

บทความที่น่าสนใจประจำเดือน ตุลาคม 2557

Title :	Influence of hepatic impairment on lenvatinib pharmacokinetics following single-dose oral administration
Author :	Robert Shumaker, Jagadeesh Aluri, Jean Fan, Gresel Martinez, Helen Pentikis and Min Ren
Journal :	The Journal of Clinical Pharmacology: Article first published online: 25 SEP 2014 DOI: 10.1002/jcph.398
Abstract :	<p>This open-label, single-dose study assessed lenvatinib pharmacokinetics (PK) in subjects with normal hepatic function (n = 8) and mild, moderate, or severe hepatic impairment (n = 6 each). Subjects received 10 mg oral lenvatinib, except those with severe hepatic impairment (5 mg). Plasma and urine samples were collected over 14 days; free and total lenvatinib and its metabolites were analyzed using validated chromatography/spectrometry. PK parameters were estimated using noncompartmental analysis. There were no clinically meaningful effects of mild or moderate hepatic impairment on lenvatinib PK. Dose-normalized C_{max} for free lenvatinib was 7.0, 3.7, 5.7, and 5.6 ng/mL in subjects with normal hepatic function, mild, moderate, and severe hepatic impairment, respectively. There was no consistent trend, although dose-normalized C_{max} was lower for all subjects with hepatic impairment. AUCs increased 170% and t_{1/2} increased (37 versus 23 hours) in subjects with severe hepatic impairment. Changes in exposure based on total plasma concentrations were generally less than those based on free concentrations, suggesting changes in plasma protein binding in subjects with severe hepatic impairment. Lenvatinib was generally well tolerated. Subjects with severe hepatic impairment should begin lenvatinib treatment at a reduced dose of 14 mg versus 24 mg for subjects with normal liver function and subjects with mild or moderate hepatic impairment.</p>
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Title :	Nestin is a Marker of Lung Remodeling Secondary to Myocardial Infarction and Type I Diabetes in the Rat
Author :	Andréanne Chabot, Marc-Andre Meus, Patrice Naud, Vanessa Hertig, Jocelyn Dupuis, Louis Villeneuve, Nabel El Khoury, Celine Fiset, Stanley Nattel, Jean-Francois Jasmin and Angelino Calderone
Journal :	Journal of Cellular Physiology: January 2015, Volume 230, Issue 1, pages 170–179 (Article first published online: 29 SEP 2014 DOI: 10.1002/jcp.24696)
Abstract :	<p>Upregulation of the intermediate filament protein nestin was identified in a subpopulation of fibroblasts during reactive and reparative fibrosis and directly contributed to the enhanced proliferative phenotype. The present study tested the hypothesis that nestin was expressed in lung fibroblasts and the pattern of expression represented a distinct marker of pulmonary remodeling secondary to myocardial infarction and type I diabetes. Nestin(+) fibroblasts were detected in rat lungs and a subpopulation exhibited a myofibroblast phenotype delineated by the co-expression of smooth muscle [alpha]-actin. In the lungs of myocardial infarcted rats, interstitial collagen content and nestin mRNA/protein levels were significantly increased despite the absence of secondary pulmonary hypertension, whereas smooth muscle [alpha]-actin protein expression was unchanged. Exposure of rat pulmonary fibroblasts to pro-fibrotic stimuli angiotensin II and transforming growth factor-β significantly increased nestin protein levels. In the lungs of type I diabetic</p>

	rats, the absence of a reactive fibrotic response was associated with a significant downregulation of nestin mRNA/protein expression. Nestin was reported a target of miR-125b, albeit miR-125b levels were unchanged in pulmonary fibroblasts treated with pro-fibrotic stimuli. Nestin(+) cells lacking smooth muscle [alpha]-actin/collagen staining were also identified in rodent lungs and a transgenic approach revealed that expression of the intermediate filament protein was driven by intron 2 of the nestin gene. The disparate regulation of nestin characterized a distinct pattern of pulmonary remodeling secondary to myocardial infarction and type I diabetes and upregulation of the intermediate filament protein in lung fibroblasts may have facilitated in part the reactive fibrotic response.
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Title :	Development of High-Throughput Glass Inkjet Devices for Pharmaceutical Applications
Author :	Touraj Ehtezazi, Nicola M. Dempster, Graham. D. Martin, Stephen D. Hoath and Ian. M. Hutchings
Journal :	Journal of Pharmaceutical Sciences: Article first published online: 29 SEP 2014 DOI: 10.1002/jps.24192
Abstract :	The application of the inkjet method to pharmaceutical products is promising. To make this realistic, not only does the throughput of this method need to be increased, but also the components should be inert to pharmaceutical preparations. We present designs of glass-based inkjet devices that are capable of producing droplets at high rates. To achieve this, inkjet devices from glass capillary tubes were manufactured with orifice diameters of 5, 10 and 20 μm and were actuated with diaphragm piezoelectric disks. Also, a pressure capsule was formed by creating a manifold at a distance from the orifice tip. Placing the piezoelectric disk at 0.5 mm distance from the tip allowed the formation of a jet at 3.2 MHz in certain designs, but for a short period of time because of overheating. The length of the pressure capsule, its inlet diameter, and the nozzle tip geometry were crucial to lower the required power. Actuating an inkjet device with 10 μm orifice diameter comfortably at 900 kHz and drying the droplets from 1% salbutamol sulphate solution allowed the formation of particles with diameters of $1.76 \pm 0.15 \mu\text{m}$ and the geometric standard deviation of 1.08. In conclusion, optimising internal design of glass inkjet devices allowed the production of high-throughput droplet ejectors.
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Title :	Hydrated/Dehydrated Lipid Phase Transitions Measured Using Nanocalorimetry
Author :	Feng Yi, Il Kyoon Kim, Song Li and David A. Lavan
Journal :	Journal of Pharmaceutical Sciences: Article first published online: 24 SEP 2014 DOI: 10.1002/jps.24187
Abstract :	The phase transition evolution with hydration of a model system, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), was investigated with a fast nanocalorimetry system. Using nanocalorimetry, it is possible to measure the gel to liquid phase transitions that occur on millisecond to second time scales and quantify the time to recover the hydrated state. The results show the phase transition occurring in a few milliseconds and the relaxation or recovery time from the dehydrated state back to original hydrated state occurring with times dependent on the local humidity. With relative humidity (RH) of 43% or higher, the recovery time can be less than a few seconds. With RH of 11% or lower, the recovery time is extended

	to greater than a minute. The recovery process is controlled by mechanisms that depend on the lipid molecular repacking and water transport from the environment. Nanocalorimetry provides a powerful method to investigate the kinetics of such transformations in lipids and other biological and pharmaceutical moieties.
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Title :	Prospective, non-randomised, open-label study of homeopathic Zingiber officinale (ginger) in the treatment of acne vulgaris
Author :	Anjali Miglani and Raj K Manchanda
Journal :	Focus on Alternative and Complementary Therapies : Article first published online: 26 SEP 2014 DOI: 10.1111/fct.12140
Abstract :	<p>Background Zingiber officinale (ginger) has a long history of use in traditional medicine, including homeopathy. Studies carried out so far have validated some of the ethno-medicinal observations.</p> <p>Objective To determine the effectiveness of homeopathic Z. officinale for the treatment of acne vulgaris and to identify its prescribing indications.</p> <p>Methods A prospective, non-randomised open-label study was conducted on human participants with acne vulgaris. Homeopathic Z. officinale was prescribed in different potencies (6C up to 1M) over a period of 6 months. Outcomes included changes in lesion counts, Global Acne Grading System (GAGS) score, and Acne-Specific Quality of Life (Acne-QoL) score. Data were analysed using paired t-tests, Wilcoxon signed-rank tests and Pearson's correlation tests.</p> <p>Results Thirty-two participants enrolled in the study; data for 31 participants were analysed. Statistically significant ($P < 0.001$) changes in lesion counts, GAGS scores and Acne-QoL scores were observed.</p> <p>Conclusion Homeopathic Z. officinale demonstrates encouraging results in the treatment of facial acne. Further investigation, using a randomised placebo-controlled trial design and a larger sample size is now required to draw firmer conclusions about the effectiveness of this intervention.</p>
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Title :	Neck manipulation, stroke and the precautionary principle
Author :	Samuel Homola
Journal :	Focus on Alternative and Complementary Therapies : Article first published online: 26 SEP 2014 DOI: 10.1111/fct.12141
Abstract :	In view of the increasing number of case reports associating stroke with neck manipulation, it is essential that patients and providers alike be made aware of the risk involved when undergoing or providing such treatment. A plausible

	explanation of how upper neck manipulation can cause stroke by damaging vertebral or internal carotid arteries begs for use of the precautionary principle when considering use of neck manipulation for any reason.
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Title :	Adrenaline (epinephrine) microcrystal sublingual tablet formulation: enhanced absorption in a preclinical model
Author :	Mutasem Rawas-Qalaji, Ousama Rachid, Belacryst A. Mendez, Annette Losada, F. Estelle R. Simons and Keith J. Simons
Journal :	Journal of Pharmacy and Pharmacology: Article first published online: 25 SEP 2014 DOI: 10.1111/jphp.12312
Abstract :	<p>Objectives For anaphylaxis treatment in community settings, adrenaline (epinephrine) administration using an auto-injector in the thigh is universally recommended. Despite this, many people at risk of anaphylaxis in community settings do not carry their prescribed auto-injectors consistently and hesitate to use them when anaphylaxis occurs. The objective of this research was to study the effect of a substantial reduction in adrenaline (Epi) particle size to a few micrometres (Epi microcrystals (Epi-MC)) on enhancing adrenaline dissolution and increasing the rate and extent of sublingual absorption from a previously developed rapidly disintegrating sublingual tablet (RDST) formulation in a validated preclinical model.</p> <p>Methods The in-vivo absorption of Epi-MC 20 mg RDSTs and Epi 40 mg RDSTs was evaluated in rabbits. Epi 0.3 mg intramuscular (IM) injection in the thigh and placebo RDSTs were used as positive and negative controls, respectively.</p> <p>Key findings Epimean (standard deviation) area under the plasma concentration vs time curves up to 60 min and C_{max} from Epi-MC 20 mg and Epi 40 mg RDSTs did not differ significantly ($P > 0.05$) from Epi 0.3 mg IM injection. After adrenaline, regardless of route of administration, pharmacokinetic parameters were significantly higher ($P < 0.05$) than after placebo RDSTs administration (reflecting endogenous adrenaline levels).</p> <p>Conclusion Epi-MC RDSTs facilitated a twofold increase in Epi absorption and a 50% reduction in the sublingual dose. This novel sublingual tablet formulation is potentially useful for the first-aid treatment of anaphylaxis in community settings.</p>
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Title :	Factors affecting adherence and access to the recommended level of diabetes care in adults with type II diabetes
Author :	Smeet Gala and Wenchen Wu
Journal :	Journal of Pharmaceutical Health Services Research: Article first published online: 9 SEP 2014 DOI: 10.1111/jphs.12066
Abstract :	Objectives

	<p>To assess realized access and equity of access to three components of diabetes care – daily self-monitoring of blood glucose (SMBG), annual dilated eye examination and biannual glycosylated haemoglobin (HbA1c) testing – and to find the factors affecting adherence to these.</p> <p>Methods In this retrospective database analysis, data was obtained from the Behavioral Risk Factor Surveillance System survey. Andersen's behavioural model of health was used to determine the factors that might affect the utilization of the three components of diabetes care. Hierarchical logistic regression was used to determine equity of access to recommended diabetes care. Data analysis was performed using SAS version 9.2.</p> <p>Key findings Realized access was highest for biannual HbA1c testing, followed by annual dilated eye examination and daily SMBG. Enabling resources drove access to daily SMBG and annual HbA1c testing, while access to annual eye exams was driven by predisposing characteristics. Uninsured individuals and those who did not receive diabetes education were less likely to adhere to diabetes care.</p> <p>Conclusions Measures are needed to increase realized access and equity of access to recommended diabetes care.</p>
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Title :	Identification of key factors affecting the oral absorption of salts of lipophilic weak acids: a case example
Author :	Orestis Petrakis, Maria Vertzoni, Alexandros Angelou, Filippou Kesisoglou, Kimberly Bentz, Konstantinos Goumas and Christos Reppas
Journal :	Journal of Pharmacy and Pharmacology: Article first published online: 23 SEP 2014 DOI: 10.1111/jphp.12320
Abstract :	<p>Objectives Evaluate the ability of biorelevant media to adequately predict solubility in human gastrointestinal aspirates collected in the fasted state for the sodium salt of a highly dosed, Biopharmaceutics Classification System II (BCS II) compound with weakly acidic properties (L-870,810, pKa 7.3, HA (5-(1,1-dioxothiazinan-2-yl)-N-((4-fluorophenyl)methyl)-8-hydroxy-1,6-naphthyridine-7-carboxamide)). Identify key luminal processes that dictate the behaviour of sodium salt of HA (NaA), after single-dose administrations of high (relatively to solubility limit) doses corresponding to 400 and 800 mg of HA in the fasted state.</p> <p>Methods Aspirates from stomach and upper small intestine were collected from eight healthy fasted adults, after administration of 240 ml of water. Solubilities of NaA and HA were measured in aspirated samples and biorelevant media. Dissolution experiments of NaA granules were performed in biorelevant media. Prediction of oral pharmacokinetics was evaluated in silico using Stella software.</p> <p>Key findings Equilibrium solubility of NaA in fluids aspirated from the upper gastrointestinal tract is more transient than of HA. Solubility in upper gastrointestinal lumen was</p>

	<p>adequately estimated by data in biorelevant media. Supersaturation, followed by precipitation, which did not fully revert to the equilibrium solubility of HA, was observed during the dissolution of NaA granules in biorelevant media. Physiologically based pharmacokinetic modelling indicated that while intragastric processes had no significant impact on absorption kinetics, dissolution kinetics, kinetic solubility, radial transport rates and, for the 800-mg dose, precipitation kinetics in the small intestine had the greatest impact on absorption profiles.</p> <p>Conclusions Adequate prediction of the average plasma profile, after administration of NaA, required consideration of region-dependent dissolution rates and/or solubilisation.</p>
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Title :	LIGHT is a crucial mediator of airway remodeling
Author :	Jen-Yu Hung, Shyh-Ren Chiang, Ming-Ju Tsai, Ying-Ming Tsai, Inn-Wen Chong, Jiunn-Min Shieh and Ya-Ling Hsu
Journal :	Journal of Cellular Physiology: Accepted manuscript online: 24 SEP 2014 12:46AM EST DOI: 10.1002/jcp.24832
Abstract :	<p>Chronic inflammatory airway diseases like asthma and chronic obstructive pulmonary disease are major health problems globally. Airway epithelial cells play important role in airway remodeling, which is a critical process in the pathogenesis of diseases. This study aimed to demonstrate that LIGHT, an inflammatory factor secreted by T cells after allergen exposure, is responsible for promoting airway remodeling. LIGHT increased primary human bronchial epithelial cells (HBECs) undergoing epithelial-mesenchymal transition (EMT) and expressing MMP-9. The induction of EMT was associated with increased NF-κB activation and p300/NF-κB association. The interaction of NF-κB with p300 facilitated NF-κB acetylation, which in turn, was bound to the promoter of ZEB1, resulting in E-cadherin downregulation. LIGHT also stimulated HBECs to produce numerous cytokines/chemokines that could worsen airway inflammation. Furthermore, LIGHT enhanced HBECs to secrete activin A, which increased bronchial smooth muscle cell (BSMC) migration. In contrast, depletion of activin A decreased such migration. The findings suggest a new molecular determinant of LIGHT-mediated pathogenic changes in HBECs and that the LIGHT-related vicious cycle involving HBECs and BSMCs may be a potential target for the treatment of chronic inflammation airway diseases with airway remodeling.</p>
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