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PHARMACOKINETICS ABS PHARMACODYNAMICS OF BIWH 3 IN HEALTHY DUFFY ANTIGEN POSITIVE AND DUFFY ANTIGEN NEGATIVE MALE VOLUNTEERS. J. Hilbert, J. Schnee, MD, U. Rummerstorfer, BSc, B. Jilma, MD, Boehringer-Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim Austria GmbH, Medical University Vienna, Ridgefield, CT.

BACKGROUND/AIMS: BIWH 3 is a recombinant pyro-glu monocyte chemotactic protein-1 (MCP-1). Based on arteriogenic effects of MCP-1 in animals, MCP-1 was developed for critical limb ischemia. This study investigated safety, tolerability, and PK of BIWH 3 after single 1-hr iv infusions of 20 ng/kg - 2 μg/kg in healthy males. Since the Duffy Antigen Receptor of Chemokines might be an important scavenger of MCP-1, BIWH 3 PK was assessed in Duffy positive and negative subjects.

METHODS: This was a randomized double-blind dose escalation study. 3 Duffy positive subjects each were enrolled at 20 and 60 ng/kg doses (2:1 active:placebo). At higher doses, 5 Duffy positive and 5 Duffy negative subjects were enrolled at each dose (4:1 active:placebo). Safety and tolerance were assessed for each dose. Plasma samples were collected for PK analysis and for PD of markers of leukocyte, coagulation, platelet and endothelial activation.

RESULTS: MCP-1 concentrations increased in a dose-proportional manner, and were rapidly cleared with a half-life of 0.4-0.5 h. There were no PK differences between Duffy negative and positive subjects. There was no consistent relationship of any PD markers to the PK of BIWH 3, except for the PD of MCP-1 induced monocytosis.

CONCLUSIONS: BIWH 3 was well tolerated by the study subjects in single iv infusions up to 20 μg/kg. Exposure was dose proportional, and didn't change with Duffy antigen status. PK-PD data were in line with the chemoattracting actions of BIWH 3 on monocytes *in vitro* and in animal studies.

PII-61

MODELLING CATEGORICAL RESPONSE DATA: PROFILE LIKELIHOOD AS AN ALTERNATIVE TO THE GOODNESS-OF-LINK TEST. A. Dunne, PhD, UCD Dublin, Dublin, Ireland.

BACKGROUND: Modelling a categorical response involves the use of a link function which links the response and the independent variables. This project examines a profile likelihood based method for choosing the most appropriate link function and compares it with the standard goodness-of-link test.

METHODS: The data are a subset of those collected during a randomised, double-blind, placebo controlled, forced dose escalating, clinical trial of oral oxybutynin tablets for the treatment of urinary incontinence and kindly supplied by Alza Corp. At the end of each week patients recorded the severity of dry mouth during the week. The severity of dry mouth on an ordinal scale was used to represent the adverse effect. The present study used the adverse effect data from 32 patients.

RESULTS: The goodness-of-link test underestimated the value of the parameter in the link function and had a larger standard error than the likelihood based estimate. The profile likelihood gives the maximum likelihood estimate without any approximation.

CONCLUSIONS: The profile likelihood approach to deciding on the link function is superior to the goodness-of-link test because it provides the actual maximum likelihood estimate of the link function parameter. In addition it gives a visual indication of how sensitive the likelihood is to changes in this parameter.

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EVALUATION OF IN VITRO INHIBITORY EFFECT OF ITOPRIDE ON CYTOCHROME P450. J. Spenard, PhD, J. Lin, H. Shen, B. Yuska, B. Chien, Quest Pharmaceutical Services, Axcan Pharma, Mont-Saint-Hilaire, PQ, Canada.

AIMS: Itopride, a new prokinetic drug, is mainly metabolized by FMO3. This *in vitro* study assessed the inhibitory potential of itopride on the main human CYP450 drug metabolizing isozymes.

METHODS: The isozymes activity was evaluated in pooled human hepatic microsomes at itopride concentration up to 100 μM. Probe substrates, phenacetin for CYP1A2, coumarin for CYP2A6, bupropion for CYP2B6, paclitaxel for CYP2C8, tolbutamide for CYP2C9, S-mephenytoin for CYP2C19, dextromethorphan for CYP2D6, chlorzoxazone for CYP2E1, midazolam and testosterone for CYP3A4/5 were used. The formation of the metabolites reflected CYP450 activity. Positive controls were also used for each isozyme.

RESULTS: Itopride showed no inhibition on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP3A4/5 activities at 100 μM. The percent of control enzyme activity was 93%, 106%, 73%, 101%, 105%, 104%, 92%, 99%, and 107% when tested at 100 μM, respectively. Itopride was a CYP2D6 inhibitor with calculated IC_{50} value of 8.81 μM. Inhibition around the usual Cmax of itopride at therapeutic concentration (0.62 μM) was about 30%.

DISCUSSION/CONCLUSIONS: Itopride has a small inhibitory effect on CYP2D6. Since the IC_{50} value is about 10 times higher than the Cmax and the other isozymes are not affected, the clinical significance of the inhibitory effect on the metabolism of drug by CYP2D6 will be minimal for most patients. Itopride will not inhibit the metabolism of drugs relying on CYP3A4 or isoenzymes other than CYP2D6.

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THE EFFECT OF DULOXETINE, ESCITALOPRAM, AND SERTRALINE ON CYP 2D6 FUNCTION. S. H. Preskorn, MD, B. Baker, MSM, A. Klick-Davis, RN, M. Ramadan, MD, L. Coyner, MD, D. A. Flockhart, MD, Z. Desta, PhD, R. Yang, T. Burt, MD, D. J. Greenblatt, MD, Clinical Research Institute, University of Kansas School of Medicine, Indiana University School of Medicine, Pfizer Global Pharmaceuticals & Columbia University College of Physicians & Surgeons, Tufts University, Wichita, KS.

Prior to this study there had been no studies directly comparing the relative effects of duloxetine, escitalopram or sertraline on the functional activity of cytochrome P450 enzyme, 2D6. In this study metoprolol was used as the model substrate drug for CYP2D6. Single-dose pharmacokinetics of metoprolol were measured before and after 17 days of treatment with escitalopram 20 mg/day, duloxetine 60 mg/day or sertraline 100 mg/day in young healthy male and female volunteers (n=54). The outcome measures were changes in metoprolol peak plasma levels (C_{max}), area under the plasma concentration-time curve (AUC) and clearance. The results were tested using paired t-tests and independent t-tests. The addition of each drug produced statistically significantly changes in metoprolol pharmacokinetics. The rank order for the change in metoprolol AUC was duloxetine (180%) > escitalopram (89%) > sertraline (48% and 67%). Duloxetine, compared to sertraline, produced statistically significantly larger changes in metoprolol pharmacokinetic parameters. The differences between the changes produced by escitalopram and sertraline were not significant. In summary, each drug produced mild to moderate inhibition of CYP2D6 as reflected in a change in the pharmacokinetics of metoprolol.