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Liver Digest

A weekly update of PLRC happenings

December 12, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Eric Lagasse

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Next Week's Seminar

PLRC Seminar Series

Tue, 12/17/2019
12:00 to 1:00 pm
S123 BST

Takanori Takebe, MD
Assistant Professor, University of Cincinnati, Department of Pediatrics
Associate Professor, Department of Regenerative Medicine, Yokohama City University, Japan

The Promise and Impact of Organoid Medicine

Pizza will be provided.

This activity has been approved for AMA PRA Category 1 credit. #6242-Liver Center Seminars.

The full schedule of Enrichment activities is posted on **https://www.livercenter.pitt.edu/events**.

Requesting PLRC Core Services

As a reminder, when requesting services from one of the PLRC Cores, please use the designated request process. This allows our Core Directors and Managers to keep accurate records of usage. Thank you!

Advanced Cell & Tissue Imaging Core: If you are a PLRC member or Associate member and are going to be a new user of the ACTI, please contact Dr. Donna Stolz (**donna.stolz@pitt.edu**). If you're already a user and interested in starting a new project or expanding an existing one, discuss it with your primary contact in the CBI.

Biospecimen Respository & Processing Core: Please download and complete the request form (available here: **https://www.livercenter.pitt.edu/sites/default/files/Pittsburgh%20Liver%20Research%20Center%20Request%20Form%2009.24.2019.pdf**) and send to Kate Smith (**smithkm13@upmc.edu**) .

Genomics & Systems Biology Core: Please review the services available (**http://www.livercenter.pitt.edu/genomics-and-systems-biology-core-0**) and contact either Dr. Takis Benos (**benos@pitt.edu**) or Dr. Jianhua Luo (**luoj@upmc.edu)** directly to request.

Clinical Component: Please download and complete the request form (available here: **https://www.livercenter.pitt.edu/sites/default/files/CC%20meeting%20form.pdf**) and send to Ann Vinski (**vinskiam@upmc.edu**).

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Varelas LJ, Klinge MJ, Malik SM, **Borhani AA**, Neal M. Idiopathic Pneumatosis Intestinalis Secondary to Lactulose Use in Patients with Cirrhosis. J Gastroenterol Hepatol. 2019 Nov 6. doi: 10.1111/jgh.14920. PubMed PMID: 31692099.

ABSTRACT

BACKGROUND & AIMS: Few case reports exist that link lactulose use with pneumatosis intestinalis in cirrhotics. This study investigates the relationship between lactulose use and idiopathic pneumatosis intestinalis in a cohort of cirrhotic patients.

METHODS: This case series considers several notable cases of patients with idiopathic pneumatosis intestinalis and concurrent lactulose use. Idiopathic pneumatosis intestinalis was defined as pneumatosis intestinalis with no identifiable etiology. A cohort of 119 patients with cirrhosis and pneumatosis intestinalis were identified in a tertiary care setting, via chart review by a multidisciplinary team. Eleven of these patients were found to have idiopathic pneumatosis intestinalis. Nine of these patients were being treated with lactulose.

RESULTS: Six out of 9 patients with idiopathic pneumatosis intestinalis that were being treated with lactulose saw resolution of pneumatosis intestinalis following discontinuation of treatment.

CONCLUSION: The etiology of idiopathic pneumatosis intestinalis is likely multifactorial, but lactulose might play a preventable role in its formation.

For full text, please **click here**.

Original Article:

Raphael BP, Mitchell PD, Gura KM, Potemkin AK, **Squires RH**, Puder M, Duggan CP. Growth in Infants and Children with Intestinal Failure Associated-Liver Disease Treated with Intravenous Fish Oil. J Pediatr Gastroenterol Nutr. 2019 Nov 6. doi: 10.1097/MPG.0000000000002551. PubMed PMID: 31703040.

ABSTRACT

BACKGROUND: Infants with intestinal failure (IF) and IF-associated-liver disease (IFALD) are at risk for poor somatic growth due to increased metabolic demands, inadequate intake, intestinal malabsorption, chronic liver disease and other co-morbidities. There are limited data on the nutritional adequacy of intravenous fish oil lipid emulsion (FOLE) compared with standard soybean oil lipid emulsion (SOLE) in the setting of intestinal failure.

AIMS: To describe growth patterns in a large cohort of infants with IFALD treated with FOLE.

METHODS: We compared growth data from infants enrolled in a single center, prospective FOLE study to published norms, as well as to a multicenter, historical cohort of infants with IF treated with SOLE.

RESULTS: 138 infants with IFALD were treated with FOLE and 108 with SOLE. Compared to normative growth curves from WHO and published pre-term data, infants in both groups from 6 to 11 months post-menstrual age exhibited declines in mean weight- and length-for-age Z-scores. At 24 months post-menstrual age compared with WHO growth data, infants treated with FOLE had a mean (95% confidence interval) weight-for-age Z-score of 0.13 (-0.18, 0.45) and length-for-age Z-score of 0.07 (-0.33, 0.47). In comparison, at 24 months post-

menstrual age, infants treated with SOLE had a mean weight for age Z-score of -0.93 (-1.20, -0.67) and mean length for age Z-score of -2.33 (-2.75, -1.91). Independent predictors of higher weight, length and head circumference Z-scores included older post-menstrual age at baseline, fewer central line-associated blood stream infections, resolution of cholestasis, type of intravenous fat emulsion (FOLE vs. SOLE) and female sex.

CONCLUSIONS: Infants with IFALD treated with FOLE showed comparable somatic growth to those treated with SOLE in early infancy, and improved somatic growth up to 24 months of age, supporting its wider use in this patient population.

For full text, please **click here**.

Review Article:
Dai H, **Thomson AW**, Rogers NM. Dendritic Cells as Sensors, Mediators, and Regulators of Ischemic Injury. Front Immunol. 2019 Oct 15;10:2418. doi: 10.3389/fimmu.2019.02418. eCollection 2019. Review. PubMed PMID: 31681306; PubMed Central PMCID: PMC6803430.

ABSTRACT
Dendritic cells (DCs) are highly specialized, bone marrow (BM)-derived antigen-processing and -presenting cells crucial to the induction, integration and regulation of innate, and adaptive immunity. They are stimulated by damage-associated molecular patterns (DAMPS) via pattern recognition receptors to promote inflammation and initiate immune responses. In addition to residing within the parenchyma of all organs as part of the heterogeneous mononuclear phagocyte system, DCs are an abundant component of the inflammatory cell infiltrate that appears in response to ischemia reperfusion injury (IRI). They can play disparate roles in the pathogenesis of IRI since their selective depletion has been found to be protective,

deleterious, or of no benefit in mouse models of IRI. In addition, administration of DC generated and manipulated ex vivo can protect organs from IRI by suppressing inflammatory cytokine production, limiting the capacity of DCs to activate NKT cells, or enhancing regulatory T cell function. Few studies however have investigated specific signal transduction mechanisms underlying DC function and how these affect IRI. Here, we address current knowledge of the role of DCs in regulation of IRI, current gaps in understanding and prospects for innovative therapeutic intervention at the biological and pharmacological levels.

For full text, please **click here**.

Original Article:

Staufner C, Peters B, Wagner M, Alameer S, Barić I, Broué P, Bulut D, Church JA, Crushell E, Dalgıç B, Das AM, Dick A, Dikow N, Dionisi-Vici C, Distelmaier F, Bozbulut NE, Feillet F, Gonzales E, Hadzic N, Hauck F, Hegarty R, Hempel M, Herget T, Klein C, Konstantopoulou V, Kopajtich R, Kuster A, Laass MW, Lainka E, Larson-Nath C, Leibner A, Lurz E, Mayr JA, **McKiernan P,** Mention K, Moog U, Mungan NO, Riedhammer KM, Santer R, Palafoll IV, **Vockley J**, Westphal DS, Wiedemann A, Wortmann SB, Diwan GD, Russell RB, Prokisch H, Garbade SF, Kölker S, Hoffmann GF, Lenz D. Defining clinical subgroups and genotype-phenotype correlations in NBAS-associated disease across 110 patients. Genet Med. 2019 Nov 25. doi: 10.1038/s41436-019-0698-4. PubMed PMID: 31761904.

ABSTRACT

PURPOSE: Pathogenic variants in neuroblastoma-amplified sequence (NBAS) cause an autosomal recessive disorder with a wide range of symptoms affecting liver, skeletal system, and brain, among others. There is a continuously growing number of patients but a lack of systematic and quantitative analysis.

METHODS: Individuals with biallelic variants in NBAS were recruited within an international, multicenter study, including novel and previously published patients. Clinical variables were analyzed with log-linear models and visualized by mosaic plots; facial profiles were investigated via DeepGestalt. The structure of the NBAS protein was predicted using computational methods.

RESULTS: One hundred ten individuals from 97 families with biallelic pathogenic NBAS variants were identified, including 26 novel patients with 19 previously unreported variants, giving a total number of 86 variants. Protein modeling redefined the β-propeller domain of NBAS. Based on the localization of missense variants and in-frame deletions, three clinical subgroups arise that differ significantly regarding main clinical features and are directly related to the affected region of the NBAS protein: β-propeller (combined phenotype), Sec39 (infantile liver failure syndrome type 2/ILFS2), and C-terminal (short stature, optic atrophy, and Pelger-Huët anomaly/SOPH).

CONCLUSION: We define clinical subgroups of NBAS-associated disease that can guide patient management and point to domain-specific functions of NBAS.

For full text, please **click here**.

Original Article:
Wu X, Zhang H, Miah MK, Caritis SN, **Venkataramanan R**. Physiologically Based Pharmacokinetic Approach Can Successfully Predict Pharmacokinetics of Citalopram in Different Patient Populations. J Clin Pharmacol. 2019 Nov 21. doi: 10.1002/jcph.1541. PubMed PMID: 31750550.

ABSTRACT

A physiologically based pharmacokinetic model (PBPK) was built for citalopram using Simcyp-based absorption, distribution, metabolism, and excretion simulator. Various physicochemical properties of citalopram were obtained from the published literature. The in vitro-in vivo extrapolation method was used to predict clearance in humans from recombinant enzyme data. Tissue distribution was predicted using parameter estimation function to fit the developed model to the observed concentration-versus-time data using nonlinear mixed-effects modeling approach. The model was verified by comparing the PBPK-based predictions with the observed pharmacokinetic (PK) profiles of citalopram in 26 clinical studies across a dose range of 10 to 60 mg. The predicted PK parameters of citalopram after intravenous dosing were within the -10% to 22% of the corresponding PK parameters obtained from the studies with quantified data sets. Most of the predicted PK parameters of citalopram after single-dose oral administration were within the 70%-130% range of the corresponding PK parameters obtained from observed data from 8 studies. After multidose oral administration, percentage error of Cmax and AUC was between -21% and 25% and -31% and 21%, respectively. Most of the observed data were within the 5th and 95th percentile interval of the variability around the predicted plasma concentrations. With the established model, the PK profiles in geriatric populations, populations with cytochrome P450 (CYP) 2C19 and/or 2D6 extensive metabolizers or poor metabolizers were predicted, and the predictions were in good agreement with the observed data. The model developed is robust to represent the absorption and disposition of citalopram and can predict the impact of patient covariates, such as age and genetic polymorphism of CYP2C19 and CYP2D6, on exposure of citalopram.

Funding Opportunity

AGA Student Abstract Award

American Gastroenterological Association (AGA)

Our mailing address is:

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