PI-72

PANCREATIC EXOCRINE INSUFFICIENCY: SECOND-GENERATION ANTIPSYCHOTIC DRUGS AND RECEPTOR BINDING PROFILES. J. F. Knudsen, MD, PhD, G. H. Sokol, MD, FCP, New Hope Cancer Center, Hudson, FL.

BACKGROUND/AIMS: Exocrine acinar cellular enzyme-secretory response and gallbladder motility are regulated by CCK and the muscarinic (M1-5) system. Metabolic consequences due to islet cell dysfunction have been reported with clozapine (C), risperidone (R), olanzapine (O), and quetiapine (Q). We believe a parallel distortion of islet and acinar cell function exists with antipsychotic drug (APD) use.

METHODS: We examined structural activity relationships, receptor binding (RB) profiles, and pancreatitis (increased amylase/lipase). "Radar" representations exemplifying similarities/differences among the APDs at RB sites were constructed to visualize APD binding profiles. Databases (joplink.net, pancreasweb.com) were evaluated for signals of acinar cell insufficiency.

RESULTS: Configurational comparisons revealed a 7-atom diazepine ring and a piperazinyl group as constant features (C, O, Q) associated with pancreatic exocrine insufficiency. The rank order of radar binding profiles (Ki values) were C > O > Q > R; a hierarchical drug cluster for classes of M1-5 receptors. Reports of increased amylase/lipase showed a preponderance for these agents, regardless of marketing exposure.

CONCLUSIONS: Our observations raise mechanistic questions about signal transduction interplay between exocrine and endocrine pancreas and the gallbladder; postprandial emptying is decreased with cholinergic antagonists. Biliary stones are a common cause of pancreatitis, and increased BMI is associated with cholesterol gallstones.

PI-73

EFFECTS OF CHRONIC HEPATIC IMPAIRMENT ON THE PHARMACOKINETICS AND SAFETY OF DESVENLAFAXINE SUCCINATE EXTENDED RELEASE. S. Baird-Bellaire, PhD, A. A. Patat, MD, N. Fauchoux, MD, C. Reh, MD, A. I. Nichols, PhD, J. A. Behrle, MS, Wyeth Pharmaceuticals France, Biotrial, Pharmacon, Wyeth Research, 92931 Paris, La Defense, Cedex, France.

BACKGROUND/AIMS: To assess the pharmacokinetics (PK) of desvenlafaxine in subjects with chronic hepatic impairment and matched healthy adults, following administration of desvenlafaxine succinate extended release (DVS).

METHODS: Hepatically impaired subjects (8 Child-Pugh class A, 8 Child-Pugh class B, and 8 Child-Pugh class C) and 12 matched healthy adults received 1 × 100-mg oral dose of DVS. Blood and urine samples were obtained over 96 hours and analyzed. A model-independent method was used to derive single-dose PK parameters of desvenlafaxine from plasma concentration vs time data. Statistical comparisons were made among groups using a 1-factor analysis of variance.

RESULTS: There were no statistically significant differences >50% for C_{max}, AUC_T, AUC_∞ or CL/F of desvenlafaxine for hepatically impaired vs healthy subjects. Median T_{max} of desvenlafaxine ranged from 6-9 hours and was similar for all groups. Mean C_{max} of desvenlafaxine in hepatically impaired subjects was ≤25% higher than in healthy subjects. Mean AUC_∞, CL/F and $t_{1/2}$ of desvenlafaxine were similar for subjects with Child-Pugh A hepatic impairment and healthy subjects. There was a higher mean AUC_∞, lower clearance, and longer $t_{1/2}$ in subjects with Child-Pugh B or C hepatic impairment.

CONCLUSION: Administration of single doses of DVS SR was safe and well tolerated in healthy and hepatically-impaired subjects. Moderate to severe hepatic impairment may alter the PK of DVS.

PI-74

INFLUENCE OF ITOPRIDE ON IN VITRO PROTEIN BINDING OF DIGOXIN AND WARFARIN. J. Spenard, PhD, W. Liu, PhD, H. Shen, PhD, L. Venkatarangan, PhD, B. Aungst, PhD, N. McAleer, BS, R. Luzietti, BS, B. Chien, PhD, Quest Pharmaceutical Services, Axcan Pharma, Mont-Saint-Hilaire, PQ, Canada.

AIMS: Itopride, a new prokinetic drug, is highly bound to plasma proteins. This study aimed at assessing the influence of itopride on the protein binding of two drugs with narrow therapeutic indices: digoxin and warfarin.

METHODS: *In vitro* protein binding in human plasma was determined using an equilibrium dialysis method after incubation at 37°C for 3 hours for warfarin and 6 hours for digoxin. Drugs were assayed in plasma and phosphate buffer by LC/MS/MS. Itopride and digoxin were tested at concentrations close to low, middle, and high therapeutic range, namely: 100 ng/mL, 250 ng/mL and 500 ng/mL for itopride and 0.8 ng/mL, 1.7 ng/mL and 2.5 ng/mL for digoxin. Warfarin was tested at concentration close to low and high therapeutic range, 1.8 μg/mL and 2.6 μg/mL. Each value is the mean of three assays.

RESULTS: Mean (S.D.) % of free digoxin or warfarin in human plasma at equilibrium

Itopride (ng/mL)	Digoxin (0.8 ng/mL)	Digoxin (1.7 ng/mL)	Digoxin (2.5 ng/mL)	Warfarin (1.8 μg/mL)	Warfarin (2.6 μg/mL)
0	99.3 (23.4)	71.4 (9.1)	81.5 (32.8)	1.4 (0.4)	1.7 (0.8)
100	120.0 (22.4)	92.8 (1.3)	79.2 (3.5)	2.6 (1.0)	2.4 (1.2)
250	107.5 (41.7)	80.0 (8.2)	90.7 (13.6)	2.0 (1.0)	1.7 (0.8)
500	78.3 (12.2)	90.0 (14.0)	73.4 (14.8)	1.9 (0.7)	1.7 (0.8)

CONCLUSIONS: These data suggest that itopride is not at risk of producing a clinically significant drug-drug interaction with digoxin. The clinical relevance of the increase seen with warfarin at itopride concentration of 100 ng/mL remains to be clarified.

PI-75

AN IMPROVED LIQUID CHROMATOGRAPHY/TANDEM MASS SPECTROMETRY METHOD FOR DETECTING ACTINOMYCIN-D AND VINCRISTINE IN PLASMA. J. M. Skolnik, J. I. Lee, J. S. Barrett, P. C. Adamson, Children's Hospital of Philadelphia, Philadelphia, PA.

BACKGROUND: Actinomycin-D (Act-D) and vincristine (VCR) are used in treating pediatric cancer. Empiric dosing continues due a lack of information on drug disposition. We report a major modification to our published Act-D and VCR LC/MS/MS assay that has reduced our lower limit of quantification (LLOQ), and decreased run time.

METHODS: The HPLC system consists of a Waters 2690 LC separation module coupled to an API 4000 MS/MS spectrometer, with a Thermo Hypurity analytical column. Mobile phase consists of water with ammonium formate 5 mM at pH 3.5 (A), and methanol: acetonitrile in a 60:40 (v:v) mix (B). Gradient elution rate is 0.15 μL/min, and run time is 9 minutes. Act-D elutes at 7.4 minutes, and its internal standard elutes at 6.3 minutes; VCR and its internal standard elute at 2 minutes. Mass spectroscopy is carried out under positive electrospray ionization and multiple reaction monitoring (MRM) mode. Nitrogen is used as a nebulizer gas. Ion recording uses the Q3 ion of Act-D and its internal standard at *m/z* 858.3 and 873.2, respectively, and *m/z* 765.4 and 751.4, for VCR and its standard, respectively.

RESULTS: The standard curve is linear from 0.1 to 10 ng/mL for Act-D and VCR, representing a five-fold lowering in LLOQ from prior assays.

CONCLUSIONS: We have improved upon our previous LC/MS/MS method, and are capable of quantifying Act-D and VCR in plasma to 0.1 ng/mL, in half the time previously required. This method will be used in our planned multicenter population PK trial of these agents in children with cancer.