Hot Articles

"June|2017"

Health Science

[Health Science]

Title: Influence of Meals and Glycemic Changes on QT Interval Dynamics

Author: Brenda Cirincione, Philip T. Sager, Donald E. Mager

Journal: Clinical Pharmacology

Volume: First Published: 22 May 2017

Doi: 10.1002/jcph.933

Abstract

Thorough QT/QTc studies have become an integral part of early drug development programs, with major clinical and regulatory implications. This analysis expands on existing pharmacodynamic models of QT interval analysis by incorporating the influence of glycemic changes on the QT interval in a semimechanistic manner. A total of 21 healthy subjects enrolled in an open-label phase 1 pilot study and provided continuous electrocardiogram monitoring and plasma glucose and insulin concentrations associated with a 24-hour baseline assessment. The data revealed a transient decrease in QTc, with peak suppression occurring approximately 3 hours after the meal. A semimechanistic modeling approach was applied to evaluate temporal delays between meals and subsequent changes that might influence QT measurements. The food effect was incorporated into a model of heart rate dynamics, and additional delayed effects of the meal on QT were incorporated using a glucose-dependent hypothetical transit compartment. The final model helps to provide a foundation for the future design and analysis of QT studies that may be confounded by meals. This study has significant implications for QT study assessment following a meal or when a cohort is receiving a medication that influences postprandial glucose concentrations.

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[Health Science]

Title: Identifying the prevalence of adverse drug events associated with potentially inappropriate medications using the Screening Tool of Older Persons' Prescriptions criteria

Author: Celeste M. Vinluan, Monique G. Aldaz, Nicole Dominguez and Elizabeth C. Ha

Journal: Journal of Pharmaceutical Health Services Research

Volume: Version of Record online: 29 MAY 2017

Doi: 10.1111/jphs.12179

Abstract

Objectives

The study's primary objective was to determine the prevalence of adverse drug events (ADEs) that could be identified using the Screening Tool of Older Persons' Prescriptions (STOPP) criteria. Secondary objectives included characterizing and identifying the prevalence of potentially inappropriate medications (PIMs) and ADEs in the study population, classifying each of the identified ADE using the Naranjo scale, and identifying the time required to use this tool in the clinical setting.

Methods

The STOPP criteria were used to identify PIMs in elderly patients' charts with a documented ADE. Patients who were found to have at least one PIM were reviewed to determine whether the documented ADE could be attributed to the PIM.

Key findings

A total of 290 PIMs were identified across three points of care: admission, hospital stay and discharge. The most prevalent types of PIMs were proton pump inhibitors (21%), benzodiazepines (14.1%) and duplicate drug class (7.9%). The most common ADEs that could be attributed to a PIM were incontinence associated with alpha-blockers (37.5%) and constipation associated with calcium-channel blockers (14.6%). The median time required for chart review on admission, hospital stay and discharge was 2, 2, and 1 minute, respectively.

Conclusions

The study suggests a large number of patients are affected by PIMs and secondary ADEs. With the short time that is needed to review patients' medications, the STOPP criteria may be beneficial in reducing the number of ADEs associated with PIMs.

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[Health Science]

Title: Hydroxychloroquine affects bone resorption both in vitro and in vivo

Author: Tim Both, M. Carola Zillikens, Marijke Koedam, Marijn Vis, Wai-Kwan Lam, Angelique E.A. M. Weel, Johannes P.T. M. van Leeuwen, P. Martin van Hagen, Bram C.J. van der Eerden and Paul L.A. van Daele

Journal: Journal of Cellular Physiology

Volume: Accepted manuscript online: 30 MAY 2017

Doi: 10.1002/jcp.26028

Abstract

We recently showed that patients with primary Sjögren syndrome (pSS) have significantly higher bone mineral density (BMD) compared to healthy controls. The majority of those patients (69%) was using hydroxychloroquine (HCQ), which may have favorable effects on BMD. The aim of the study was to evaluate whether HCQ modulates osteoclast function. Osteoclasts were cultured from PBMC-sorted monocytes for 14 days and treated with different HCQ doses (control, 1 and 5 μg/ml). TRAP staining and resorption assays were performed to evaluate osteoclast differentiation and activity, respectively. Staining with an acidification marker (acridine orange) was performed to evaluate intracellular pH at multiple timepoints. Additionally, a fluorescent cholesterol uptake assay was performed to evaluate cholesterol trafficking. Serum bone resorption marker β-CTx was evaluated in rheumatoid arthritis patients. HCQ inhibits the formation of multinuclear osteoclasts and leads to decreased bone resorption. Continuous HCQ treatment significantly decreases intracellular pH and significantly enhanced cholesterol uptake in mature osteoclasts along with increased expression of the lowdensity lipoprotein receptor. Serum β-CTx was significantly decreased after six months of HCQ treatment. In agreement with our clinical data, we demonstrate that HCQ suppresses bone resorption in vitro and decreases the resorption marker β-CTx in vivo. We also showed that HCQ decreases the intracellular pH in mature osteoclasts and stimulates cholesterol uptake, suggesting that HCQ induces osteoclastic lysosomal membrane permeabilization (LMP) leading to decreased resorption without changes in apoptosis. We hypothesize that skeletal health of patients with increased risk of osteoporosis and fractures may benefit from HCQ by preventing BMD loss.

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[Health Science]

Title: Biological roles of glial fibrillary acidic protein as a biomarker in cartilage regenerative medicine

Author: Sanshiro Kanazawa, Satoru Nishizawa, Tsuyoshi Takato and Kazuto Hoshi

Journal: Journal of Cellular Physiology

Volume: Version of Record online: 1 JUN 2017

Doi: 10.1002/jcp.25771

Abstract

Glial fibrillary acidic protein (GFAP) is an intermediate filament that is expressed in specifically expressed auricular chondrocytes, which are good cell sources of cartilage regenerative medicine. Although our group uses GFAP as a biomarker of matrix production in the cultured auricular chondrocytes, the biological roles of GFAP in auricular chondrocytes has remained unknown. In this study, we demonstrated the biological functions of GFAP in the human and mouse derived auricles to clarify the significance and role with the chondrocytes of GFAP in order to provide useful information for reliable and safe regenerative medicine. We examined the cell responses to stretch stress for these chondrocytes and completed a nuclear morphological analysis. Based on these results, GFAP seems to support the resistance to severe mechanical stress in the tissue which physiologically suffers from a stretch overload, and plays pivotal roles in the conservation of cell structures and functions through the maintenance of nuclear morphology.

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[Health Science]

Title: Daily oral administration of low-dose methotrexate has greater antirheumatic effects in collagen-induced arthritis rats

Author: Aoi Koyama, Aki Tanaka and Hideto To

Journal: Journal of Pharmacy and Pharmacology

Volume: Version of Record online: 31 MAY 2017

Doi: 10.1111/jphp.12752

Abstract

Objectives

Methotrexate (MTX) is administered once or thrice weekly to patients with rheumatoid arthritis (RA). Even though RA continually progresses, MTX is not administered daily. Therefore, we investigated whether the daily administration of a low dose of MTX inhibits the progression of arthritis in collagen-induced arthritis (CIA) rats.

Methods

Methotrexate was orally administered once weekly, thrice weekly and once daily to CIA rats, and arthritis scores were measured.

Key findings

When the same dose of MTX was administered, the exacerbation of arthritis was inhibited significantly more in the once-daily group than in the other groups. When the dose in the once-daily group was reduced to one-fourth that of the current standard dosing method, arthritis scores were markedly lower in the once-daily group than in the once and thrice-weekly groups.

Conclusions

The daily administration of a low dose of MTX not only maintained normal levels that estimated adverse effects but also suppressed the progression of arthritis significantly more than the current standard dosing method. The results indicate that the reconsideration of dosing schedules based on the characteristics of MTX will lead to more effective RA therapy than that currently used in clinical practice.

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[Health Science]

Title: Factors affecting a face-to-face learning event

Author: Ricarda Micallef and Reem Kayyali

Journal: International Journal of Pharmacy Practice

Volume: Version of Record online: 17 MAY 2017

Doi: 10.1111/ijpp.12373

Abstract

Background

Pharmacy professionals have multiple opportunities to attend learning events run by a series of providers. However, there has never been a large-scale evaluation of events. Currently, formats of learning sessions differ by provider with no optimum model identified. Pharmacy Education South London was formed in April 2014 for the provision of education and training for pharmacy professionals in South London, running sessions multiple times across various locations.

Objective

The objective of this work was to identify factors that influence the perceived success of a face-to-face supplementary education and training event from the perspective of attendees.

Methods

Evaluation forms from 600 participants at training events followed by semi-structured individual interviews with 11 participants.

Key findings

Participants over 55 years were more likely to attend lecture style events versus those aged under 25 years who attended more workshops ($P < 0.001$); there was no correlation with gender. About 57.3% (n = 344) of participants agreed fully that the event increased their understanding of the topics, although only 38.5% (n = 231) stated that it would change their practice. Themes influencing an event fell into three broad themes: personal reasons affecting attendance, success factors for the session and application of learning, all with related subthemes. Subthemes included commitments, convenience, awareness, topic and personal relevance, content and delivery and reference, review and action.

Conclusions

In publicising events, the topic, including the driver for the topic and the skills that will be obtained, the speaker and their experience plus how learning can be applied after the event should be included.

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[Health Science]

Title: A Broader Bioethics: Topic Selection and the Impact of National Bioethics Commissions

Author: Jason L. Schwartz

Journal: Hastings Center Report

Volume: Version of Record online: 22 MAY 2017 (pages S17–S19)

Doi: 10.1002/hast.713

Abstract

Comparative assessments of national bioethics commissions in the United States commonly look at the differences among these groups over their forty-year history. A particular focus has been differences in the membership, mission, methods, and reports of the President's Council on Bioethics, which was active from 2001 until 2009, compared to those of its predecessors and the recent Presidential Commission for the Study of Bioethical Issues, active from 2009 until 2016. The differences are real, but disproportionate attention to them can obscure the substantial similarities in commissions' structure and function throughout the history of expert bioethics advice to government. As the Trump administration considers what role, if any, a bioethics commission will play in its work, it would be well served to consider how choices regarding the design of such a group and the topics it examines can best facilitate the unique contributions it can make to the government and to the country.

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[Health Science]

Title: The Rapid Recovery Progression Measure: A Brief Assessment of Biopsychosocial Functioning During Substance Use Disorder Recovery

Author: Sarah Elison , Stephanie Dugdale , Jonathan Ward & Glyn Davies

Journal: Substance Use & Misuse

Volume: Published online: 30 May 2017

Doi: 10.1080/10826084.2017.1299183

Abstract

Background: There is debate in the literature around how to measure outcomes in treatment and recovery from substance use disorder (SUD). Various constructs have been suggested as appropriate including "recovery capital" and "treatment progression." To contribute to this debate, the construct of "recovery progression" has been suggested by the authors, and a psychometric assessment, the Recovery Progression Measure (RPM). Although published psychometrics data have demonstrated the RPM to be reliable, at 36-item long, it may be too lengthy to complete in clinic environments. Therefore, a shorter version has been developed, the Rapid RPM. **Objectives**: To examine reliability, validity, sensitivity and specificity of the Rapid RPM via data from 9208 service users. Methods: Data were collected from service users accessing the Breaking Free Online (BFO) treatment and recovery program, which has within its baseline assessment the six-item, 11-point Likert scale Rapid RPM. Psychometric properties were examined. **Results**: Internal reliability of the Rapid RPM was excellent, α =.92. The Rapid RPM also had good concurrent and predictive validity, with baseline scores, and changes in scores to follow-up, being significantly associated with scores on standardized measures of common mental health sequela, severity of substance dependence and quality of life, and changes in self-reported substance use. The Rapid RPM was also able to differentiate between participants scoring above thresholds on these measures for clinically relevant substance dependence and mental health difficulties. **Conclusions:** This study provides data to support reliability, validity, sensitivity and specificity of the Rapid RPM, indicating potential as a clinical tool.

Database

Taylor & Francis

[Health Science]

Title: Executive function and attention in patients with stress-related exhaustion: perceived fatigue and effect of distraction

Author: David Krabbe, Susanne Ellbin, Michael Nilsson, Ingibjörg H Jonsdottir & Hans Samuelsson

Journal: Stress

Volume: Accepted author version posted online: 29 May 2017

Doi: 10.1080/10253890.2017.1336533

Abstract

Cognitive impairment has frequently been shown in patients who seek medical care for stress-related mental health problems. This study aims to extend the current knowledge of cognitive impairments in these patient by focusing on perceived fatigue and effects of distraction during cognitive testing. Executive function and attention was tested in a group of patients with stress-related exhaustion (n = 25) and compared with healthy controls (n = 25). Perceived fatigue was measured before, during and after the test session, and some of the tests were administered with and without standardized auditory distraction. Executive function and complex attention performance was poorer among the patients compared to controls. Interestingly, their performance was not significantly affected by auditory distraction but, in contrast to the controls, they reported a clear-cut increase in mental tiredness, during and after the test session. Thus, patients with stress-related exhaustion manage to perform during distraction but this was achieved at a great cost. These findings are discussed in terms of a possible tendency to adopt a high-effort approach despite cognitive impairments and the likelihood that such an approach will require increased levels of effort, which can result in increased fatigue. We tentatively conclude that increased fatigue during cognitive tasks is a challenge for patients with stress-related exhaustion and plausibly of major importance when returning to work demanding high cognitive performance.

Database

Taylor & Francis

[Health Science]

Title: Comprehensive DNA methylation study identifies novel progression-related and prognostic markers for cutaneous melanoma

Author: Jasper Wouters, Miguel Vizoso, Anna Martinez-Cardus, F. Javier Carmona, et. al.

Journal: BMC Medicine

Volume: 2017 **Issue:** 15 **Page:** 101 (Published: 5 June 2017)

Doi: 10.1186/s12916-017-0851-3

Abstract

Background

Cutaneous melanoma is the deadliest skin cancer, with an increasing incidence and mortality rate. Currently, staging of patients with primary melanoma is performed using histological biomarkers such as tumor thickness and ulceration. As disruption of the epigenomic landscape is recognized as a widespread feature inherent in tumor development and progression, we aimed to identify novel biomarkers providing additional clinical information over current factors using unbiased genome-wide DNA methylation analyses.

Methods

We performed a comprehensive DNA methylation analysis during all progression stages of melanoma using Infinium HumanMethylation450 BeadChips on a discovery cohort of benign nevi (n = 14) and malignant melanoma from both primary (n = 33) and metastatic (n = 28) sites, integrating the DNA methylome with gene expression data. We validated the discovered biomarkers in three independent validation cohorts by pyrosequencing and immunohistochemistry.

Results

We identified and validated biomarkers for, and pathways involved in, melanoma development (e.g., HOXA9 DNA methylation) and tumor progression (e.g., TBC1D16 DNA methylation). In addition, we determined a prognostic signature with potential clinical applicability and validated PON3 DNA methylation and OVOL1 protein expression as biomarkers with prognostic information independent of tumor thickness and ulceration.

Conclusions

Our data underscores the importance of epigenomic regulation in triggering metastatic dissemination through the inactivation of central cancer-related pathways. Inactivation of cell-adhesion and differentiation unleashes dissemination, and subsequent activation of inflammatory and immune system programs impairs anti-tumoral defense pathways. Moreover, we identify several markers of tumor development and progression previously unrelated to melanoma, and determined a prognostic signature with potential clinical utility.

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