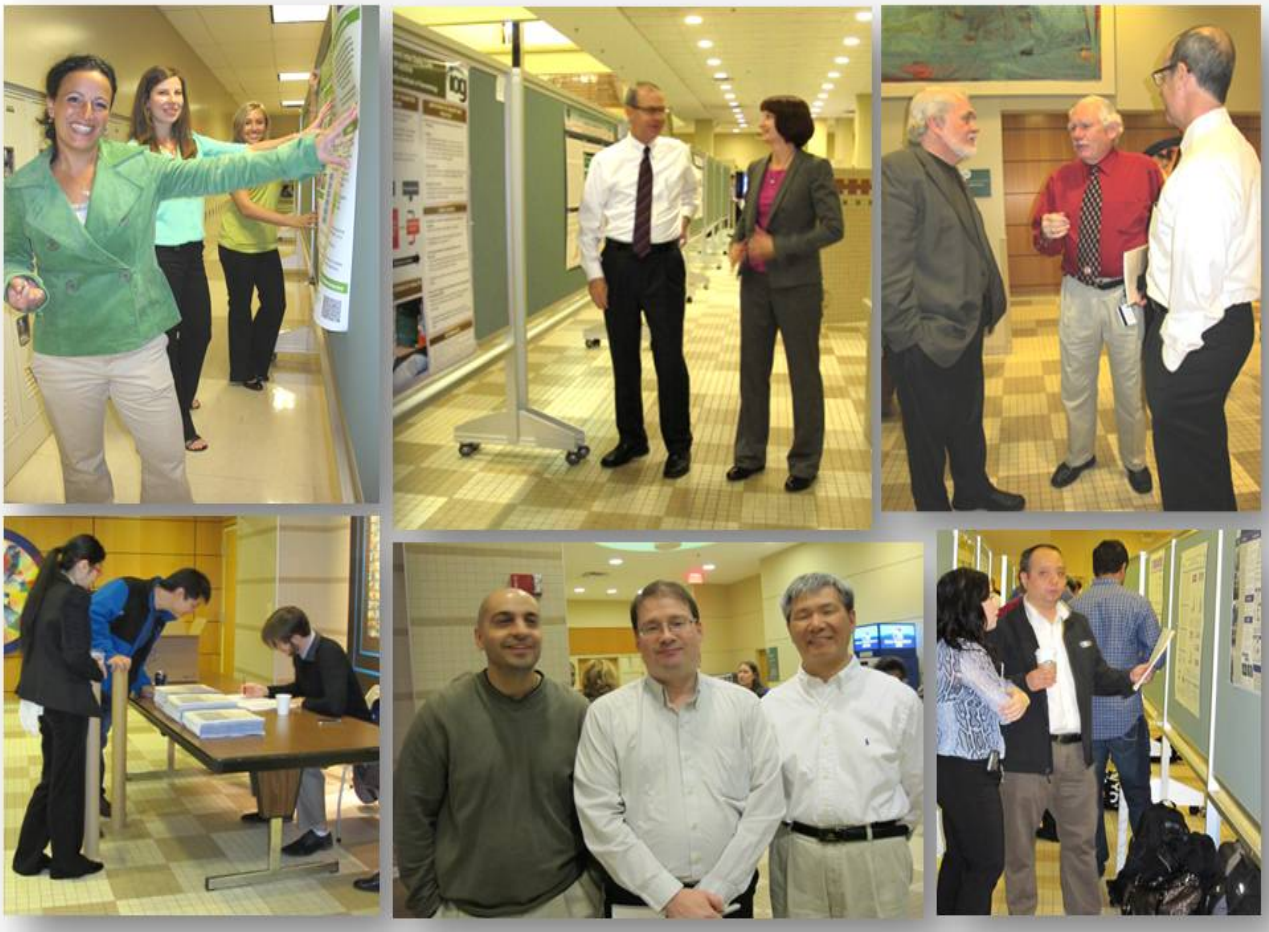
WAYNE STATE UNIVERSITY

EUGENE APPLEBAUM COLLEGE OF PHARMACY AND HEALTH SCIENCES

11th Annual Research Forum

2014



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11th Annual Research Forum

2014

Table of Contents:

Agenda:

8:00 AM Poster Setup

9:00 AM Student Poster Judging

11:00 AM Welcome:

Deepak K. Bhalla Ph.D., Associate Dean for Research

11:15 AM Key Note Speaker:

George C. Prendergast, Ph.D.

"IDO pathways in inflammation, immune escape and therapy of cancer"

12:00 PM Presentation of Awards:

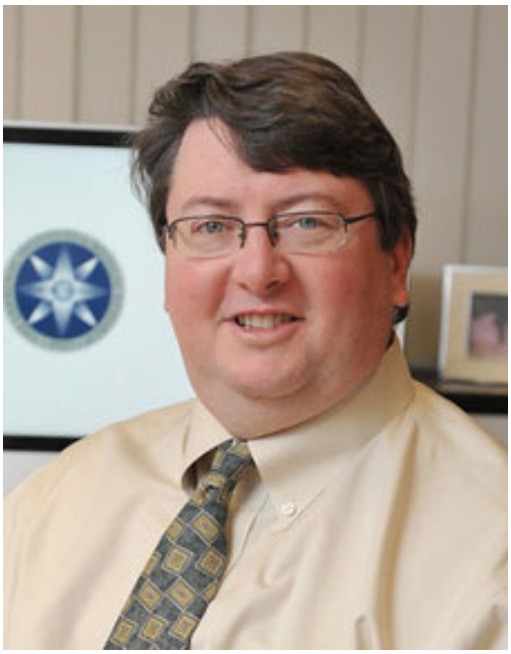
Cathy Lysack, Ph. D., Dean

12:30 PM Lunch

12:30 PM – 3:00 PM

Poster Display and Presentation

Keynote Speaker:



George C. Prendergast, Ph.D.:

IDO pathways in inflammation, immune escape and therapy of cancer

George C. Prendergast, Ph.D. is a Professor of Pathology, Anatomy and Cell Biology in the Jefferson Medical School, Thomas Jefferson University. He also holds the position of President and CEO of the Lankenau Institute for Medical Research and currently serves as the Editor-in-Chief of Cancer Research, the most-cited journal in the field. Dr. Prendergast graduated magna cum laude from the University of Pennsylvania in 1983 as a Benjamin Franklin Scholar with a BA in biochemistry. He earned an MS in molecular biophysics from Yale University in 1984 and a PhD in Molecular Biology from Princeton University in 1989. After receiving his doctorate, he continued his research as an American Cancer Society Postdoctoral Fellow at the Howard Hughes Medical Institute at NYU Medical Center.

In 1991, Dr. Prendergast joined the Department of Cancer Research at Merck Research Laboratories as a staff scientist. In 1993, he returned to academic research at The Wistar Institute in Philadelphia as an Assistant Professor. He rose through the ranks to become an Associate Professor and Assistant Chair of the Tumor Biology Group. While at Wistar, in 1995, Dr. Prendergast was designated a Pew Scholar in the Biomedical Sciences. In 1999, he left Wistar to become Senior Director of the Cancer Research Group at DuPont Pharmaceuticals Company. In 2002 he moved to Lankenau Institute for Medical Research (LIMR) as a Senior Investigator, and in 2004 he was appointed President and CEO of LIMR. In 2008, recognizing his contributions to cancer research, Dr. Prendergast was designated one of the 250 most historically influential alumni of Princeton University, and in 2012 he was named as the Inventor of the year by the Jefferson Kimmel Cancer Center.

Dr. Prendergast's research has contributed to the discovery and study of oncogenes and tumor suppressor genes in cancer, and more recently to understanding of the role of the immune system in cancer progression and treatment. His work has advanced the understanding of how cancer cells create barriers against the immune system. His group has developed an approach to degrade these barriers and stimulate the immune system in combination with chemotherapy. He is the author of 150 peer-reviewed publications and 74 book chapters, editorials and monographs. He has edited three books and holds several U.S. patents.

Poster Abstracts

Abstracts

Abstract No. 1 (Faculty)

Title

A pilot study on exercise prescription for patients with dysferlinopathies

Affilliations

Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences, Department of Health Care Sciences, Physical Therapy Program, Detroit, MI 48201, USA.

Authors

Morium Begam, BS
Amani A. Alkayyali, BS
Sujay S. Galen, PT, PhD
Joseph A. Roche, PT, PhD

Abstract

Background: Dysferlinopathies are adult-onset, non-lethal, progressive, muscle wasting syndromes that are associated with mutations in the dysferlin (DYSF) gene, which cause severe loss of muscle function leading to compromised functional independence. There are currently no known ways to reduce disease severity in patients with dysferlinopathies, and the role of physical exercise in the rehabilitation of patients with dysferlinopathies is debated. Our earlier work suggests that dysferlinopathic muscle undergoes extensive delayed-onset muscle fiber damage and inflammation following a single bout of eccentrically-biased exercise. Our current studies are aimed at testing in suitable mouse models, the effects of a 12-wk exercise program that predominantly involves maximal concentric, isometric or eccentric contractions. Hypothesis: We hypothesize that, concentrically-biased exercise is protective to dysferlinopathic muscle, whereas eccentrically biased exercise is damaging. Methods: Dysferlin-deficient A/J mice and dysferlin-sufficient CrAJ mice (males, 3-4 months) are randomly assigned to one of 4 groups, namely, ConEX (concentric exercise), IsoEx (isometric exercise), EccEx (eccentric exercise) and NonEx (no exercise) groups (N = 96 mice per strain). Each group has 3 subgroups - one to study the effects of a single bout of exercise, another to study changes induced by 12-wk of exercise, and a third Eccentric Challenge subgroup to test if 12-wk of exercise can protect muscle against damage from a single bout of eccentric exercise. The tibialis anterior muscle (TA), which is the primary ankle dorsiflexor in both mice and humans, is studied using electrophysiological, histological and biochemical methods to monitor contractile torque, muscle fiber morphology and protein levels, respectively. Results: A single bout of ConEx, IsoEx and EccEx performed by A/J muscle resulted in 0.71 ± 0.42, 3.07 ± 1.1 and 37.25 ± 3.42 damaged muscle fibers in the TA 3 days after a single bout of exercise. Conclusion: Our preliminary data suggest that concentrically-biased exercise and reduced eccentric loading might help patients with dysferlinopathies maintain muscle mass and strength, and minimize muscle damage.

Funded by a Research Grant to JAR from the Jain Foundation Inc.

Abstract No. 2 (Student_Graduate)

Title

Identification of Protein Interaction Partners of Protein Phosphatase 2A Catalytic Subunit Using Quantitative Mass Spectrometry

Affilliations

1Wayne State University, Detroit, MI ... 2University of Michigan, Ann Arbor, MI

Authors

Divyasri Damacharla1 ... Xiangmin Zhang1 ... Danjun Ma1 ... Monique Lewis1 ... Michael Caruso1 ... Wissam Anteer1 ... Yue Qi1 ... zhao yang1 ... Rodney Berry1 ... Abdullah Mallisho1 ... Zaher Msallaty1 ... Sorin Draghici1 ... Jeffrey Horowitz2 ... Berhane Seyoum1 ... Zhengping Yi1

Abstract

Introduction
The serine/threonine protein phosphatase 2A (PP2A) is a heterotrimeric complex comprising a 36KDa catalytic subunit C Regulatory subunits A and B. PP2A accounts for approximately 80% of total serine/threonine phosphatases in mammalian cells, and plays critical roles in cell functions through regulating the phosphorylation state of proteins involved in various signaling pathways. Growing evidence suggests that PP2A is hyperactivated in liver, muscle, retina and the pancreatic islet under glucolipotoxicity and type 2 diabetes (T2D). However, it remains unknown how PP2A plays the role in the development of skeletal muscle insulin resistance, a primary defect in T2D. Here, we aimed to identify the PP2Ac interaction partners involved in insulin signaling or other pathways related to the development of insulin resistance.
Methods
Eight obese/overweight non-diabetic participants (BMI: 26.7 to 36.7, ages: 29 to 57 years) were recruited and skeletal muscle biopsies were obtained before insulin infusion (basal) and after 2 hour insulin infusion in vivo. Biopsies were homogenized for immunoprecipiation with antibody against normal IgG (served as a control to filter out non-specific binders) followed by PP2Ac. The co-immunoprecipitates were resolved by 1D-SDS-PAGE and followed by analysis with HPLC/nano-ESI-LTQ-Orbitrap Elite. The Xcalibur ‘RAW’ files were searched against the Uniprot database (Homo Sapiens) using the MaxQuant. The LFQ intensity of each protein was normalized against the total intensity of proteins identified in each sample. The normalized LFQ intensity was used to determine enrichment ratio of PP2Ac-specific binding (PP2Ac/NIgG) for each protein identified. Proteins which showed a 1.5 fold change between basal and 2h biopsy samples are also determined.
Preliminary Data
PP2Ac was detected in PP2Ac immunoprecipitates from all 16 biopsies used for the study, but was not detected at all in the NIgG immunoprecipitates. Totally, 2057 proteins were identified with minimum of two unique peptides and false discovery rate at 0.01. Among them, approximately 586 proteins showed 10-fold higher binding to PP2Ac than the normal IgG control at basal and/or insulin stimulation states ($P < 0.05$). Of these, 188 proteins were identified with a peak area in more than half of the PP2Ac IP samples, which represent the largest PP2Ac interactome in vivo in human tissues to date. Multiple known PP2Ac interaction partners were identified, such as the PP2A subunit A and B, which serves as a positive control for our approach, since this is the first time PP2Ac interaction

partners were studied in human tissue using Co-immunoprecipitation and HPLCE-ESI-MS/MS. Furthermore, a large number of novel PP2Ac interaction partners were identified. Ingenuity pathway analysis for PP2Ac interactome revealed multiple significantly enriched pathways in human skeletal muscle. These results imply that PP2Ac plays an important role in many biological processes. Our results may help to pin-point the specific abnormalities in the pathways in specific to insulin resistance and type 2 diabetes. We anticipate that the novel PP2Ac interaction partners identified in human skeletal muscle tissue may help understand the various roles that PP2Ac plays in physiological and pathophysiological conditions in muscle and other tissues/organs.

Abstract No. 3 (Student_Graduate)

Title

Fluoroquinolone Sequential Therapy for Helicobacter pylori

Affilliations

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Authors

Sheila Wilhelm, Pharm.D., BCPS1, Anela Mihaescu, Pharm.D. Candidate2 and Pramodini Kale-Pradhan, Pharm.D.3

Abstract

Purpose: Resistance of Helicobacter pylori (H. pylori) to first line standard therapy is increasing globally leading to exploration of alternative treatment regimens. Once such alternative is a fluoroquinolone-based sequential regimen which consists of 5-7 days of proton pump inhibitor and amoxicillin therapy followed by 5-7 days of proton pump inhibitor, fluoroquinolone and metronidazole or tinidazole therapy. This meta-analysis compares quinolone-based sequential therapy to first-line treatment for H. pylori infection.

Methods: Medline, PubMed, and Cochrane Library CENTRAL database were searched for randomized controlled trials (RCTs), published in full in English. Included trials compared fluoroquinolone-based sequential therapy to guideline recommended first line treatment regimens in H. pylori treatment-naive adults. All selected trials confirmed H. pylori infection prior to treatment as well as post-treatment eradication. Meta-analysis was performed with Review Manager 5.2. Treatment effect was determined with a random effects model by the Mantel-Haenszel method and reported as a risk ratio (RR) with 95% confidence interval (CI).

Results: Six RCTs met the inclusion criteria. 648 of 729 patients receiving fluoroquinolone-based sequential therapy and 521 of 724 patients receiving standard regimens achieved eradication (RR 1.21 ... 95% CI: 1.08-1.35). Adverse effects reported in three of the trials were comparable for all treatments (RR 0.99 ...

95% CI: 0.76-1.29). Additionally, there was not a statistical difference in the adverse effects prompting the discontinuation of therapy (RR 1.03 ... 95% CI: 0.34-3.09). Eradication rate appeared similar among the trials with respect to duration of therapy and daily dose of fluoroquinolone.

Conclusion: Fluoroquinolone-based sequential therapy is a reasonable treatment alternative for first line eradication of H. pylori.

Abstract No. 4 (Post_Doctoral_Fellow)

Title

Dysfunctional Protein Phosphatase 2A in Human Skeletal Muscle in Type 2 Diabetes

Affilliations

1 Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy/Health Sciences, Wayne State University, Detroit, MI ... 2 Department of Physiology, Wayne State University School of Medicine, Wayne State University, Detroit, MI ... 3Department of Computer Science, College of Engineering, Wayne State University, Detroit, MI ... 4 Division of Kinesiology, University of Michigan, Ann Arbor, MI

Authors

Xiangmin Zhang1, Divyasri Damacharla1, Michael Caruso1, Monique Lewis1, Danjun Ma1, Zhao Yang1, Yue Qi1, Rodney Berry1, Berhane Seyoum2, Zaher Msallaty2, Wissam Al-janabi1, Rebecca Tagett3, Sorin Draghici3, Jeffrey F. Horowitz4, and Zhengping Yi1

Abstract

Protein phosphatase 2A (PP2A), a major serine/threonine phosphatase, regulate multiple cellular events such as insulin signaling. PP2A can inactivate/activate multiple kinases (e.g. Akt, GSK3), and emerging evidence suggests hyperactivation of PP2A in liver, muscle, retina and islets under the duress of glucolipotoxicity. Nonetheless, most experiments regarding PP2A activity and regulation were carried out in cell/animal models. Whether these findings can be translated into humans is currently unknown. Recently, we identified the catalytic subunit of PP2A (PP2Ac) and the 65 kDa regulatory subunit A alpha (PP2Aa) as novel IRS1 interaction partners in human skeletal muscle, and demonstrated increased interactions of these PP2A subunits with IRS1 in muscle of type 2 diabetic subjects (T2D) compared to lean controls (LC). Here, we further explored the activity and regulation of PP2A in T2D. 1st, we assessed overall PP2A activity in muscle biopsies from 4 LC and 4 T2D subjects. The PP2Ac activity was significantly lower after 2h insulin infusion in LC, while unchanged in T2D between basal and 2h biopsies. 2nd, we determined the level of carboxylmethylation of leucine309 (mLeu309) of PP2Ac (known to activate PP2A) from 4 LC and 3 T2D. There is a trend of decrease for mLeu309 in LC after 2h insulin infusion. However, insulin did not reduce mLeu309 in T2D at all. 3rd, proteomics analysis on muscle biopsies from 5 participants revealed 89 PP2Ac interaction partners, including PP2Aa, and protein phosphatase methylesterase 1 that activates PP2Ac through mLeu309 of PP2Ac. In summary, these results provided the 1st experimental evidence that insulin's ability to suppress PP2A activity (possibly through suppressing mLeu309 of PP2Ac) is impaired in T2D muscle, and provided the largest

PP2Ac interaction network in skeletal muscle in humans. These novel findings may facilitate the design of new drugs to restore abnormal PP2Ac activity and improve insulin signaling, resulting in the treatment/prevention of T2D.

Abstract No. 5 (Faculty)

Title

Older Adult Home Visit: Real Life Interprofessional Education

Affilliations

Wayne State University, Physician Assistant Studies, Pharmacy Practice, Occupational Therapy, School of Medicine
University of Florida Department of Physical Therapy

Authors

Stephanie J. Gilkey, M.S., P.A.-C., DFAAPA, Mary Beth O'Connell, Pharm.D., BCPS, FASHP, FCCP, Gerry Conti, PhD, OTRL, FAOTA, FMiOTA, Kim Dunleavy, Ph.D., Jennifer Mendez, Ph.D.

Abstract

Purpose:
To analyze Physician Assistant Studies students' (PAS) opinions of expectations and fulfillment of learning objectives (i.e. healthy aging, interprofessional team care, and home visits) from an interprofessional team visit (IPTV).

Methods:
Forty-three PAS were matched with a medical and pharmacy student to visit as a team an independently living older adult. Student teams participated in pre-visit orientation, post-visit discussion, and post-visit debriefing ... completing a learning survey after each activity. Survey options were strongly agree, agree, disagree or strongly disagree. The PAS were assigned a tool to obtain a family health history ... other students performed nutrition, prevention screening, and medication review. Descriptive statistics and qualitative analysis of open-ended questions were conducted. Qualitative comments were coded and analyzed for themes related to learning objectives. Differences between expectations (pre) and learning (post) were analyzed with the related-sample Wilcoxon signed rank test ... $p < 0.05$ significant.

Results:
Forty-three student teams met with older adults, mean age 77.8 years, in the older adult's home (79%), or non-clinical settings. PAS (100%) agreed that teamwork skills are vital and believed they would be more effective within a healthcare team (93%). Most students (91%) learnt about older adult issues from observing other healthcare student assessments, and thought more positively about other healthcare professionals after the visit (95%). Most IPTV expectations were generally similar to post-experience opinions, except one related to the ability to solve the older adult health problems from the assessments conducted by other health care students ... they did not believe the IPTV increased their ability to do so: 95% pre visit versus 80% post visit ($p=.005$). PAS expressed dissatisfaction with the genogram assessment tool. Eighty-one percent wanted more team learning experiences.

Discussion: The older adult home visit IPTV program provides unique exposure to the interprofessional health team and is perceived by students to facilitate learning.

PAS participation will continue with a change in the assessment tool.

Abstract No. 6 (Student_Graduate)

Title

Arsenic-induced reactive oxygen species in Akt activation and cell migration

Affilliations

Department of Pharmaceutical Sciences, Wayne State University

Authors

Lingzhi Li, Ph.D ... Yongju Lu, Bachelor ... Fei Chen, Ph.D

Abstract

We have previously reported that arsenic, a well-known environmental carcinogen, induces phosphorylation of several putative Akt substrates. In the present report, we characterized one of these substrates by immunoprecipitation and mass spectrometry. The results indicate that a cytoskeleton remodeling protein, filamin A, with a molecular weight of 280kD, is phosphorylated by Akt in HEK-293 cells treated with arsenic, which was also confirmed in human bronchial epithelial cell line, BEAS-2B cells. Additional biochemical and biological studies revealed that serine 2152 (S2152) of filamin A is phosphorylated by Akt in cellular response to arsenic. Inhibition of the reactive oxygene species by NAC attenuated arsenic-induced Akt activation and filamin A phosphorylation. Thus, these data suggest that Akt dependent filamin A phosphorylation may be one of the key events in mediating arsenic-induced carcinogenesis. Antioxidant that antagonizes reactive oxygen species can ameliorate arsenic-induced Akt activation and filamin A phosphorylation, which may serve as a molecular targeting strategy for malignancies associated with environmental arsenic exposure.

Abstract No. 7 (Student_Graduate)

Title

Characterization of Isu1 Scaffold Protein Structure and Function In Vitro

Affilliations

Wayne State University
Wayne State University
University of Pennsylvania

Authors

Stephen Dzul
Timothy Stemmler, PhD
Andrew Dancis, MD

Abstract

Friedreich’s ataxia (FRDA) is a debilitating neurodegenerative disease currently affecting 6,000 Americans. Recent progress in FRDA research has linked pathogenesis of FRDA to the absence of Frataxin (Fxn), a protein that regulates iron-sulfur cluster (Fe-S) biosynthesis, possibly by serving as a regulator of the pathway or as an iron chaperone that delivers metal to protein partners in the Fe-S cluster bioassembly (ISC) pathway. In eukaryotes, the predominant ISC assembly pathway is located within the mitochondria and driven by coordinated association with a scaffold

protein (Isu1), a cysteine desulfurase that provides atomic sulfur (Nfs1), an accessory protein (Isd11) and frataxin (Yfh1). This project aims to characterize the active site of the Isu1 protein in addition to the overall ISC assembly complex. The findings of this study will help in the development of strategies to augment the activity of this pathway in the absence of frataxin. All studies will be performed in the yeast system, where the genetics of Fe-S cluster assembly have been well established. Our preliminary hypothesis is that Fxn provides two Fe(II) atoms and Nfs provides two sulfur atoms at distinct sites on Isu1. Subsequent Isu1 rearrangement brings both sulfur and Fe(II) species together at Isu1's active site to accomplish cluster assembly. This proposal follows two specific aims. Firstly, Isu1 will be manipulated to identify and characterize critical residues essential for Fe-S assembly. Secondly, a multi-protein expression plasmid, with all ISC complex proteins present, will be utilized to determine how Isu1, Nfs1, Isd11 assemble in the presence/absence of frataxin.

Abstract No. 8 (Student_Graduate)

Title

siRNA Targeted Delivery to Ovarian Cancer Cells via Folate Conjugated Triblock Co-polymer

Affilliations

- Department of Oncology, Wayne State University School of Medicine, Detroit, MI 48202
- Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy & Health Sciences, Detroit, MI, 48201

Authors

Steven K. Jones - B.S Biochemistry, Ph.D in progress
Olivia Merkel - Ph.D

Abstract

Purpose: Our project had two purposes. First, we wanted to use our Folate conjugated tri-block co-polymers to increase the targeted delivery of siRNA to cancer cells that over-express Folate Receptor α ... (FRα ...). Secondly, by co-encapsulating Paclitaxel (PTX) and siRNA targeting certain proteins such as Toll-Like Receptor 4 (TLR4) or Multidrug Resistance Gene (MDRG), we aim to sidestep challenges in standard treatment of ovarian cancers ... such as chemo-resistance, relapse and toxicity.
Methods: Our tri-block copolymer consists of polyethyleneimine-graft-polycaprolactone-block-poly(ethylene glycol), or folate coupled PEI-g-PCL-b-PEG-Fol. In our work, we looked at these polymers with different molecular weights of PEG, as well as different grafting degrees of the (g-PCL-b-PEG-Fol) chains to PEI to find the optimal delivery mechanism for siRNA uptake into the cancerous cells. For characterization of the polymers we used Dynamic Light Scattering, Transmission Electron Microscopy, Confocal Microscopy, NMR, and other biological assays for determining optimal polymer-to-siRNA (N/P) ratios for best siRNA uptake. Biological techniques such as MTT, qRT-PCR, and flow cytometry help assess the efficacy of co-delivery of our folate conjugated tri-block copolymers with siRNA and PTX.
Results: The different PEI-g-PCL-b-PEG-

Fol conjugates that were tested showed suitable sizes below 260nm, especially at N/P 5 which also allowed for full siRNA condensation. Furthermore, at N/P 5, each polymer was able to deliver the siRNA effectively in comparison to our positive control PEI. Confocal and Transmission microscopy showed the particle sizes, siRNA condensation, and delivery ability. Preliminary experimental data suggests that by using our polymers to knockdown TLR4, we can effectively side step chemo-resistance seen to PTX.
Conclusion: We have demonstrated that our polymers are effectively able to condense and deliver siRNA and achieve knockdown within the cell. This suggests that our polymers could be a good mechanism to deliver siRNA for oncogene knockdown and avoid chemo-resistance.

Abstract No. 9 (Student_Graduate)

Title

Training Urban Older Adults on Internet Use via Computers and iPads: Quality of Life Outcomes

Affilliations

Occupational Therapy Master of Science Program

Authors

Nancy Vandewiele Milligan PhD, OTRL Widad Asoufy,BS Amanda Kokas,BS Ling Vuong,BS and Sarah Wojciechowski,BS

Abstract

Technology is one of the fastest growing industries in the country. One reason is the convenience and ease of it ... technology makes it possible to do things that once took hours or even days, in a matter of minutes. Examples include the ability to immediately pay bills, send emails, access information on any topic, and video chatting, among many others. A rapidly growing population in the United States is that of the elderly. According to the Department of Health & Human Services, the older population — persons 65 years old or older — numbered 39.6 million in 2009. The elderly represent 12.9% of the U.S. population, approximately one in every eight Americans. People 65 and older are expected to grow to 19% of the population by 2030 (Aging Statistics, 2014). There is a great disconnect between senior citizens and the use of technology, specifically the Internet. The elderly have consistently fallen behind their younger counterparts when it comes to using computers and the Internet. Smith (2014) found that many seniors remain unattached from technology — 41% do not use the Internet at all, 53% do not have broadband access at home, and 23% do not use cell phones. The growth of our elderly population means there is an increasing need for healthcare services. Technology is beginning to play a larger role in the delivery of these services, as well as the availability of healthcare related resources. Over the past 20 years, Internet technology has increased access to health-related and non-health related information, facilitated communication and social connections (Choi & DiNitto, 2013).
The purpose of the study is to educate older urban adults on how to use the Internet to connect with others and to access information. Participants in the study are trained on using either iPads and laptops. The primary research question: What are the benefits of training older adults to browse the Internet? This will be assessed using multiple tests and questionnaires. We also

examine whether or not Internet training promotes an elderly person to take a more active role in their healthcare through access to health information websites, since accessing healthcare information is much easier when done online ... this fact is underscored when it can be done in the comforts of one's own home. The study also examines if computer training assists a senior to develop new leisure activities and interests, and whether or not computer training increases a person's quality of life. Past studies imply there should be a positive correlation in this area.
The second research question examined is: Which is a better mode of training this population to browse the Internet: iPad or Laptop? The participants will be using both devices and will be questioned about which one is easier to use.

Abstract No. 10 (Student_Graduate)

Title

Large Scale Kinome Analysis of Human Skeletal Muscle using ATP Probes and HPLC-ESI-MS/MS

Affilliations

1 Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy/Health Sciences, Wayne State University, Detroit, MI. 2 Department of Physiology, Wayne State University School of Medicine, Wayne State University, Detroit, MI. 3 Department of Computer Science, College of Engineering, Wayne State University, Detroit, MI.

Authors

Yue Qi1 ... Danjun Ma1 ... Michael Caruso1 ... Monique Lewis1, Xiangmin Zhang1 ... Wissam Al-janabi1 ... Divyasri Damacharla1,Zhao Yang1, Rodney Berry1 ... Abdullah Mallisho2 ... Zaher Msallaty2 ... Sorin Draghici3 ... Assia Shisheva2 ... Berhane Seyoum2 ... Zhengping Yi1

Abstract

Protein kinases play important roles in regulation of phosphorylation-based signal transduction, which significantly impact insulin signaling and glucose metabolism. Abnormal kinase abundance and activity is observed in insulin resistance in skeletal muscle, a primary defect in overweight/obese population.. However, these studies are mainly performed in cell cultures or animal models, targeting only a limited number of known kinases. No large scale kinome analysis has been reported in skeletal muscle in human. We hypothesize the kinases involved in insulin signaling and glucose metabolic pathways will be significantly enriched in human skeletal muscle due to its critical role in these two pathways.
Skeletal muscle biopsies from 8 non-diabetic participants were homogenized and desalted by ZebaTM Spin desalting Columns. The muscle lysates were labeled with ActivX Desthiobiotin-ATP Probe, followed by in-solution tryptic digestion overnight. The desthiobiotin labeled peptides were pulled down by Streptavidin agarose resin and desalted by C18 Ziptip, followed by mass spectrometry analysis using NanoHPLC-LTQ-Orbitrap Elite. Full scan was acquired using the Orbitrap mass analyzer to obtain high mass accuracy and high mass resolution data. Meanwhile, up to 20 peptides are selected for fragmentation by a second mass analyzer (LTQ). Linear gradient, mobile phase ACN in 0.1%FA started from 10 to 35% for 180 minutes, flow rate, 200nl/min. The raw files were analyzed by the MaxQuant software.

The ActivX Desthiobiotin-ATP Probe is designed to specifically bind to highly conserved lysine in ATP binding sites, therefore, kinases containing active ATP binding pockets may be pulled down by this probe. Using a combination of the ATP probe and proteomics, in small skeletal muscle biopsies from 8 participants, we identified 123 unique kinases in human skeletal muscle tissue, which is a task currently cannot be achieved using Western blot analysis due to the limited amount of human tissue. These 123 kinases constitutes approximately 24% of the human kinome (with 518 total kinases), and is the largest catalogue of kinases identified in human skeletal muscle tissue to date. Multiple kinases known to regulate insulin action and to be impaired in skeletal muscle insulin resistance were identified, such as AKT2, MAPK1, MTOR, PDPK1, PIK3CG and PRKAG. Gene Ontology analysis for the 123 kinases indicated that 13 of them are involved in glucose metabolic process (E.g., PDPK1, MTOR, MAPK1, AKT2, PRKAG2 and GSK3A). Furthermore, Ingenuity pathway analysisfor these kinases revealed multiple significantly enriched pathways in human skeletal muscle, such as insulin receptor signaling (with 14 kinases assigned to this pathway), mTOR Signaling (with 15 kinases assigned to this pathway), and PI3K/AKT Signaling (with 11 kinases assigned to this pathway), which play an important role in insulin signaling and glucose metabolism. The present results suggest that ATP Probes combined with HPLC-ESI-MS/MS may be an efficient way for kinome profiling. Further study will focus on quantitative human kinome analysis among lean, overweight/obese and diabetic subjects to discover abnormal kinase signatures in obesity and type 2 diabetes.
Identified 123 kinases in human skeletal muscle tissue, the largest catalogue of kinases identified in human tissue to date.

Abstract No. 11 (Student_Graduate)

Title

Identification of the mdig interaction partners through proteomics

Affilliations

1.Department of Pharmaceutical Sciences, Wayne State University ...
2.Wuhan University

Authors

Wei Wang, Bachelor Degree ... Yongju Lu ... Kai Wu ... Fei Chen, Phd.

Abstract

Increased expression of the mineral dust-induced gene (mdig, also named as mina53, MINA, or NO52) has been implicated in the pathogenesis of a number of human cancers. How mdig contributes to the cancer cell growth or epigenetic regulation of genes remains to be fully understood. Previous studies suggested that mdig protein may be involved in the demethylation of the tri-methyl lysine 9 of histone H3 (H3K9me3) through its JmjC domain. However, distinguishing from typical histone demethylases, the mdig protein lacks chromatin-binding domains, such as WD repeats and/or PHD fingers. Thus, the activities of mdig on chromatin or histone proteins are most likely achieved through its interaction with other chromatin binding partners. To test this hypothesis, we performed proteomics analyses for the protein complexes that were

immunoprecipitated from lung cancer cell line A549 cells. On SDS-PAGE gels, three to five unique protein bands were consistently presented in the complexes pulled-down by mdig antibody, but not the control IgG. In addition to the target protein mdig, several chromatin binding proteins, including XRCC5, XRCC6, RBAP46/48, CBX8, and TDRD, were identified by the proteomics analyses using liquid chromatograpy-tandem mass spectrometry in three independent experiments. The interaction of mdig with some of these chromatin binding proteins was further validated by co-immunoprecipitation using antibodies against mdig and its partner proteins, respectively. These data, thus, provide evidence showing that mdig interacts with other chromatin binding proteins to accomplish its functions on epigenetic regulation, DNA replication, DNA repair, and cell growth.

Abstract No. 12 (Post_Doctoral_Fellow)

Title

Deficiency in mdig gene ameliorates silica-induced pulmonary fibrosis by altering balance between Th17 and Treg T cells and reducing lung infiltration of the Th17 cells

Affilliations

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3 Respiratory Medicine, The 4th Affiliated Hospital, China Medical University, Shenyang, Liaoning Province, China ...
4 The Central Laboratory of the Wuhan Central Hospital, Tongji Medical School, Huazhong University of Science and Technology, Wuhan, Hubei 430014, China

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Michael Wolfarth2,
Jiaying Sun1,3,
Yadong Zhang2,4,
Yongju Lu1,
Lori Battelli2,
Dale W. Porter2,
Fei Chen1,2

Abstract

Mineral dust-induced gene (mdig, also named Mina53) was first identified from alveolar macrophages of the coal miners with chronic lung inflammation or fibrosis, but how this gene is involved in lung diseases is poorly understood. To investigate whether mdig contributes to the pathogenesis of lung inflammation and/or fibrosis, we established a heterozygotic mdig gene knockout mouse strain (mdig+/-) and evaluated the degree of lung fibrosis induced by silica in both wild type (WT) and mdig+/- mice. We found that silica exposure through pharyngeal aspiration induced severe lung damage in both WT and mdig+/- mice that advanced with the exposure time and silica dose.However, relative to the WT mice, lungs from silica-exposed mdig+/- mice showed a reduced macrophage infiltration, coinciding with a significant attenuation of the lung fibrosis as determined by the collagen deposition. Additional tests revealed that partial deficiency of the mdig gene weakens T helper 17 (Th17) T cell infiltration into the

lung as well as decreases IL-17 levels in the bronchoalveolar lavage (BAL) fluids in response to silica. In contrast, an increased infiltration of the T regulatory (Treg) cells to the lung intestitium was observed in the mdig+/- mice treated with silica. Thus, these results suggest that mdig may contribute to silica-induced lung fibrosis by altering the balance between Th17 and Treg cells. Genetic deficiency of mdig impairs Th17 cell infiltration and function, but favors infiltration of the Treg cells, the immune suppressive T cells that are able to limit the inflammatory responses by repressing the Th17 cells and macrophages. In other words, the presence of mdig gene favors the formation of lung fibrosis induced by silica through promoting the Th17 cells, the most important T lymphocytes that drive inflammation and fibrosis. These results may be clinically relevant for designing sufficient treatment strategies against pulmonary fibrogenesis or other allergic diseases by targeting mdig and the Th17 T cells.

Abstract No. 13 (Post_Doctoral_Fellow)

Title

Increased expression of mdig predicts poorer survival of the breast cancer patients

Affilliations

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Authors

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Abstract

Breast cancer is the most common cancer and the second leading cause of cancer death among women of all races and Hispanic origin populations in the United States. In the present study, we reported that the survival time of the breast cancer patients is influenced by the expression level of mdig, a previously identified lung cancer-associated oncogene encoding a JmjC-domain protein. By checking the expression levels of mRNA and protein of mdig through both RT-PCR and immunohistochemistry in samples from 204 patients, we noticed that about 30% of breast cancer samples showed increased expression of mdig. Correlation of the mdig expression levels with the survival time of the breast cancer patients indicated a clear inverse relationship between mdig expression and patient survival, including poorer overall survival, distant metastasis free survival, relapse free survival, and post-progression survival. Taken together, these data suggest that an increased expression of mdig is an important prognostic factor for poorer survival time of the breast cancer patients.

Abstract No. 14 (Student_Graduate)

Title

The prevalence of anterior pelvic tilt in the prosthetic-wearing lower limb amputee

Affilliations

Wright & Filippis - Warren, MI

Authors

Jenna Barbour, SPT ... Brooke Binder, SPT ... Alyssa Paglia, SPT ... Kristina Reid, M.S., P.T.

Abstract

Background: Approximately 1 in 190 Americans are living with a lower limb amputation.1 Prosthetic devices improve functioning level of these individuals. As they increase use of their prosthetic limb during daily tasks, abnormal tissue loading and deformation of structures can occur. These changes can result in altered alignment at the pelvis such as anterior pelvic tilt causing increased lumbar lordosis. This alteration can lead to increased low back pain (LBP) in this population.

Objective: To investigate if there is a difference in anterior pelvic tilt (APT) between the sound limb and the amputated limb in transfemoral amputees (TFA) and transtibial amputees (TTA). Our second objective is to investigate if a relationship exists between APT and LBP in amputees.

Methods: Seventeen participants (N=17) were randomly assigned to a sequence of four conditions in which their APT was measured 3 times bilaterally. The four conditions included: static standing, sit to stand, walking 10 feet, and marching in place 20 times. Participants were also asked to complete the Oswestry Disability Index (ODI) and Prosthetic Evaluation Questionnaire (PEQ).

Results: The results revealed no statistically significant difference from sound side to amputated side in any of the 4 conditions for both the TFA and TTA populations (p=0.621-0.671). Results also showed no statistically significant relationship between APT and LBP in TTA sample. A correlation exists between the ODI and PEQ questionnaires for being a predictor for LBP (r=-0.602, p=0.050).

Conclusion: Based on the results, there is no significant difference in APT between the sound side and amputated side in the transtibial amputees in this study which may indicate that there is no effect from the biomechanical alignment of the socket to APT in this population. The findings also suggest no correlation between increased APT and the prevalence of LBP. Due to limited sample size, more research is needed regarding APT in the TFA population.

Abstract No. 15 (Student_Graduate)

Title

Feasibility of the Lower Extremity Fugl Meyer Assessment in Acute Stroke

Affilliations

Wayne State University

Authors

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Katherine Reyes, SPT
Allon Goldberg, PT, PhD
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Abstract

Purpose/Hypothesis: The Fugl-Meyer Assessment Scale (FMA) is a standardized quantitative outcome measure that assesses motor function following a stroke. The lower extremity subscale (FMA-LE) has been studied in chronic stroke and found to have good reliability and concurrent validity. The feasibility of using the FMA-LE for the acute stroke population has not been studied to date. The purpose of this study was to determine the feasibility (patient tolerance, duration of testing) of the FMA-LE in individuals with acute stroke in an inpatient rehabilitation setting.

Number of Subjects: Twenty-one participants with acute stroke (mean 17.95 days post-stroke) resulting in unilateral hemiparesis were recruited from an inpatient rehabilitation setting in the Metro Detroit area.

Materials/Methods: Participants were assessed using the FMA-LE, twice on the same day with at least a 5 minute rest in between assessments. The duration of each FMA-LE assessment was recorded. Blood pressure (BP), heart rate (HR), oxygen saturation (SpO2) and pain were measured before, during the 5 minute rest, and after the two trials. Rate of perceived exertion (RPE) was measured before, during and after each trial of the FMA-LE. The primary investigator reviewed medical records to determine mobility status, length of inpatient rehab stay, and discharge disposition.

Results: The mean time to complete the FMA-LE for each trial was 9.45 and 8.85 minutes. Mean changes in vitals were very small: systolic BP less than 1.33 mmHg (SD 11.66), diastolic BP less than 4.86 mmHg (SD 8.11), HR less than 2 beats/minute (SD 8.06), SpO2 less than 0.6% (SD 1.25). Using the visual analog scale, mean change in pain was less than 0.3 (SD 1.31). The average RPE throughout the assessment was 7.74, with a mean change of less than 1.5 units (SD 1.53). Participants scored between 10 and 34 out of a possible 34 points on the FMA-LE. The subjects' primary therapist used the following measures of motor recovery: 43% used the Chedoke-McMaster Stroke Assessment, 0% used the FMA-LE or Brunnstrom staging, and 57% used manual muscle testing.

Conclusions: The amount of time necessary to perform the FMA-LE (less than 10 minutes) in the acute stroke population demonstrates that this is an outcome measure that can be incorporated into the initial assessment of the inpatient rehabilitation population. The minimal changes in vitals, pain and RPE demonstrate the FMA-LE is tolerated well by the acute stroke population in the inpatient rehabilitation setting. The medical record review indicates that the FMA-LE is not used, with over half of the subjects having their motor recovery measured by manual muscle testing.

Clinical Relevance: In patients with acute stroke in an inpatient rehabilitation setting, the FMA-LE was shown to be feasible, well tolerated by this patient population and not time consuming for the therapist. These preliminary results should be used to encourage clinicians to use the FMA-LE when assessing motor recovery in the acute stroke population.

Abstract No. 16 (Student_Graduate)

Title

Use of Complementary and Alternative Medicine (CAM) in an Urban Teaching Hospital

Affilliations

Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences, Harper University Hospital.

Authors

Sheila Wilhelm, Pharm.D. ... Mandy Khemmoro, Pharm.D. Candidate 2016 ... Alyssa McKay, Pharm.D. Candidate 2016, Jesse Shuster, Pharm.D.

Abstract

Introduction: Complementary and Alternative Medicine (CAM) covers a broad range of practices and products. The National Center for Complementary and Alternative Medicine (NCCAM) categorizes CAM into two subgroups: natural products or mind and body practices. The natural product group includes a wide variety of options, such as herbals, vitamins, minerals and probiotics. Mind and body practices include various groups of procedures or techniques, such as acupuncture and massage therapy. Data from the 2007 National Health Interview Survey (NHIS) found that almost 4 out of 10 American adults use CAM therapy. However, the patterns of CAM use in urban populations have not been extensively studied.
Purpose: to prospectively categorize and assess an urban patient population's current and past use of CAM therapies. Also, the study aims to determine whether pharmacists who are conducting medication history interviews are gathering complete and accurate information regarding their patients' use of CAM therapies.
Methods: This single-group, descriptive study will involve interviewing a sample of patients admitted to Harper University Hospital who have had a pharmacy driven medication history interview completed and documented in the electronic medical record in the past 24-72 hours. Pharmacists who conduct medication interviews will introduce the study to their patients and, after generating a medication list, will make a copy for research use and to recruit patients eligible for study. The research interviews regarding CAM use will be live, verbal, face-to-face, and will be conducted by research personnel using a standardized CAM questionnaire and script. The CAM questionnaire was developed based on the results of the comprehensive NHIS, cross referenced with published surveys that assessed more specific aspects of CAM use. The research personnel reviewed and revised the resulting survey tool and any disagreements were resolved through discussion and consensus. The types of CAM therapies that are included in the questionnaire were selected based on data from the NHIS survey and a list of the most common CAM therapies published on the NCCAM website. During the interview, the research personnel will record anonymous patient responses on hard-copy survey forms. No protected health information will be collected or accessed for this survey. After the interview, the research personnel will compare the patient's responses to the de-identified, already completed pharmacy medication history to determine whether medication history interviews conducted by pharmacy personnel are complete and accurate with regard to information on CAM therapies.
Results: Results are expected Spring 2015.

Abstract No. 17 (Student_Graduate)

Title

Feasibility of Inter-professional Team-Based Screening for Hepatitis C Infection Among Patients in Ambulatory Care Settings

Affilliations

(1) Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Science and (2) the Department of Internal Medicine, School of Medicine, Wayne State University, Detroit, MI.

Authors

Xinwei Gu, Pharm. D. Candidate, 2016 (1), Prateek Lohia, M.D. (2), Abdulbaset Salim, M.B.Ch.B., M.P.H.(1), Carolyn Archer, M.Sc., (1), Paul E. Kilgore, M.P.H., M.D. (1)

Abstract

Background:
The reported rate of chronic hepatitis C virus (HCV) infection in Detroit is 172 per 100,000 vs. 81 per 100,000 in Michigan. To our knowledge, there has been no study looking at an integrated strategy to screen for HCV among a lower income population in primary care settings. The objective of this study is to determine the feasibility of an interdisciplinary screening program for HCV in Detroit.

Methods:
This study has been submitted to Detroit Medical Center/Wayne State University (DMC/WSU) institutional review boards. This pilot study is designed for conduct in the DMC/WSU general medicine ambulatory (GMAP) clinic. Adult patients aged 49-69 years are eligible for inclusion in this study. For detection of antibody to HCV, the OraQuick HCV rapid antibody test (OraSure Technologies, Inc., Bethlehem, PA) will be performed on oral swab specimens. A standardized algorithm for education, consent, testing and post-test counseling was established in accordance with current guidelines from the US Centers for Disease Control and Prevention and the Infectious Disease Society of America. Patients who test positive will undergo post-test counseling with a primary care provider. If appropriate, confirmatory nucleic acid detection test will be performed. Test results and counseling activities will be documented in patients' electronic medical record. During screening and HCV testing, patients will undergo a brief survey to assess the presence of potential risk factors for HCV.

Results:
During development and feasibility stages of this pilot study, an intensive literature review identified the use of several different HCV test kits. However, no studies evaluated use of a HCV test in a low income urban population.
An environmental review of the clinic setting was performed to ensure staff support and identify the most efficient strategy for patient education, consenting, testing and post-test counseling.
Upon arrival, eligible patients are triaged according to standard clinic procedures. A medical assistant or nurse will check vital signs and a pharmacist will guide patients through the informed consent process. Consenting patients will then undergo oral swab collection and the sample will be placed into the Developer Vial. Development of the sample takes 20 to 40 minutes. Once the test result is obtained, patients will be invited to a clinic examination room for discussion of their test results and post-test counseling.

We also reviewed HCV educational materials published by various organizations. Most of them are readily accessible online. These materials provide information on diagnosis and treatment of HCV, as well as various sources of support, such as toll-free consultation from Hep-4-Help and HCV community by American Liver Foundation. CDC has the most comprehensive educational materials and HCV statistics. The Michigan Department of Community Health website provides additional HCV statistics specific to the State of Michigan.

Conclusion:
The GMAP clinic provides a suitable environment with excellent logistics to conduct an inter-professional pilot survey of outpatient HCV screening and education among an urban population. Experience in this pilot study will be used to scale-up HCVscreening across other primary care settings in Detroit.

Abstract No. 18 (Faculty)

Title

Hand use and the control of grasp-force post-stroke - a pilot study

Affilliations

Physical Therapy Program - Matthew Pierce, SPT, Ken White, SPT, Anthony Ruvolo, SPT, Vicky Pardo PT, DHS,Diane E. Adamo

Institute of Gerontology - Diane E. Adamo PhD

School of Medicine, Department of Neurology - Kumar Rajamani MD, DM,

Authors

Matthew Pierce, SPT, Ken White, SPT, Anthony Ruvolo, SPT, Vicky Pardo PT, DHS, Kumar Rajamani MD, DM, Diane E. Adamo PhD

Abstract

The extent of hand use and grasping ability post stroke may be related to hand preference which is seldom taken into consideration when implementing treatment programs. The purpose of this study was to investigate how shifts in hand preference are related to motor recovery and the ability to perform grasp force matching tasks in right handed stroke survivors.
Methods: Twenty-one participants, (13 with right hemisphere stroke ... 8 with left hemisphere stroke) performed hand grasp tasks. Pre/post stroke hand preference, maximum voluntary grip exertions and the Upper-Extremity Fugl-Meyer were administered to the participants. For grasping tasks, participants matched a 20% reference force established with their affected and less affected hand, then matched with the same and opposite hand. The matching force, quantified as the Constant Error (CE), indicated whether the participant overshot or undershot the reference force. Relative error (RE) was quantified as the % target difference between the reference and matching force.
Results: Findings showed that right side affected individuals used their right hand less after their stroke
($p < .01$), and left side affected individuals tended to use their right hand more after their stroke ($p = .30$). Right (29.6 ± 11.5kg) and left (20.2 ± 12.2kg) maximum grip strengths were significantly different
($p < .01$) only for participants with left hemiplegia. Post-stroke hand preference and Fugl-Meyer scores were strongly correlated

(r = .72 ... p < .05) only for right side affected (those with right hemiplegia). For CE, left side affected showed right hand overshoots (23.4 ± 4.6N) and left hand undershoots (-6.3 ± 3.7N) and right side affected showed left hand overshoots (19.4 ± 6.8N) and right hand undershoots (-4.5 ± 5.9N). When matching with the same, there were no significant differences for between the groups. Overall, greater RE was found in those with right side affected (p < .05). Discussion: Shifts in handedness scores indicated more use of non-affected hand post stroke to perform everyday tasks. Prior to testing many participants reported they rarely used their affected hand, however findings from this showed that shifts in hand preference were related to motor recovery and contributed to asymmetries in grasp force matching ability. Of particular interest was the observation that generating reference forces less than 4kg in their more affected hand provided enough motor information that allowed them to remember and reproduce forces in the opposite - less affected hand. These findings suggest that some level of force perception is preserved following a stroke. Using force matching paradigms offers promising alternatives to traditional treatment interventions. Further, by providing visual feedback during force generation, individuals were better able to realize their potential for improving grasp control in both hands. Lesion location and hand preference are factors to consider in designing hand rehabilitation programs that may benefit from using visual feedback in the restoration of unimanual and bimanual grasp force control.

Abstract No. 19 (Student_Graduate)

Title

Biophysical Characterization of the Frataxin-bypassing mutant, Isu1 M107I

Affilliations

(1) Wayne State University
(2) University of Pennsylvania

Authors

April L. Kusowski (1)
Ashoka Kandegedara (1)
Andrew Dancis (2)
Timothy L. Stemmler (1)

Abstract

Iron-sulfur (Fe-S) clusters are utilized ubiquitously in nature to provide diverse functionality as cofactors bound to proteins that drive in some regard nearly every biochemical pathway. In eukaryotes, the mitochondrial Fe-S cluster bioassembly pathway provides the majority of the Fe-S clusters required by cells. This pathway is driven within the mitochondrial matrix by the cofactor assembly scaffold protein, Isu1 (in
yeast). Isu1 receives iron and sulfur from protein partners and will assemble the 2Fe-2S cluster, which it can then provide for downstream insertion into proteins that require
the cofactor for activity. The protein Frataxin, which when deficient is the direct cause
of the neurodegenerative disease Friedreich's Ataxia, acts in some capacity with other
proteins to regulate Isu1 activity. Recently, the Dancis laboratory has discovered a supressor mutant of Isu1 that

functions in the absence of Frataxin. This Isu1 bypass mutant, M107I, rescues iron homeostasis and Fe-S cluster assembly activity that is impaired in Frataxin-deleted cells. The goal of this work is to characterize the biophysical properties and reactivity of the suppressor mutant in order to provide an enhanced understanding of the role of Frataxin in driving eukaryotic Fe-S cluster assembly.

Abstract No. 20 (Student_Graduate)

Title

Modified Cysteine conjugated pro-drug of neuroprotective antiparkinsonian drug D-264: Synthesis and pharmacological characterization for the treatment of Parkinson’s disease

Affilliations

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Authors

1Fahd Dholkawala, 1Chandrashekhar Voshavar, 1Liping Xu, 1Aloke Dutta

Abstract

Parkinson's disease (PD) is a complex neurodegenerative disorder with progressive loss of dopamanergic neurons in the substantia nigra region of the brain and accumulation of intracytoplasmic inclusions called ‘Lewy bodies’. PD is characterized by tremors, rigidity, slowness of movement, bradykinesia and postural imbalances. Although the etiology of PD is not well understood, it is well established that oxidative stress, mitochondrial dysfunction, alpha-synuclein aggregation play a central role in the pathogenesis of PD. Current treatment methods are based on symptomatic relief without addressing the underlying pathophysiological factors responsible for the disease. It is important to develop therapies which can address these complex pathogenesis of the disease process and providing symptomatic relief as well. Towards development of novel multifunctional dopamine D2/D3 agonist drugs for the treatment of Parkinson’s disease (PD), D-264 was previously synthesized in our lab. D-264, a potent D3 preferring agonist, is one of our lead compounds which showed high neuroprotection in MPTP & Lactacystin PD animal models. However, this drug seems to have minimal brain penetration. In order to further enhance the efficacy and bio-availability of D-264 in the brain, we have designed a cysteine based D-264 prodrug as a substantial amount of research points out an important role of antioxidants such as L-cysteine in reducing the oxidative stress associated with PD .
To this end, we have evaluated the ex vivo hydrolysis pattern of synthesized prodrug to yield active D-264 in brain & plasma solutions using RP-HPLC. In order to evaluate the efficiency of prodrug in crossing blood-brain barrier, in vivo brain penetration studies were performed and efficiency of hydrolysis was quantified using RP-HPLC. Further, DPPH based anti-oxidant assay was performed to evaluate the anti-oxidant property of prodrug. Details of prodrug design, synthesis and pharmacological evaluation will be presented. This work is supported by NS047198 (AD)

Abstract No. 21 (Post_Doctoral_Fellow)

Title

NOVEL HIGH AFFINITY MULTIFUNCTIONAL D2/D3 AGONIST D-512 WITH POTENT NEUROPROTECTION PROPERTY: MECHANISTIC EVALUATION OF MULTIFUNCTIONAL PROPERTIES

Affilliations

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Authors

Chandrashekhar Voshavar, Mrudang Shah, Liping Xu, Aloke Dutta*

Abstract

Parkinson's disease (PD) is a heterogeneous, progressive neurodegenerative disorder that results from the degeneration of dopaminergic (DA) neurons within the substantia nigra region of the midbrain. Mitochondrial dysfunction and oxidative stress are strongly implicated in the pathogenesis of PD. Glutathione metabolism is thought to play a key role in the pathology of the disease process also. In our overall goal to develop bifunctional/ multifunctional drugs as neuroprotective treatment agents for PD, we have developed dopamine D2/D3 agonist molecules with potent antioxidant activity. Such molecules should not only address symptomatic aspect of the disease by normalizing motor dysfunction but also at the same time should slow down or stop the process of degeneration. In this regard, we have evaluated one of our lead compounds D-512, a novel potent D2/D3 receptor selective agonist, for potential symptomatic and neuroprotection treatment agent for PD. To this end, we have evaluated the neuroprotective effect of D-512 in PC12 cells (rat pheochromocytoma) against 6-OHDA induced cytotoxicity. D-512 also shows the free radical scavenging property in PC12 cells against sodium nitroprusside induced lipid peroxidation. In order to evaluate the mechanisms of neuroprotection of D-512, we have carried out a series of experiments involving detection of modulation of level of glutathione and MAP kinase activities upon treatment with D-512. Furthermore, in order to evaluate whether D-512 could confer any protection against DNA cleavage, DNA laddering assay was carried out. Details of study, design and the results will be presented. Supported by NS047198 (AKD).

Abstract No. 22 (Post_Doctoral_Fellow)

Title

Further Structure Activity Relationship (SAR) study of novel hybrid N6-(2-(4-(1H-Indole)piperazine-1-yl)ethyl)-N6-propyl-4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine analogues: Development of highly potent and selective D3 receptor preferring agonist molecules.

Affilliations

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Authors

1Seenuvasan Vedachalam, 1Banibrata Das, 2Tamara Antonio, 2Maarten. E. A. Reith, 1Aloke Dutta

Abstract

Parkinson's disease (PD) is an age-related and progressive movement disorder that is characterized by dopaminergic neuronal loss in the substantia nigra region of the brain. Dopamine modulates movement, cognition, and emotion through activation of dopamine receptors in the brain. PD is a multifactorial disease caused by oxidative stress and mitochondrial dysfunction in neuronal cells with subsequent reduction of the dopamine level. An interesting development in the use of dopamine receptor agonists for the treatment of PD is that some of them may prove to be neuroprotective such as D3 receptor preferring agonists. Targeting dopamine D3 receptor, a subfamily of dopamine D2-class of receptors, for various CNS disorders is drawing much attention because of its unique location of D3 receptor. It has also been shown that selective D3 receptor agonists can provide neuroprotection in PD by inducing brain derived neurotrophic factors (BDNF). Much of the pharmacological actions mediated by D3 receptor are still unresolved because of the lack of highly potent and selective D3 receptor agonist. In our previous communication, we described the development of a series of hybrid molecules for D2 and D3 receptors that showed high agonist potency by combining pharmacophoric elements of aminothiazole and piperazine molecular fragments derived from known dopamine receptor agonist and antagonist molecules. In our present SAR study, we used N6-(2-(4-(1H-Indole)piperazine-1-yl)ethyl)-N6-propyl-4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine analogues to design such drugs. In these molecules, we specifically introduced various indole derivatives as accessory binding sites which led to the discovery of highly potent and selective molecules for D3 receptor. Compounds were characterized both in the in vitro binding and functional assays. Synthesis and in vitro binding and functional characterization will be presented. This work is supported by NS047198 (AD).

Abstract No. 23 (Post_Doctoral_Fellow)

Title

Chemical Synthesis, Characterization and Biological Evaluation of 3-Substituted Isatin Inhibitors of N5-CAIR Synthetase

Affilliations

Department of Pharmaceutical Sciences
College of Pharmacy and Health Sciences

Authors

Shiv K. Sharma PhD, Melissa Topper PhD, Maria Fawaz MS, and Steven M. Firestine PhD

Abstract

Antibiotics are arguably one of the most important discoveries in modern medicine. Unfortunately, their dominance is slowly being eroded by the rise of organisms resistant to antimicrobial drugs. Thus, there is clearly a need for the continued development of novel antibiotics that target previously under-explored pathways. One such pathway is de novo purine biosynthesis. Previous research has shown

that the pathway is fundamentally different between microorganisms and humans. The divergence is centered on the microbial enzyme, N5-carboxyaminoimidazole ribonucleotide (N5-CAIR) synthetase. Humans do not require this enzyme nor do they possess a homolog of the protein. Previous research in our laboratory has discovered that isatin and its analogs inhibit N5-CAIR synthetase. We discovered that: (a). small substituents off of N1 are preferred ... (b). the amide carbonyl group at C2 is required ... (c). electron-withdrawing groups are preferred on the aromatic ring ... and (d). preferred substitution on the aromatic ring is 5≈ ... 7>6>>4 ... 5,7-disubstitution is tolerated. To further investigate the substitution effect on the 3-position on these inhibitors, we have synthesized 3-phenylamino, and 3-phenylhydrazino and their analogs and examined their ability to inhibit N5-CAIR synthetase. We have found that phenylamino and phenylhydrazino moieties though big in size compared to corresponding keto group but are well tolerated on the 3-position on isatin and these compounds are good inhibitors. The antibacterial properties of these compounds against Staphylococcus aureus were also examined. We found that several compounds inhibited bacteria ... however, growth inhibition could not be recovered by the addition of purines indicating that the antibacterial effects of these agents was not due to inhibition of the purine pathway. Details biological results along with chemical synthesis of isatin analogs will be presented.

Abstract No. 24 (Faculty)

Title

An Epigenome-Wide Assessment of Atypical Antipsychotic Side Effects in Bipolar Disorder

Affilliations

[1] Wayne State University Eugene Applebaum College of Pharmacy and Health Sciences, Department of Pharmacy Practice ... [2] University of Michigan School of Public Health, Department of Environmental Sciences ...
[3] University of Michigan, College of Pharmacy, Department of Clinical Social and Administrative Sciences and [4] University of Michigan, School of Medicine, Department of Psychiatry

Authors

Kyle J. Burghardt, Pharm.D.[1], Jacyln M. Goodrich, Ph.D.[2], Dana C. Dolinoy, Ph.D.[2] Vicki L. Ellingrod, Pharm.D.[3,4]

Abstract

Background: Atypical antipsychotic (AAP) use has become increasingly common over the past 10 years in both the acute and maintenance phases for patients with bipolar disorder, which has brought with it an increase in cardiovascular mortality. While many different risk factors are thought to be at the root of this medication related adverse event, little work has investigated environment and gene interactions. Investigating AAPs' effects on DNA methylation or, pharmacoepigenetics, incorporates the effect of the environment on genetic manipulation and may allow for identification of new biomarkers for AAP metabolic side effects. How AAPs influence

DNA methylation in bipolar subjects is currently unknown. Our group has previously reported that bipolar subjects treated with AAPs carrying the highest risk for metabolic side effects have low global DNA methylation using the LUminometric Methylation Assay (LUMA). Therefore the aim of this investigation was to examine differences in global DNA methylation in bipolar subjects treated with AAPs or lithium monotherapy using the Illumnia 450K BeadChip.
Methods: DNA was collected as part of a larger study assessing metabolic syndrome in bipolar disorder. All subjects (n = 96) had clinical and fasting metabolic measurements taken within 3 hours of their normal waking time. Subjects also underwent a brief dietary and exercise assessment. Bipolar disorder diagnosis was verified by a structured clinical interview and medical chart review. Illumina 450K data was preprocessed using several bioinformatics strategies including: 1) removal of poor quality probes, 2) removal of SNPs found on array, 3) probe-to-probe normalization and 4) batch normalization. Subjects were grouped based on Lithium or AAP use and compared using R statistical software packages and controlling for age, gender, diet and exercise.
Results: Of the 96 bipolar subjects included, 66 were on AAPs and 30 were on lithium monotherapy. The average age was 44.9±11.2 years, 62.5% were female and 90% were Caucasian. No other significant demographic differences between the groups were found. No samples were removed after reviewing data quality from array. Preliminary results have identified a probe contained within the Protein Tyrosine Phosphatase Receptor Type N Polypeptide 2 (PTPRN2) gene that was hypomethylated in the AAP population (corrected p-value = 0.02) compared to those receiving lithium. This gene is associated with autoantibody production in type I diabetes. Analysis is ongoing and future work will investigate differentially methylated regions based on treatment type.
Conclusions: This work is the first to investigate DNA methylation of bipolar subjects based on AAP use. We have identified a potential target in a gene associated with aberrant glucose regulation in type I diabetes. Future work will be to identify the top 5 differentially methylated regions of interest and use these results to look at gene methylation more in depth at the single nucleotide level. Identification of a new biomarker linked to AAP metabolic side effects in bipolar disorder is exciting and important as it may lead to personalized medicine therapy and therapy targeted at treating the altered methylation seen in a particular gene (e.g., methyl-donor therapy).

Abstract No. 25 (Post_Doctoral_Fellow)

Title

The induction of immune tolerance to Type II Collagen through anterior chamber associated immune deviation

Affilliations

Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA.

Authors

Shukkur M Farooq, Ph.D.
Hossam M Ashour, Ph.D.

Abstract

Type II Collagen (CII) is a structural protein in cartilage and plays important roles in joint function, arthritis, and aging. In studying the ability of CII to induce eye-mediated specific immune tolerance, we studied the ability of CII to induce eye-mediated immune tolerance in different strains of mice. We hypothesized that CII induces anterior chamber associated immune deviation (ACAID) through the AC route (direct injection) or the intravenous route (adoptive transfer of in vitro-generated CII-specific ACAID macrophages or of CII-specific in vitro-generated T regulatory cells). Specific immune tolerance induction was assessed using both delayed-type hypersensitivity (DTH) and local adoptive transfer (LAT) assays. Results indicated the generation of CII-specific ACAID-mediated immune tolerance in vivo and in vitro in all tested strains of mice. These findings could be beneficial in studies of immune tolerance induction using CII.

Abstract No. 26 (Student_Graduate)

Title

Development of a Fluorescent Competitive Binding Assay Utilizing Fragments of the First Known Selective N5-CAIR Mutase Inhibitor

Affilliations

(1) Department of Pharmaceutical Sciences - EACPHS WSU
(2) MD/PhD Program - WSU SOM

Authors

Cale C. Streeter (1,2), Shiv K. Sharma PhD (1) and Steven M. Firestine PhD (1)

Abstract

Microbes have developed resistance mechanisms to every clinically relevant anti-microbial therapeutic agent. Bacterial strains resistant to daptomycin and linezolid, the only two FDA approved anti-microbial agents in the past decade, were discovered within 5 years of clinical use. Drug resistant microbial infections result in higher mortality rates, increased duration of hospital stays and increased health care costs.
The development of a novel anti-microbial agent, leveraging the divergence in de novo purine biosynthesis between bacteria, fungi and lower eukaryotes and higher eukaryotes, is a promising route of investigation. Microorganisms produce carboxyaminoimidazole ribonucleotide (CAIR) from the unstable intermediate, N5-carboxyaminoimidazole ribonucleotide (N5-CAIR), via the action of the enzyme N5-CAIR mutase. In contrast, vertebrates produce CAIR from aminoimidazole ribinucleotide (AIR), via the action of the enzyme AIR carboxylase. Development of a fluorescent competitive binding assay for the N5-CAIR mutase reaction will be useful for investigating known inhibitors as well as adaptation for high throughput screening. Chiral fragments of compound 1 show increased inhibition of N5-CAIR mutase over the original compound (Ki of 10 µM compared to 26 µM). The fluorophore dansyl chloride was conjugated to the “l” enantiomer fragment (SKS-IV-24) and demonstrates a Kd of 121 µM with N5-CAIR mutase. Assay conditions are being investigated to maximize the fluorescent shift between the bound and unbound state of SKS-IV-24 to N5-CAIR mutase.

Abstract No. 27 (Faculty)

Title

Immediate Effect of Whole Body Vibration on Gait in Patients with Incomplete Spinal Cord Injury: Preliminary Results.

Affilliations

1. Rehabilitation Institute of Michigan, Detroit.
2. Physical Therapy Program, EACPHS.

Authors

Diane Patzer, MPT ... Phuong Vu, MPT ... Vicky Pardo, PT DHS ... Sujay Galen, PT PhD.

Abstract

Background
Whole body vibration (WBV) is relatively a new intervention that is being increasingly used in the rehabilitation of spinal cord injured (SCI) patients. An important observation that was recently made in patients with incomplete SCI was the reduction in spasticity in their lower extremities immediately following the application of WBV, especially within the first 15 minutes. However to date there have been no scientific investigations that have studied the immediate effect of reduction in spasticity following WBV on walking in patients with incomplete SCI (ISCI).
Aim

The aim of this study was to investigate the immediate effects of WBV on gait in Incomplete SCI patients

Methods
A cross over design was adopted to research the immediate effects of WBV following two types of WBV interventions (Type A and Type B). All subjects received the two types of intervention twice over a 4 week period ... however the order in which these interventions were delivered were randomized. Type A intervention consisted of four bouts of WBV lasting 45 s each with three 60s rest periods interspersed between each bout. Type B intervention consisted of a WBV dosage (number of bouts of WBV) matched to the severity of the subject's lower extremity (LE) spasticity. Subjects assessed as having mild, moderate or severe LE spasticity received two, three or four bouts of WBV respectively. A rest period of 60s was interspersed between each bout of WBV. The spatio-termporal gait parameters (walking speed, stride length, stance time, swing time, double support time, and foot contact pattern) were recorded before and after WBV intervention using an insole based wireless gait assessment tool (Wi-GAT). Subjects were randomly tested either immediately after the WBV intervention (test 1) or following a 15 minute delay (test 2). A total of 10 subjects participated in this study and 9 have completed the study.

Results
The preliminary results seem to suggest that WBV may have beneficial effects on gait in individuals with incomplete Spinal Cord Injury. These are only trends identified from a preliminary analysis and therefore needs to be interpreted with caution.

Gait parameters seem to show greater improvements when they were recorded after a 15 minute delay compared to immediately after WBV. This finding is in agreement with a previous study that found a greater reduction in muscle tone following a 15 minute delay.

Conclusions

These are preliminary results and therefore must be interpreted with caution. The results so far seem to suggest that WBV as a pre-gait intervention may be useful for patients with incomplete spinal cord injuries.

Abstract No. 28 ()

Title

COMPARING EMG AMPLITUDE PATTERNS OF RESPONSES DURING DYNAMIC EXERCISE: POLYNOMIAL VERSUS LOG-TRANSFORMED REGRESSION

Affilliations

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Authors

Robert J. Blaesser, SPT, Lauren M. Couls, SPT, Carolyn F. Lee, SPT, Jorge M. Zuniga, PhD and Moh H. Malek, PhD

Abstract

The purposes of this study were to determine if 1) the log-transformed model can be applied to dynamic exercise and 2) the slope and y-intercept terms can provide additional information above and beyond the polynomial regression analyses. Eleven physically active individuals performed incremental cycle ergometry on a single occasion. Electromyographic (EMG) electrodes were placed on the three superficial quadriceps muscles to record muscle activation during the exercise test. The patterns of responses for EMG amplitude versus power output were analyzed with polynomial and log transformed regression models. The results of the polynomial regression for the composite data indicated that the best-fit model for the vastus lateralis muscle was linear ($R2 = 0.648$, $p < 0.0001$), whereas the best-fit model for the rectus femoris ($R2 = 0.346$, $p = 0.013$) and vastus medialis ($R2 = 0.764$, $p = 0.020$) muscles was quadratic. One-way repeated measures analyses indicated no significant differences ($p > 0.05$) across the three superficial quadriceps muscles for the slope and y-intercept terms. These findings suggest that the log-transformed model may be a more versatile statistical approach to examining neuromuscular responses during dynamic exercise.

Abstract No. 29 (Student_Graduate)

Title

RELIABILITY OF THE LOG-TRANSFORMED EMG AMPLITUDE-POWER OUTPUT RELATIONSHIP FOR INCREMENTAL KNEE-EXTENSOR ERGOMETRY

Affilliations

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Authors

Travis Eason SPT, Christine R. Gavel SPT, Kyle A. Hawley SPT, Sujay S. Galen PhD PT, and Moh H. Malek PhD

Abstract

The purpose of this investigation was to determine the reproducibility of the log transformed model for the EMG amplitude during incremental single-leg knee extensor exercise. Eight healthy college-aged men performed three incremental tests using a Monday Wednesday Friday schedule on the knee-extensor ergometer. The EMG amplitude was analyzed using the log-transformed model for each participant on each occasion for the rectus femoris and vastus medialis muscles. In addition, we examined the EMG response at four different exercise power outputs (30%, 50%, 70%, and 90%) corresponding to each participant's maximal power output. Furthermore, intraclass correlation coefficients (ICC) were determined for the slope and y-intercept terms derived from the log-transformed EMG amplitude-power output relationship for each muscle. The ICC values for the rectus femoris (slope = 0.779 ... and y intercept = 0.787) and vastus medialis (slope = 0.756 ... and y intercept = 0.763) muscles were high. The results of this study indicate that the log-transformed EMG amplitude-power output relationship for EMG amplitude during incremental single-leg knee extensor exercise is a reliable index of measuring motor unit activation.

Abstract No. 30 (Post_Doctoral_Fellow)

Title

Design, synthesis and pharmacological evaluation of novel multifunctional dopamine D2/D3 agonists with iron chelation property: potential implication in symptomatic and neuroprotective treatment of Parkinson's disease

Affilliations

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Authors

1Banibrata Das, 1Liping Xu, 2Tamara Antonio, 2Maarten E. A. Reith, 1Aloke K. Dutta

Abstract

Parkinson's disease (PD) is the second most common form of neurodegenerative disorders that results from the progressive loss of dopaminergic neurons in the midbrain substantia nigra pars compacta (SNpc) triggering profound motor perturbation, as well as cognitive, sensory and mood deficits. Although extensive research has been done to elucidate the underlying molecular events leading to neuronal death, yet the cause and individual steps in the pathogenesis of the disease are still not understood well and thus, PD remains a progressive and incurable condition. It is generally believed that oxidative stress, neuroinflammation, compromised natural antioxidant defense, protein aggregation and impaired mitochondrial functions are the mainstream predisposing factors implicated in the pathogenesis of PD. Due to complexity of the pathogenesis of PD, it is increasingly evident that drugs targeting only a single site may not be sufficient to slow the disease progression and alleviate motor dysfunction at the same time. In our overall goal to develop multifunctional drugs as neuroprotective treatment agents for PD, we designed novel dopamine D2/D3 agonist molecules with a capacity to address some underlying pathological factors in PD

including chelating iron to reduce oxidative stress. The molecules exhibited high affinity for both D2 and D3 receptors where as in GTPγ ... S functional assay, the lead compound (-)-D-583 showed potent agonist activity at both D2 and D3 receptors (EC50 (GTPγ ... S) ... D2 = 3.14 nM and D3 = 0.62 nM). Furthermore, the lead molecules demonstrated potent antioxidant activity in DPPH assay and also exhibited iron chelation property. In PD animal model study, both lead molecules (-)-D-583 and (-)-D-607exhibited potent in vivo activity in reversing hypolocomotion in reserpinized rats. In cell culture study, the selected compounds demonstrated significant reduction of toxicity induced by treatment with 6-hydroxy dopamine, thereby, producing neuroprotection effect. This work is supported by grants from NINDS (NS 047198, AKD).

Abstract No. 31 (Student_Graduate)

Title

Nephrotoxicity Risk and the Use of Concomitant Vancomycin and Piperacillin/Tazobactam

Affilliations

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2.Oakwood Hospital and Medical Center, Dearborn, Michigan

Authors

Areej Kattan PharmD candidate (1,2), Aamna Khan Pharm D.(2), Francine Salinitri PharmD(1,2), Raymond Cha PharmD(1,2) , Lama Hsaiky PharmD(2).

Abstract

Background: The incidence of drug-induced nephrotoxicity has been known to increase morbidity and prolong hospitalization. In current literature, there is a 1.0-42.6% rate of vancomycin-associated nephrotoxicity (VAN) amongst a variety of patient populations. Recent reports suggest that piperacillin/tazobactam may be associated with higher rates of nephrotoxicity when used in combination with vancomycin. There is however, a lack of reporting on patient specific risk factors that pre-dispose a patient to nephrotoxicity associated with piperacillin/tazobactam and vancomycin. Identifying these risk factors could potentially improve antimicrobial stewardship and minimize nephrotoxicity when prescribing empiric antibiotics in hospital acquired infections.
Objective: this study aims to identify risk factors predisposing patients to nephrotoxicity with the combination of piperacillin/tazobactam and vancomycin.
Methods: This is a retrospective case-control study that compares the incidence of predetermined risk factors in cases of nephrotoxicity and controls in 200 patients who received vancomycin and piperacillin/tazobactam between January 2013 and May 2014 for at least 24 hours. The primary endpoints are the incidence of nephrotoxicity among piperacillin/tazobactam recipients and the incidence of patient specific risk factors such as hemodynamic instability, age, admission unit, dose, and trough prior to nephrotoxicity.
Data collected includes baseline demographic data as well as lab values at initiation and completion such as blood pressure, serum creatinine, BUN/SCr Ratio, albumin, ect. Other major variables include co-morbid disease states, indication for antibiotic use, duration and dose of

vancomycin, vancomycin levels, duration and dose of piperacillin/tazobactam, number of days of concomitant therapy, number and names of concomitant nephrotoxic agents used before and during therapy, need for dialysis, ICU status, APACHE II scores, and Charleston Comorbidity Index.
Logistic Regression will be used to determine factors that are correlated with nephrotoxicity.
Results: Out of 71 patients who received the combination of vancomycin and piperacillin/tazobactam, nephrotoxicity occurred in 21 patients (30%). Patients who experienced nephrotoxicity were in the Risk (60%), Injury (30%), or Failure (10%) categories per RIFLE criteria. Patients who developed nephrotoxicity were mostly above 60 years of age (70%) ... were more obese with an average difference of 38 kg between the two groups, and had a longer hospital stay (5 days on average). They also had a higher APACHE II score (13 in the nephrotoxicity group vs. 11.5) and higher Charleston Comorbidity Index (55% in the nephrotoxicity group vs. 44%). Also, compared to the non-nephrotoxicity group, 27 (76%) of patients who experienced nephrotoxicity were on greater than three concomitant nephrotoxic agents during therapy.
Conclusion: Findings from the study suggest there might be potential risk factors contributing to the nephrotoxicity associated with the vancomycin and piperacillin/tazobactam combination. Identifying these risk factors could potentially minimize nephrotoxicity when prescribing empiric antibiotics in hospital acquired infections. More data is needed to identify whether the combination of piperacillin/tazobactam is an independent risk factor for nephrotoxicity.

Abstract No. 32 (Post_Doctoral_Fellow)

Title

DEVELOPMENT OF PHARMACOPHORE MODEL AND ASYMMETRIC SYNTHESIS OF NOVEL TETRAHYDROFURAN DERIVATIVES ENROUTE TO TRIPLE REUPTAKE INHIBITORS AS ANTI-DEPRESSANT AGENTS

Affilliations

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Authors

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Abstract

Unipolar depression, caused by an imbalance of monoamine neurotransmitters in brain, is ranked as the most prevalent of all somatic and psychiatric illness. It is estimated that about 40 % of patients remains refractory to treatment thereby limiting the use of current antidepressant drugs. Moreover, because of relapse and unwanted side effects of existing drugs there is an unmet need to discover novel agents for the treatment of this devastating mental disorder. Current treatment aims at alleviating extraneuronal concentration of serotonin (5-HT) and /or norepinephrine (NE) (Figure 1). Tricyclic antidepressants

were among the first class to have been discovered but due to their nonspecific side effects they have limited use in clinics. They have been largely replaced by second-generation antidepressants including selective serotonin reuptake inhibitors (SSRI, e.g., fluoxetine, Figure 2), selective norepinephrine reuptake inhibitors (NRI, e.g. reboxetine, Figure 2), and serotonin and norepinephrine reuptake inhibitors (SNRI, venlafexine, Figure 2).

Abstract No. 33 (Student_Graduate)

Title

Target trough achievement using a vancomycin nomogram versus individualized pharmacokinetic dosing

Affilliations

1 Wayne State University
2 St. John Hospital and Medical Center

Authors

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Abstract

Purpose: To evaluate achievement of target vancomycin trough levels using a vancomycin nomogram versus individualized pharmacokinetic dosing

Methods: This single-center, retrospective cohort study will be conducted at a 772 bed community teaching hospital. Patients ≥ ... 18 years will be included if they received pharmacy managed vancomycin dosing for greater than 48 hours from January 2011 to June 2014 . Patients will be excluded if they received dialysis or have a creatinine clearance (CrCl) <30 mL/min.. The following patient information will be collected: age, weight, sex, type of infection, serum creatinine, nephrotoxicity, duration of vancomycin, and initial vancomycin trough concentration. CrCl will be calculated using the Cockcroft-Gault equation. Baseline demographics and clinical outcomes will be analyzed using the chi-squared test for nominal variables and student's t-test for continuous variables using SPSS v. 20.0.

Preliminary Results: 396 were screened with 60 patients entering the nomogram group and 40 patients in the pharmacokinetic group. Average troughs in the nomogram versus pharmacokinetic group versus were 11.7 ug/ml and 12.8 ug/ml, respectively. Over 95% of goal troughs for patients in either group were in the 15-20 ug/ml range. Target trough levels of 15-20 ug/ml were obtained in 20.7 % (12/58) of the nomogram group and 31.6% (12/38) of the pharmacokinetic group.

Conclusions: Preliminary findings show a trend towards under-dosing of vancomycin with the nomogram versus individualized pharmacokinetic dosing.

Abstract No. 34 (Student_Graduate)

Title

Evaluation of Vancomycin Dosing per Nomogram: A Tale of Two Institutions

Affilliations

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3 Providence Hospital, Southfield, MI

Authors

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Abstract

Purpose: To evaluate obtainment of target vancomycin trough levels using two different vancomycin dosing nomograms.

Methods: This two-center, retrospective cohort study will be conducted at two community teaching hospitals. Patients ≥ ... 18 years with a documented vancomycin trough will be included if they received pharmacy managed vancomycin dosing for greater than 48 hours from January 2011 to June 2014. Patients will be excluded if: creatinine clearance (CrCl) < 30 mL/min, receiving dialysis, vancomycin dosed based on random levels, or admitted to ICU. The following patient information will be collected: age, weight, sex, type of infection, length of hospital stay (LOS), baseline serum creatinine (SCr), dose, duration of therapy, and initial trough level. CrCl will be calculated by using the Cockcroft-Gault equation. Baseline demographics and clinical outcomes will be analyzed using the chi-squared test for nominal variables and student's t-test for continuous variables using SPSS v. 20.0.

Preliminary Results: 211 patients were screened ... 24 and 16 were included at Hospital 1 and Hospital 2, respectively. Target trough was obtained in 29.2% (7/24) of patients at hospital A with an average level of 12.7mg/L and 31.3% (5/16) of patients at hospital B with an average level of 14.1mg/L.

Conclusions: Preliminary results suggest both nomograms are not attaining the target concentrations.

Abstract No. 35 (Student_Graduate)

Title

The Influence of Oligospermine Architecture on their Suitability for siRNA Delivery

Affilliations

Department of Oncology, Department of Pharmaceutical Sciences

Authors

Dan Feldmann, B.S. ... Maha Elsayed, B.S ...
Kim, Rohit Kolhatkar,PhD ... Olivia M Merkel, PhD

Abstract

Spermines are naturally abundant polyamines, which partially condense nucleic acids and exhibit the”proton-sponge effect” in an acidic environment. However, spermine shows limited transfection efficiency of nucleic acids due to its low molecular weight. Therefore, spermines need to be modified to be used as non-viral vectors for nucleic acids. Here, we synthesized and studied linear bisspermine, linear tetraspermine and dendritic tetraspermine with different molecular architecture to be used as self-assembled polyplexes that are cable of delivering siRNA. The structure-activity relationship of the oligospermines was evaluated in terms of their efficiency to deliver siRNA in a non-small cell lung carcinoma cell line. Oligospermines displayed minimal cytotoxicity and efficient siRNA condensation with better stability against polyanions than polyethylenimine. The morphology of the polyplexes was strongly affected by the oligospermine architecture. Linear tetraspermine/siRNA polyplexes showed the best gene silencing efficiency among the oligospermines tested on both the mRNA and protein expression levels which suggests the most favorable structure for siRNA delivery. In order to increase the efficiency and specificity of these spermines, we have coupled the glycoprotein transferrin to linear tetraspermines. After transferrin conjugation, we then characterized the polyplex size and the ability for it to deliver siRNA to the lung carcinoma cells.

Abstract No. 36 (Post_Doctoral_Fellow)

Title

Beta-lactam combinations with daptomycin (DAP) provide synergy against vancomycin-resistant Enterococcus faecalis (Efc) and Enterococcus faecium (Efm)

Affilliations

Wayne State University

Authors

Jordan R Smith, PharmD ... Katie E Barber, PharmD ... Animesh Raut, BS ... Michael J Rybak, PharmD, MPH

Abstract

Background:
Efc and Efm are frequently resistant to vancomycin (VAN) and beta-lactam (BL) antibiotics. In vitro data suggest potent synergy between several BLs and VAN or DAP. Our objective was to evaluate BL synergy with DAP against resistant enterococci.

Methods:
Two Efc strains (R6981 and R7808), and one isogenic non-DAP-R/DAP-R Efm strain pair (8019/5938) were evaluated. DAP MICs were obtained via microdilution in the absence and presence of ceftaroline (CPT), ertapenem (ERT), cefepime (FEP), ceftriaxone (CRO), cefotaxime (CTX), cefazolin (CFZ), and ampicillin (AMP). All combinations were evaluated for synergy using time-kills. DAP at 0.5 x MIC was used in combination with BL at either biologic free concentration or 0.5 x MIC. R6981 and 8019 were evaluated for response to LL-37, a human cationic peptide with a similar

mechanism to DAP, in the presence and absence of ERT and AMP. 96h, in vitro models were run with DAP 10 mg/kg/day (fCmax 11.3 mg/L), CPT 600 mg q8h (17.04), AMP 2 g q4h (70), and ERT 1 g q24h (15.5) both alone and in combination against R6981 and 8019.

Results:
CPT reduced DAP MIC values the most against all strains. In time-kills, CPT, ERT, FEP, CRO, and AMP demonstrated synergy with DAP against all strains, CFZ demonstrated none, and CTX demonstrated synergy against only 8019. Bacterial reduction at 24h was statistically greater for DAP + CPT, ERT, FEP, CRO, or AMP for all strains compared to any single agent or DAP + CFZ or CTX ($p<0.001$). ERT and AMP similarly augmented LL-37 killing against strain 6981. In 8019, ERT aided LL-37 killing more than AMP ($p<0.001$). PK/PD models demonstrated bactericidal activity with DAP and CPT (-4.7 log10 CFU/ml at 96h), AMP (-4.9) or ERT (-4.1) against strain 8019 ($p<0.001$ and log10 CFU/ml reduction >2 compared to any single agent). Against strain R6981, DAP and AMP demonstrated no synergy (-1.7 log10 CFU/ml compared to most active single agent), while the combinations of DAP and CPT (-5.1) or ERT (-4.9) were both bactericidal and demonstrated synergy at 96 hours ($p<0.001$).

Conclusions:
The data support the potential use of DAP/BL combination therapy in VRE. Combination regimens provide better kill and prevent resistance compared to DAP alone. Further clinical research involving DAP combination therapy is warranted.

Abstract No. 37 ()

Title

Reported incidence of nausea, vomiting, and pain after receiving Ofirmev in patients undergoing laparoscopic sleeve gasterectomy

Affilliations

Wayne State University

Authors

Mary Rabina SRNA, Cynthia Taasn SRNA, Rachna Desa SRNA, Kristine Faust, CRNA

Abstract

PURPOSE
Evaluate the effectiveness of intravenous acetaminophen (Ofirmev) in patients undergoing laparoscopic sleeve gasterectomy, roux-en-y gastric bypass and any other bariatric surgeries at a single center. To assess this, a prospective chart analysis will be performed to evaluate: pain scores on visual analogue scale, administration of rescue opioid analgesics, and incidence of nausea/vomiting requiring administration of anti-emetics.

Abstract No. 38 (Post_Doctoral_Fellow)

Title

Surface modified PEI as targeted siRNA delivery system for GASC1 oncogene in breast cancer

Affilliations

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Authors

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2-Zeng-Quan Yang,PhD
3-Olivia M. Merkel,PhD

Abstract

This study is aimed to establish active targeting gene delivery system (Transferrin-PEI conjugate) that efficiently delivery small interference RNA (siRNA) against the histon-modifying enzyme GASC1 in breast cancer, with an emphasis on the highly lethal, advanced basal breast cancer subtype for which effective treatments are urgently needed.

RNA interference (RNAi) therapy is a promising strategy in cancer gene therapy. But its clinical translation is hampered by the lack of biocompatible and efficient siRNA delivery systems.
Polymer-mediated siRNA delivery systems have shown favorable results. Cationic polymers encapsulate the siRNA via electrostatic interactions by simple mixing. Additionally, the presence of targeting ligands on the polymer chains can increase the siRNA uptake and specificity.
Transferrin is a glycoprotein that transports iron into cells. The iron loaded Tf binds to the transferrin receptor (TfR, CD71) and the Tf-TfR complex is internalized into the cell by receptor-mediated endocytosis. The high expression of TfR on cancer cells and its ability to internalize make the transferrin receptor a great target for drug or gene delivery to cancer cells.

The polymer was established by conjugation of transferrin to a 5kDa PEI via the crosslinking agent N-succinimidyl-3-(2-pyridldithio) propionate (SPDP). The purification was performed by membrane ultrafiltration and ion exchange FPLC. The determination of siRNA-condensing properties was examined by SYBR Gold assays at various polymer amine to siRNA phosphate (N/P) ratios. The expression of the transferrin receptor in the breast cancer cell-line HCC1954 was confirmed using a CD-71 antibody labeled with PE by flow cytometry. For uptake experiments by flow cytometry, the conjugate was mixed with AlexaFluor 488 labeled siRNA. Finally, gene knock-down on the mRNA level was determined with quantitative RT-PCR.

SYBER Gold Assays showed the best siRNA condensation properties of the Tf-PEI conjugate at N/P ratios ranging from 10 to 15. As the triple negative cell line HCC1954 showed a significantly higher transferrin receptor expression compared to MCF-10A, it was chosen for active targeting siRNA delivery. Furthermore, the transferrin-conjugated PEI demonstrated increased siRNA uptake than just PEI by itself in TfR overexpressing HCC1954 cells

but not in the normal breast cell line MCF-10A. The increased siRNA delivery to HCC1954 cells with the conjugate was confirmed by confocal microscopy. Finally, gene knock-down studies revealed that Tf-PEI is as effective as Lipofectamine 2000 as standard transfection reagent.

We show an enhanced specific uptake in TfR expressing breast cancer cells with the Tf-PEI conjugate. Our delivery system can be exploited to examine the effect of GASC1 inhibition on cancer phenotypes and pathways in basal breast cancer. Further work on the optimization of siRNA sequences and transfection parameters are currently under way.

Abstract No. 39 (Student_Graduate)

Title

Ceramide synthase inhibitor fumonisin B1 inhibits apoptotic cell death in SCC17B human head and neck squamous carcinoma cells after Pc4 PDT

Affilliations

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Authors

Nithin B. Boppana,PhD student ... Duska Separovic,PhD

Abstract

The sphingolipid ceramide modulates stress-induced cell death and apoptosis.We have shown that ceramide generated via de novo sphingolipid biosynthesis is required to initiate apoptosis after photodynamic therapy(PDT).The objective of this study was to define the role of ceramide synthase(CERS) in PDT-induced cell death and apoptosis using fumonisin B1(FB),a CERS inhibitor.Silicon phthalocyanine Pc4 for PDT, and SCC17B cells, a clinically-relevant model of human head and neck squamous carcinoma were used in this study.zVAD-fmk, a pan-caspase inhibitor,as well as fumonisin B1,protected cells from death after PDT indicating the role of ceramide synthase and caspase activation in PDT-induced cell death.In contrast,ABT199,an inhibitor of the anti-apoptotic protein Bcl2,enhanced cell killing after PDT.PDT-induced accumulation of ceramide in the endoplasmic reticulum and mitochondria were inhibited by fumonisin B1.PDT-induced Bax translocation to the mitochondria, cytochrome c release and caspase-3 activation were also inhibited by fumonisin B1.These novel data suggest ceramide synthase/ceramide as a modulator in PDT-induced apoptotic cell death and emphasizes ceramide synthase as a potential druggable target that could control the effectiveness of PDT.

Abstract No. 40 ()

Title

Benefits of Training Educators in Sensory Integration for Students Who Have Experienced Trauma

Affilliations

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Authors

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Sarah Dill, OT Student
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Erica Berghoff, OT Student

Abstract

This study focuses on the benefits of training educators who work with high school girls at Clara B Ford Academy with histories of trauma in sensory integration techniques. In this non-experimental mixed study, all staff and paraprofessionals working with students in a residential treatment facility will receive 7 hours of training over the course of 7 weeks. The staff will rate their levels of knowledge, confidence and willingness in the use of sensory integration techniques with students using a pre- and post-test questionnaire. Focus groups will be conducted to gain further insight on educators' use of SI techniques. It is expected that there will be an overall increase in these measures. Implications for future research and limitations of the study are discussed.

Abstract No. 41 (Student_Graduate)

Title

Use and interpretation of quasi-experimental studies in pharmacy

Affilliations

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Authors

Shawn M. Bockelman, Matthew S. Duprey, Jamie L. Wagner, Susan L. Davis

Abstract

Purpose: Quasi-experimental (QE) studies are useful for situations where randomization is neither feasible nor ethical. Research in infectious disease, infection control, and medical informatics literature has shown that QE are often misreported. This leads to underreporting of associated limitations inherent to the study design, which include lack of randomization, potential for regression to the mean, opportunity for confounding by temporal or seasonal factors, and confounding due to maturation. Our objective is to evaluate the use and quality of the QE study design in pharmacy literature and to determine characteristics that constitute high quality reporting.
Methods: This is a systemic review of articles published from 1 January 2010 through 31 December 2012 in Pharmacotherapy, Annals of Pharmacotherapy and American Journal of Health-System Pharmacy. Articles were selected if they were self-identified as "quasi-experimental", "pre-post intervention", or "before-after intervention", or those papers which were deemed by the research team to be QE from evaluation of the study design. Each paper was evaluated by two investigators to determine the type of QE study, if the paper justified its use for a QE study design, if it was correctly identified as a QE study, and whether or not it included limitations associated with QE studies. Additional information collected included subject area, multicenter design,

corresponding author demographics, and practice site region. The characteristics collected about these studies were analyzed to determine patterns which may influence the quality of reporting.
Results: This review of three years of pharmacy journal publications yielded 2,302 unique articles. Five hundred eighty (25%) articles were determined to be original research, and 87 (15%) were determined to be QE and therefore included in this study. Of the 87 papers reviewed, only 1 (1%) included justification for use of the QE study design, 58 (85%) did not utilize any QE nomenclature, nor did the authors list any QE limitations to the study. However, 8 (42%) studies were correctly identified as a QE and listed at least one QE specific limitation (p=0.021). No specific QE design was associated with identification as a QE or addressing QE specific limitations (p=0.615).
Conclusion: This study identified significant deficiencies in the reporting of QE in the pharmacy literature. While a significant difference was not identified between a specific QE study design, there is still a large discrepancy in the authors who can appropriately identify and describe the QE design. QE are very useful within the field of pharmacy, and in order to improve the quality of scientific writing in this field, it is important to carefully select the most appropriate study design to provide the greatest impact possible.

Abstract No. 42 (Student_Graduate)

Title

Synthesis of fluorescein-labeled polylactide polymers for fabrication of Nanoparticles encapsulating anti-cancer drug

Affilliations

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Authors

Avinash Ande, Dr.Shiv kumar sharma PhD, Dr.Steven Firestine PhD, Dr.Joshua Reineke PhD

Abstract

Nanoparticles are one of the most promising approaches for fighting cancer. Passive targeting of nanoparticles (such as the enhanced permeation and retention effect) results in many positive gains such as achieving very high drug concentrations at the tumor site and eliminating any addition of targeting ligand. Major hurdles in exploiting the passive targeting is understanding the pharmacokinetics, in vivo degradation and drug release profiles in specific tissues. Fabricating nanoparticles with a novel co-polymer that has a flurophore in its backbone and can deliver a therapeutic cargo to the desired site will be helpful in determination of those important pharmacokinetic parameters We aimed at (1)synthesizing a novel co-polymer that has flurophore in its backbone (2)fabrication of nanoparticles encapsulating an anticancer drug with the novel polymer and finally (3)determining the important pharmacokinetic parameters such as bio-distribution, degradation and drug release

profiles in various tissues. We seek to utilize this information regarding the various pharmacokinetic parameters for fabricating nanoparticles that deliver the therapeutic cargo to the diseased tissues at higher concentrations. We successfully conjugated flurophore (Di-carboxy fluorescein) to an amine compound (1, 3 Dioxolane-2, 2 dimethyl-4 methyl, methanamine) which serves as one of the monomers for our desired co-polymer synthesis. Lactide (3,6 dimethyl-1,4-dioxan-2,5-dione) will be used as second monomer for the synthesis of the novel co-polymer. We developed a standard protocol for the polymerization process by successfully synthesizing polylactide polymer from lactide monomer. Meanwhile, we fabricated poly lactic co-glycolic acid (PLGA) nanoparticles encapsulating model anticancer drug paclitaxel which are similar to the desired nanoparticles and characterized them. Various pharmacokinetic studies, such as bio-distribution, in vivo degradation and drug release will be performed for these nanoparticles. This information will be utilized in predicting and performing the pharmacokinetic studies in future for the nanoparticles fabricated from the novel co-polymer.

Abstract No. 43 (Student_Graduate)

Title

EHT-1864, a small molecule inhibitor of Rac family GTPases, inhibits glucose-induced insulin secretion in pancreatic beta-cells.

Affilliations

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Authors

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Rajakrishnan Veluthakal, Ph.D
Khadija Syeda, M. Pharm
Anjan Kowluru, Ph.D

Abstract

Glucose-stimulated insulin secretion [GSIS] in the pancreatic β ... -cells underlies a variety of signaling mechanisms including activation of small GTP-binding proteins [G-proteins]. Previous studies from our laboratory in human islets, rodent islet and clonal β ... -cells have demonstrated that G-proteins [e.g., Arf6, Cdc42 and Rac1] play novel roles in cytoskeletal remodeling, which is a critical step in the membrane trafficking of insulin-laden granules for fusion with plasma membrane and release of insulin. Recently, we have also identified Tiam1 as one of the guanine nucleotide exchange factors [GEF] for glucose-induced Rac1 activation and insulin secretion [GSIS]. To further understand regulatory roles of Rac1 in GSIS, we utilized, herein, a small molecule inhibitor, EHT-1864, which inhibits Rac1 by a GEF-independent mechanism. We demonstrate that EHT-1864 [10μM] markedly attenuated GSIS in INS-1 832/13 cells without significantly affecting insulin release elicited by a membrane depolarizing concentration [40mM] of KCl [KSIS]. Interestingly, higher concentrations [20μM] of EHT-1864 potentiated both GSIS and KSIS, suggesting that additional regulatory mechanisms might mediate insulin secretion under those conditions. Furthermore, we observed a significant reduction in glucose-induced activation and membrane association [translocation] of

Rac1 by EHT-1864. Lastly, EHT-1864 inhibited glucose-induced phosphorylation and activation of extracellular signal-regulated kinases [ERK1/2]. Together, these observations suggest that EHT-1864 inhibits glucose-induced Rac1 activation and membrane association and downstream ERK1/2 activation, thereby reducing cytoskeletal remodeling and exocytotic secretion of insulin.

Abstract No. 44 ()

Title

Inhibition of protein farnesylation promotes islet β ... -cell dysfunction via caspase-3 activation and lamin B degradation

Affilliations

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Authors

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Anjan Kowluru, PhD

Abstract

Protein farnesylation is a post translational modification (PTM), wherein small molecular weight G-proteins, the γ ... -subunits of trimeric G-proteins and nuclear lamins are subjected to the addition of a 15-carbon “farnesyl” moiety. The enzyme farnesyltransferase (FTase) plays a critical role in the execution of this PTM. Such a modification increases the lipophilicity of these proteins and targets them towards the membrane region where they localize and interact with effector proteins involved in downstream signaling events. A growing body of evidence suggests that prenylation (farnesylation and geranylgeranylation) is required for the physiological function of the β ... -cell (eg: insulin secretion) and that short term exposure to high glucose conditions activates prenyltransferases in islet β ... -cells. The nuclear lamins, which undergo farnesylation, are intermediate filaments that form a network, the nuclear lamina, surrounding the nucleoplasm, lying on the interior of the nuclear membrane. We have previously shown using INS-1 832/13 cells that glucotoxic conditions (20 mM for 12-48 hr) induce caspase-3 activation which results in the cleavage of its substrate proteins including the nuclear lamin B. Herein, we demonstrate that inhibition of protein prenylation by exposing β ... -cells to FTI-277, a specific inhibitor of FTase (10 μM for 24 hr) promotes caspase-3 activation and cleavage of lamin B. In addition, using phase partitioning with Triton X114, we observed an increase in the level of degraded fragment of lamin B in the cytosol. A significant decrease in the metabolic cell viability was also noted under these conditions. Taken together, these observations collectively indicate that farnesylation is a necessary PTM for maintaining integrity of the nucleus, which is crucial in the normal functioning and viability of pancreatic β ... -cells.

Abstract No. 45 (Student_Undergrad)

Title

Occupational Therapy Activities for Children Residing in a Detroit Homeless Shelter

Affilliations

Wayne State University Master Of Occupational Therapy

Authors

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Kassandra Bradley, Occupational Therapy Student
Kelly Bridge, Occupational Therapy Student
Marissa Ford, Occupational Therapy Student
Rana Karcho, Occupational Therapy Student
Rebekah Mohney, Occupational Therapy Student
Kathryn Thornsberry, Occupational Therapy Student

Abstract

The purpose of this research project was to explore the play occupations of children residing in a Detroit area homeless shelter. The main focus was to determine if children in temporary shelters have a preference between three different types of play and leisure experiences: fine motor, gross motor, and food-based activities. At the end of the five one-hour weekly sessions, children compared each set of activities. They had to indicate which they enjoyed most and which they enjoyed least. Results showed a slightly higher preference for food-based activities as hypothesized. Recommendations for future research include modifying the rating scale for younger children, collecting data immediately following activities and increasing group time to 90 minutes.

Abstract No. 46 (Student_Graduate)

Title

Validity of a Wireless Gait Analysis Tool (Wi-GAT) in assessing spatio-temporal gait parameters during Slow, Preferred and Fast walking speeds.

Affilliations

Physical Therapy Program ... Wayne State University, Detroit, MI.

Authors

Ashley Des Jardins, SPT ... Enas Eraqi, SPT ... Amanda Samuels, SPT ... Martha Schiller, DPT, MSA ... Sujay Galen PT, PhD

Abstract

INTRODUCTION/CLINICAL RELEVANCE:
Assessment of spatio-temporal parameters of gait can help the Physical Therapist identify the presence of any movement deviations or abnormalities that may be linked to a particular injury or disease. However due to time, cost and space constraints, performing these assessments in a clinical setting can be challenging. A low cost wireless gait analysis tool (Wi-GAT) was developed to meet these challenges. A recent study comparing the measures of the Wi-GAT with those of a 3D motion capture system, showed excellent agreement, thereby establishing validity of the Wi-GAT measures. However the validity of the Wi-GAT measures is yet to be established

during slow and fast walking speeds. The purpose of this study was to establish the validity of the Wi-GAT measures recorded during preferred, fast and slow gait speeds in healthy adults.
METHODS: Twenty-five healthy adult volunteers with no musculoskeletal or neurological conditions participated in this study. The spatio-temporal gait parameters of each subject were concurrently recorded using the GaitRite instrumented walkway (CIR systems Inc, Sparta, NJ) and the Wi-GAT system while they walked at their preferred, fast and slow gait speeds. Three trials took place for each of the three walking speeds. Both absolute measurement errors and percentage errors were computed for all the recorded gait parameters. Interclass correlation coefficient (ICC) 2,k were computed to assess the level of agreement between the gait parameters recorded concurrently by the two systems.
RESULTS: Twenty two subject's (13 female, mean age: 25.7 + 5.3 years) data were used in the final analysis because 3 subject's data showed a noisy signal. Walking speed measured both by the Wi-GAT and the Gaitrite systems showed excellent agreement for preferred (ICC = 0.979 $p<0.001$), slow (ICC = 0.989 $p<0.001$) and fast (ICC = 0.967$p<0.001$) walking speeds. Overall most gait parameters recorded during slow walking speed showed good (ICC > 0.70) to excellent (ICC>0.85) agreement. Gait parameters recorded during fast walking speed showed the least agreement between the two systems.
DISCUSSION: The Gait parameters recorded during slow walking speed showed the greatest agreement between the two systems, compared to fast or preferred walking speeds. The Wi-GAT is limited by its slow sampling speed of 30 samples a second because of the wireless Bluetooth connection that it uses to send the data to a laptop computer. This we believe directly contributed to some of the poor agreements in the recorded gait parameters during the fast walking speed.
CONCLUSION: The findings of this study indicate that the gait parameters recorded by the Wi-GAT system may be more valid for slow walking speeds compared to fast walking speeds. Design considerations that will increase the sampling frequency of the Wi-GAT system is currently being considered to improve its accuracy in measuring gait parameters during fast walking speeds.

Abstract No. 47 (Student_Graduate)

Title

Validity of performing an Interactive Functional Reach Test (I-FRT) using the Microsoft Kinect® Sensor

Affilliations

Physical Therapy Program, Wayne State University, Detroit, Michigan

Authors

Andrew Diamond,SPT ... Victor Brodith,SPT ... Douglas Wyatt,SPT ... Alexey Pavlov, BSc ... Vicky Pardo, PT DHS, Sujay Galen, PT, PhD

Abstract

Introduction/Clinical Relevance: Video games such as Microsoft Kinect® are increasingly used by Physical Therapists. The limitation of "off the shelf" video games is that they do not provide performance measures that are clinically relevant. We have now developed software called the Interactive Functional Reach

Test(I-FRT) enables the Microsoft Kinect® Sensor to assess a patient's balance using a Functional Reach Test (FRT). Physical Therapists can perform an I-FRT using voice activated commands and a stick figure avatar provides real time feedback to the patients on their movements. The aim of this study was to test the concurrent validity of the I-FRT by using a 3D motion capture system as a criterion reference. The secondary aim was to establish the feasibility of performing the I-FRT in adults with mild balance impairments secondary to neurological impairments,
Methods: The concurrent validity of the IFRT measures were assessed in 20 healthy adults (14 women and mean age of 25.8 years (SD- 3.4 years). The 3D position of the subject's wrist and upper extremity were simultaneously tracked using the IFRT software and an Optotrak Certus 3D motion-capture system, while the subjects performed a FRT. Subjects completed a total of 9 FRT trials with the Microsoft Kinect® Sensor placed at a distance of 2.0m(3 trials), 2.5m(3 trials) and 3.0m(3 trials) from the subject. The absolute measurement error was calculated for each FRT trial and an interclass correlation (ICC) was performed to establish the agreement between the two systems. In addition 10 adults with mild balance impairments provided qualitative feedback on performing an I-FRT using the NASA- task load index tool.
Results: The absolute errors in FRT measurement as measured by the IFRT software for the three Microsoft Kinect® Sensor positions 2.0 m, 2.5 m and 3.0 m were 6.01 + 4.47 cm, 4.92+ 4.13 cm and 4.82 + 4.31 cm respectively. Statistical analysis using ICC showed moderate to good agreement between the two measurement systems. The greatest agreement between the two measurement system was found with the Microsoft Kinect® Sensor placed at a distance of 2.5m (ICC2,k=.786, p<.001) from the subject. The qualitative feedback provided by adults with mild balance impairments indicated that performing the I-FRT placed only a low level mental and physical demand on the subject.
Discussion: This preliminary study showed that the IFRT software provided the best estimate of FRT measures with the Microsoft Kinect® Sensor placed at a distance of 2.5m. The measurement errors were consistent with previous studies that have validated the Kinect for assessing human movement. This study has demonstrated the potential of the I-FRT software to provide a clinically relevant measure that can be embedded into the gaming platform with an ability to assess clients/patients balance performance.
Conclusions: Microsoft Kinect® Sensor in combination with the I-FRT software provides a low cost and user friendly clinical measure in assessing the patient's balance performance. The measurement errors are likely to reduce with therecent introduction of the Xbox One sensor which has a better resolution than the current Microsoft Kinect® Sensor.

Abstract No. 48 (Student_Graduate)

Title

Multifunctional Dopamine Agonist D-520 with Modulation of Alpha-synuclein Aggregation and Toxicity: Implication in the Neuroprotective Treatment of Parkinson's Disease

Affilliations

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Authors

Dan Luo, Chandrashekhar Voshavar, Liping Xu, Aloke Dutta*

Abstract

Parkinson's disease (PD) is a neurodegenerative disorder with a progressive loss of dopaminergic neurons and the presence of "Lewy bodies" as its pathogenic hallmarks. Studies have revealed that the pathogenesis of PD, although not well understood, is multifactorial and complex. Oxidative stress, protein aggregation, mitochondrial dysfunction, and genetic/environmental factors are strongly implicated in the PD progression. Due to multifactorial nature of PD pathogenesis, treatments targeting multiple pathogenic factors could be more promising in terms of symptomatic and neuroprotective treatment of PD which should overcome the shortcomings presented by the current therapies. Alpha synuclein (ASN), as the main component of Lewy bodies, has been one of the major targets for the development of PD therapeutics. Our goal is to develop multifunctional agents with modulation of alpha–synuclein aggregation derived toxicity while maintaining the potent D2/D3 agonistic activity. Based on our hybrid molecular template, we have developed D-520, a lead compound which modulated toxicity derived from alpha-synuclein aggregation. Initially, we have evaluated D-520 in modulating the ASN fibrils formation (60 μ ... M) and inhibition of toxicity in PC12 cells. Morphology studies have also been conducted by using transmission electron microscopy (TEM) to investigate the effect of D-520 on altering ASN aggregation kinetics. Further, we have focused on preparation of highly toxic alpha-synuclein oligomeric species at 14 μ ... M concentration which is close to physiological concentration in the brain. We are evaluating D-520 against oligomers induced toxicity. Details of in vitro toxicity assays, morphological studies (TEM) will be presented. Supported by NS047198 (AKD).

Abstract No. 49 (Student_Graduate)

Title

Mdig facilitates oncogenic crosstalk between c-myc and IL-6 pathways in multiple myeloma

Affilliations

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Authors

Kai Wu,PhD candidate ... Xintong Chen, PhD candidate ... Yongju Lu, ... Bachelor ... Chitra Thakur, PhD ... Fei Chen, PhD

Abstract

Multiple myeloma (MM) is a malignant tumor derived from plasma cells located within the bone-marrow compartment. Among complex genetic abnormalities, a critical role of collaboration between dysregulated c-myc and hyperactivated interleukin-6 (IL-6) pathway has been highlighted in the development of MM. However, the mechanisms underlying such oncogenic crosstalk remain to be fully elucidated. In this study, we demonstrate that overexpression of a c-myc downstream regulator, mineral dust-induced gene (mdig, also known as mina53, MINA, or NO52), is closely related to the pathogenesis of MM.

Co-immunoprecipitation experiment confirmed a robust physical binding between mdig and c-myc in a human MM cell line. Further genetic silencing of mdig led to down- regulated glycoprotein 130 (also known as gp130, IL6ST, IL6-beta or CD130) expression and thus inhibited the activity of major downstream regulators in IL-6 pathway, including STAT3 and Akt. Thus, these data suggest a pivotal role of mdig in synergizing c-myc and IL-6 pathways to promote malignant transformation of the plasma cells and therefore provide a promising target for future anti-tumor therapy against MM.

Abstract No. 50 (Post_Doctoral_Fellow)

Title

Experience with ceftaroline fosamil for methicillin-resistant Staphylococcus aureus (MRSA) blood stream infections (BSI)

Affilliations

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Authors

Evan Zasowski, Pharm.D. ... Anthony M. Casapao, Pharm.D. ... Kenneth P. Klinker, Pharm.D. ... Susan L. Davis, Pharm.D. ... Michael J. Rybak, Pharm.D.,M.P.H.

Abstract

Background: Vancomycin is considered the treatment of choice for MRSA BSI. However, vancomycin failure rates in some cohorts exceed 40%. With increased characterization of reduced vancomycin susceptibility phenotypes, novel treatments for MRSA BSI are needed. Ceftaroline fosamil, the pro-drug of ceftaroline, is an advanced generation cephalosporin antibiotic with MRSA activity. While not FDA approved for BSI, it's increasingly used for MRSA BSI, particularly following failure of initial/alternative regimens. This study will describe the use of ceftaroline for treatment of MRSA BSI.
Methods: A retrospective observational study was completed at three academic medical centers between 1/2011 and 6/2013. Inclusion criteria: age ≥ ... 18 years ... ≥ ... 1 blood culture positive for MRSA ... receipt of ceftaroline for ≥ ... 72 hours for MRSA BSI. Exclusion criteria: blood cultures clear prior to ceftaroline ... polymicrobial BSI ... receipt of concurrent daptomycin, vancomycin, linezolid, sulfamethoxazole/trimethoprim, or clindamycin for ≥ ... 24 hours. Descriptive statistics and patient outcomes were analyzed.
Results: A total of 43 patients were included. Demographics and clinical characteristics: Mean (SD) age 55.6 (17.3) ... 62.8% male ... 93% complicated BSI ... 23.3% infective endocarditis ... 30.2% osteomyelitis ... 23.3% pneumonia ... 7% skin/soft tissue ... 20.9% other/unknown ... Mean (SD) APACHE II 14.17 (6.29) ...

27.9% intensive care unit (ICU). Reason for ceftaroline: 2.3% empiric coverage ... 9% toxicity of prior therapy ... 88.3% failure of prior therapy. Outcomes: Median (IQR) hospital-length of stay (LOS) 24 (16,34) ... Median (IQR) ICU-LOS 9 (5,21) ... 25.6 % composite clinical failure ... 14% in-hospital mortality ... median (IQR) duration of BSI prior to ceftaroline 5 (3,9) ... median (IQR) duration of BSI after ceftaroline 3 (1,4). Conclusions: Ceftaroline was primarily used for MRSA BSI following prior treatment failure, including episodes secondary to osteomyelitis and infective endocarditis. Composite failure rates, in-hospital mortality rates, and length of BSI after ceftaroline suggest ceftaroline is a viable option for therapy of MRSA BSI, particularly after prior treatment failure.

Abstract No. 51 (Post_Doctoral_Fellow)

Title

HPLC-ESI-MS/MS Analysis of Insulin-Stimulated Akt2 Protein Interaction Partners in L6 Myotubes

Affilliations

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Authors

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Abstract

Insulin resistance and Type 2 diabetes are characterized by an aberrant response in the insulin signaling network. The isoform-specific serine/threonine kinase Akt2 has been implicated to play a key role in insulin-stimulated skeletal muscle glucose uptake. Activation of Akt2 is regulated via phosphorylation — notably Thr309 and Ser478 — whereas dephosphorylation has been shown to decrease Akt2 activity. Insulin-stimulated L6 myotubes were used to examine Akt2 protein interaction partners utilizing co-immunoprecipitation coupled with HPLC-ESI-MS/MS analysis. The pull-down assay displayed specificity for the Akt2 isoform ... Akt1 and Akt3 were not detected. Nearly 100 proteins indicated a significant difference ($n=7$ ... $p<0.05$) between basal and insulin-stimulated conditions. Of the potential insulin-responsive Akt2 interaction partners, several notable kinases and phosphatases were detected: protein kinase A (PKA) ... mitogen-activated protein kinase (MAPK) 1 and 3 ... 5'-AMP-activated protein kinase alpha 1 (AMPK) ... serine/threonine protein phosphatase alpha (PP1A) ... phosphatidylinositide phosphatase (SAC1) ... all of which decreased following insulin stimulation. The insulin-stimulated decrease in Akt2 kinase and phosphatase interaction partners may have the potential to mediate site-specific Akt2 phosphorylation affecting insulin signaling transduction, as well as alternative signaling pathways through Akt2 substrate interaction. These data suggest that several novel proteins may associate with endogenous Akt2 under basal, as well as insulin-stimulated conditions, and may provide further insight into the insulin

signaling network.

Abstract No. 52 (Student_Graduate)

Title

Toxic effects of the widely used antibiotics and emerging contaminants, triclosan and triclocarban, on Daphnia pulex

Affilliations

1 - Department of Pharmaceutical Sciences, 2 - Department of civil and environmental enngineering, 3 - Department of Biological Sciences

Authors

1Vibhuti Matta, 2Shawn McElmurry(PhD), 3 Donna Kashian(PhD), 1David Pitts(PhD)

Abstract

Triclosan (TCA) and triclocarban (TCC) are polychlorinated aromatic antibiotics that are widely used in the U.S. These antibiotics can be found in ‘antibacterial’ soaps (75% of liquid soap and 29% of bar soap), toothpaste, clothing, plastics, paint, and detergents (Halden, 2014). These compounds are now considered emerging contaminants (http://toxics.usgs.gov/regional/emc/), and have been found in surface water (Kolpin et al., 2002) and ground water, wastewater, and drinking water, and a number of studies suggest toxic effects in humans (Halden, 2014). TCA and TCC are subject to photocatalytic degradation in the environment, and generate transformation products when exposed to sunlight (Miranda-Garcia et al., 2011). Although there is some data on the toxicity of the parent compounds, the toxicity of the parent compounds still needs to be further evaluated. The toxicity of the transformation products has not been well characterized. A medium throughput bioassay utilizing the keystone species and freshwater crustacean, Daphnia pulex, has been developed by the laboratory to evaluate the toxicity of emerging contaminants. Daphnia have been routinely used in assessing water quality, using standard protocols developed by the Environmental Protection Agency (EPA). These EPA assays focus on survival, growth and fecundity. New assay systems that are able to detect sublethal behavioral effects, and that can rapidly screen a larger number of compounds are needed in order to evaluate the aquatic toxicity of emerging contaminants. We have developed an assay that evaluates Daphnid swimming behavior and focuses on two different variables, accumulated distance and angular change. Our preliminary results indicate that both TCC and TCA affected Daphnid swimming behavior significantly. The effect was similar across the two concentrations studied: 0.1 and 10 μ ... M. There appeared to be some initial transient stimulation of swimming by TCC and TCA, but this finding will require a more detailed analysis of the video recordings. A similar decrease in cumulative swimming distance over time was elicited by exposure to both TCA and TCC, and this was not concentration-dependent, occurring in a similar manner for both concentrations studied (time x chemical, $P<0.001$ ... time x chemical x concentration, $P>0.50$). In addition, a similar time-dependent increase in mean angle over time was elicited by both TCA and TCC, and this was also not concentration-dependent, occurring in a similar manner for both concentrations (time x chemical, $P<0.001$ ... time x chemical x concentration, $P>0.30$). The significant increase in mean angle suggests that some spinning behavior may have occurred, however this will

require more detailed analysis of the video recordings. Based on the responses to insecticides known to affect the cholinergic system, these effects on swimming behavior will likely lead to animal immobility and death. However, this endpoint has not yet been assessed in our studies. Our results suggest that these relatively low concentrations of TCC and TCA are toxic to Daphnia pulex. A lower concentration range needs to be explored in order to identify a no-effect level. In addition, we plan to examine the toxicity of the photocatalytic transformation products in future experiments.

Abstract No. 53 (Student_Graduate)

Title

Urine trouble: inappropriate use of antibiotics for asymptomatic bacteriuria

Affilliations

Henry Ford Hospital, Wayne State University

Authors

Kyle Mangan, Andrea Johnson, Katie Parrish, Jamie Wagner, Vasilios Athans, Susan Davis

Abstract

Purpose
The inappropriate screening and treatment of urine cultures in asymptomatic patients is a global problem which predisposes patients to multi-drug resistance, Clostridium difficile infection, adverse drug effects, and excess cost. As such, targeting urine cultures in patients with asymptomatic bacteriuria (ASB) is a potentially valuable intervention for antimicrobial stewardship programs. The purpose of this study was to characterize inappropriate antimicrobial use in patients with ASB at our institution.

Methods
The institutional review board approved this retrospective cohort study including patients with ASB, defined as lack of urinary symptoms and positive urine culture (>10^5 cfu/mL), at Henry Ford Hospital from January 2014 to May 2014. Patients were excluded if they presented with urinary symptoms according to strict pre-defined criteria, were pregnant females, less than 18 years of age, had another indication for antibiotics, had an absolute neutrophil count <1000 cells/mm^3, if their review of systems was unavailable, or if they underwent a urologic procedure during the index visit. Data collected included: patient characteristics, antibiotics used for treatment, and clinical outcomes. Clinical outcomes included hospital admission or emergency department (ED) revisit , C. difficile infection, or adverse drug effect attributed to antibiotic therapy within 30 days of discharge.

Results
We screened 1,287 patients and 79 (6.1%) patients met strict inclusion criteria for ASB. Demographics: mean age 65 [SD: 17] years, 58 (73.4%) male, 0 (0%) urinary stent present, 1 (1.3%) kidney transplant, 29 (36.7%) diabetes mellitus. Urinary characteristics: 16 (20.3%) indwelling catheter prior to culture, 37 (46.8%) urinalysis with >10 WBC. Microbiology characteristics: 2 (2.5%) prior positive urine culture in preceding 90 days, 3 (3.8%) prior treatment for urinary tract infection in preceding 90 days, 7 (89%) polymicrobial urine culture. Treatment characteristics: 53/79 (67.0%) patients inappropriately

received antibiotics for a median duration of 3 days. The most commonly prescribed agents were: 17 (21.5%) ciprofloxacin, 17 (21.5%) ceftriaxone, 10 (12.7%) cefepime, 6 (7.6%) cephalexin, 6 (7.6%) trimethoprim/sulfamethoxazole. Clinical outcomes at 30 days post-discharge: 14 (17.7%) hospital admission or ED revisit, 1 (1.3%) C. difficile infection, 2 (2.5%) adverse drug effects attributed to antibiotic therapy.

Conclusion
We found that over half of the ASB patients included received unnecessary antibiotic therapy. This confirms our hypothesis that treatment of ASB is a high-yield area for antimicrobial stewardship intervention. Based on these results, we plan to implement a targeted stewardship intervention aimed at reducing unnecessary antimicrobial use in patients with ASB.

Abstract No. 54 (Student_Graduate)

Title

Obeying the Antibiotic Police: Do Antimicrobial Stewardship Metrics Matter?

Affilliations

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Roua Dabal: Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, MI
Fatimah Farhat: Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, MI
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Authors

Sarah Elhalis
Roua R. Dabal
Fatimah Farhat
Jamie L. Wagner
Susan L. Davis

Abstract

Purpose: Antimicrobial stewardship programs (ASPs) aim to improve patient outcomes through better use of antibiotics. Pharmacist participation in ASPs may often involve the use of care bundles to assess surrogate markers of patient outcomes. The ASP Care Bundle at Henry Ford Hospital includes documented indication at start of therapy, appropriate cultures collected, empiric therapy according to guideline, and appropriate de-escalation therapy when cultures available. The objective of this study was to determine the relationship between these bundle metrics and patient outcomes, such as discharge disposition, adverse events, and 30-day readmission.

Methods: This retrospective cohort included adult patients admitted from 2012 through 2013 meeting the following criteria: receipt of IV antibiotics for >= 72 hours and location in one of three designated patient care units participating in a prospective interventional study (methods described elsewhere). Exclusion criteria: absolute neutrophil count < 1000 cells/mm^3 or pregnant. The ASP care bundle metrics were extracted from the electronic medical record for the duration of antimicrobial therapy. Clinical success was defined as discharged alive without adverse drug reaction and not

readmitted within 30 days of discharge. Additional data collected included patient demographics, comorbidities, and infection characteristics.

Results: 319 patients were enrolled in the study. Mean age was 62.8 +/- 17 years and 142(44%) were males. The median Charlson Score was 3, 71(22%) had ESRD/CKD, and 105(33%) were in the ICU at the time of antibiotic initiation. Major infection types included 117(37%) lower respiratory tract, 100(31%) genitourinary, and 56(18%) abdominal. When assessing the care bundle, 297/318(93%) had a documented indication for therapy, 252/314(80%) had appropriate cultures obtained at baseline, 232/306(76%) had appropriate empiric therapy at baseline, 123/145(85%) had appropriate de-escalation performed ... 160/305(52%) met all care bundle metrics. 197/319(62%) achieved clinical success. Completion of all care bundle metrics was not associated with clinical success (p = 0.464). ID consult was not a significant indicator of clinical success (45% vs 55%, p=0.06).

Conclusion: Although there was good compliance with each metric, compliance with all indicators concurrently was poor when there was no active stewardship audit and feedback. Compliance with all metrics did not improve clinical outcome. Further studies are needed to identify process measures to serve as appropriate surrogate markers for clinical outcome and to guide antimicrobial stewardship interventions.

Abstract No. 55 (Student_Graduate)

Title

Characterization of Yeast and Fruit fly Cysteine Desulfurase Complexes for Fe-S cluster Biogenesis

Affilliations

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Authors

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Abstract

Iron-Sulfur (Fe-S) clusters are a versatile class of inorganic cofactors that are essential in vital biochemical tasks in every living cell. Due to the ubiquitous usage of Fe-S clusters in a number of biochemical activities, Fe-S cluster biogenesis in mitochondria is an indispensable function for the viability of cells. Defects in this pathway are now recognized as the cause for several human diseases and among them is Friedreich’s ataxia (FRDA) a debilitating disease in which the patients accumulate extensive amounts of iron in mitochondria in the heart and CNS causing oxidative damage to nerve cells. Developing treatments for FRDA suffer from lack of molecular level understanding of the proteins involved in Fe-S cluster biogenesis pathway and our

goal is to provide insights into biophysical and functional characters of core proteins involved in it.
ISC pathway not only assembles mitochondrial Fe-S proteins but also is crucial in the formation of cytosolic and nuclear Fe-S proteins in yeast and mammalian cells. Among other key players in this pathway, Nfs1-Isd11 (Cysteine desulfurase and desulfurase interacting protein) pair generates a persulfide from free Cysteine to provide the sulfur component for Fe-S clusters and Frataxin provides iron for the process. Here we characterize the molecular details of the cysteine desulfurase reaction mechanism by exploring the role of interactions between Nfs1, Isd11 and Frataxin in both yeast and Drosophila systems. Our hypothesis is that Frataxin binds in the Nfs1 flexible active site loop following persulfide formation and stimulates loop stabilization, orientating the loop to accommodate for sulfur transfer concurrent with iron delivery. Isd11, which is already bound to Nfs1, orchestrates the orientation and energetics driving frataxin binding.

Abstract No. 56 ()

Title

Barriers and facilitators to diabetes self-management in Arab Americans: Pharmacy student participation in the research process

Affilliations

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Authors

Malak Abbas, BS1 ... Rana Fayad1 ... Mohamad Kaafarani1 ... Khalil Chahine, BS1 ... Heather Fritz, PhD2 ... Elizabeth Conger, PharmD3 ... Judith Arnetz, PhD4 ... Catherine L. Lysack, PhD5 ... Fredrick D. Pociask, PhD6 ... Rosanne DiZazzo-Miller, DrOT6 ... Linda A. Jaber, PharmD3

Abstract

Background

Diabetes self-management (DSM) is an essential part of treatment but is composed of lifestyle behaviors that are inherently influenced by culture. Diabetes prevalence in the Arab American community is reported to be higher than other ethnic groups (1) ... however there is a lack of data about how Arab culture influences DSM in this population. The principal aim of this study is to identify barriers and facilitators to DSM perceived by Arab Americans and their healthcare providers.

Methods

Twenty-three Adult Arab Americans with diabetes on multiple medications

participated in 3 focus group sessions: two mixed gender groups (N=15) and one female-only (N=8). Inclusion of a female-only group was based on our previous data suggesting 'female silencing' may occur in mixed gender Arab American groups. In addition, data were collected from healthcare providers (N=8), who practice in a pre-defined geographical area of Dearborn, in two English-language focus group sessions. A female Arabic-speaking trained moderator conducted all sessions, typically lasting 90-minutes each. All focus group discussions were transcribed verbatim and patient sessions were translated from Arabic to English. Each transcript was reviewed by the moderator to ensure accuracy. Transcripts are currently undergoing content analysis to identify themes and assess concordance between patient and provider perceptions.

Student Involvement

Bilingual Arab American student pharmacists completed IRB requirements and were trained in focus group methodology, note-taking and debriefing. Student pharmacists attended pharmacies located in Dearborn, Michigan to recruit providers and patients. Students also contributed to the development of informed consents in the Arabic language. Students attended the focus groups, administered patient consents and surveys, and participated in session note-taking during and debriefing immediately after focus groups. Students also transcribed all sessions and translated patient transcripts before moderator review.

Future Direction

Once content analysis is complete, common themes identified will be used to develop a novel questionnaire. This tool will further pinpoint barriers and facilitators of diabetes self-management in Arab Americans and will aid providers in identifying effective and individualized DSM education for their patients.

1. Jaber LA, Brown MB, Hammad A, Nowak SN, Zhu Q, Ghafoor A, Herman WH. Epidemiology of diabetes among Arab Americans. Diabetes Care 2003 ... 26 (2): 308-13.

Abstract No. 57 (Student_Graduate)

Title

Targeted deliver therapeutic siRNA into activated T cell by Tf-SPDP-PEI conjugate for therapy of asthma

Affilliations

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Authors

Yuran Xie 1, Na Hyung Kim 1, Venkatareddy Nadithe 1, Archana Thakur 1,2, Lawrence G. Lum 1,2, David JP Bassett 1, Olivia M Merkel 1,2

Abstract

With increasing environment problems and air pollution asthma has become a major public health problem which affects 235 million people worldwide. Asthma is characterized by chronic airway inflammation caused by infiltration of the lung by immune cells including T helper 2 cells (TH2). TH2 cells can induce airway

inflammation via the production of interlukines. GATA-3 is a key transcription factor to control TH2 interlukines production. Therefore a potential therapy of asthma is the delivery of GATA-3 siRNA to inhibit the expression of GATA-3 protein. However, TH2 cells do not readily uptake siRNA. To enhance siRNA delivery we designed a novel targeted delivery system Transferrin- N-Succinimidyl-3-(2-pyridyldithio)-propionate-polyethyleneimine (Tf-SPDP-PEI). In this system we utilized transferrin protein to target the TH2 cells which overexpress the transferrin receptor and “gold standard transfection reagent” polyethyleimine as a carrier of siRNA. The delivery system is also equipped with a bioreducible linker will be cleaved after endocytosis by the TH2 cells. My hypothesis is the novel delivery system could selectively target and deliver siRNA to TH2 cells and could potentially be used to treat asthma.
Here we successfully synthesized the Tf-SPDP-PEI conjugate and characterized the size and zeta-potential of Tf-SPDP-PEI/siRNA polyplex via dynamic light scattering(DLS). Measured the condensation efficiency of Tf-SPDP-PEI by using SYBR Gold assay. Furthermore, we investigated whether Tf-SPDP-PEI siRNA delivery system is efficacious in both human primary T-cells and a mouse asthma model via flow cytomertry. Finally, real time PCR was using to quantify its efficiency to knock down mRNA of GAPDH, a universal housekeeping gene, by delivery of GAPDH siRNA to human activated T cells.
Results show that the zeta-potential of Tf-SPDP-PEI/siRNA is neutral and its size is less than 100nm as well as it shows comparable siRNA condensation ability with polyethylenimine. The result also indicats it can effectively deliver siRNA to activated human primary T-cells (a TH2 cells model) and mouse T-cells in murine asthma model. Furthermore, it can specifically reduce GAPDH in mRNA level. In conclusion, we have demonstrated Tf-SPDP-PEI can efficiently and specifically siRNA delivery to TH2 cells in vitro and in vivo. Our targeted delivery system could be an innovative and promising asthma therapy in future.

Abstract No. 58 ()

Title

Neurotoxic Administration of Methamphetamine Alters Microtubules within Rat Striatal Dopamine Axons

Affilliations

Pharmaceutical Sciences Department
Wayne State University

Authors

Bryan Killinger, MA
Anna Moszczynska, PhD

Abstract

Methamphetamine (METH) is a commonly abused psychostimulant, which can induce neurotoxicity to dopaminergic (DAergic) terminals in the striatum without affecting DA cell bodies in the substantia nigra pars compacta (SNc). METH neurotoxicity is primarily characterized by reductions in striatal DAergic markers such as dopamine transporter (DAT) and tyrosine hydroxylase (TH) that indicate loss of DAergic axons. Multiple studies have demonstrated that striatal DAergic markers partially recover in experimental animals and humans, given a sufficient period of abstinence from METH. Most striatal DAergic markers require

axonal transport to be replenished ... therefore,we have hypothesized that the deficits in striatal DAergic markers are, in part, due to dysfunction of axonal transport in surviving DAergic axons. Currently, it is unknown whether METH alters axonal transport in striatal DAergic neurons. To test our hypothesis, we assessed post translational modifications (PTMs) of α ... -tubulin and neuron specific tubulin isoform ßIII tubulin in lysates from the whole striatum and within rat striatal DAergic axons at 3 days following neurotoxic METH administration (4 x 10mg/kg, every 2h, i.p.). In lysates, there was a statistically significant loss of detyrosinated α ... -tubulin (-14%, $p<0.05$) whereas the levels of acetylated α ... -tubulin, tyrosylated α ... -tubulin and ßIII tubulin remained unchanged. The decrease in detyrosinated α ... -tubulin was concurrent with significant reductions in striatal tissue levels of both TH and DAT (-43% and -68%, $p<0.05$). None of the assessed indices were affected in the SNc. DAergic axons constitute less than 1% of striatal components. To determine whether alterations in tubulin PTMs occur in DAergic axons, we employed immunofluorescence confocal microscopy. Double labeling of striatal slices for TH and PTMs revealed a loss of acetylated α ... -tubulin ($R = 0.24$, Saline vs. $R = 0.075$, METH, $p<0.05$, Pearson's correlation) and overall α ... -tubulin ($R = 0.28$, Saline vs. $R = 0.19$, METH, $p<0.05$) in METH-treated rats as compared to saline controls. Furthermore, we observed a selective increase in cololocalization of ßIII tubulin with TH ($R = 0.14$, Saline vs. $R = 0.07$, METH, $p<0.05$) in the striatum following METH. No such differences were found in the SNc. Our results suggest that neurotoxic METH causes persistent changes to structure and stability of microtubules within surviving DAergic axons. This data supports the hypothesis of axonal transport impairment in striatal DAergic axons following neurotoxic METH.

Abstract No. 59 ()

Title

EMERGING CONTAMINANTS AND DAPHNIA:EFFECTS OF DIAZINON ON SWIMMING BEHAVIOR

Affilliations

1Department of Pharmaceutical Sciences, 2Pharmacy and Health Sciences, 3Department of Civil and Environmental Engineering, 4Department of Biological Sciences

Authors

1Vibhuti Matta, 2Alexandra Wierbicki, 2Karim Mouabbi, 2Omar Jadallah, 3Shawn Mcelmurry, 4Donna Kashian, 1David Pitts

Abstract

Emerging contaminants such as pharmaceuticals and personal care products (PPCPs), herbicides, pesticides, plasticizers, fire retardants, polycyclic aromatic hydrocarbons (PAHs), and other organic waste are increasingly being detected in surface water and ground water. These contaminants can enter into the environment through wastewater treatment plant effluent and agriculture runoff. Many of these emerging contaminants tend to be biologically active at very low concentrations, typically occur in water as part of complex mixtures, and may impact biota at concentrations not detected using traditional toxicity tests (e.g. LC 50 tests). A previous study by our group (Zein et al.,

2014) described a prototypical high-throughput optical assay for tracking freely swimming aquatic animals called Daphnia pulex. Daphnia are small planktonic crustaceans found in freshwater ecosystems, and are considered a keystone species and NIH model organism. The purpose of the present study was to re-examine the effects of the organophosphate acetylcholinesterase inhibitor, diazinon, at environmentally relevant concentrations over a longer time-course. A significant concentration- and time-dependent effect of diazinon (0.125 to 500 nM) on swimming behavior was found with significant changes in both mean cumulative distance and mean angle (ANOVA, $P<0.001$ for all factors). The lowest concentration studied (125 pM or 38 ppt) is environmentally relevant, and it significantly stimulated swimming behavior after approximately 6 hours of exposure. A no-observed-adverse-effect-level (NOAEL) has not yet been identified. When present, this study suggests that environmentally relevant concentrations of diazinon can significantly alter Daphnid behavior, and therefore may have a significant impact on freshwater ecosystems.

Abstract No. 60 (Student_Graduate)

Title

A RETROSPECTIVE COHORT STUDY OF TREATMENT OUTCOMES IN PATIENTS WITH ST131 VERSUS NON-ST131 ESBL-PRODUCING E.COLI

Affilliations

WAYNE STATE UNIVERSITY

Authors

Pansy Awasthy, Kayoko Hayakawa (MD, PhD), Dror Marchaim, Jason Pogue, Steven Firestine (PhD), Keith Kaye, Emily Martin (PhD)

Abstract

OBJECTIVE: E.coli ST131 multi-locus sequence type (MLST) have been associated with extended spectrum β ... -lactamase (ESBL) production, conferring antimicrobial resistance, with increased virulence and with healthcare-associated infection. The high prevalence of multidrug antimicrobial resistance in ESBL-producing ST131 E.coli infections creates unique challenges in the studying patient outcomes and analysis are required to study ST131 E.coli amongst a large population of ESBL-producers. Present study was carried out to check whether the samples were ST131 or not.
METHOD: E.coli samples were grown using broth culture and DNA was extracted. Isolates were screened for ST131 characterization using rapid multiplex PCR detection (pabB for O25-ST131 and trpA for an E. coli-specific internal control) and high resolution two locus clonal typing (for H30 sub clone).
RESULTS: All isolates were found positive with the assay and all are H30-O25-ST131.
FUTURE DIRECTIONS: The rate of treatment failure among patients with infection due to ST131 E.coli will be compared to the patients with infection due to non-ST131 E.coli.

Abstract No. 61 (Student_Graduate)

Title

Daptomycin in combination with beta-lactams demonstrates synergistic activity against several resistant Enterococcus faecalis and Enterococcus faecium in time kill assays and combination broth microdilution

Affilliations

Wayne State University

Authors

Mostafa Aboutaleb ... Ruffa Diones-Villota ... Victor Nguyen ... Animesh Raut ... Jordan R. Smith ... PharmD ... Michael J. Rybak, PharmD, MPH

Abstract

Background:
Enterococcus faecalis (Efc) and Enterococcus faecium (Efm) are frequently resistant to vancomycin and beta-lactam antibiotics. In MRSA with reduced glycopeptide susceptibility, and in enterococci resistant to vancomycin and beta-lactams, increased beta-lactam susceptibility has been documented. This phenomenon is known as the “seesaw effect”. In vitro data suggest potent synergy between several beta-lactams and lipopeptides and glycopeptides against these resistant pathogens. Our objective was to conduct time-kill experiments involving multiple bacterial strains and antibiotic combinations to evaluate synergy with daptomycin (DAP).

Methods:
15 Enterococcus faecalis and 20 Enterococcus faecium strains were evaluated for DAP MIC in the presence and absence of several beta-lactam antibiotics including ampicillin (AMP), ceftaroline (CPT), ertapenem (ERT), ceftriaxone (CRO), cefepime (FEP), cefotaxime (CTX), and cefazolin (CFZ). Two Enterococcus faecalis (R6981 and R7808) and two Enterococcus faecium (8019 and 5938) were evaluated in 24-hour time-kill assays against these beta-lactams in combination with DAP. DAP exposures were 0.5 x the MIC, and beta-lactam exposures were the lower of 0.5 x the MIC or biologic free peak. Synergy was defined as >2 log10 reduction from the most active single agent.

Results:
Against Efm, CPT demonstrated the greatest reduction in DAP MIC value (2.3 + 0.48 average 2-fold reductions from baseline DAP MIC). The other antimicrobials were similar in MIC reduction (1.6 + 0.84, 1.4 + 0.7, 1.2 + 0.92, 1.2 + 1.14, and 1.1 + 1.2 for CRO, ERT, FEP, CFZ, and CTX, respectively. Against Efc, CPT and FEP demonstrated the greatest reduction in DAP MIC from baseline (3.8 + 1.94 and 3.3 + 2.58 average 2-fold reductions, respectively). The other antimicrobials demonstrated less reduction (2.2 + 2.04, 2 + 0.89, 2 + 1.1, and 0.7 + 0.82 for CRO, CFZ, ERT, and CTX, respectively). In time-kill experiments, CPT, ERT, FEP, CRO, CTX, and AMP demonstrated synergy with DAP against all strains, while CFZ demonstrated none. In strains R6981 (Efc) and 5938 (Efm), ERT demonstrated more synergy with DAP compared to other strains. All other combinations, except CFZ, displayed similar synergy.

Conclusions:
The data demonstrate the ability of beta-lactams to enhance the activity of daptomycin against resistant enterococci. Especially impressive are the MIC

reductions possible with CPT and FEP. Since each beta-lactam binds to different penicillin binding proteins preferentially, it is possible that this is part of the mechanism that may enhance daptomycin's activity. Further clinical research involving these combinations is warranted.

Abstract No. 62 (Student_Graduate)

Title

Novel combinations of beta-lactam antibiotics demonstrate synergistic activity against Enterococcus faecalis and Enterococcus faecium

Affilliations

Wayne State University

Authors

Ruffa Diones-Villota ... Victor Nguyen ... Mostafa Aboutaleb ... Animesh Raut ... Jordan R. Smith, PharmD ... Michael J. Rybak, PharmD, MPH

Abstract

Background:
Enterococci are often resistant to several antibiotics, including vancomycin and beta-lactam agents. Ceftaroline (CPT), a recently developed cephalosporin with anti-MRSA activity, has demonstrated activity against resistant penicillin binding proteins (PBPs) within enterococci as well. Combined with previous data suggesting the ability of ampicillin (AMP) and ceftriaxone (CRO) to provide synergistic activity against Enterococcus faecalis, our objective was to determine if synergy is present with any of the combinations of these beta-lactams against resistant Enterococcus faecalis and Enterococcus faecium.

Methods:
Three Enterococcus faecalis (R7202, R7203, and R7600) and six Enterococcus faecium (8019, 5938, R6295, R6370, R7172, and R7555) strains were evaluated for combination minimum inhibitory concentration (MIC) of AMP and CPT. Two Enterococcus faecalis (R7600 and R7635) and two Enterococcus faecium (R6370 and R7172) were evaluated in 24-hour time-kill assays against AMP, CPT, and CRO alone and against the combinations of AMP and CPT, AMP and CRO, and CPT and CRO. All isolates were resistant to all beta-lactam agents (AMP MIC >64, CPT MIC >32, CRO MIC >256). Concentrations of antibiotics were biologic free peaks (AMP 70 µg/ml, CPT 17.04 µg/ml, CRO 25.7 µg/ml). Synergy was defined as >2 log10 reduction from the most active single agent.

Results:
AMP reduced the CPT MIC for all Enterococcus faecalis strains (5.67 2-fold reductions on average) and for all Enterococcus faecium strains (4.5). CPT reduced the AMP MIC for all Enterococcus faecalis strains (2) and for all Enterococcus faecium strains (4.67). In combination time-kill assays, all combinations demonstrated synergistic activity against R7635 (Enterococcus faecalis). Against R7172 (Enterococcus faecium), the combinations of AMP and CPT and CRO and CPT demonstrated synergy, while the combination of AMP and CRO demonstrated no synergy. Against strains R6370 (Enterococcus faecium) and R7600 (Enterococcus faecalis), however, no time-kill synergy was demonstrated for any combinations.

Conclusions:
The data demonstrate the potency of the combinations of beta-lactams against enterococci, even those that harbor resistant MIC values. It is possible that the unique PBP binding profiles of each beta-lactam provide additive effects against these organisms. Going forward, it will be interesting to research beta-lactam combinations in combination with other antimicrobials.

Abstract No. 63 (Student_Graduate)

Title

Insulin infusion Protocol in post cardiac surgery

Affilliations

Oakwood Hospital Dearborn

Authors

Nissan, Marwin ... Wong, Judy PharmD ... Wilpula, David PharmD

Abstract

Postoperative hyperglycemia is associated with an increased risk of infection cardiothoracic surgery patients. Measure SCIP-Inf-4 of the Surgical Care Improvement Project (SCIP) describes new post-operative glucose targets, specifying blood glucose less than or equal to 180 mg/dl within 18 to 24 hours after anesthesia. This study will describe the safety and effectiveness of routine postoperative insulin infusion in cardiothoracic patients. This is a retrospective, serial cross-sectional study evaluating post-operative glucose control in cardiac surgery patients at Oakwood Hospital Dearborn, a community teaching hospital in southeast Michigan. Data will be obtained from electronic medical records from January 2014 through August 2014. Inclusion criteria consist of patients undergoing cardiothoracic surgery. Patients excluded are those who are less than 18 years of age, patients admitted for greater than 120 days, those with pre-operative infections, burn and transplant patients, patients that undergo CPR, surgery, discharge, patients that expire and patients who voluntarily leave 24 hours after anesthesia end time. Patient's diabetes history, weight, age, gender, and anesthesia end time will be collected in the study population which includes data prior to revision to the infusion protocol. Point of care glucose levels during insulin infusion, duration of post-op insulin infusion, and the amount and type of nutritional subcutaneous insulin will also be analyzed. Outcome measures include the total area under the glucose concentration-time curve for 24 hours post anesthesia end time (AUC0-24), hyperglycemic index (represented as AUC of glucose values above 180 mg/dl), SCIP-Inf-4 success, hypoglycemia and insulin utilization. Descriptive statistics utilizing 95% confidence intervals will be used to compare outcomes time periods . The results of this study will lead to the optimization of postoperative insulin infusion protocols resulting in lower hyperglycemic indexes and a decreased prevalence of hypoglycemia in post operative patients.

Abstract No. 64 (Student_Graduate)

Title

Clinical outcomes in patients with vancomycin heteroresistant Staphylococcus aureus (hVISA) lower respiratory tract infections

Affilliations

Wayne State University
Anti-Infective Research Laboratory

Authors

Alison Gravelin, PharmD Candidate ... Kimberly Claeys, PharmD, BCPS ... Abdalhamid Lagnf, MPH ... Michael Rybak, PharmD, MPH

Abstract

INTRODUCTION: Vancomycin remains the mainstay of treatment for methicillin-resistant Staphylococcus aureus (MRSA) infections, including pneumonia. High use of this antibiotic has caused the emergence of resistant strains, including heterogenous vancomycin-intermediate Staphylococcus aureus (hVISA), a problematic infection associated with vancomycin treatment failure despite having MICs within the susceptible range. Lower respiratory infections are of particular concern due to their high rates of morbidity and mortality. This study evaluated the clinical outcomes of patients with hVISA pneumonia compared to those with MRSA pneumonia.

METHODS: This was a retrospective cohort study of patients treated for MRSA lower respiratory infections (LRTIs) at the Detroit Medical Center between 2005 and 2014. Patients included had a diagnosis of MRSA infection with the lower respiratory tract as the primary site, blood or respiratory isolates available for analysis, and received anti-MRSA therapy for at least 72 hours. Determination of MRSA or hVISA was done by the 48 hour PAP-AUC method. A sample size of 87 patients was determined a priori to meet the primary outcomes. The primary outcomes were treatment failure and inpatient mortality. Differences in patients with hVISA versus non-hVISA were compared by Chi-squared and Fisher exact test for categorical variables and student t-test or Mann–Whitney U for continuous variables. Multivariable logistic regression was performed to determine independent risk factors for treatment failure/mortality.

RESULTS: Eighty-one patients with MRSA LRTIs have been identified. Of these patients, 21 (26%) were found to have hVISA by 48 hour PAP-AUC. No significant difference in baseline characteristics, including ICU admission or need for mechanical ventilation, was found between non-hVISA and hVISA groups. Overall, inpatient mortality was found to be significantly associated to the presence of hVISA, the hVISA group had a mortality rate of 47.6% versus 23.3% in the non-hVISA group ($p = 0.033$). However, multivariable regression analysis failed to confirm hVISA as an independent predictor of mortality. The only independent predictor of mortality found was the presence or absence of an infectious disease consult, wherein the presence of an infectious disease consult decreased mortality.

CONCLUSIONS: Lower respiratory tract infections are associated with high morbidity and mortality, which almost 50% of hVISA patients experiencing inpatient mortality. hVISA could not be confirmed as a independent predictor of mortality in LRTI, despite having a statistically

significant correlation, this is likely due to the small sample size at this time.

Abstract No. 65 (Post_Doctoral_Fellow)

Title

Burden of Illness Associated with Acute Bacterial Skin and Skin Structure Infections Evaluated in the Emergency Department (ED) or Observational Unit (OU): Experience at the Detroit Medical Center

Affilliations

Wayne State University
Anti-Infective Research Laboratory

Authors

Kimberly Claeys, PharmD, BCPS ... Abdalhamid Lagnf, MPH ... Susan Davis, PharmD ... Micheal Rybak, PharmD, MPH

Abstract

Background: Acute Bacterial Skin and Skin Structure infections (ABSSSIs) represent one of the most common infections encountered in hospitals, with the majority treated in emergency departments (EDs) with outpatient antibiotics. Currently, there is a lack of data regarding the burden of illness of low acuity patients not admitted. This study aims to describe ABSSSI management in patients treated and discharged from EDs/OUs.

Methods: Cohort study at Detroit EDs April 2012-13. Included adults treated in ED for ABSSSI, received less than 24 h intravenous (IV) antibiotics, and discharged from ED or OU without hospital admission. Demographics, location of care, consultations, antibiotics received, and patient outcomes were collected. The primary outcome of interest was ED re-visit/admission within 96 hours.

Results: A total of 289 patients were reviewed with 200 included. The median age was 41.5 years, 77% were African American, 36% were uninsured, and 74% were treated in the ED. The median time in the ED was 2.9 hours and OU was 20.4 hours. The most common type of lesions were uncomplicated abscess (36.5%), complicated abscess (21.5%). Uncomplicated abscesses were significantly more likely to be treated in the ED. Surgery consults occurred in 46% of patients, tissue cultures were obtained from 21% of patients, equally between ED and OU. Incision and drainage was the most common intervention. All patients received at least one dose of IV therapy ... clindamycin was the most common (51%), followed by vancomycin (25%). Discharge antibiotics included oral clindamycin (43%), cephalexin (21%), trimethoprim-sulfamethoxazole (16%), and nothing (11%). Twenty-three patients (11.5%) revisited the ED within 96 hours of being released, numerically more were seen in the ED compared to the OU.

Conclusions: There is a relatively low admission rate of patients with no significant differences noted between different types of skin lesions or setting of care.

Abstract No. 66 (Faculty)

Title

Student feedback of a newly developed advanced diabetes elective in pharmacy practice

Affilliations

1. Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences
2. Health Centers Detroit Medical Group

Authors

Helen Berlie, PharmD, CDE, Libby Conger, PharmD, Linda Jaber, PharmD

Abstract

Objective: Evaluate a newly developed advanced diabetes elective course and a patient simulation assignment within the course.

Design: A total of 8 third year pharmacy students were enrolled in the elective course during Winter 2014. Students participated in an active learning simulation, which entailed living as a patient with diabetes and wearing an insulin pump for 3 days. Students were trained on issues related to pump use including insulin adjustments and calculating carbohydrate intake. They kept a blood glucose log, and recorded nutrition intake and activity level. They also completed reflection questions via email on 2 separate days (3 questions on day 1 and 5 questions on day 2), to solicit their perceptions of their experiences. At the end of the course, an evaluation was administered via a 30-minute electronic survey (SurveyMonkey®). Reflections and evaluations are undergoing content analysis by 2 independent coders.

Assessment: Preliminary analysis of the active learning assignment revealed the following themes: clinical knowledge/ability, empathy, and personal risk. All 8 students provided positive feedback regarding the tested active learning experience. The course evaluations will provide future direction for course content and delivery as well as insights into to the students' perceptions of class impact on professional development. Data analysis is in progress.

Conclusion: Students' positive feedback reinforce the need for future implementation of the living with diabetes assignment. Upon data analysis completion, specific course changes will be identified and incorporated into future offerings of the course.

Abstract No. 67 (Student_Graduate)

Title

Flight! Beta-Testing to Improve Forearm Rotation

Affilliations

Occupational Therapy Program1, College of Engineering2

Authors

Missler, N.1, Albertson, N.1, Sivakumar P.2, Burford, C.2., and Conti, G., PhD1

Abstract

Flight! is a serious rehabilitation video game that requires precise supination and pronation to control virtual plane flight

through constantly changing smoke rings. Supination and Pronation were selected for game development because these motions are critical to effective hand placement during daily life tasks. Game play criteria included the use of intense, active, high-repetition movements, with motivating and engaging activities that encourage continued supination/pronation exercise. The purpose of this project was to 1) collect normative game data using guided participant movement, generating clinically meaningful instrumental outcome measures (IOMs) from a variety of users and 2) receive feedback from users on elements of game play in order to develop an improved “next generation” video game.
34 healthy young adults participated in this study. Participants attached the Yei 3 space sensor to the wrist and used supination and pronation of the forearm to maneuver an airplane through a series of rings. During game play, participants were challenged to fly through all of the rings included in each level for a maximum of 10 levels of play (increasing in difficulty from easier to harder). At the conclusion of the testing, each user completed a survey about the experience. Instrumental Outcome Measures were automatically collected by the computer throughout game play. Our research found that the range of forearm supination and pronation was 0-104 degrees and 0-106 degrees, respectively. A small amount of pitch and yaw was associated with supination and pronation movements, even when standardized protocol was strictly observed and compensatory movement limited. The Flight! video game received positive feedback and generated interest and repetition of supination and pronation in all participants. This game may provide a new and exciting intervention option for occupational therapists.

Abstract No. 68 ()

Title

Treatment of Acute Bacterial Skin and Skin Structure Infections Seen in the Emergency Department or Observational Unit

Affilliations

Wayne State University
Anti-Infective Research Laboratory

Authors

Trishna Patel, PharmD Candidate ... Manu Jacob, PharmD Candidate ... Kimberly Claeys, PharmD, BCPS ... Abdalhamid Lagnf, MPH ... Susan Davis, PharmD, Micheal Rybak, PharmD, MPH

Abstract

BACKGROUND: Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) are common infections encountered in emergency departments (EDs) and observational units (OUs). The most common organisms responsible for causing ABSSSIs are Streptococcus pyogenes and Staphylococcus aureus, of particular concern however is methicillin-resistant S. aureus (MRSA). The ongoing problem of antibiotic resistance presents a continuous challenge to the management of ABSSSIs, therefore, by understanding how treatment for ABSSSI cases are approached, as well as the rationale for specific treatment regimens, progress can be made to help improve care and curb the problem of resistance. Additionally, there is little data regarding decision strategies for ED versus OU treatment. Therefore, the objective of this investigation is to determine the burden of illness and services received for patients with less than 24 hours of intravenous

therapy for ABSSSIs before being discharged from EDs or OUs.

METHODS: This was a retrospective observational study that focused on adult patients (> 18 years) that presented to EDs and OUs of the Detroit Medical Center (DMC) with diagnosis of ABSSSI between April 2012 to 2014. The primary endpoint of interest is 96 hour ED re-visit/admission. Additional data of interested included the type of ABSSSI, empiric treatment received, differences in treatment between ED and OU, and types of discharge antibiotics received. Severity of illness was determined by the CREST classification and Dundee score and compared for ED versus OU. Continuous variables were compared with T-test or Wilcoxon rank sum and categorical variables were compared using Chi squared or Fisher's exact test in order to compare factors regarding readmission.

RESULTS:
A total of 120 patients were analyzed. There was no statistical significance in terms of patients' co-morbid conditions or presenting types of ABSSSI between the ED vs. OU. Additionally, there was no difference in 96-hour ED revisit between the ED and OU, but patients with complicated cellulitis were more likely to revisit. There was a statistically significant difference in severity of illness by the Dundee Score between ED and OU ($p = 0.034$). The most common empiric antibiotic regimens were clindamycin followed by vancomycin and ampicillin/sulbactam.

CONCLUSIONS: The primary outcome has not met statistical significance, likely because the standard of care was appropriate to prevent revisit or readmission to the hospital.

Abstract No. 69 (Student_Graduate)

Title

Save the carbapenems! Preliminary results from the MAD-ID research network world's largest MUE

Affilliations

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Jamie Wagner, PharmD

Abstract

Purpose:
Carbapenems are a class of broad-spectrum antimicrobials that are often reserved for the management of multidrug-resistant organisms. While antimicrobial benchmarking studies can demonstrate the total amount of carbapenems used across the country, data on the indication and outcome of antibiotic use is lacking. We are conducting a national, multicenter medication use evaluation of carbapenems through the MAD-ID research network. The objective of the present study, completed in two of the participating centers, is to characterize the organisms/susceptibilities of patients treated with carbapenems and determine the impact of microbiology on outcomes of therapy.

Methods:
This is a retrospective observational cohort including adult inpatients receiving any systemic carbapenem antibiotic from 2011-2013. Data collected included: demographics, comorbidities, antimicrobial therapy, infection sites, microbiology, and outcomes. Clinical outcomes assessed were: discharge disposition and 30-day readmission. Optimization of antibiotics was defined as narrowest spectrum possible OR compliant with institutional criteria PLUS active in vitro activity against the pathogen PLUS de-escalated within 72h, if possible.

Results:
50 patients were included. Median (IQR) age 66 (47-80), 29(58%) males. 25(50%) had prior hospitalization in the 180d, 22 (44%) with prior infection with Gram negative bacilli (GNB) ... 10 (20%) nursing home residents. Carbapenems used: 26 (52%) meropenem, 17 (34%) ertapenem, 7 (14%) imipenem/cilastatin. Forty-five organisms were cultured in 33/50 patients. The most common organisms isolated were: 12 (27%) Pseudomonas aeruginosa, 7 (15%) Klebsiella species, and 7 (15%) Escherichia coli. Ertapenem MIC distribution was: 0.5 mg/L (6 organisms), 2 mg/L (1 organism), 4 mg/L (4 organisms). Meropenem MIC distribution was: 0.25 mg/L (22 organisms), 0.5 mg/L (2 organisms), 1 mg/L (3 organisms), 8 mg/L (3 organisms). Antibiotics were completely optimized in 10 (20%). Most common missed opportunities for optimization: compliance with institutional guidelines, use of narrowest spectrum therapy, and timely de-escalation. Clinical outcomes: 43 (86%) were discharged alive and 13 (26%) had 30-day readmission, 8 of these were infection-related readmissions.

Conclusion:
Carbapenems are frequently used for a variety of Gram negative pathogens, including some with elevated carbapenem MICs. We identified many opportunities for improving carbapenem use, including choice according to guidelines and de-escalation of therapy. Future research will benchmark these findings against a cohort from over 20 hospitals.

Abstract No. 70 (Student_Graduate)

Title

The effects of nicotine on the feeding current and respiration in the freshwater crustacean, Daphnia pulex, are attenuated by the ganglionic blocker, mecamylamine.

Affilliations

1 - College of Pharmacy and Health Sciences(Pharm.D), 2 - Department of Pharmaceutical Sciences, 3 - Department of Biological Sciences, 4 - Department of Civil and Environmental Engineering

Authors

1Yasmin Saleh, 2Bryan Hannan, 1Batool Jafri, 1Ghadeh Dari, 1Alexandra Wierbicki, 2Vibhuti Matta, 3Donna Kashian, 4Shawn McElmurry, 1David Pitts

Abstract

Daphnia are freshwater crustaceans known as zooplankton. They are primary grazers of phytoplankton (algae), and are considered a keystone species. Environmental impacts on keystone species can negatively affect the functioning of ecosystems. D. pulex and D. magna are often used in standardized aquatic toxicity assays (e.g., EPA). The D. pulex genome has been sequenced, and it is

considered to be a model organism by the NIH and is an ideal organism for toxicogenomic studies. Daphnia pulex, is a species found in the Great Lakes region. Insecticides are frequently found as a contaminant in both surface water and ground water. Many of these insecticides target the cholinergic nervous system of insects either by inhibiting the degradative enzyme, acetylcholinesterase (AChE-I), or by causing excessive direct stimulation of nicotinic receptors (neonicotinoids). Although these substances are designed to kill insects as pests, non-target organisms such as Daphnia are also very sensitive to the toxic effects of these insecticides. Little is known about how motor function is regulated by the cholinergic system in Daphnia.

Recent studies conducted in our laboratory by Bryan Hannan et al. have enhanced our understanding of the functioning of the cholinergic system in Daphnia. Bryan Hannan et al. found that both muscarinic and nicotinic receptor activation by oxotremorine and nicotine, respectively, elicited pronounced inhibition of the appendage beat rate (ABR) responsible for the 'feeding current' generated by appendages, which is used for both feeding on algae and for respiration. Bryan et al., were able to demonstrate that the muscarinic antagonist, atropine, attenuates the effects of the AChE-I, physostigmine, and oxotremorine. However, the effect of known antagonists of the vertebrate nicotinic NN receptor on nicotine-induced inhibition of ABR has not been studied. This study examines the effect of the known NN receptor antagonist and ganglionic blocker, mecamylamine, on D. pulex ABR.

D. pulex or D. magna were fixed in an aquatic chamber using a very small drop of cyanoacrylate applied to the dorsal side of their exoskeleton. Two parameters, heart rate and ABR, were monitored through their translucent exoskeleton at 40x magnification using a digital camera attached to a brightfield microscope. As previously shown by Hannan et al., the ABR of D. pulex was more sensitive to the inhibitory effect of a 16M nicotine challenge than D. magna. The heart rate in both species was less affected than ABR by the nicotine challenge. Pretreatment of both D. pulex and D. magna with 50M mecamylamine was found to significantly attenuate the inhibitory effect of 16 ... μ ... M nicotine on ABR (parameter x antagonist concentration, $P< 0.01$ ... parameter x antagonist concentration x time $P<0.001$ ... parameter x antagonists concentration x time x species, $P>0.50$). These results suggest that the inhibitory effect of nicotine on ABR may be mediated by vertebrate-like NN nicotine receptors. Since the neonicotinoid and organophosphate insecticides have been found as water contaminants in many surface water samples, these contaminants may have significant effects on a keystone species, and therefore on freshwater ecosystems.

Abstract No. 71 (Post_Doctoral_Fellow)

Title

Combination Daptomycin and Trimethoprim/Sulfamethoxazole on Clinical Outcomes in Methicillin-Resistant S. aureus Infections

Affilliations

Wayne State University
Anti-Infective Research Laboratory

Authors

Kimberly Claeys, PharmD, BCPS ... Susan Davis, PharmD, Michael Rybak, PharmD, MPH

Abstract

Introduction: Complicated S. aureus infections, including bacteremia, are often associated with treatment failure, prolonged hospital stays, and the emergence of resistance to therapy. Daptomycin (DAP) is often used as salvage therapy after vancomycin (VAN) failure for the treatment of MRSA infections. Unfortunately, the emergence of daptomycin resistance (DNS), especially in deep-seated infections, has been reported prompting the need for alternative or combination therapy. Numerous antibiotic combinations with DAP have been investigated both clinically and in vitro. Of interest, the combination of DAP and trimethoprim/sulfamethoxazole (TMP/SMX) has proven to be rapidly bactericidal in vitro to strains that are both susceptible and non-susceptible to DAP. However, there is limited clinical evidence supporting the use of this combination to date.

Methods: This is a multi-center, retrospective, case-series of patients treated with the combination of DAP and TMP/SMX for at least 72 hours. The objective of this study is to describe the safety and effectiveness of this regimen in clinical practice.

Results: For the majority of patients, TMP/SMX was added to daptomycin because of persistent bacteremia and/or progressive signs and symptoms of infection. Microbiological eradication was demonstrated in 24 out of 28 patients and in vitro synergy was demonstrated in 17 of the 17 recovered isolates, including DNS isolates.

Conclusion: The combination of TMP/SMX and DAP is promising for difficult to treat, deep-seated infections and shows good activity against DNS isolates. Further research with this combination is necessary to describe the optimal role and its impact on patient outcomes.

Abstract No. 72 (Faculty)

Title

Design and Simulation of Customizable Self-Assembling Nanosystems Using ‘Clickable’ Hyaluronic Acid-Based Functional Macrostructures for Diverse Drug Encapsulation and Delivery

Affilliations

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Authors

Arun Iyer* PhD, Abhishek Samanta MS, Faryal Mir BS, Ganesan Venkatesan MS, Ravi Sundaram PhD & Mansoor Amiji PhD

Abstract

Purpose: Hyaluronic acid (HA) is a polysaccharide present in the extracellular matrix and synovial fluids. It is

biodegradable, non-toxic, non-immunogenic and specifically recognizes CD44 receptors that are overexpressed in many tumors including tumor-initiating (stem) cells, that makes it an ideal polymer for designing targeted drug delivery systems.

Method: Based on a customizable combinatorial library approach, we report for the first time, a series of lipid modified, PEGylated and thiol-functionalized HA macrostructures constructed using copper (Cu+1) catalyzed 'click' chemistry for efficient encapsulation of diverse drug and gene payloads by self-assembly. The physicochemical properties of self-assembled nanostructures were determined by DLS and the morphology of the nanoparticles was visualized using TEM. A diverse class of anticancer compounds was encapsulated in functional HA macrostructures and correlated with Matlab® simulation using logP of drug and lipid modified HA as the variables. In vitro cytotoxicity (MTT) assays using SKOV3 ovarian cancer cells were performed to assess targeted intracellular uptake and cell killing efficiency (IC50) of the various anticancer drug loaded HA nanosystems.

Results: By judicious selection of the functionalized-HA polymer, its lipid chain length, charge, degree of modification, molecular weight, logP value of the drug, drug class and other pertinent variables, the HA derivatives could be tailored to encapsulate various drug payloads. Furthermore, the Matlab® simulation results correlated well with the experimental results obtained on drug encapsulation and loading.

Conclusion: The design synthesis and simulation results obtained from the current study hold promising potentials for the future development of in silico models for development of customizable targeted-nano drug and gene delivery systems.

Abstract No. 73 (Post_Doctoral_Fellow)

Title

Type 2 Diabetes Phosphotyrosines in Human Skeletal Muscle

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Authors

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Samra2,6, Wissam Al-janabi1, Rodney O Berry1, Kurt Højlund7, Jeffrey F. Horowitz8, Rebecca Tagett9, Sorin Draghici9, Zhengping Yi1*

Abstract

The prevalence of type 2 diabetes (T2D) has reached 340 million people worldwide. Genomics and transcriptomics studies have provided valuable information regarding the pathogenesis of T2D, such as the discovery of T2D genes. However, they provide no information regarding protein phosphorylation, which plays a key role in insulin signaling and the development of T2D. We performed the first differential tyrosine phosphoproteome study of skeletal muscle from lean healthy controls and T2D participants, and identified 530 phosphotyrosine sites, which represents the largest skeletal muscle tyrosine phosphoproteome to date in humans. Furthermore, we generated the first global picture of regulation of tyrosine phosphorylation by insulin in lean controls, and how it differs in T2D participants. Interestingly, 86 phosphotyrosine sites were insulin-responsive in lean only, but not in T2D participants, suggesting wide-spread insulin resistance in phosphotyrosine-mediated signaling. These novel abnormalities in T2D patients, type 2 diabetes phosphotyrosines, may provide drug targets for T2D.

Abstract No. 74 (Student_Graduate)

Title

Family Quality of Life of Persons with Dementia

Affilliations

Authors

Hilary Diacono ... Chet Privett ... Erin Skotzke ... Preethy Samuel, PhD, OTRL ... Rosanne DiZazzo-Miller, DrOT, OTRL, CDP

Abstract

Introduction
Dementia is a disease that causes a decline in cognition, hindering a person's functional ability to perform everyday activities (Alzheimer's Association, 2014). 15.2 million family and friends provide 17.4 billion hours of unpaid care to those with Alzheimer's & other dementias, with their care valued at 210.5 billion dollars (Alzheimer's Association, 2012). Although it is clear the quality of life of the person with dementia and the primary caregiver is adversely affected, we have little empirical information about the quality of life of the entire family of the main caregiver of a person with dementia. Since the family is the primary environment of the person with dementia, it is essential to study the family as a whole. An appropriate measurement of the multidimensional social construct of Family Quality of Life (FQOL) is an essential prerequisite to improving the quality of holistic care of people with of dementia. Therefore, the aim of this study is to measure FQOL of people with dementia.
Methods
A cross-sectional survey research was conducted using a convenience sample of primary caregivers of persons with dementia. The Family Quality of Life Survey (FQOLS-2011) was used to collect data on 10 domains [Health, Finances, Family, Supports (Practical, Emotional and Services), Values, Careers, Leisure, Community]. Each of these domains was

measured using six items [Importance, Opportunity, Initiative, Stability, Attainment, and Satisfaction]. Descriptive and Pearson correlation analysis were used to compare the mean ratings of the dimensions across all domains and their associations with global FQOL.
Results
Of the 28 respondents, 17 reported to be a primary caregiver of a parent with dementia, 70% of whom were reported to have Alzheimer's disease. More than half (57%) of the respondents were females, 39% were African American, and had a median annual household income of 60,000 dollars. The domains of Health, Family Relationships, Influence of Values, and Leisure and recreation were significantly correlated ($r=.62-.56$ ... $p < 0.01$) to global FQOL. The domains of Financial well-being, Service support and Community participation were also found to have weaker but significant correlations ($r=.45-.40$, $p<0.05$) with global FQOL. However, the domains of Careers, Practical, and Emotional Supports were not significantly associated with global FQOL. It was interesting to note that the domains that affect the family unit internally had a stronger association with global FQOL. In terms of dimensions, we found that the level of initiative varied by importance of a domain in 7 of the 10 domains and it varied by the perception of available opportunities in 5 of 10 domains.
Clinical Implications
There is a clear need to educate families on existing opportunities in domains important to their FQOL, especially in the domains of Leisure and Health, which have the strongest association with global FQOL. Given the progressive nature of dementia, the need to pursue healthy, meaningful, inclusive leisure participation is crucial to early stage dementia caregivers. Our findings highlight the need for holistic family-centered interventions driven by community-based models of care when working with people with dementia.

Abstract No. 75 (Student_Graduate)

Title

Effects of Methamphetamine in Protein Levels on Isolated Mitochondria from Rat Striatum

Affilliations

Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University

Authors

Jessica Patel, PharmD Candidate ... Anna Moszczynska, PhD Neurochemistry

Abstract

Methamphetamine (METH) is a strongly addictive psychostimulant. Its abuse has been a public health concern in the US for decades. In addition to triggering addictive behavior, METH is neurotoxic to the brain in experimental animals and humans. One of the mechanisms mediating METH neurotoxicity is damage to mitochondria while one of the neuroprotective strategies is increasing the levels of E3 ligase parkin. The mechanisms underlying parkin neuroprotection from METH toxic effects have not been fully elucidated. Exposure of cultured non-neuronal cells to METH causes depolarization of their mitochondria and decreases the levels of mitochondrial proteins. This mitochondrial impairment is mediated, at least in part, by reactive oxygen species (ROS). Mitochondria depolarized by ROS are known release cytochrome c and

attract parkin to their membrane for a repair. We hypothesized that exposure of isolated mitochondria to METH will lead to decreased levels of mitochondrial proteins and translocation of parkin to mitochondria. To test our hypothesis, we isolated mitochondria from rat striata and suspended them in the cytosol. Half of mitochondrial suspension was treated with 10 µ ... M METH, while the remaining half was treated with saline (the control group). Gel electrophoresis and western blotting techniques were used to determine the effects of METH on parkin trafficking, release of cytochrome c, and the levels of several mitochondrial proteins. Contrary to our hypothesis, there was no translocation of parkin from cytosol to mitochondria. Instead, the levels of mitochondrial parkin decreased. The levels of all investigated mitochondrial proteins also decreased, namely complex I, complex II, complex III and VDAC. The cytochrome c levels decreased in mitochondria and increased in cytosol. Our data suggest that METH enters mitochondria and causes loss of mitochondrial function.

Abstract No. 76 (Student_Graduate)

Title

Encapsulation of SV7 as novel antibiotic drug in biodegradable PLGA nanoparticles

Affilliations

Department of Pharmaceutical Sciences, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI

Authors

Kathrin Gasteyer, Pharmacy Resident
Venkatereddy Nadithe, PhD, PostDoc
Shiv Sharma, PhD, PostDoc
Steven Firestine, PhD, Assistant Professor
Olivia Merkel, PhD, Assistant Professor

Abstract

Summary
The synthetic drug SV7 has been developed in the constant need for new antibiotics. Due to its poor solubility, ways need to be found to improve this feature and therefore find a formulation to administer it.

Introduction
Since SV7 is a poorly soluble drug and cannot be administered in organic solvents, new formulations were searched to improve its bioavailability while maintaining biocompatibility. The drug has been encapsulated in poly-L-lactic-co-glycolic acid (PLGA) nanoparticles. In former experiments the ratio of drug encapsulated per polymer was optimized regarding particle size, polydispersity index, zetapotential and encapsulation efficiency (EE).
Poly-vinyl-alcohol has been discovered to be a good emulsifier for the hydrophobic PLGA particles to form a dispersion of the particles in water.

Methods
Particle production: The particles were produced by adding a SV7 in DMSO solution to a PLGA in Acetone solution. This was added to PVA in water, exposed to ultrasonication and left stirring for the acetone to evaporate. The particles were washed and lyophilized to get a dry and stable product.
Size measurement: Size was determined using dynamic light scattering.

Encapsulation efficiency: Two methods were used, an indirect and a direct one. For the indirect one, the washing solutions of the nanoparticle preparations were combined and analyzed. The direct method uses the particles dispersed in dichloromethane, extracting the drug with HCl solution.
Release studies: To determine how much drug can be released after encapsulation, the release percentage from the particles over an extended period was analyzed. Particles were dispersed in a HCl solution and incubated at 37°C over a months' period. Samples were taken regularly during this time.
Antibiotic tests: Methicillin Sensitive Staphylococcus Aureus, a gram positive strain of bacteria, was used. They were cultivated, exposed to different concentrations of free or encapsulated drug and incubated. The blue dye Resazurin was added and the plate again incubated. Viable bacteria reduce the dye to its complementary pink version. The plates were read at 580 nm in a Minimum Inhibitory Concentration assay to show the concentrations that are needed to kill the bacteria population.
MTT assay: To test toxicity towards mammalian cells, 8000 cells/well were seeded and incubated. PLGA was used as a control. Untreated cells were considered to show 100% viability (with MTT), while the 0% viability control didn't get MTT treatment. The samples were incubated with several concentrations of SV7.

Conclusion
The experiments show that particles with a main population at around 300 nm were obtained with the previously optimized formulation. To determine the EE, the direct method is preferred due to a lower possibility for errors. The EE ranged between 40-55%. The cumulative release was shown to be 39% of the encapsulated drug.

SV7 encapsulated in PLGA has a good antibiotic effect, while the cytotoxicity towards mammalian cells is rather low compared to the amount needed to get an effective bacterial killing. It therefore possesses the two main features an antibiotic drug needs: ability to kill a harmful bacteria population, while being rather innocuous towards the bodies' own cells.

Abstract No. 77 (Student_Undergrad)

Title

Escape! Beta-Testing of a Fine Motor Coordination Assessment

Affilliations

Wayne State University

Authors

K. Paternoster, C. Sheena, P. Janiczek, R. Erlandson, PhD, G. Conti, PhD

Abstract

"Escape!" is a computerized assessment tool that measures fine motor coordination (FMC) with the arm positioned in space. During this game-like assessment, participants move their finger through mazes of differing complexity, with the shoulder and elbow unsupported. This design was selected to mimic the FMC requirements of many daily life tasks. The purpose of this study is to identify normative movement data of healthy young adults, and to examine this first version of the assessment for

usability.
Participants were selected by convenience sampling, and consisted of 40 young healthy adults, 20 males and 20 females, between the ages of 18-28y. “Escape!” is played with a custom-designed touch screen monitor connected to a laptop that controls the settings and automatically gathers performance data during play, including temporal and spatial accuracy. Participants were seated with the touch screen positioned in front of him/her at a comfortable distance. In this study, three different pathways, and varying instructions were used to increase complexity. Responses to the survey and verbal feedback showed that the assessment was enjoyable, with an overall mean of 3.74 out of 4, and without the need for major revision. Post-processing and data analysis is ongoing.

Abstract No. 78 (Student_Graduate)

Title

Daptomycin combinations with beta-lactams demonstrate synergy against resistant mutant strains of Enterococcus faecalis and Enterococcus faecium

Affilliations

Wayne State University

Authors

Animesh Raut ... Jordan R. Smith, PharmD ... Michael J. Rybak, PharmD, MPH

Abstract

Background:
Enterococcus faecalis and Enterococcus faecium are often resistant to multiple antibiotics. These resistant enterococci have several mutations that confer resistance and nonsusceptibilities. Daptomycin (DAP), one of few agents with bactericidal activity against these multidrug resistant enterococci. Unfortunately, enterococci resistance to DAP has been reported. Recent data demonstrates that ampicillin (AMP), a beta-lactam antibiotic, restores DAP activity against E. faecium strains with mutations in the LiaFSR region, a mutation frequently observed in DAP-nonsusceptible enterococci. This synergy has been documented in the presence of LiaFSR with a DAP MIC of 3-4 µg/ml. However, synergy has not yet been demonstrated in the presence of other mutations or in the presence of DAP MICs that exceed 3-4 µg/ml. Our objective was to determine if AMP, along with the other beta-lactams such as ceftaroline (CPT) and ertapenem (ERT), demonstrates enhanced DAP activity against enterococci with multiple resistance mutations and elevated DAP MIC values.

Methods:
One clinical strain of E. faecalis (s613) and one clinical strain of E. faecium (s447), along with isogenic mutants of these strains recovered over the course of a 2-week, in vitro model, were tested for DAP MIC in the absence and presence of 0.5 x the MIC of AMP, CPT, and ERT. Within the mutants obtained from s613 E. faecalis, mutations were observed in the cls and LiaFSR regions. However, these mutations were not observed in the s447 E. faecium strain or its derived DAP resistant mutants.

Results:
Initial MIC values for s613 and s447 were 1 µg/ml and 2 µg/ml, respectively. For strain s613 E. faecalis, mutant MIC values ranged from 4 µg/ml to 32 µg/ml. For strain s447 E. faecium, mutant MIC values ranged from 4 µg/ml to 128 µg/ml. Against E. faecalis

s613, AMP, CPT, and ERT were able to reduce DAP MIC values 16-128 fold, with the greatest effect coming against a mutant strain with MIC 32 µg/ml (128-fold). This strain also carried a LiaF insertion mutation, demonstrating the ability of beta-lactams to possibly restore DAP activity against this resistance mutation. The beta-lactams were also effective against the three strains with cls mutations. Against E. faecium s447, AMP, CPT, and ERT reduced DAP MIC values 2-128 fold, with AMP demonstrating greater reduction on average than either of the other two agents (40-fold, 31-fold, and 23-fold average reduction for AMP, CPT, and ERT, respectively).

Conclusions:
The data demonstrate the ability of beta-lactams to enhance the activity of DAP against resistant enterococci with varying MIC values. Against E. faecalis, all beta-lactams tested appear to share similar MIC reduction activity. E. faecium, however, appears to be best targeted with ampicillin in combination. Our data suggest that beta-lactams, in general, have the ability to restore DAP activity in the presence of previously defined resistance mutations and against elevated DAP MIC values up to 128 µg/ml. Further research is necessary to study these interesting combinations.

Abstract No. 79 (Post_Doctoral_Fellow)

Title

COMPARISON OF RISK FACTORS AND OUTCOMES ASSOCIATED WITH POLYMICROBIAL AND MONOMICROBIAL ENTEROCOCCAL INFECTION

Affilliations

Anti-Infective Research Laboratory
Eugene Applebaum College of Pharmacy and Health Sciences
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Authors

Abdalhamid M. Lagnf, MPH
Anthony M. Casapao, Pharm.D.
Kimberly C. Claeys, Pharm.D., BCPS
Michael J. Rybak, Pharm.D., MPH

Abstract

Enterococci are the second most common pathogen to cause of nosocomial bloodstream infections (BSI). Of interest, 82.6% and 9.5% of E. faecium and E. faecalis bloodstream isolates are resistant to vancomycin, respectively. Polymicrobial BSI frequencies have been increasing, ranging from 6% to 32% of all BSI episodes. Coupled with the rise in the incidence of enterococci BSI (EBSI) and the development of resistance to multiple antimicrobial agents there has been a growing concern surrounding this organism. The aims of this study were to determine the 30-day mortality and potential risk factors for polymicrobial versus monomicrobial EBSI in an area where antimicrobial resistance is of concern.

Methods: Patients with monomicrobial EBSI (control group) was matched 1:1 against patients with polymicrobial EBSI (case group) ... By: age ± 10, source of EBSI, pitt bacteremia score, and enterococcal species. Bivariate and multivariable analyses were performed to explore factors predicting for 30-day of all-cause mortality and occurrence of polymicrobial BSI.

Results: A total of 276 patients were

successfully matched and evaluated. With respect to 30-day mortality, advance age (aOR, 1.95 ... 95% CI, 1.10-3.61 ... p = 0.031), admission/transfer to intensive care unit (aOR, 3.67 ... 95% CI, 1.93-6.98 ... p = 0.001), renal disease (aOR, 4.17 ... 95% CI, 1.87-9.26 ... p = 0.001) were all risk factors for 30-day mortality. The overall mortality rate was 24.8%, 26% with monomicrobial EBSI vs. 19.5% with polymicrobial EBSI. Regarding the factors predicting for polymicrobial EBSI, African American race was an independent risk factor (aOR, 2.9 ... 95% CI, 1.29-4.08 ... p = 0.005), whereas renal disease with dialysis was protective factor (aOR, 0.51 ... 95% CI, 0.31-0.84 ... p = 0.008).

Conclusion: Polymicrobial EBSI was not an independent predictor of mortality. However, African American race was found to be an independent risk factor for polymicrobial BSI. The highlighted risk factors identified in this study could be targeted for additional treatment strategies to reduce the likelihood of mortality.

Abstract No. 80 (Post_Doctoral_Fellow)

Title

Evaluation of Colistin and Meropenem against Clinical Isolates of Extensively Drug-Resistant Pseudomonas Aeruginosa and Carbapenem-Resistant Enterobacteriaceae

Affilliations

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Authors

Juwon Yim, PharmD
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Keith Kaye, MD, MPH
Paul Lephart, Ph.D.
Michael J Rybak, PharmD, MPH

Abstract

Objective
The treatment of extensively drug-resistant (XDR)- Pseudomonas aeruginosa and carbapenem-resistant Enterobacteriaceae (CRE) poses a significant clinical challenge. Various colistin-based combination antimicrobial therapies have been studied against these extensively drug-resistant pathogens. However, the most effective combinations are yet to be determined. The objective of this in-vitro study is to evaluate the synergistic effect of an antimicrobial combination with colistin and meropenem against these extensively drug-resistant gram-negative bacteria.

Methods
For three clinical isolates, including XDR-P. aeruginosa (R#8381), and two isolates of carbapenem-resistant Klebsiella pneumoniae (R#8375 and 8376), minimum inhibitory concentrations (MICs) were determined with colistin and meropenem for each strain by broth microdilution. Colistin and meropenem MICs were measured in the presence of 0.25- to 0.5- x the MIC of the other antibiotic to determine the ability to lower MIC values. MIC reductions were

measured by serial 2-fold dilutions. Time-kill assays were performed with each agent alone and in combination to evaluate a potential for synergistic interactions. Additive and synergistic effect was defined as 1- to 2-log10 and ≥ ... 2-log10 reductions in CFU/ml from the most active single agent.
Results
MIC testing and time-kill assays were performed against three clinical isolates. Two- to four-fold decreases in colistin and meropenem MICs were observed in combination with the other agent, when compared with each agent alone. Colistin in combination with meropenem demonstrated synergistic activity against XDR-P. aeruginosa (R#8381) and an additive effect against a K. pneumoniae (R# 8376) at 24 hours in time-kill analysis.

Conclusion
Our preliminary data indicate that the combination of colistin and meropenem demonstrate bactericidal additive or synergistic effect against extensively drug-resistant gram-negative bacteria. The combination might be a promising therapeutic option for treatment of extensively drug-resistant gram-negative bacteria.

Abstract No. 81 (Student_Graduate)

Title

Evaluation of University HealthSystem Consortium Metric for Hospital Acquired Hemorrhage Related to Anticoagulation Therapy

Affilliations

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Authors

Alex C. Chaben,a Nadia J. Aneese, PharmD,b Janet L. Hoffman, PharmD,a.b Maureen A. Smythe, PharmD,a,b

Abstract

Introduction: Hemorrhage, the most concerning anticoagulant adverse effect, can increase mortality, morbidity and healthcare associated costs. In 2010, the University HealthSystem Consortium (UHC), an alliance with academic medical centers aimed at improving the quality, safety and cost-effectiveness of care, introduced a new metric to capture the frequency of inpatient anticoagulant hemorrhage. Patients with presumed bleed are identified through electronic medical record review to capture patients on an anticoagulant with both an ICD-9 code for bleeding and a code for anticoagulant causing harm (E-code). From October 2010 through December 2013, the UHC metric identified 71 patients with anticoagulant hemorrhage. Although UHC has charged institutions with a goal of decreasing the frequency of hemorrhage by 40% from baseline, this new metric has not been validated. The objectives of this study were to determine if the UHC metric accurately captures patients with inpatient anticoagulant hemorrhage, classify hemorrhage severity and assess preventability.

Methods: This study was a retrospective medical record review of the 71 patients

identified with presumed inpatient anticoagulant hemorrhage. Each patient was assessed for anticoagulant exposure, bleed confirmation including a temporal relationship of the anticoagulant with bleed, bleed severity and preventability. Accurate capture verified the bleed occurred after anticoagulant exposure, was not present prior to anticoagulant exposure and appeared potentially related to inpatient anticoagulant therapy. The severity of the hemorrhage was categorized as major, (based on the International Society on Thrombosis and Haemostasis definitions), clinically relevant non-major, or minor. A preventability assessment form was developed apriori for each anticoagulant based upon pharmacokinetics, pharmacodynamics, and institution guidelines for use. A systematic data abstraction form was used to extract relevant patient data and descriptive statistics were performed.

Results: Preliminary results are reported for 59 patients who received a heparin product. Accurate capture occurred in 53/59 patients (89.8%). The average age was 74.1 ± 11.4 years. Over one third of patients, (21/53, 39.6%) had renal impairment with 9.4% (5/53) on dialysis. Mean creatinine clearance was 50.3 ± 27.6 ml/min. Major bleeding accounted for 64.2% (34/53) of hemorrhages, and clinically relevant non-major bleeding accounted for 35.8% (19/53). Gastrointestinal and epistaxis were most common sites. Concurrent anticoagulation without indication was present in 3/53 (5.7%). Concurrent antiplatelet therapy occurred in 36/53 (67.9%). An inadequate hold time prior to an invasive procedure was evident in 2/53 patients (3.8%) while an incorrect heparin dose occurred in 4/53 (7.5%). For those on IV heparin, inadequate monitoring was present in 7/45 (15.6%) while noncompliance with the recommended protocol occurred in 10/45 (22.2%). Overall, after comprehensive case review 44/53 (82.9%) cases were classified as not preventable.

Conclusion: Ten percent of patients captured by the UHC metric are found not to have inpatient anticoagulant hemorrhage. Over 60% of bleeds were major. The mandate of a 40% reduction in hemorrhage rate requires re-evaluation as < 20% of all bleeds were preventable. Opportunities exist to reduce the inpatient anticoagulant bleeding rate. These will be explored through policy and procedure/guideline re-evaluation and education.

Abstract No. 82 (Student_Graduate)

Title

Testing Multiple PCR Techniques for Sepsis Detection

Affilliations

Eugene Applebaum School of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan
Detroit Medical Center, Detroit, Michigan

Authors

Linda Arrabi PharmD candidate 2018, Gilad Ben-Yehuda MS, Timothy Burger MS, John P McRoberts BS, Paul Lephart PhD, Keith Kaye MD MPH, Emily Martin MPH PhD, Tal Mann MD

Abstract

Background: Traditionally, roll plate method is used to detect the presence of bacterial infections in the peripheral venous blood culture. These cultures also allow detection of bacterial organisms on the lumen of the catheter tips inserted into patients while admitted to hospitals. PCR has the ability to detect sepsis presence faster and is also suspected to be more sensitive. RT-PCR used is a technique used for accurate quantification and characterization of bacterial DNA presence. This process take about 2 hours and 45 minutes. The FilmArray extracts and purifies all nucleic acids from the sample and its software generates a report of the detected pathogens. The estimated time for testing each sample is 1 hour.

Methods: RT-PCR was completed using 7 sets of primers that targeted the bacterial or fungal chromosomal DNA for the following species: Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Staphylococcus epidermidis, Proteus mirabilis, Enterococcus faecalis, and Candida albicans. Genomic DNA was extracted from blood samples and the tip solution was lysed at 96 °C for 5. RT-PCR was performed on both the extracted blood samples and the lysed saline solution. FilmArray was completed using the prepared pouches that detect up to 21 pathogens. We are using samples from 22 different patients that have been admitted to the Detroit Medical Center Intensive Care Unit. Using the blood sample and the saline solution containing the catheter tip of patients known to have one of the specific bacteria listed above, we tested the validity of RT-PCR and FilmArray for identification of the bacteria.

Results: Out of the 22 blood samples collected, PCR identified 3 samples (13.63%) as positive for S. aureus or 1 sample (4.54%) positive for K. penumoniae. PCR did not detect any organism from the remaining 18 blood samples (81.83%). On the other hand, clinical results show positive results for S. aureus in 2 samples (9.09%), 2 samples (9.09%) positive for E. faecalis, and 1 sample (4.54%) positive for K. pneumoniae. Only 2 cases of S. aureus were detected successfully by both methods. Out of 22 CVC tip solutions, clinically 2 samples (9.08%) were identified as positive for S. aureus, 1 sample (4.54%) was identified as positive for K. pneumonia, and 1 sample was positive for S. epidermidis. PCR was able to identify only 1 CVC tip solution with S. aureus infection and the 21 remaining samples (95.45%) were negative for the organisms tested. This CVC sample was the only sample detected as positive for S. aureus using both methods.

Discussion: Our results showed 81.39% concordance with the results determined by traditional culture methods performed at the Detroit Medical Center Clinical Microbiology Laboratory. Our PCR technique, with improvement, will be able to identify specific infections from catheter related blood streams. This assay may be introduced in hospital for sepsis detection. It has the ability to shorten the time for sepsis detection compared to traditional cultures methods used today. This allows faster infection diagnosis, allowing optimal treatment plans for hospitalized patients.

Abstract No. 83 (Faculty)

Title

Myofiber Damage Precedes Macrophage Infiltration after Contraction-Induced Injury in Dysferlin-null Muscle

Affilliations

1. Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences, Department of Health Care Sciences, Physical Therapy Program, Detroit, MI 48201, USA.
2. University of Maryland School of Medicine, Division of Pulmonary and Critical Care, Baltimore, MD 21201, USA.

Authors

1. Joseph A. Roche, PT, PhD
2. Mohan E. Tulapurkar, PhD

Abstract

Mutations in the DYSF gene that encodes the protein, dysferlin, lead to late-onset, human muscular dystrophies known as dysferlinopathies. The dysferlin-deficient A/J mouse spontaneously develops a mild dysferlinopathy around 6 months of age and at younger ages models the subclinical phase of the human disease. We subjected 3-4 month old A/J mice to in vivo large-strain injury (LSI) from eccentric (lengthening) contractions and studied the role of inflammation in the onset of muscle damage and recovery thereafter. We show that post-LSI, myofiber damage in the tibialis anterior muscle occurs prior to inflammatory cell infiltration. Indeed, most edema and inflammation, monitored by T2-weighted MRI and by immunofluorescence labeling of neutrophils and macrophages, respectively, develops 24-72 hr after LSI, well after the appearance of damaged myofibers. The cytokines IL-1A, MCP-1, and MCSF are elevated several-fold at 72 hr after injury, consistent with extensive macrophage infiltration. Control A/WySnJ mice show much less myofiber damage, much less inflammation and much lower cytokine levels after LSI than A/J. Depletion of monocytes and macrophages by systemic clodronate administration, fails to suppress myofiber damage or to accelerate functional recovery in A/J mice. Our studies suggest that, although macrophage infiltration is prominent in A/J muscle following LSI, it is the consequence and not the primary cause of progressive myofiber damage.

Funded by a Research Grant to JAR from the Jain Foundation Inc.

Abstract No. 84 (Student_Graduate)

Title

Three-layered Biodegradable Micelles composed of PEI-PEG block Copolymers for local Drug and Gene delivery

Affilliations

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Department of Chemistry, The University of Memphis, Memphis, TN 38152, USA

Authors

Rima Kandil, Daniel G. Abebe, Teresa Kraus, Maha Elsayed, Tomoko Fujiwara and Olivia M. Merkel

Abstract

Cationic block copolymers have been intensively studied as scaffoldings for non-viral gene delivery systems. They show many advantageous characteristics, such as their capability to form poly-ion complexes, self-assembly into micelle-forms, but also their safe and well-known structures. Poly(ethylene-imine)-b-poly(ethylene-glycol), PEI-PEG is one of the most explored block polymers used as gene carriers. The aim of this work is to establish novel nanosized three-layered PLLA(polylactid acid)-PEI-PLLA and PLLA-PEG-PLLA micelles that can be employed as carriers for local drug and gene delivery.
The process of DNA encapsulation and formulation of the micelles is accomplished in two consecutive steps. First we condensate the DNA and build its complex with PLLA-PEI-PLLA during a dialysis step which results in the formation of organo micelles. Then the outer layer of PLLA-PEG-PLLA is added by exchanging the solvent in an evaporation procedure. With the help of transmission electron microscopy images we were able to demonstrate how the micelles are constructed: the inner core consists of the DNA/PEI polyplex which is coated by the inner shell of hydrophobic PLLA segments as well as the outer shell built up of the hydrophilic PEG parts. We observed spherical particles with hydrodynamic diameters around 220 nm and an average polydispersity index of 0,156. Besides its high condensation competency and superior transfection efficiency, PEI has shown to prevent DNA complexes from aggregation or premature release, which is still a major hurdle to overcome for therapeutic applications. The combination with the covalently attached protectice layer of PEG supports this effect by averting DNA release and eventual degradation in the endosome. Moreover the incorparated PLLA forms an impermeable barrier and effectively shields the polyplex core from competing polyanions. We were able to show that this hydrophobic inner shell provides a sealed barrier for polyanions and therefor dramatically increases the stability of the micelles in neutral pH by protecting the condensed DNA. In spite of these findings we observed a favorable DNA release behaviour under slightly acidic conditions which are able to simulate the environment of the late endosomes from which the drug carriers would be released. Furthermore the DNA encapsulation efficiency and cell toxicity of the three-layered micelles were examined and the uptake of the particles into cells is currently investigated.

Abstract No. 85 (Student_Undergrad)

Title

Changes in Recovery Following ACL Repair: A Case Study

Affilliations

Wayne State University Occupational Therapy Program, Wayne State University Division of Kinesiology, Health and Sport Studies, DMC Sports Medicine

Authors

By N. Bally, B. Rosinski, A. Esquivel, PhD, K. Hefferan, PA, H. Goitz, MD, G. Conti, PhD

Abstract

The purpose of this study was to capture anthropometric data prior to anterior cruciate ligament (ACL) repair and two-weeks after surgery and link it to changes in self-care, mobility, pain, and fatigue. To collect the anthropometric data, the Vitus XXL 3D Body Scanner3 used laser technology to obtain 140 anthropometric data points of the body in approximately 11 seconds. The International Knee Document Committee (IKDC) survey was given at each session to collect ordinal responses on self-care, mobility, pain, and fatigue. The body scanner data showed that area above the patella had greater differences in swelling than the area below/lower part of the patella on the affected leg after surgery. After two-weeks post-surgery, the participant report reflected a significant loss of energy, increased pain levels, decreased ability to perform self-care, and a significant loss of mobility. This may reflect not only an inflammatory response to the surgical repair, but also a loss of muscle mass. Further assessments are expected to show decreasing circumferential measurements and improved mobility, as would be expected with improved muscle function.

Abstract No. 86 (Student_Graduate)

Title

Learning from a Pharmacy Culture Sensitivity Elective Course

Affilliations

Eugene Applebaum College of Pharmacy and Health Sciences Pharmacy Program

Authors

Sarah Eisho, Pharm.D. 3 Candidate
Claudia Hanni, Pharm.D. 3 Candidate
Mary Beth O'Connell, Pharm.D., BCPS, FASHP, FCCP

Abstract

BACKGROUND: The United States has great religious diversity. Religious beliefs influence health behaviors and decision making. Practitioners need to be culturally sensitive and work with patients from different religions. Using multiple learning techniques can alter ideologies and behaviors in regards to cultural sensitivity. Therefore, a pharmacy culture elective was created.

PURPOSE: The purpose of this study was to evaluate student cultural learning about religion and its application to care.

METHODS: First and second year student pharmacists participated in interactive presentations about various religions including the religion's specific beliefs on health from birth to death, adjustments to practice based on these beliefs, and use of complementary and alternative forms of healing including prayer. Students wrote a 1 page reflection on each religion using the what (knowledge), so what (importance), now what (application) format. Prior to and after the course, students completed two validated cultural sensitivity surveys on SurveyMonkey. Mixed methods analysis was conducted on the reflections simultaneously by two researchers to create themes. Project was IRB approved.

RESULTS: The students (N=30) were 63% women (N=19) ... 17% born outside the United States (N=8) ... 73% affiliated with a religion [Christian (N=14), Muslim (N=6),

Judaism (N=1), Hinduism (N=1), Buddhism (N=1)] ... race 83% white (N=25), 17% Asian (N=3)/Hawaiian (N=1) ... ethnicity 27% Arab American (N=8) ... and 13% previous culture training (N=4). For the Muslim, Catholic, and Judaism religions, the most common themes were ideas to improve practice (34-54% focused codes) and patient interviewing (14-20% focused codes) skills, and changing attitudes (12-19% focused codes).

Survey Item Responses Pre Course Post Course
(# Extremely and very confident)
1.Comfortable interacting with patients 17 26
from diverse religious backgrounds
2.Recognize assumptions/generalizations 11 22
you have or make about different groups of people
3.Identify the influence of stereotypes 8 24
on your thoughts, feelings, and behaviors toward different groups of people while providing patient care or education
4.Accurately list and describe elements 2 20
of culturally competent health care
5.Elicit a patient's perspective of 5 17
healing and medication therapy during a patient encounter or consultation
6.Effectively monitor the therapy of a 8 20
patient from a background different from your own
7.Effectively counsel a patient from a 10 20
background different from your own on their medications or supplements
(# Strongly disagree)
8.A particular lifestyle or culture is 5 16
irrelevant when it comes to good medical care
9.I believe that race, religion and 3 12
culture should play little or no part in the assessment and treatment of patients
(# Strongly agree and agree)
10.I have a variety of techniques that 7 29
I can use to help treat patients from diverse backgrounds
11.I relate to patients differently 13 20
depending on their race, religion and culture
12.At least initially, cultural 6 16
competency is more important than technical competency

CONCLUSION: Students reported becoming more culturally competent and provided specific applications to individualize care for each religion.

Abstract No. 87 (Student_Graduate)

Title

An Outbreak of Legionnaires' Disease in Michigan: Lessons from Case Studies

Affilliations

Oakwood Hospital Dearborn
Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University

Authors

Megan Paleno, PharmD Candidate
Rama Thyagarajan, MD
Raymond Cha, PharmD
Lama Hsaiky, PharmD

Abstract

Background: Legionnaires' disease (LD) is a serious, sometimes fatal, bacterial infection that is responsible for approximately ~2-10% of all community acquired pneumonia (CAP) cases. Clinical treatment for LD has been established with macrolides and quinolones. Large outbreaks of LD are rare,

but when they occur they may provide the opportunity to enhance our understanding of risk factors and treatment outcomes.

Methods: In this retrospective case cohort, patients >18 yo with confirmed Legionnaires' disease through positive serology were identified at Oakwood Health System from May 1, 2013 to August 1, 2013. Patients were analyzed for their various characteristics including: demographics, Legionnaires' clinical presentation (sign, symptoms, pertinent laboratory values), risk factors (immunosuppression, co-existing lung disease, BMI, comorbidities), treatment (azithromycin or levofloxacin) and treatment outcomes (length of stay, clinical efficacy).

Results: Preliminary results of 25 patients are characterized by an overall mean age of 56 years. 44% were female and 56% were male. 68% of all subjects were current or former smokers and 68% were overweight or obese (BMI>25 kg/m2). Mean duration of therapy with macrolide or quinolone was 7 days ± 3.5 days. Mean length of stay (LOS) was 8 days ± 4 days. Overall, all patients' experienced clinical success with no mortalities or readmissions.

Conclusion: Preliminary results suggest patients receiving levofloxacin therapy had a shorter length of stay (<7 days LOS). An additional analysis of a larger cohort is forthcoming.

Abstract No. 88 (Student_Graduate)

Title

Effects of Ertapenem on the Resolution of an Osteomyelitis Infection: A Retrospective Review

Affilliations

Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences
Oakwood Hospital and Medical Center, Dearborn

Authors

Elena Saveska, PharmD Candidate 2015
Alison Britt, PharmD Candidate 2016
Francine Salinitri, PharmD
Raymond Cha, PharmD
Lama Hsaiky, PharmD

Abstract

Background: The pharmacotherapeutic management of osteomyelitis may be complicated by assessment of efficacy and duration of therapy. Broad-spectrum antibiotics with favorable safety profiles can be used as therapy for this infection. As a result, Ertapenem is one agent which has been utilized in the treatment of osteomyelitis ... however, little data exists to support this indication. The objective of this study is to determine the efficacy of ertapenem in the treatment of osteomyelitis, as well as, to evaluate factors that influence outcomes of osteomyelitis in patients treated with ertapenem.

Methods: A retrospective analysis was performed on patients, admitted from 2009 to present, diagnosed with osteomyelitis and treated with ertapenem. The duration of treatment with ertapenem was at least two weeks without other similar-spectrum antibiotic treatment for greater than one week. Data collected included baseline demographic data (age, sex, weight, height, etc.), osteomyelitis infection parameters such as white blood count, infection site, microbiology reports and imaging results, and antibiotic-related information such as

dosing regimen and renal function. Outcome measures include the resolution, improvement or persistence of osteomyelitis at follow-up. Pearson's correlation will be used to assess the association between factors and osteomyelitis outcome.

Results: A total of thirty-three osteomyelitis patients successfully completed ertapenem therapy and were included in this study. In this study population, 27 (82%) were males. The weight was 92 ± 38.44 kilograms. When evaluating underlying co-morbidities, diabetes mellitus was most common, corresponding to 76% of patients, followed by peripheral vascular disease (48%). In more than 75% of patients, osteomyelitis was limited to the foot/toe while only 15% had concurrent bacteremia. A total of 30 patients received ertapenem at 1 gram daily dose, and the remaining received ertapenem at 500 milligram daily dose. The average duration of treatment was 33 ± 9.60 days. Finally, 7 patients were receiving concomitant therapy with vancomycin and 3 patients were receiving concomitant therapy with daptomycin.

Abstract No. 89 (Student_Undergrad)

Title

"Hey, Where's the Party?!" The Effects of Texting and DUI Simulation on Driving Performance in the Human Driving Simulator

Affilliations

1Department of Pharmaceutical Sciences, EACPHS ... 2Department of Health Care Sciences, EACPHS

Authors

Theresa J Palumbo1, Doreen Head2, Jeremy Ing1, Cindy Ngo1, Matthew Surducan1, Eric Lahoud1, Brenna Johnson1, Benjamin Mackie1 and Randall L. Commissaris1

Abstract

Background and Rationale: Alcohol and texting each have serious effects on driving ability, leading to crashes and fatalities. The combined effects of alcohol intoxication and texting on driving behavior have not been well-studied. The present studies utilized 'Beer Goggles' to test the hypothesis that the visual perception disturbances typically observed with ethanol intoxication potentiate the disruptive effects of texting while driving.

Subjects: Subjects were students, faculty and staff from EACPHS, 18–51 years of age.

Experimental Design: While 'driving' on a straight road, subjects were engaged in four brief text conversations with a member of the research team. Subjects wore normal safety goggles for two drives and 'Beer Goggles' (Fatal Vision, Inc.) for two drives ... Beer Goggles simulated the visual disturbance associated with 0.07-0.1 % EtOH (legally drunk).

Data Collection and Analysis: The primary dependent variables were (1) the position of the car on the road and (2) eye glances on the phone –v- the road during texting. Both measures were archived on videotape and scored by a trained observer (blind to the treatment condition). Driving during texting was rated using a 1-4 scale (1=no weaving ... 2=weaving, but remained in the proper lane ... 3=excursion outside the driving lane ... 4= multiple excursions outside the driving lane. For each instance of texting while

driving, the sequence of eye glance behavior during texting (looking at phone ... at road ... at phone ... at road ... etc) was scored to a resolution of 0.033 sec (1 video frame). The primary eye glance measures for each texting and driving episode were (1) the mean (and median) glance duration on the phone, (2) the number of glances on the phone and (3) the total duration of eyes off the road (TEOR). The effects of Beer Goggles –v- Control on driving performance during texting were analyzed using the Wilcoxin Matched Pairs Sign Text. The effects of Beer Goggles –v- Control on eye glance measures were analyzed using paired t-tests.

Results: In all subjects, texting while driving was associated with a series of glances back and forth between the phone and the road, with approximately half this time (Overall Control Mean TEOR = 8.9 sec) spent looking at the phone and NOT at the road. Texting alone significantly impaired driving. Beer Goggles alone did not negatively affect driving. Beer Goggles significantly increased the disruptive effects of texting on driving performance and also increased (1) mean (and median) glance duration, (2) the number of glances/text and finally (3) total duration of eyes off the road (TEOR).

Discussion and Conclusions: The present studies confirm past reports that texting impairs driving performance. Moreover, the present study demonstrates that the effects of texting on driving are dramatically worse when vision has been moderately impaired. Given the high likelihood of texting while driving and after drinking, these data suggest that 'No Texting While Driving' education and public service messages need to be continued, and they should be expanded to focus on the negative interaction between texting, drinking and driving.

Abstract No. 90 (Student_Graduate)

Title

Risk Factors Associated with Breakthrough Influenza following Receipt of Influenza Vaccine

Affilliations

Wayne State University, Oakwood Hospital and Medical Center

Authors

Kathleen Beydoun, PharmD Candidate2015 ... Raymond Cha, PharmD ... Joyce Mitchell, BS ... Emily Martin, PhD ... Carolyn Archer, MSc ... Paul Kilgore, MD, MPH1

Abstract

Purpose: Influenza is a major cause of acute respiratory infections and is a major source of morbidity and mortality among children and adults globally. Despite recognition of influenza as a common cause of severe respiratory tract disease, factors associated with breakthrough influenza and are not widely understood. This study will evaluate the relationship between patient demographic characteristics, underlying medical conditions and the occurrence of laboratory-confirmed influenza disease among patients who have and have not received influenza vaccine.
Methods: This case control study will identify cases of laboratory confirmed influenza among patients in the Oakwood health system using electronic records of the central microbiology laboratory. Influenza cases will then be matched to Oakwood patients who present for care of a non-respiratory disease. Influenza cases will be

identified from influenza seasons (2010-2011 through 2013-2014). Non-identifying patient information will be collected from influenza cases and control subjects using a standardized data collection instrument and data will be inspected for completeness and well as range and consistency errors prior to analysis. Adjusted and unadjusted odds ratios will be estimated to describe the association between the occurrence of laboratory confirmed influenza and receipt of the influenza immunization. Multivariate analysis will be performed to control for potential confounders and estimate odds ratios with 95% confidence intervals.
Preliminary Results: Of the 34 patients with influenza we studied, 33 tested positive for influenza A, while 1 tested positive for influenza B. Mean age was 64.1 years, 70.5% were female and 5% were admitted to the intensive care unit. 55.9% had hypertension, 32.3% had COPD, 29.4% had cardiovascular disease, 26.4% of patients had diabetes, and 2.9% had asthma. 11.7% of cases received an influenza vaccine prior to admission.
Discussion: Preliminary results suggest that patients with hypertension, COPD, cardiovascular disease, diabetes and/or female gender may be at higher risk of developing breakthrough influenza.
Conclusion: Risk factors associated with increased risk of breakthrough influenza among adults age 50 and older may include female gender, hypertension, COPD, cardiovascular disease and diabetes. In continuing to evaluate patients, it is our goal to further investigate these risk factors in order to help guide future planning of influenza immunization programs, as well as to assist in creating health educational messaging for influenza vaccination programs in the USA.

Abstract No. 91 (Student_Graduate)

Title

Variability of Spatiotemporal Gait Parameters of 3 and 5 year-old Children at Slow, Self-Selected, and Fast Speeds: A Pilot Study

Affilliations

Physical Therapy Program, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University

Authors

Alisa Barlage, Courtney Ehred, Patricia Isaac, Krista Marck, Susan Ann Talley, PT, DPT

Abstract

INTRODUCTION: Gait variability refers to the amount of variance comparing different steps in one individual. Variability is necessary to perform tasks. However, excessive variability is associated with instability and fall risk in older adults. Gait variability decreases with maturation ... speed variability decreases 75% by age 8. Research has not examined changes in variability in children at different speeds. This study's purpose is to examine how variability of 8 spatiotemporal gait parameters change across age and speed for 3 and 5 year-olds at slow (SL), self-selected (SS) and fast (F) speeds. METHODS: Twenty (17 five year olds [YO] and 3 three YO) subjects were recruited from two pre-schools. Participants walked on the GAITRite following a demonstration at each speed. Practice trials, followed by three trials for data collection at each speed were completed. Means and standard deviations were computed for spatiotemporal gait

parameters. Variability was computed using the Coefficient of Variability (CV) for parameters at each speed (CV = standard deviation / mean * 100). A repeated measures ANOVA was used to compare CV across speeds with post hoc analysis completed with Bonferroni corrections. Wilks-Lambda was used when data did not meet the sphericity assumption for ANOVA. Alpha was set at 0.05. RESULTS: Significant differences in 4 gait parameters across speeds in the 5YO group occurred. Variability of velocity was significantly greater during SL compared to SS. Variability of double support was significantly greater at F than SL and SS speeds. Variability of step time was significantly greater at SL compared to SS speeds. Stance time showed significantly greater variability at F compared to SS speeds. DISCUSSION: Variability of gait velocity in this study is comparable to the 50th percentile CV for 3YO (14.79% vs. 12.86%) and 5YO (6.69% vs. 11.52%) in previous research. Variability was greater for Base of Support and Double Support in 5YO and may be due to a lack of path efficiency or a lack of mature postural control. In 6 parameters, the CV was lowest at the SS speed in 5YO. While not significant in most comparisons, this is expected as SS speeds are typically more efficient than SL or F speeds and deviations from SS speeds require greater postural control. Although the 3YO sample size is too small to analyze, the CVs were larger for 3YO across most (18 of 24 [75%]) parameters when compared to the values for 5YO. This mirrors prior research that variability in speed decreases with maturation. Future studies should be conducted with larger sample sizes and age ranges to understand how variability is influenced by speed and age. CONCLUSION: Understanding how variability of gait parameters change with age and speed can help clinically assess gait and understand how variability impacts activities and participation in daily function.

Abstract No. 92 (Post_Doctoral_Fellow)

Title

Characterization of Nigrostriatal Dopamine System in Park2 Gene Knockout Rats

Affilliations

Department of Pharmaceutical Sciences, EACPHS, Wayne State University, Detroit, USA

Authors

Jickssa Gemechu,Phd
Anna Moszczynska,PhD

Abstract

Parkin is an E3 ubiquitin-protein ligase associated with the ubiquitin-proteasome system. Mutations in parkin gene (Park2) are linked to early-onset autosomal recessive Parkinson’s disease (PD) and lead to degeneration of dopaminergic neurons. Conversely, overexpression of parkin protects against a variety of cellular insults. Our lab has shown the involvement of parkin in binge methamphetamine (METH) neurotoxicity and that overexpression of parkin plays an important role in protection of the nigrostriatal dopaminergic system from toxicity of the drug. Therefore, phenotypic characterization of parkin knockout (KO) rats is necessary before they can be used as a model for studying the role

of parkin in PD and potential parkin-mediated survival and recovery mechanisms during METH neurotoxicity. We characterized the nigrostriatal dopaminergic system in two months-old male parkin KO and Long Evans wild-type (wt) rats by assessing the levels of dopamine (DA), DA metabolites, and the levels of other dopaminergic markers in the striatum, substantia nigra, and frontal cortex. Activity of one striatal DA-metabolizing enzyme, monoamine oxidase (MAO) was assessed using spectrophotometric-based enzymatic analysis. The neurochemical analysis based on high performance liquid chromatography (HPLC) technique indicated a reduction in striatal DA levels in parkin KO rats when compared to wt counterparts. Interestingly, DA metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC) showed a two fold increase in the parkin KO rats. The imunoblot analysis revealed reduction in the levels in other dopaminergic markers, i.e tyrosine hydroxylase (TH), DA transporter (DAT), and vesicular monoamine transporter (VMAT2) as well as a reduction in MAO activity. Altogether, our findings demonstrate that loss of parkin gene in rats produces a significant reduction in some dopaminergic markers, and increased DA metabolism. This finding agrees with the deficit in MAO activity. We conclude that parkin KO rats are useful as a model to investigate the mechanisms underlying PD and METH neurotoxicity.

Abstract No. 93 (Student_Undergrad)

Title

Comparison of Legibility Scoring between ETCH and a Commercial Software Program

Affilliations

Authors

H. Xu, S. Dankovic, N. Falls, E. Iacoban, M. Minard, P. Sivakumar, R. Erlandson, PhD, G. Conti, PhD

Abstract

Handwriting legibility is an important issue because illegible text can result in the occurrence of dangerous errors in the workplace or poor scholastic performance. There is currently no known literature comparing manual word and letter legibility assessments with software-produced legibility assessments. As occupational therapists spend 30-50 minutes per child in legibility assessment, and as each therapist typically works with 100 or more children in a school year, the use of a software-based analysis program could make available more time for intervention rather than assessment. The purpose of this research is to compare handwriting legibility scores of young adults between the Evaluation Tool of Children's Handwriting (ETCH) and the MyScript Text SDK software program. The prospective cross-sectional data that is being collected in Fall 2014 will be analyzed both digitally by the Myscript Text SDK program and manually using the ETCH. The scores will be compared using an independent t-test. The expected outcome of this research project is that this information will inform the next steps in the development of a clinically relevant software-based writing assessment.

Abstract No. 94 ()

Title

Minimum detectable change in balance and mobility tests in young adults

Affilliations

Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences

Authors

Susan Talley, Principle Investigator ... Ashley Grant, SPT ... Tahmina Rahman, SPT ... and India Stanford, SPT

Abstract

Introduction: Balance and mobility tests such as Five Times Sit to Stand and Timed Up and Go are assessment tools accessible to clinicians that assist in determining the effectiveness of treatment interventions. Minimum detectable change (MDC) values for these tests can be utilized to help clinicians assess whether change in performance following an intervention is due to real change and not measurement error. Many studies have been published quantifying MDC values for various balance and mobility tests in the older adult population, but there is a significant lack in literature determining these values in the young adult population. MDC scores from a healthy young adult population or "controlled gold standard population" can be used to interpret older adult MDC scores. The purpose of this study was to determine MDC for several balance and mobility tests used clinically by physical therapists ... including, Five Times Sit to Stand (5STS), Maximal Step Length (MSL), Four Square Step (4SST), Timed Up and Go (TUG), Stair Climb, and 20-meter Gait Tests in a "gold standard" population.
Methods: The study consisted of 30 healthy young adults between the ages of 18 and 30 (50% male, mean age = 24.3+ 1.94 years). Participants were recruited from Eugene Applebaum College of Pharmacy and Health Science to complete two trials of a battery of physical performance and functional measures separated by a 30 second interval. Inclusion criteria for the study were participants were able to walk 30 meters unassisted and stand independently for 10 minutes. Participants were excluded if they had a current injury or medical condition which limited their ability to walk and complete testing. MDC values were calculated for each outcome measure.
Results: ICC2, 1 values for the tests of mobility and balance ranged from .65 (4SST) to .94 (MSL-Right) ... indicating excellent relative reliability for 7 of 8 outcome measures. ICC2, 1 values for the FSST indicate moderate reliability. MDC scores at 95% confidence intervals were as follows ... 1.22 seconds for 5STS, 5.88 and 7.84 inches for MSL Right and Left respectively, 1.19 seconds for 4SST, 0.61 seconds for TUG, 0.53 seconds for Stair Climb Test, 1.16 seconds for Comfortable Gait Speed Test and 1.08 for Fast Gait Speed Test. Small SEM% and low MDC95% values for 7 of the 8 tests indicate these measures have good absolute reliability and are likely to be sensitive to detecting change in performance in the clinical setting. The 4SST produced high MDC95% and SEM% values indicating it is unlikely to be sensitive to detecting change and may not be useful indicators of change in balance and mobility in the younger adult population.
Conclusion: Small measurement error and low minimum detectable change percent values for FSTS, TUG, Stair Climb Test,

Comfortable MSL, and Fast Gait Speed indicate that these measures have good absolute reliability and are likely to be sensitive to detecting change in performance in a clinical setting. Clinicians can use these balance and mobility tests in young adults to evaluate the effectiveness of therapeutic interventions.

Abstract No. 95 (Student_Graduate)

Title

Continuity of care in human immunodeficiency virus (HIV) outpatient therapy

Affilliations

Wayne State University, Oakwood Hospital and Medical Center

Authors

Jennifer Froomkin, PharmD Candidate ...
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Raymond Cha, PharmD

Abstract

The dawn of new antiretroviral formulations has simplified the treatment landscape of human immunodeficiency virus (HIV). Although these pills are easier to manage, the antiretroviral drug components are still vulnerable to developing resistance. Continuity of care in HIV patients in the ambulatory care setting becomes essential because adherence is important to prevent resistance. We know that transition of care is necessary when patients are going from an inpatient setting to a community setting, but there is no literature about patients managed in an ambulatory care setting. This is an observational, retrospective, non-interventional cohort study that will evaluate the impact of continuity of care on HIV pharmacotherapy. The patient populations studied are those older than 18 years of age diagnosed with HIV and those who are receiving antiretroviral treatments at the Oakwood Hospital HIV ambulatory care clinic. The primary assessment in this study is effectiveness of continuity of care, which will be measured by patient surveys and information from the community pharmacy where prescriptions are being filled. The patient survey will quantify and qualify patient level of understanding of treatment details, treatment interruptions and their reasons, educational interventions, heath care utilization, social work services, geographic location, and comorbidities including substance abuse. The information gathered from community pharmacies include: patient refill history, inventory maintenance, refill programs, education programs. Continuity of care in an ambulatory care setting is challenging and preventing treatment interruptions in antiretroviral therapy is imperative. Assessment of continuity of care for optimization opportunities sets the stage for future research.

Abstract No. 96 (Student_Graduate)

Title

Impact of Obesity on Treatment Parameters in Pneumonia

Affilliations

Wayne State University ... Oakwood Hospital Dearborn

Authors

Ayesha Noorulla, PharmD Candidate ... Jillian James, PharmD Candidate ... Cassandra Petros, PharmD Candidate ... Joseph Fava, PharmD ... Lama Hsaiky, PharmD ... Raymond Cha, PharmD

Abstract

Obesity is a growing epidemic around the world. Not only does obesity alter immunologic responses in infection, it also affects the pharmacokinetic disposition of antimicrobials. The objective of this study is to analyze the treatment outcomes of pneumonia infection in patients with a BMI that categorizes them as overweight or obese.
This is a non-interventional, retrospective cohort study performed at Oakwood Hospital Dearborn, a community teaching hospital in Michigan. Patients greater than 18 years of age, have a BMI >= 25kg/m2 (subgroups: BMI of 25-29.9, 30-39.9, >40kg/m2), diagnosed with pneumonia, and received antimicrobials for >2 days are included. The primary endpoints included 30 day mortality and readmission, length of hospital stay (LOS), and time to clinical improvement (CI). Additional variables included: comorbidities, sepsis, surgery, renal function, antimicrobial regimens, microbiology, and infection parameters. Discriminant factor analysis was performed on infection parameters with obese subcategories as independent risk factors. Kruskal-wallis was performed on treatment characteristics.
Twenty-nine subjects with documented pneumonia were evaluated in the study: 6 in 25-29.9kg/m2, 18 in 30-39.9kg/m2, 5 in >40kg/m2. No statistical differences were noted between BMI categories for diabetes, heart failure, lung disease, immunosuppression, kidney disease, and other infections with the exception of sepsis with the largest proportion in the lower BMI category (67 vs. 22 and 20%). Ceftriaxone was used most often (48%), followed by broad-spectrum beta-lactams (31%) and vancomycin (24%). Fifty-two percent of vancomycin troughs achieved levels of 15-20mcg/mL. Seventy-six percent of subjects received the maximal prescribing dose of antimicrobials. No statistical difference ($p<0.05$) was noted between groups for mortality (0 vs. 1 vs. 2), readmission (2 vs. 6 vs. 1) and time to CI (7.1 vs. 8.6 vs. 6.4days) while a difference was identified for LOS (9.7 vs. 11.8 vs. 7.0days). In the current analysis, no variable was statistically linked to LOS.
The heightened potential of more obese patients on antimicrobial therapies require expanded assessment into the design of individualized dosing. The impact of lower antimicrobial exposures, as witnessed in this study, requires further exploration in larger sample sizes, other infections, additional controls, and with pharmacodynamic comparisons.

Abstract No. 97 (Student_Graduate)

Title

Medication Use Evaluation of Ticagrelor 180mg and Aspirin 81mg

Affilliations

Wayne State University

Authors

Shadi Shamsedean PharmD Candidate 2015 and Larry Diamond PharmD

Abstract

Purpose: Patients presenting with acute coronary syndromes, be it unstable angina, NonSTEMI or STEMI require dual antiplatelet therapy with or without an intervention. In the Plato trial, it was concluded that Ticagrelor 90mg twice a day combined with Aspirin 81mg daily was superior to Clopidogrel 75mg daily and Aspirin 81mg daily for decreasing the composite endpoint of myocardial infarction, stroke, and death in patients with acute coronary syndromes (UA, NSTEMI, STEMI). Ticagrelor should only be given with an Aspirin dose of 81mg, as a higher dose of Aspirin 325mg showed a higher incidence of cerebrovascular events.

Methods: This medication use evaluation is for the use of Ticagrelor for acute coronary syndrome patients at Oakwood Hospital in Dearborn, Michigan from October 2013 to September 2014. We looked at how many therapies were written for Ticagrelor 90mg twice daily and Aspirin 81mg, and how many therapies required the Aspirin dose to be reduced from 162mg or 325mg to 81mg.

Results: Of the 382 Ticagrelor therapies prescribed during the analyzed period, 18 (4.7%) of them required the dose of Aspirin to be reduced to 81mg by a pharmacist, and 2(0.5%) had a contraindication to aspirin due to allergies. Overall, providers at Oakwood Hospital were able to achieve an optimal therapy rate of 99.5%.

Conclusion: The 99.5% optimal therapy rate is indicative of the efficacy of the medication reminder system that is embedded in EPIC, it also proves that having a pharmacist overlook these therapies leads to optimal therapy.

Author Index