บทความที่น่าสนใจประจำเดือนกันยายน 2558

สาขาวิทยาศาสตร์สุขภาพ

Title :	Ceftolozane/tazobactam pharmacokinetic/pharmacodynamic-derived dose justification for phase 3 studies in patients with nosocomial pneumonia
Author :	Alan J. Xiao, Benjamin W. Miller, Jennifer A. Huntington and David P. Nicolau
Journal :	The Journal of Clinical Pharmacology: Article first published online: 25 AUG 2015 | DOI: 10.1002/jcph.566
Abstract :	Ceftolozane/tazobactam is an antipseudomonal antibacterial approved for the treatment of complicated urinary tract infections (cUTIs) and complicated intra-abdominal infections (cIAIs) and in phase 3 clinical development for treatment of nosocomial pneumonia. A population pharmacokinetic (PK) model with the plasma-to-epithelial lining fluid (ELF) kinetics of ceftolozane/tazobactam was used to justify dosing regimens for patients with nosocomial pneumonia in phase 3 studies. Monte Carlo simulations were performed to determine ceftolozane/tazobactam dosing regimens with a >90% probability of target attainment (PTA) for a range of pharmacokinetic/pharmacodynamic targets at relevant minimum inhibitory concentrations (MICs) for key pathogens in nosocomial pneumonia. With a plasma-to-ELF penetration ratio of approximately 50%, as observed from an ELF PK study, a doubling of the current dose regimens for different renal functions that are approved for cUTIs and cIAIs is needed to achieve >90% PTA for nosocomial pneumonia. For example, a 3-g dose of ceftolozane/tazobactam for nosocomial pneumonia patients with normal renal function is needed to achieve a >90% PTA (actual 98%) for the 1-log kill target against pathogens with an MIC of ≤8 mg/L in ELF, compared with the 1.5-g dose approved for cIAIs and cUTIs.
Database :	Wiley Online Library

Title :	Osteosarcoma Stem Cells Have Active Wnt/β-Catenin and Overexpress SOX2 and KLF4

Author :	Sara R. Martins-Neves, Willem E. Corver, Daniela I. Paiva-Oliveira, Brendy E.W.M. van den Akker, Inge H. Briaire-de-Bruijn1, et. al.
Journal :	Journal of Cellular Physiology: Accepted Article (Accepted, unedited articles published online and citable. The final edited and typeset version of record will appear in future.) -- DOI: 10.1002/jcp.25179
Abstract :	Osteosarcoma is a bone tumor displaying significant cellular and histological heterogeneity and a complex genetic phenotype. Although multiple studies strongly suggest the presence of cancer stem cells in osteosarcoma a consensus on their characterization is still missing. We used a combination of functional assays (sphere-forming, Aldefluor and side-population) for identification of cancer stem cell populations in osteosarcoma cell lines. Expression of stemness-related transcription factors, quiescent nature, in vivo tumorigenicity and Wnt/β-catenin activation were evaluated. We show that different cancer stem cell populations may co-exist in osteosarcoma cell lines exhibiting distinct functional properties. Osteosarcoma spheres are slowly-proliferating populations, overexpress SOX2 and KLF4 stemness-related genes and have enhanced tumorigenic potential. Additionally, spheres show specific activation of Wnt/β-catenin signaling as evidenced by increased nuclear β-catenin, TCF/LEF activity and AXIN2 expression, in a subset of the cell lines. Aldefluor-positive populations were detected in all osteosarcoma cell lines and overexpress SOX2, but not KLF4. The side-population phenotype is correlated with ABCG2 drug-efflux transporter expression. Distinct functional methods seem to identify cancer stem cells with dissimilar characteristics. Intrinsic heterogeneity may exist within osteosarcoma cancer stem cells and can have implications on the design of targeted therapies aiming to eradicate these cells within tumors.
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Title :	A combination SMS and transportation reimbursement intervention to improve HIV care following abnormal CD4 test results in rural Uganda: a prospective observational cohort study
Author :	Mark J. Siedner, Data Santorino, Alexander J. Lankowski, Michael Kanyesigye, Mwebesa B. Bwana, Jessica E. Haberer and David R. Bangsberg

Journal :	BMC Medicine: 2015, 13:160 doi:10.1186/s12916-015-0397-1
Abstract :	Background Up to 50 % of HIV-infected persons in sub-Saharan Africa are lost from care between HIV diagnosis and antiretroviral therapy (ART) initiation. Structural barriers, including cost of transportation to clinic and poor communication systems, are major contributors. Methods We conducted a prospective, pragmatic, before-and-after clinical trial to evaluate a combination mobile health and transportation reimbursement intervention to improve care at a publicly operated HIV clinic in Uganda. Patients undergoing CD4 count testing were enrolled, and clinicians selected a result threshold that would prompt early return for ART initiation or further care. Participants enrolled in the pre-intervention period (January – August 2012) served as a control group. Participants in the intervention period (September 2012 – November 2013) were randomized to receive daily short message service (SMS) messages for up to seven days in one of three formats: 1) messages reporting an abnormal result directly, 2) personal identification number-protected messages reporting an abnormal result, or 3) messages reading “ABCDEFG” to confidentially convey an abnormal result. Participants returning within seven days of their first message received transportation reimbursements (about $6USD). Our primary outcomes of interest were time to return to clinic and time to ART initiation. Results There were 45 participants in the pre-intervention period and 138 participants in the intervention period (46, 49, and 43 in the direct, PIN, and coded groups, respectively) with low CD4 count results. Median time to clinic return was 33 days (IQR 11–49) in the pre-intervention period and 6 days (IQR 3–16) in the intervention period ($P < 0.001$); and median time to ART initiation was 47 days (IQR 11–75) versus 12 days (IQR 5–19), ($P < 0.001$). In multivariable models, participants in the intervention period had earlier return to clinic (AHR 2.32, 95 %CI 1.53 to 3.51) and earlier time to ART initiation (AHR 2.27, 95 %CI 1.38 to 3.72). All three randomized

	message formats improved time to return to clinic and time to ART initiation (P < 0.01 for all comparisons versus the pre-intervention period). Conclusions A combination of an SMS laboratory result communication system and transportation reimbursements significantly decreased time to clinic return and time to ART initiation after abnormal CD4 test results.
Database :	BioMed Central Ltd

Title :	The most important tasks for peer reviewers evaluating a randomized controlled trial are not congruent with the tasks most often requested by journal editors
Author :	Anthony Chauvin, Philippe Ravaud, Gabriel Baron, Caroline Barnes and Isabelle Boutron
Journal :	BMC Medicine: 2015, 13:158 doi:10.1186/s12916-015-0395-3
Abstract :	Background The peer review process is a cornerstone of biomedical research publications. However, it may fail to allow the publication of high-quality articles. We aimed to identify and sort, according to their importance, all tasks that are expected from peer reviewers when evaluating a manuscript reporting the results of a randomized controlled trial (RCT) and to determine which of these tasks are clearly requested by editors in their recommendations to peer reviewers. Methods We identified the tasks expected of peer reviewers from 1) a systematic review of the published literature and 2) recommendations to peer reviewers for 171 journals (i.e., 10 journals with the highest impact factor for 14 different medical areas and all journals indexed in PubMed that published more than 15 RCTs over 3 months regardless of the medical area). Participants who had peer-reviewed at least one report of an RCT had to classify the importance of each task relative to other tasks using a Q-sort technique. Finally, we evaluated editors' recommendations to authors to determine which tasks were clearly requested by editors in their recommendations to peer reviewers.

	Results The Q-sort survey was completed by 203 participants, 93 (46 %) with clinical expertise, 72 (36 %) with methodological/statistical expertise, 17 (8 %) with expertise in both areas, and 21 (10 %) with other expertise. The task rated most important by participants (evaluating the risk of bias) was clearly requested by only 5 % of editors. In contrast, the task most frequently requested by editors (provide recommendations for publication), was rated in the first tertile only by 21 % of all participants. Conclusions The most important tasks for peer reviewers were not congruent with the tasks most often requested by journal editors in their guidelines to reviewers.
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Title :	Formulation and evaluation of tacrolimus-loaded galactosylated Poly(lactic-co-glycolic acid) nanoparticles for liver targeting
Author :	Nishita P. Mistry, Jagruti L. Desai and Hetal P. Thakkar
Journal :	Journal of Pharmacy and Pharmacology: Article first published online: 5 MAY 2015 | DOI: 10.1111/jphp.12430
Abstract :	Objective The aim of this investigation was to formulate liver targeted tacrolimus-loaded nanoparticles for reducing renal distribution and thereby decreasing nephrotoxicity. Method Poly lactic-co-glycolic acid (PLGA) was galactosylated, and confirmation of galactosylation was performed by Fourier transform infrared spectroscopy and nuclear magnetic resonance spectroscopy. Tacrolimus-loaded PLGA nanoparticles (Tac-PLGA NP) and galactosylated PLGA nanoparticles (Tac-Gal-PLGA NPs) were prepared by ultrasonic emulsification solvent evaporation technique and characterized.

	Key findings The size of both the formulations was below 150 nm and negative zeta potential indicated the stability and reticuloendothelial system targeting efficiency. The in-vitro release and pharmacokinetics showed sustained release of tacrolimus from nanoparticles in comparison to plain drug solution. The biodistribution studies revealed the potential of both the nanoparticulate systems to target tacrolimus to the liver for prolonged periods of time compared with the plain drug solution. However, significantly higher liver and spleen targeting efficiency of Tac-Gal-PLGA NPs compared with Tac-PLGA NPs was evident indicating its active targeting. Significantly lower distribution in the kidney from nanoparticles indicated the possibility of reduced nephrotoxicity – the principal reason for patient non-compliance. Both nanoparticles showed stability at refrigerated condition (5°C ± 3°C) upon storage for 1 month. Conclusion Galactosylated PLGA nanoparticles seem to be a promising carrier for liver targeting of tacrolimus.
Database :	Wiley Online Library

Title :	Development of glutathione-conjugated asiatic acid-loaded bovine serum albumin nanoparticles for brain-targeted drug delivery
Author :	Nisith Raval, Tejas Mistry, Niyati Acharya and Sanjeev Acharya
Journal :	Journal of Pharmacy and Pharmacology: Article first published online: 27 AUG 2015 | DOI: 10.1111/jphp.12460
Abstract :	Objective Asiatic acid, a well-known plant-based neuroprotective pentacyclic triterpenoid, has major limitation for its bioavailability in the brain. The objective of this study is to develop novel bovine serum albumin (BSA) nanoparticles coupled with glutathione (natural tripeptide) to enhance drug delivery to brain. Methods

	Asiatic acid-loaded BSA nanoparticles were prepared by using modified desolvation technique. Conjugation of glutathione with asiatic acid-loaded BSA nanoparticle was done by carbodiimide reaction using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDAC). In-vivo biodistribution study of asiatic acid solution, and conjugated and unconjugated asiatic acid-loaded BSA nanoparticles, at the dose equivalent to 75 mg/kg was evaluated, through intravenous administration to Wistar rats. Asiatic acid has very weak chromophore so high-pressure liquid chromatography-based novel pre-derivatization method was developed using p-toluidine as a coupling agent to improve sensitivity. Key findings The results showed 10-fold more bioavailability of asiatic acid in the brain after 5 h with glutathione-conjugated asiatic acid-loaded BSA nanoparticles as compared with asiatic acid solution with 627.21% drug targeting efficiency to the brain. Conclusion The present investigation demonstrated enhanced delivery of asiatic acid using glutathione and hence served as a potential ligand to improve brain targeting efficiency.
Database :	Wiley Online Library

Title :	Pharmacokinetics of metoprolol during pregnancy and lactation
Author :	Rachel J. Ryu, Sara Eyal, Thomas R. Easterling, Steve N. Caritis, Raman Venkataraman, Gary Hankins, Erik Rytting, Kenneth Thummel, Edward J. Kelly, Linda Risler, Brian Phillips, Matthew T. Honaker, Danny D. Shen and Mary F. Hebert
Journal :	The Journal of Clinical Pharmacology: Accepted manuscript online: 7 SEP 2015 05:43AM EST | DOI: 10.1002/jcph.631
Abstract :	The objective of this study was to evaluate the steady-state pharmacokinetics of metoprolol during pregnancy and lactation. Serial plasma, urine and breast milk concentrations of metoprolol and its metabolite, α-hydroxymetoprolol, were measured over one dosing interval in women treated with metoprolol (25-750 mg/day) during early- (n = 4), mid- (n = 14) and late-pregnancy (n = 15), as

	well as postpartum (n = 9) with (n = 4) and without (n = 5) lactation. Subjects were genotyped for CYP2D6 loss-of-function allelic variants. Utilizing paired analysis, mean metoprolol apparent oral clearances were significantly higher in mid-pregnancy (361 ± 223 L/hr, n = 5, $p < 0.05$) and late-pregnancy (568 ± 273 L/hr, n = 8, $p < 0.05$) compared to ≥ 3 months postpartum (200 ± 131 L/hr and 192 ± 98 L/hr, respectively). When the comparison was limited to Extensive Metabolizers (EMs), metoprolol apparent oral clearance was significantly higher during both mid- and late-pregnancy ($p < 0.05$). Relative infant exposure to metoprolol through breast milk was < 1.0% of maternal weight-adjusted dose (n = 3). Due to the large, pregnancy-induced changes in metoprolol pharmacokinetics, if inadequate clinical responses are encountered, clinicians who prescribe metoprolol during pregnancy should be prepared to make aggressive changes in dosage (dose and frequency) or consider using an alternate β-blocker.
Database :	Wiley Online Library

Title :	Association Between Vitamin D Status and Age-Related Macular Degeneration by Genetic Risk
Author :	Amy E. Millen, Kristin J. Meyers, Zhe Liu, Corinne D. Engelman, et. al.
Journal :	JAMA Ophthalmol. Published online August 27, 2015. doi:10.1001/jamaophthalmol.2015.2715
Abstract :	Importance: Deficient 25-hydroxyvitamin D (25[OH]D) concentrations have been associated with increased odds of age-related macular degeneration (AMD). Objective: To examine whether this association is modified by genetic risk for AMD and whether there is an association between AMD and single-nucleotide polymorphisms of genes involved in vitamin D transport, metabolism, and genomic function. Design, Setting, and Participants:

Postmenopausal women (N = 913) who were participants of the Carotenoids in Age-Related Eye Disease Study (CAREDS) (aged 54 to <75 years) with available serum 25(OH)D concentrations (assessed October 1, 1993, to December 31, 1998), genetic data, and measures of AMD (n = 142) assessed at CAREDS baseline from May 14, 2001, through January 31, 2004, were studied.

Main Outcomes and Measures:
Prevalent early or late AMD was determined from graded, stereoscopic fundus photographs. Logistic regression was used to estimate odds ratios (ORs) and 95% CIs for AMD by the joint effects of 25(OH)D (<12, ≥12 to <20, ≥20 to <30, and ≥30 ng/mL) and risk genotype (noncarrier, 1 risk allele, or 2 risk alleles). The referent group was noncarriers with adequate vitamin D status (≥30 ng/mL). Joint effect ORs were adjusted for age, smoking, iris pigmentation, self-reported cardiovascular disease, self-reported diabetes status, and hormone use. Additive and multiplicative interactions were assessed using the synergy index (SI) and an interaction term, respectively. To examine the association between AMD and variants in vitamin D–related genes, age-adjusted ORs and 95% CIs were estimated using logistic regression.

Results:
Among the 913 women, 550 had adequate levels of vitamin D (≥20 ng/mL), 275 had inadequate levels (≥12 to <20 mg/mL), and 88 had deficient levels (<12 ng/mL). A 6.7-fold increased odds of AMD (95% CI, 1.6-28.2) was observed among women with deficient vitamin D status (25[OH]D <12 ng/mL) and 2 risk alleles for CFH Y402H (SI for additive interaction, 1.4; 95% CI, 1.1-1.7; P for multiplicative interaction = .25). Significant additive (SI, 1.4; 95% CI, 1.1-1.7) and multiplicative interactions (P = .02) were observed for deficient women with 2 high-risk CFI (rs10033900) alleles (OR, 6.3; 95% CI, 1.6-24.2). The odds of AMD did not differ by genotype of candidate vitamin D genes.

Conclusions and Relevance:

	In this study, the odds of AMD were highest in those with deficient vitamin D status and 2 risk alleles for the CFH and CFI genotypes, suggesting a synergistic effect between vitamin D status and complement cascade protein function. Limited sample size led to wide CIs. Findings may be due to chance or explained by residual confounding.
Database :	(The American Society for Nutrition) – Web of Science

Title :	Amino Acid Intake Is Inversely Associated with Arterial Stiffness and Central Blood Pressure in Women
Author :	Amy Jennings, Alex MacGregor, Ailsa Welch, Phil Chowienczyk, Tim Spector, and Aedín Cassidy
Journal :	The Journal of Nutrition: September 2015, 145 (9)
Abstract :	Background: Although data suggest that intake of total protein, and specific amino acids (AAs) reduces blood pressure, data on other cardiovascular disease risk factors are limited. Objective: We examined associations between intake of AAs with known mechanistic links to cardiovascular health and direct measures of arterial stiffness, central blood pressure, and atherosclerosis. Methods: In a cross-sectional study of 1898 female twins aged 18–75 y from the TwinsUK registry, intake of 7 cardioprotective AAs (arginine, cysteine, glutamic acid, glycine, histidine, leucine, and tyrosine) was calculated from food-frequency questionnaires. Direct measures of arterial stiffness and atherosclerosis included central systolic blood pressure (cSBP), mean arterial pressure (MAP), augmentation index (AI), pulse wave velocity (PWV), and intima–media thickness (IMT). ANCOVA was used to assess the associations between endpoints of arterial stiffness and intake (per quintile), adjusting for potential confounders.

	Results: In multivariable analyses, higher intake of total protein and 7 potentially cardioprotective AAs was associated with lower cSBP, MAP, and PWV. Higher intake of glutamic acid, leucine, and tyrosine was most strongly associated with PWV, with respective differences of −0.4 ± 0.2 m/s (P-trend = 0.02), −0.4 ± 0.2 m/s (P-trend = 0.03), and −0.4 ± 0.2 m/s (P-trend = 0.03), comparing extreme quintiles. There was a significant interaction between AA intake and protein source, and higher intake of AAs from vegetable sources was associated with lower central blood pressure and AI. Higher intake of glutamic acid, leucine, and tyrosine from animal sources was associated with lower PWV. Conclusions: These data provide evidence to suggest that intake of several AAs is associated with cardiovascular benefits beyond blood pressure reduction in healthy women. The magnitude of the observed associations was similar to those previously reported for other lifestyle factors. Increasing intake of these AAs could be an important and readily achievable way to reduce cardiovascular disease risk.
Database :	(The American Society for Nutrition) – Web of Science

Title :	Stress-Induced Activation of Apoptosis Signal-Regulating Kinase 1 Promotes Osteoarthritis
Author :	Qian-Shi Zhang, Gregory J. Eaton, Carol Diallo and Theresa A. Freema
Journal :	Journal of Cellular Physiology: Accepted Article (Accepted, unedited articles published online and citable. The final edited and typeset version of record will appear in future.) -- DOI: 10.1002/jcp.25186
Abstract :	Apoptosis signal-regulated kinase 1 (ASK1) has been shown to affect a wide range of cellular processes including stress-related responses, cytokine and growth factor signaling, cell cycle and cell death. Recently, we reported that lack of ASK1 slowed chondrocyte hypertrophy, terminal differentiation and apoptosis resulting in an increase in trabecular bone formation. Herein, we investigated the role of ASK1 in the pathogenesis of osteoarthritis (OA). Immunohistochemistry performed on articular cartilage samples from patients with OA showed ASK1 expression

	increased with OA severity. In vitro analysis of chondrocyte hypertrophy, maturation and ASK1 signaling in embryonic fibroblasts from ASK1 knockout (KO) and wild type (WT) mice was examined. Western analysis demonstrated an increase in ASK1 signaling commensurate with chondrogenic maturation during differentiation or in response to stress by the cytokines, tumor necrosis factor alpha or interleukin 1 beta in WT, but not in ASK1 KO embryonic fibroblasts. Surgically induced moderate or severe OA or OA due to natural aging in WT and ASK1 KO mice was assessed by microCT of subchondral bone, immunohistochemistry, histology and OARSI scoring. Immunohistochemistry, microCT and OARSI scoring all indicated that the lack of ASK1 protected against OA joint degeneration, both in surgically induced OA and in aging mice. We propose that the ASK1 MAP kinase signaling cascade is an important regulator of chondrocyte terminal differentiation and inhibitors of this pathway could be useful for slowing chondrocyte maturation and cell death observed with OA progression.
Database :	Wiley Online Library