

PII-01

INFLIXIMAB USE IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE AND THE RISK OF SERIOUS BACTERIAL INFECTIONS. S. Schneeweiss,¹ D. H. Slomon,¹ J. Korzenik,² C. Canning,¹ B. Bressler³; ¹Brigham & Women's Hospital, Harvard Medical School, Boston, MA, ²Mass General Hospital, Harvard Medical School, Boston, MA, ³University of Vancouver, Vancouver, BC, Canada

BACKGROUND: The association between infliximab use and serious bacterial infections is controversial in patients with Inflammatory Bowel Disease (IBD). We sought to assess the association between the use of infliximab, systemic corticosteroid use, or immunosuppressant use and the risk for serious bacterial infections that led to hospital admissions among patients with IBD.

METHODS: We identified patients 18+ from British Columbia administrative databases who had five recorded diagnoses of IBD from 1996 - 2005. 11,479 patients entered the cohort at their fifth recorded diagnosis and were required to be free of cancer or HIV/AIDS. Primary outcome was first hospitalization with a primary discharge diagnosis for bacterial infections.

RESULTS: We identified 16,699 new treatment episodes with either of the three drug classes and observed a total of 104 serious bacterial infections. The combination of infliximab and glucocorticoid use doubled the risk of serious bacterial infections compared with immunosuppressive agents (RR=2.0; 0.9-4.5), independent of prior infections, disease activity and drug use. The use of infliximab alone did not increase the risk (RR=1.0; 0.1-7.1). The effect of combined use of infliximab and glucocorticoid was stronger when the analysis was restricted to bacteremia (RR=3.9; 1.6-9.6). Steroid use may increase the risk for clostridium difficile infection (RR=2.2; 0.9-5.3) based on only 32 outcomes.

CONCLUSION: In a large cohort of patients with IBD, initiation of corticosteroids alone and in combination with infliximab were associated with an increased risk of serious bacterial infection compared with immunosuppressant therapy. Infliximab alone did not show similar increases in risk but this analysis may be based on too few outcomes and assessment of disease severity may be incomplete.

PII-02

NSAID SWITCHING AND SHORT-TERM EFFECTS ON GASTROINTESTINAL OUTCOMES AFTER THE WITHDRAWAL OF ROFECOXIB. S. Schneeweiss,¹ R. J. Glynn,¹ J. Avorn,¹ M. Mamdani,² H. Mogun,¹ D. H. Solomon¹; ¹Brigham & Women's Hospital, Harvard Medical School, Boston, MA, ²University of Toronto, Toronto, ON, Canada

BACKGROUND: Rofecoxib was withdrawn from the market on September 30, 2004 because of its cardiac risk. We sought to estimate the effect of switching from selective Cox-2 inhibitors to nsNSAIDs on the incidence of GI adverse events following the withdrawal of rofecoxib on September 30, 2004

METHODS: From a US managed care database containing health care utilization information of enrollees, we identified a cohort of 33,045 patients with osteoarthritis or rheumatoid arthritis and chronic use of a selective Cox-2 inhibitor before the rofecoxib withdrawal. We calculated monthly rates of hospitalization for GI adverse events or upper GI endoscopy for the 6 months before and 3 months after the switching and compared the time trends in outcomes. Switching from rofecoxib to another coxib was considered the reference group.

RESULTS: Of 15,916 patients using rofecoxib immediately before its withdrawal, 2,626 (16%) switched to nsNSAIDs without co-prescribing of a gastroprotective drug (PPI or H2RA), 146 (1%) with a gastroprotective drug, and 5,246 (33%) switched to either celecoxib or valdecoxib. Among those switching to nsNSAID without gastroprotection, time trends of GI hospitalization rates and endoscopies did not significantly increase compared with those switching to celecoxib or valdecoxib (+ 0.3 per 1,000 persons per month; 95% CI -3.0 to 3.5).

However, physician visit rates with diagnoses of peptic ulcer disease and its complications increased differentially in the group switching to nsNSAIDs without gastroprotection (+5.2 per 1,000 persons per month; 1.2 to 9.2) compared with the group switching to another coxib. Rates of colonoscopy were not affected differentially by this switching (p=0.68).

CONCLUSION: Short-term follow-up data suggest that the sudden shift to nsNSAIDs without gastroprotection may have differentially increased outpatient visits for peptic ulcer disease and its complications compared with switching to other selective Cox-2 inhibitors.

PII-03

EFFECT OF A PROTON PUMP INHIBITOR THERAPEUTIC SUBSTITUTION POLICY IN ABORIGINAL PATIENTS IN REMOTE COMMUNITIES. M. Levine,¹ K. Gaebel,² N. Toeg³; ¹McMaster University, Hamilton, ON, Canada, ²Centre for Evaluation of Medicines, Hamilton, ON, Canada, ³Aboriginal Pharmacists Association, Hamilton, ON, Canada

BACKGROUND: Proton pump inhibitors (PPIs) used to treat of gastroesophageal symptoms can vary greatly in price but are thought not to differ in clinical benefits. The Health Canada's Non-Insured Health Benefits Program instituted a therapeutic substitution policy for PPIs as a cost containment strategy. Only the two least expensive PPI products were eligible for reimbursement. The objective of this pilot study was to determine the effect of this policy on First Nations and Inuit people in northern isolated communities.

METHODS: Five pharmacies identified a sample of patients subjected to the substitution policy, i.e., were required to switch PPI products. Eligible patients who provided informed consent received a face-to-face or telephone interview with a pharmacist using a standardized questionnaire.

RESULTS: 44 of 66 patients identified consented to be interviewed and 40 were used for analyses; 70% female, mean age 57 years. 34 (85%) patients reported health problems after the required PPI switch. The frequency of new or recurrent gastroesophageal symptoms was 73%. Problems were sufficiently severe enough to require 19 (48%) patients to go to a local nursing station or physician and 6 (18%) to a hospital for assessment (with 1 patient requiring hospital admission). During the initial 15 month period of the program there was a net increment in drug costs of \$30.96 (\$CDN) per person due to drug wastage, delayed switching and switching back. A conservative estimate of additional healthcare service costs for this cohort relating to health problems perceived to be due to the switch was \$36,624.

CONCLUSION: A majority of the patients sampled experienced problems following the PPI switch, possibly associated with either diminished efficacy or adverse drug effects. While causality is not proven, patient perceptions in this sample influenced resource use resulting in no net savings (average incremental cost of \$946 per patient) during the first 15 months of the policy.

PII-04

CISAPRIDE AND VENTRICULAR ARRHYTHMIA. S. Hennessy, C. E. Leonard, C. Newcomb, S. E. Kimmel, W. B. Bilker; University of Pennsylvania School of Medicine, Philadelphia, PA

BACKGROUND: In contrast to case reports and electrophysiology studies, previous epidemiologic studies have not demonstrated an increased risk of ventricular arrhythmia associated with cisapride use. We sought to examine the association between cisapride and ventricular arrhythmia and examine the relationship with dose and with drugs that inhibit cisapride's metabolism.

METHODS: We conducted a case-control study nested within a population of Medicaid and Medicare beneficiaries of California, Florida, New York, Ohio, and Pennsylvania enrolled during 1999 and 2000, exposed to cisapride, metoclopramide, or a proton pump inhibitor (PPI). Cases were identified via hospitalization with a principal ICD9 discharge diagnosis code indicating sudden cardiac death

or ventricular arrhythmia. Controls had at least as much eligible person time following the most recent study prescription, but had not yet experienced an event at the time of sampling. Exposure to study drugs was assessed in the thirty days prior to the event date (cases) or sampling date (controls).

RESULTS: A total of 145 cases and 7,250 controls were identified. The unadjusted rate ratio for cisapride vs. PPIs was 1.49 (95% CI, 0.96 to 2.25). Compared with PPIs, the minimally-adjusted and fully-adjusted odds ratios for cisapride were 1.65 (95% CI, 1.08 to 2.51) and 2.10 (95% CI, 1.34 to 3.28), respectively. No significant association with dose or cytochrome P-450 inhibition was evident. There were no statistically significant interactions with age, gender, or calendar year.

CONCLUSION: Cisapride was associated with an approximate doubling of the risk of hospitalization for ventricular arrhythmia and sudden cardiac death. Whether the risk-benefit balance of cisapride versus its therapeutic alternatives is favorable for a particular patient is an individual risk-benefit decision. Unmeasured confounders and error in outcome ascertainment may have contributed to the observed association.

PII-05

QT PROLONGATION POTENTIAL FOR NEW MOLECULAR ENTITY DRUGS APPROVED BY FDA, 2003-2006: LABELING REVIEW. N. Gevorkian, MD, P. Sharma, MPH, E. Pinnow, MS, A. Parekh, PhD; FDA, Rockville, MD

BACKGROUND: Several drugs withdrawn from the market have shown higher adverse events in women, notably QT prolongation and torsades des points (TdP). The FDA guidance on clinical QT assessment recommends that new drugs be evaluated for effects on QT. New Drug Applications (NDAs) now contain this safety information. The goals of this study are: 1) to identify if QT-prolongation potential is addressed in labeling; 2) to evaluate the study design and results of studies in labeling.

METHODS: Drug labels for NDA New Molecular Entities (NMEs) approved by FDA between 2003-2006 was reviewed. Labels containing information on QT prolongation or TdP were identified. We abstracted information on the product indication, population studied, dose selection, study design, data analysis, results and their clinical implications for Precautions, Warnings, Contraindications and Dosage and Administration sections.

RESULTS: FDA approved 363 NDAs between 2003-2006; 88 were NMEs. Labeling for only 28 NMEs had any information about QT prolongation or TdP. Of the 28 NME labels, 18 had no information about the sex of study participants, 3 studied only men, and 7 studied men and women. Thorough QT studies (TQT), conducted in healthy volunteers with a positive control, were found in 13 NME labels; maximum dose ranged from 3 to 8 times the highest therapeutic dose. Positive controls in TQT were identified in 9 NME labels were moxifloxacin, gatifloxacin, and ibutilite. Clinical QT assessment involving patients was found in 19 NME labels. Labels provided QT information in 8 Warnings, 11 Precautions and 4 Contraindications sections of labels.

CONCLUSION: QT prolongation and TdP were critical safety issues for several drugs in the 1990's; sponsors have since conducted thorough QT assessments for new drugs. This information should be adequately captured in labeling and appropriate clinical relevance evaluated for all susceptible populations (e.g. women, elderly).

PII-06

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS DURING CORONARY ARTERY BYPASS GRAFTING DOES NOT INCREASE CARDIOVASCULAR EVENTS. K. H. Lucas,¹ B. J. Reyes,² R. D. Santos,² M. Ayoubi,² M. Broce,² D. B. Lucas²; ¹West Virginia University - Charleston Division, Charleston, WV, ²CAMC Health Education and Research Institute, Charleston, WV

BACKGROUND: COX-2 inhibitor use for CABG postoperative pain has been linked to adverse cardiovascular outcomes. An FDA *black box warning* on the use of **all** NSAIDs peri-CABG

subsequently ensued, largely based on a single study of COX-2 inhibition only. Coupled with significant postoperative CABG pain, a high opioid toxicity profile and poor efficacy of acetaminophen in this setting, further exploration of **all** NSAID use peri-CABG is warranted.

METHODS: We conducted a retrospective analysis comparing cardiovascular complications in patients undergoing CABG at a large-volume center between 2004 and 2006 that have been exposed to NSAIDs perioperatively with a propensity matched group of patients not receiving NSAIDs during the same time period.

RESULTS: Seventy-eight percent of the 894 patients included were elective CABG with 78% being male and a mean±SE age of 60±0.3. Co-morbidities include diabetes 38%, tobacco use 38%, hypercholesterolemia 86%, hypertension 79%, previous CVA 5%, previous PCI 27%, previous CABG 8% and past MI 43%. After matching, no baseline differences were observed between groups. Cardiovascular events follow for NSAID versus no-NSAID, respectively: stroke 1.3% & 1.8%, MI 1.8% & 1.6%, PE 0% & 0.2% and cardiac arrest 0.4% & 1.1%. Although all findings were statistically insignificant, 30-day mortality trended higher by more than two-fold in those patients not exposed to NSAIDs (2% versus 0.7%; p=0.14).

CONCLUSION: NSAID use was not associated with an increased cardiovascular risk. In light of the findings, postoperative management of CABG pain with NSAIDs requires further investigation before this medication class is fully abandoned.

PII-07

DOES "EPHEDRA-FREE" MEAN "TROUBLE FREE"? B. J. Gurley, L. Bryant, C. Allan, D. K. Williams; University of Arkansas for Medical Sciences, Little Rock, AR

BACKGROUND: The 2004 FDA ban on ephedra-containing dietary supplements produced an upsurge of "ephedra-free" products onto the U.S. market. Despite their "ephedra-free" designation, many of these supplements contain botanical ingredients with sympathomimetic properties (synephrine, caffeine) that may produce untoward cardiovascular effects. The purpose of this study was to examine the hemodynamic and electrocardiographic (ECG) effects of a 3-day course of 4 separate "ephedra-free" dietary supplements (Metabolift, Xenadrine EFX, Zantrex 3, Guarana).

METHODS: 12 healthy males participated in an open label study randomized for supplementation sequence. Subjects wore a Holter monitor for 24 hours before each phase (baseline) to assess ECG activity. Blood pressure (BP) and heart rate (HR) were also assessed. Subjects ingested supplements 3 times daily for 3 days. On days 1 and 3 of supplementation, Holter monitors were again placed and hemodynamic parameters evaluated. Caffeine content and serum caffeine concentrations were determined by HPLC. Possible microbial contamination was also assessed.

RESULTS: On day 1, systolic (SBP) and diastolic (DBP) blood pressures were significantly increased relative to baseline (9.8 ± 2.2 and 5.8 ± 1.7 mm Hg, respectively). By day 3, these effects were attenuated (5.1 ± 1.6 mm Hg, SBP; 3.0 ± 2.0 mm Hg, DBP) but remained significantly elevated. Only Zantrex 3 produced significant elevations in mean HR. All supplements significantly decreased bradycardia runs. Abnormal atrial and ventricular events were noted in several subjects. Gastrointestinal and sympathomimetic side effects were frequently reported. 2 supplements were contaminated with *Bacillus*, *Enterobacter*, and *Klebsiella* species.

CONCLUSIONS: "Ephedra-free" dietary supplements may not be free of adverse cardiovascular effects or microbial contamination. Accordingly, their use should be discouraged in consumers with underlying cardiovascular disease.

PII-08

REFINING AND ADVANCING METHODOLOGY FOR ABUSE LIABILITY TESTING. M. Sokolowska,¹ B. Setnik,¹ B. Chakraborty,¹ J. B. Jones,² F. Johnson,³ M. Romach,¹ E. Sellers¹; ¹DecisionLine Clinical Research Corporation, Toronto, ON, Canada, ²Alpharma Pharmaceuticals LLC, Piscataway, NJ, ³Alpharma Pharmaceuticals, LLC, Piscataway, NJ

BACKGROUND: Various measures of positive drug effects are commonly used to determine a drug's abuse potential including assessments of subjective drug effects over time using at this moment measures (e.g., Visual Analog Scale [VAS], Addiction Research Centre Inventory [ARCI] and Cole Modification of the ARCI [Cole/ARCI]). The Overall Drug Effect VAS (at either 12 or 24 hours post dose) is assumed to be a preferred summary measure but its validity has not been established.

METHODS: This was a randomized, double-blind, single-dose, crossover study. 32 subjects with a history of recreational opioid use were administered 2 x 60 mg extended release morphine sulfate pellets with naltrexone core in capsules; 120 mg morphine sulfate in solution and placebo. The capsules were given whole and crushed. Subjects completed assessments over 24 hours (VASs [for Drug Liking (at this moment), High, Good Effect and Overall Drug Liking], ARCI [MBG] and Cole/ARCI [Stimulation Euphoria and Abuse Potential] scales and estimate of Subjective Drug Value (SDV) using validated computerized tests (DecisionLine-SMS). Correlations between the measures were analyzed using Pearson correlations.

RESULTS:

- Measures of positive drug effect at this moment and overall drug effect were highly correlated ($P < 0.001$)
- VASs (at the moment) had a higher correlation with the measures of overall drug effect ($r \geq 0.53$) than the ARCI or Cole/ARCI scales ($r \leq 0.45$)
- The responses on SDV and VAS Overall Drug Effect at 12 and 24 hours post dosing were highly correlated ($P < 0.001$)
- The correlation between the scales was affected by treatment

CONCLUSION: SDV and VAS for Overall Drug Effects are equally valid summary measures in assessment of positive drug effects. However, the responses on these measures are highly correlated with at the moment measures suggesting both are not needed. VAS measures are superior to ARCI scales. The high correlation among measures indicates simpler designs of abuse liability studies are possible.

PII-09

LACK OF ASSOCIATION BETWEEN A COMMON HISTIDINE DECARBOXYLASE (HDC) GENE POLYMORPHISM AND ATOPIC DERMATITIS (AD) IN CHILDREN. C. M. Tucker,¹ A. R. Griffin,¹ M. Levy,² D. Best,³ G. Kearns,⁴ S. Jones,⁵ J. Hurwitz,⁶ M. Pansare,⁷ M. J. Kennedy¹; ¹University of Louisville, Louisville, KY, ²Baylor College of Medicine, Houston, TX, ³Children's National Medical Center, Washington, DC, ⁴Children's Mercy Hospitals and Clinics, Kansas City, MO, ⁵Arkansas Children's Hospital, Little Rock, AR, ⁶Duke University, Durham, NC, ⁷Wayne State University, Detroit, MI

BACKGROUND/AIMS: Histidine decarboxylase (HDC) is the primary enzyme responsible for the synthesis of histamine, an important biochemical mediator in atopic dermatitis (AD), a common pediatric condition. Given that genetic variability in HDC activity may contribute to disease pathogenesis, severity and/or treatment response, we investigated the association of a common HDC polymorphism, SNP rs854158, with pediatric AD.

METHODS: The study was an open-label genotyping study conducted in 7 pediatric academic medical centers. A buccal swab was performed in Caucasian, African-American and Hispanic children (6 mo-5 yr) with a diagnosis of AD (n=309) and in pediatric controls without a personal or family history of allergies or asthma (n=379). Genomic DNA was isolated and HDC genotype determined by PCR-RFLP (n=282 AD, n=335 control).

Analysis of the relationship between allele/genotype frequency and AD was completed via χ^2 analysis. Association between genotype and AD disease severity was also assessed via the Kruskal-Wallis test.

RESULTS: Allele and genotype frequencies were as follows:

	Allele Frequency (number of alleles)		Odds Ratio	95% CI	Genotype Frequency (number of subjects)			Odds Ratio	95% CI
	A	G			AA	AG	GG		
Control (n=335)	0.78 (520)	0.22 (150)			0.58 (195)	0.39 (130)	0.03 (10)		
AD (n=282)	0.79 (444)	0.21 (120)	0.94	(0.7,1.2)	0.63 (178)	0.31 (88)	0.06 (16)	0.81	(0.6,1.1) $\chi^2 = 0.2$ $p = 0.6$

No significant association between HDC genotype and AD disease severity was noted. ($p = 0.99$).

CONCLUSION: The HDC SNP rs854158 does not appear to be associated with AD in infants and children. Altered histamine exposure in pediatric AD may therefore be the result of alterations in histamine release and/or degradative pathways. Alternately, given that numerous genes contribute to AD pathogenesis and treatment response, a polygenic rather than single candidate gene approach may be superior in predicting disease severity and/or drug response. Consequently, associations between AD and multiple candidate genes are currently being investigated.

PII-10

A PEDIATRIC CLINICAL PHARMACOLOGY CONSULT SERVICE: ONE YEAR EXPERIENCE. M. J. Rieder; University of Western Ontario, London, ON, Canada

BACKGROUND: Teaching in pediatric clinical pharmacology includes education of fellows. It is unclear as to what fellowship clinical goals should be, as the spectrum of patients to be seen is not well understood, notably for in-patients. This study reviewed a mid-size Children's Hospital to determine type and scope of consultations in pediatric clinical pharmacology.

METHODS: The study was conducted at Children's Hospital of Western Ontario, a 120 bed Hospital serving 1.5 million people. All consultations for in-patients from July 1st, 2005 to June 30, 2006 were prospectively collected. The consultation service was available working hours Monday to Friday. Data were analyzed using Microsoft Excell.

RESULTS: Over the year there were 36 consultations for in-patients, evenly distributed except for September (19%) and December (3%). 30% of consults were on Friday and only 11% on Monday. Consultations came primarily from General Pediatric Wards (50%), with Pediatric Sub-Specialty services the next commonest (22%) and the ICU, Surgical Services and others accounting for the remainder. There was an equal distribution of ages from newborn to adolescents; 60% of were male. The commonest consultation was for assessment of a possible adverse drug event (64%, $p > 0.05$), with neonatal drug exposure being next commonest (28%). A change in therapy was recommended in 41% of cases; in 38% of cases drug-related causes were ruled out.

CONCLUSIONS: The commonest reason by far for consultation on a pediatric in-patient is assessment of a possible adverse drug event. Fellowship curriculum need to have a robust component for teaching this and in assessment of drug exposure during pregnancy and lactation. A consultation service can be developed at a pediatric care facility providing exposure to a wide range of patients without an overwhelming clinical burden, with the caveat - common to many services - that consultations may group themselves on Fridays.

PII-11

TOXIC EPIDERMAL NECROLYSIS IN AN INFANT DUE TO FLUOXETINE: ROLE OF REACTIVE DRUG METABOLITES. M. J. Rieder,¹ M. J. Tucker,² P. J. O'Connell³; ¹Children's Health Research Institute, University of Western Ontario, London, ON, Canada, ²University of Western Ontario, London, ON, Canada, ³Robarts Research Institute, University of Western Ontario, London, ON, Canada

BACKGROUND: Toxic Epidermal Necrolysis (TEN) is one of the most severe forms of adverse drug reactions (ADRs). A 9 month old infant developed TEN after therapy with sulfa and fluoxetine, the latter given as a result of a dispensing error. We studied the cells of the infant to investigate the possible pathogenesis of this event.

METHODS: Peripheral blood mononuclear cells were isolated and incubated with sulfa or fluoxetine in increasing concentrations in the presence and absence of a microsomal activating system. Cells were obtained from the infant, a naïve control and from a control who had tolerated fluoxetine. After 18 hr viability was determined using a tetrazolium-based assay. Expression of serotonin receptors was studied using RT-PCR. Data were analyzed using Microsoft Excell.

RESULTS: There were no differences in viability between the cells of the patient and controls when incubated with sulfas or sulfa metabolites. In contrast, the cells of the patient showed a sharp decline in viability when incubated with fluoxetine and a microsomal activation system compared to the two controls (at 50 µM, 50 ±5% versus 83 ± 4%, p>0.01). There was no difference in expression of the 5-HT 7 receptor but expression of 5-HT 1B and 2A was reduced in both the patient and in the fluoxetine-exposed control.

CONCLUSIONS: Serotonin has been shown to have a role in immune activation. The cells of the infant who developed TEN after fluoxetine exposure showed a sharp decline in viability when exposed to fluoxetine metabolites when compared to both naïve and drug-exposed controls. As well, there was reduced expression of two 5-HT receptor sub-types, but this was seen in both tolerant and intolerant patients. There were no changes in 5-HT 7, a receptor that has been shown to be linked to T-cell activation. This suggests that the pathogenesis of TEN in this infant may have been related to altered ability to detoxify reactive metabolites of fluoxetine rather than to altered immune activation.

PII-12

HOW TO DOSE DRUGS IN THE PEDIATRIC INTENSIVE CARE UNIT: CAN WE USE EXISTING FORMULARIES? S. N. de Wildt,¹ I. Ceelie,² K. Stol,² G. Koren,¹ D. Tibboel²; ¹Hospital for Sick Children, Toronto, ON, Canada, ²Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands

BACKGROUND: A safety audit on a level III pediatric ICU (PICU) showed a large number of errors related to drug dosing errors. A single PICU drug formulary used by all staff may aid to prevent such errors. To bridge the gap to an institution-specific formulary, which takes time and money to implement, can one of the already available pediatric formularies be used? We aimed to compare availability and variability of pediatric drug dosing guidelines of four formularies for drugs used in PICU.

METHODS: First, we determined all drugs prescribed in our PICU over a one-year period. For these drugs, pediatric drug dosing guidelines were searched in four formularies. i.e. internet-based: Lexicomp® (USA), Micromedex® (USA), pocketbooks: Drug doses® (Australia), WKZ Pediatric Formulary (the Netherlands). Next, dosing guidelines were compared for actual dosage, annotation, dosage specifics and specified age ranges.

RESULTS: Of all 225 drug formulations prescribed, pediatric drug dosing guidelines could be found for 80%, 71%, 86% and 67% of formulations in the respective formularies. For 45% of formulations, daily doses differed more than 100%, for 11% no pediatric dosage was available at all, for 73% different annotations (e.g. ug/kg

vs mg/m²). For 74% different dosing administration guidelines (frequency, loading dosage, etc) and for 49% different age ranges for dosing were used.

CONCLUSION: Reflective of the lack of evidence-based drug information in children, no formulary had pediatric dosages for all drugs prescribed in our PICU. Also, doses, administration guidelines and age ranges varied considerably between formularies.

An important information gap was the general lack of references to the source of the dosing guidelines. Hence, no specific formulary can be advocated. However, to bridge the gap to an evidence-based, institution-specific formulary, the choice of one of these formularies added with guidelines for the drugs not covered, seems a reasonable alternative.

PII-13

PEDIATRIC NEUROCOGNITIVE DEVELOPMENT FOLLOWING IN-UTERO EXPOSURE TO LABETALOL FOR HYPERTENSION. I. Nulman,¹ M. Barrera,¹ W. Chan,² D. Knittel-Keren,¹ G. Koren,¹ M. Rezvani¹; ¹The Hospital for Sick Children, Toronto, ON, Canada, ²Sunnybrook Health Sciences Centre, Toronto, ON, Canada

BACKGROUND: To determine the neurocognitive developmental outcomes of children following in-utero labetalol exposure in comparison to those exposed to non-teratogenic substances.

METHODS:

- *Design:* A cohort controlled study using a prospectively collected database.
- *Setting:* The Motherisk Program at The Hospital for Sick Children, and The Sunnybrook Health Sciences Centre, Toronto, Canada.
- *Participants:* Mother-child pairs exposed to labetalol (n=32), methylodopa (n=25), and non-teratogenic substances (n=53) during pregnancy.
- *Intervention:* Age appropriate psychological tests to assess children's cognitive performance. The main outcome measures were Children's Verbal IQ, Performance IQ, and Full-Scale IQ assessed with the Wechsler Preschool and Primary Scale of Intelligence. Statistical analysis included ANOVA and linear regression.

RESULTS: The IQ scores for labetalol exposed children were not different from those of children exposed to methylodopa or non-teratogenic substances. There were no statistically significant differences between the groups of labetalol, methylodopa, and non-teratogenic controls in Verbal IQ respectively (112.27±11.04; 109.64±11.00; 111.77±11.63; P= 1.00 for ANOVA). Performance IQ and Full-Scale IQ scores for children exposed to methylodopa were significantly lower than scores for non-teratogenic controls (104.80±8.67; 98.80±16.16; 109.06±12.38; P= 0.003; 109.60±8.20; 105.24±12.46; 111.85±11.04; P= 0.037). Linear regression reveals that inclusion in the methylodopa group and maternal IQ were significant predictors of children's Full-Scale IQ and Performance IQ.

CONCLUSION: In-utero exposure to labetalol does not appear to adversely affect neurocognitive development of pre-school children.

PII-14

MATERNAL CIGARETTE SMOKING DURING PREGNANCY ALTERS NEWBORN PAIN RESPONSE AND TEMPORAL ORGANIZATION OF CRY. V. Tutag-Lehr,¹ M. Mathew,¹ P. Zeskind,² R. Thomas,¹ J. V. Aranda¹; ¹Children's Hospital of Michigan, Detroit, MI, ²Carolinas Medical Center, Charlotte, NC

BACKGROUND: Effect of maternal smoking during pregnancy on newborn pain response is unknown. A way to assess newborn pain response is cry analysis. Newborns exposed to maternal smoking during pregnancy show higher pitched cry response and higher

state of arousal. Faster or higher RR has recently been documented in states of greater presumed infant distress or arousal as independently measured by Neonatal Facial Coding System (NFCS). We evaluated relationship between maternal smoking during pregnancy on newborn pain response and temporal organization of cry measured by NFCS and RR.

METHODS: As part of larger circumcision study, audio and video recordings were analyzed for 44 healthy term males (<3 days old) undergoing foreskin removal and lysis. 7/44 exposed to maternal cigarette smoking during pregnancy. Digital recordings of crying subjected to digital sound spectrographic analysis to assess number and duration of cry expirations. RR calculated as Number of Expirations/Duration (secs) crying, including in rate durations of pauses between expiratory sounds. NFCS scores independently coded from video (no audio). NFCS scores and RR compared between groups using independent samples t-test.

RESULTS: Infants of mothers who smoked were marginally heavier ($p=0.08$). Mean NFCS scores and RR were higher during foreskin removal and lysis for infants exposed to maternal smoking vs non-exposed infants suggesting lower pain threshold.

Results

Pregnancy Smoking Exposure	Weight (kg)	NFCS-Foreskin		RR-Foreskin	
		Removal	NFCS-Lysis	Removal	RR-Lysis
Yes (n=7)	3.20 ± 0.25	107.26 ± 14.7	219.65 ± 1.9	0.60 ± 0.04	0.35 ± 0.12
No (n=37)	3.12 ± 0.06	162.2 ± 50.2	247.4 ± 17.2	0.47 ± 0.24	0.19 ± 0.04

Data values are mean ± SEM

CONCLUSION: Maternal smoking during pregnancy may alter newborn pain response evidenced by higher NFCS scores and faster RR. Marginal trends in findings would achieve significance at $n=56$ per group. Provocative data warrant further investigation of effect of maternal smoking during pregnancy on infant pain.

PII-15

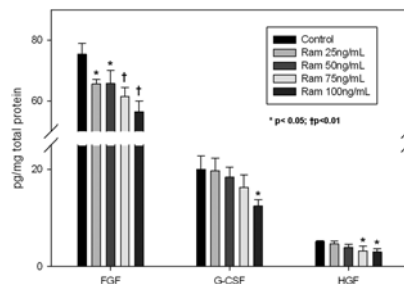
EFFECT OF RAMIPRIL ON BASAL PRODUCTION OF ENDOTHELIUM-DERIVED GROWTH FACTORS. A. L. Beitelshes, G. J. Welder, I. Zineh; University of Florida, Gainesville, FL

BACKGROUND/AIMS: Endothelial cell (EC) homeostasis is crucial for cardiovascular health. It has been reported that cytokines with mitogenic activity may be involved in cardiovascular disease pathogenesis. These growth factors are constitutively expressed in ECs, and the effects of commonly used cardiovascular drugs, such as ACE inhibitors, on these molecules are unknown. We investigated the effect of the ACE inhibitor, ramipril, on basal production of three diverse growth factors from human umbilical vein ECs (HUVECs).

METHODS: HUVECs were cultured to 80% confluence and treated with solvent control (CTL), or ramipril 25, 50, 75, or 100 ng/mL. The following growth factors were measured in cell culture supernates after 24 hours of treatment by cytometric immunofluorescence: fibroblast growth factor (FGF), granulocyte colony stimulating factor (G-CSF), and hepatocyte growth factor (HGF). All experiments were performed in triplicate and cytokines were normalized to total protein content. ANOVA with Tukey correction was performed to test drug effect across doses ($P<0.05$) and Jonckheere-Terpstra test was conducted to test for trends with increasing doses.

RESULTS: Treatment of HUVECs with ramipril resulted in reductions in all three growth factors (Figure). Ramipril 25, 50, 75, and 100 ng/mL reduced FGF by 13, 13, 19, and 25%, respectively ($p=0.001$); G-CSF by 2, 8, 19, and 38% ($p=0.014$) and HGF by 10, 23, 38, and 42% ($p=0.009$). The effect of ramipril on these growth factors was dose-dependant ($p\leq 0.002$ for ordered effect).

CONCLUSIONS: Ramipril lowers EC production of FGF, G-CSF, and HGF in a dose-dependent manner. To our knowledge, these endothelial properties of ramipril have not been previously described. The clinical relevance of this property of ramipril is unknown and should be further investigated.



PII-16

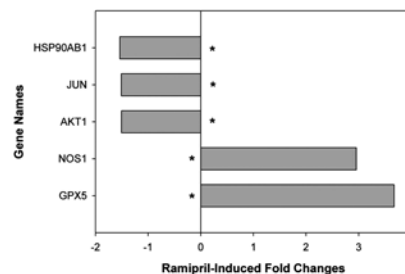
INFLUENCE OF RAMIPRIL ON NITRIC OXIDE PATHWAY GENES IN ENDOTHELIAL CELLS. A. L. Beitelshes, G. J. Welder, M. L. Hames, I. Zineh; University of Florida, Gainesville, FL

BACKGROUND/AIMS: ACE inhibitors have beneficial effects in the treatment of coronary artery disease and heart failure which are not fully understood. The nitric oxide (NO) signaling pathway has been implicated. We evaluated the effect of the ACE inhibitor, ramipril, on NO pathway genes in human umbilical vein endothelial cells (HUVECs) using a focused microarray approach.

METHODS: HUVECs were treated with ramipril 100 ng/mL or control solvent (DMSO) for 24 hours ($N=2$ experiments). RNA was isolated from HUVECs and real-time PCR was performed using an array of 84 genes whose expression is controlled by or involved in NO signaling (SuperArray Bioscience Corp., Frederick, MD). Fold changes were determined by the $2^{-\Delta\Delta Ct}$ method with $p<0.05$ considered significant.

RESULTS: Of 84 genes evaluated, 2 genes (NOS1 and GPX5) were significantly up-regulated and 3 genes (HSP90AB1, JUN, and AKT1) were significantly down-regulated with ramipril treatment compared to control ($p<0.05$). Fold changes in gene expression in response to ramipril are shown in the figure. The modulated genes are involved in NO biosynthesis and signaling and response to oxidative stress.

CONCLUSIONS: Ramipril significantly modulates genes involved in NO signaling in endothelial cells. Whether these effects contribute to the beneficial effects of ramipril in the clinical setting merits further investigation.



PII-17

EFFECTS OF DILTIAZEM ON RBC CONCENTRATIONS OF PURINE NUCLEOTIDES IN AN EXERCISE RAT MODEL FOLLOWING MULTIPLE DOSES IN VIVO. P. K. Yeung,¹ J. Howlett,² C. Schindler³; ¹Dalhousie University, Halifax, NS, Canada, ²Dalhousie University and QEII HSC, Halifax, NS, Canada, ³Technical University Dresden, Dresden, Germany

BACKGROUND: To determine the effect of diltiazem on RBC concentrations of purine nucleotides in an exercise rat model following repeated subcutaneous injections.

METHODS: Male SD rats (Charles River Laboratories) weighing between 300 - 450 g were used. Each rat received either saline (control) or 10 mg/kg of diltiazem (DTZ) subcutaneously twice daily for 5 doses (n = 6 per group). One hour after the last dose each rat was exercised on a treadmill at 7 m/min and 3 % grade. Continuous hemodynamic recordings and blood samples were collected from each rat via an indwelling catheter implanted into a carotid artery before and up to 1 hour post exercise. The samples were immediately mixed with a Stopping Solution to stabilize the purines before processing. Concentrations of ATP, ADP, AMP, GTP, GDP, and GMP in the RBC were determined by HPLC. Data between groups were analyzed by 2-sample t-test and differences between groups considered significant when $p < 0.05$.

RESULTS: Exercise increased SBP and HR in control rats ($p < 0.05$) but had no significant effect on DBP. Heart rate and systolic BP responses to exercise were significantly attenuated by DTZ ($p < 0.05$). Exercise also increased RBC concentrations of ATP in the diltiazem treated rats from 1.57 ± 0.50 to 3.45 ± 0.66 mM ($p < 0.05$). It also increased RBC concentrations of ADP, and GTP but the increases were not statistically significant ($p > 0.05$).

CONCLUSION: Diltiazem after repeated administration is associated with attenuated hemodynamic responses and increased RBC concentrations of ATP during exercise in a normal in vivo rat model. (Supported in part by a grant-in-aid from CIHR/NSHRF/PEF Regional Partnership Program)

PII-18

A RANDOMIZED, BLINDED, PLACEBO AND POSITIVE-CONTROLLED, CROSSOVER STUDY TO DETERMINE THE EFFECT OF REPEATED DOSES OF THE FACTOR XA INHIBITOR APIXABAN ON THE QTc INTERVAL. P. Wastall, Sunil Nepal, Charles Frost, Zhigang Yu, Kenneth Moore, Richard A Reeves; Bristol Myers Squibb, Princeton, NJ

BACKGROUND: Apixaban is an oral, direct and highly selective factor Xa inhibitor in late stage development for the prevention and treatment of thromboembolic disease. The primary objective of this study was to determine the effect of apixaban on QTc interval.

METHODS: In a randomized, crossover design (≥ 7 day washout), 40 healthy subjects (32 male; 8 female) received 3 days of blinded apixaban 10 mg QD, 50 mg QD (supratherapeutic), or placebo (PBO) QD, or a single dose of open label moxifloxacin 400 mg (MOXI) on Day 3. Triplicate electrocardiograms, obtained over 24 hours on Days -1 (baseline) and 3, were read by a blinded third party. The sample size provided $\geq 90\%$ power to conclude that apixaban has no clinically significant effect on QTc interval. The time-matched difference between the mean Δ QTc on apixaban or MOXI vs PBO was estimated at each time point. For the maximum difference, a one-sided upper 95% confidence interval (CI) was constructed for the difference between apixaban and PBO. If the upper 95% CI was < 10 msec, then it would be concluded that apixaban had no clinically significant effect on QTc interval. Assay sensitivity would be confirmed if the lower 95% CI was > 0 msec for MOXI vs PBO.

RESULTS: Thirty-nine subjects were included in the analysis. Fridericia's correction was chosen based on low correlation with heart rate on Day -1. The maximum PBO-adjusted Δ QTcF was 1.51 msec (upper 95% CI = 3.71 msec) after apixaban 50 mg QD; 1.36 msec (upper 95% CI = 3.54 msec) after apixaban 10 mg QD; and 10.21 msec (lower 95% CI = 8.07 msec) after MOXI. Apixaban was safe and well tolerated.

CONCLUSION: Administration of apixaban doses up to 50 mg QD for 3 days had no clinically significant effect on QTc interval in healthy volunteers. These data support further evaluation of apixaban for the prevention and treatment of thromboembolic disease.

PII-19

COUGH RESPONSE TO INHALED CAPSAICIN FOLLOWING A BLINDED, ORAL, SINGLE DOSE OF CODEINE, DEXTROMETHORPHAN, OR PLACEBO IN HEALTHY MALES. J. Gong,¹ J. Burke,² R. L. Blanchard,² P. Dicipingaitis,³ J. Palcza,² X. Yan,⁴ T. E. Bradstreet,² W. K. Kraft¹; ¹Thomas Jefferson University, Philadelphia, PA, ²Merck Research Labs, West Point, PA, ³Einstein Division/Montefiore Medical Center, New York, NY, ⁴University of Missouri-Kansas City, Kansas City, MO

BACKGROUND: Cough is one of the most common respiratory symptoms encountered in clinical practice. A provocative tussive challenge using inhaled capsaicin has been proposed to investigate cough pathophysiology. We investigated the antitussive effects of codeine and dextromethorphan hydrobromide (DM).

METHODS: 18 healthy Caucasian or African-American subjects (age 18-43) with extensive metabolizer CYP2D6 genotype received a single dose of codeine 60 mg, DM 60 mg or placebo in a double-blinded, three period, crossover study. During each period subjects underwent a baseline and a two-hour post-dose cough challenge. The cough challenge test consisted of increasing doses of inhaled capsaicin (~ 0.98 to 1000 μ M) via nebulization until the subject coughed ≥ 5 times, an endpoint defined as "C5". Nebulized saline (vehicle control) was interspersed randomly among the rising doses of capsaicin to support double-blinding and to minimize conditioned responses to capsaicin.

RESULTS: Inhaled capsaicin was well tolerated. 17 subjects were evaluable (1 did not reach C5 at baseline). From baseline levels, codeine significantly increased C5 2.79 fold ($p=0.003$), as compared to DM 1.63 fold ($p=0.14$), and placebo 1.64 fold ($p=0.15$). Between-treatment comparisons (in fold change from baseline) are shown below.

Treatment Comparison	C5 Fold Difference Between Treatments	p-value
DM vs. Placebo	0.99	0.99
Codeine vs. Placebo	1.70	0.19

Codeine increased the concentration of capsaicin at which the endpoint of C5 was reached. DM did not demonstrate inhibition of capsaicin-induced cough compared to placebo.

CONCLUSION: Codeine has a modest ability to inhibit cough in healthy volunteers. Codeine could serve as a positive control in studies employing inhaled capsaicin as a tussive challenge.

PII-20

THE INFLUENCE OF CYCLOOXYGENASE-1 A-707G AND C50T POLYMORPHISMS ON ASPIRIN RESPONSE. K. M. Momary,¹ N. L. Shapiro,¹ E. A. Nutescu,¹ L. D. Brace,¹ S. S. Shord,¹ C. M. Helgason,² L. H. Cavallari¹; ¹University of Illinois at Chicago, College of Pharmacy, Chicago, IL, ²University of Illinois at Chicago, College of Medicine, Chicago, IL

BACKGROUND/AIMS: There is substantial inter-patient variability in the inhibitory effects of aspirin on platelet aggregation. Incomplete platelet inhibition by aspirin has been associated with an increased risk of serious vascular events. We sought to determine whether the A-707G and C50T polymorphisms of the gene for cyclooxygenase-1 (*PTGS1*), the target site for aspirin, are associated with aspirin's effects on platelets.

METHODS: In this prospective cohort study, 59 subjects (including 28 blacks) on single antiplatelet therapy with aspirin for ≥ 2 weeks were enrolled. Blood was collected during a single outpatient study visit for determination of genotype (by PCR and sequencing), *ex-vivo* platelet aggregation (by the method of Born), fasting lipid profile, and salicylate concentrations (by HPLC). Aspirin response,

salicylate and lipid levels, and characteristics were compared by genotype.

RESULTS: Genotype distributions were in Hardy Weinberg equilibrium. The frequencies of the variant *PTGS1* -707G and 50T alleles were 0.12 and 0.08, respectively. No subjects were homozygous for either variant. Thirty (51%) subjects were classified as partial responders to aspirin by *ex-vivo* platelet aggregation studies. There was no association between the A-707G genotype and aspirin response. However, the frequency of partial responders to aspirin was greater among *PTGS1* 50C allele homozygotes compared to 50T allele carriers (0.57 vs. 0.20; $p=0.04$) and among subjects homozygous for the -707A/50C haplotype compared to -707G/50T allele carriers (0.59 vs. 0.0; $p=0.04$). There were no significant differences in characteristics, aspirin dose, lipids, or salicylate levels between any of the genotype groups studied.

CONCLUSIONS: Our data suggest that the *PTGS1* C50T genotype and the A-707G/C50T haplotype, but not the A-707G genotype alone, are predictive of aspirin response as measured by *ex-vivo* platelet aggregation in a racially diverse population.

PII-21

ETHNIC AND GENETIC DETERMINANTS OF CARDIOVASCULAR RESPONSE TO THE SELECTIVE α_2 -ADRENERGIC RECEPTOR AGONIST DEXMETETOMIDINE. D. Kurnik,¹ M. Muszkat,¹ G. G. Sofowora,¹ E. A. Friedman,¹ W. D. Dupont,¹ M. Scheinin,² A. J. Wood,¹ C. M. Stein¹; ¹Vanderbilt University, Nashville, TN, ²University of Turku, Turku, Finland

BACKGROUND: The α_2 -adrenoceptor agonist clonidine reduces blood pressure more effectively in white than black Americans despite similar degrees of sympatholysis. Functional genetic variation in receptor signaling mechanisms, for example in the β_3 G-protein subunit (*GNB3* C825T) and in the α_2C -adrenoceptor subtype (*ADRA2C* del322-325), may affect drug responses. We examined the hypothesis that there are ethnic differences in the responses to the highly selective α_2 -agonist, dexmedetomidine, and that these genetic variants contribute to interindividual variability in drug responses.

METHODS: In a placebo-controlled, single-masked study, 73 healthy subjects (37 whites and 36 blacks) received 3 placebo infusions and then 3 incremental doses of dexmedetomidine (cumulative dose, 0.4 mcg/kg), each separated by 30 minutes. Blood pressure, heart rate, and plasma catecholamine concentrations were determined after each infusion. We measured dexmedetomidine concentrations after the last infusion and determined *ADRA2C* del322-325 and *GNB3* C825T genotypes.

RESULTS: Dexmedetomidine lowered blood pressure and plasma catecholamine concentrations significantly (all $P<0.001$). There was substantial interindividual variability in the reduction of systolic blood pressure (range, 1 to 34 mmHg) and plasma norepinephrine concentrations (range, 24 to 424 pg/mL). However, there were no differences between black and white subjects in dexmedetomidine responses ($P>0.16$ for all outcomes) before or after adjustment for covariates. Neither *ADRA2C* del322-325 nor *GNB3* C825T genotypes affected the responses to dexmedetomidine (all $P>0.66$).

CONCLUSION: There is large interindividual variability in response to the selective α_2 -AR agonist dexmedetomidine, and neither ethnicity nor *ADRA2C* and *GNB3* genotypes contribute to it. Further studies to identify determinants of α_2 -AR-mediated responses will be of interest.

PII-22

GENOMIC REMODELING OF CARDIAC METABOLISM COMPROMISES TOLERANCE OF THE AGING HEART. A. Jahangir, C. C. Cabrera Aguilera, A. Oberlin, V. Maria, M. Ahmad, A. Gupta, M. Yousufuddin, S. Sagar, A. Terzic; Mayo Clinic, Rochester, MN

BACKGROUND: Aging is a recognized risk factor for cardiac morbidity, yet the molecular substrate underlying homeostatic failure in the senescent myocardium has not been decoded.

METHODS: Differential responsiveness of adult (6 m) and aged (24 m old) rats to stress was determined at the whole heart, isolated myocytes and mitochondria level and differences in expression of genes and proteins characterized.

RESULTS: In contrast to adult, aged rats demonstrated a reduced tolerance to ischemia-reperfusion, calcium-overload and hypoxia-reoxygenation. Protection conferred by ischemic preconditioning, robust in young, was lost in the aged heart. The energetic reserve and ionic handling capacity of aged mitochondria was reduced, associated with disruption of the myocardial capacity for transduction of stress signals into protective responses. Out of 614 genes encoding for mitochondrial proteins, 94 were differentially expressed ($p<0.01$) with 95% downregulated with aging. Changes primarily affected genes coding for mitochondrial energetics and translated into a reduced mitochondrial functional capacity, with decreased NADH dehydrogenase and F_0F_1 ATPase complex activities, and diminished capacity for ATP synthesis in the aged. Gene encoding for adenylate kinase, the stress-responsive phosphorelay coupling sites of energy production and utilization was reduced along with expression of *KCNJ11* and *ABCC9* genes that encode subunits of the K_{ATP} channel, the metabolic stress response element in the heart. Deficiency in the metabolism related defense mechanisms in the aging heart was bypassed by targeted modulation of mitochondrial membrane potential or K_{ATP} channel activation, which rescued the compromised tolerance of the aging heart to stress.

CONCLUSION: Thus, mapping of senescence-induced genomic remodeling of cardiac metabolism reveals dysfunctional pathways that can be exploited to enhance the stress-responsiveness of the vulnerable aging heart.

PII-23

THE CONTRIBUTION OF CYP3A4 AND CYP3A5 ON THE METABOLISM OF SILDENAFIL, VARDENAFIL, AND UDENAFIL. H. Ku, S. Bae, K. Seo, H. Ahn, S. Bae, J. Shon, K. Liu, J. Shin; Dept. of Pharmacology and Pharmacogenomics Research Center, Inje University College of Medicine, Busan, Republic of Korea

BACKGROUND: This study is to assess the contribution of CYP3A4 and CYP3A5 on the metabolism of phosphodiesterase-5 inhibitors (PDE5I) such as sildenafil, vardenafil, and udenafil.

METHODS: The *in vitro* incubation studies of sildenafil *N*-demethylation, vardenafil *N*-deethylation, and udenafil *N*-dealkylation were conducted using recombinant cDNA-expressed CYP3A enzymes and 15 human liver microsomes (HLM) of which CYP3A5 genotype were predetermined. PDE5Is and their metabolites were analyzed as LC/MS/MS respectively.

RESULTS: Both recombinant CYP3A4 and CYP3A5 showed profound catalytic activity of sildenafil *N*-demethylation (V_{max} : 1.0 and 1.4 μ M, K_m : 15.0 and 14.7 μ M), vardenafil *N*-deethylation (V_{max} : 1.5 and 1.8 μ M, K_m : 7.8 and 3.0 μ M), and udenafil *N*-dealkylation (V_{max} : 3.9 and 1.1 μ M, K_m : >500 and 216.4 μ M). The catalytic efficiency ($CL_{int} = V_{max}/K_m$) of recombinant CYP3A5 isoform for vardenafil *N*-deethylation showed about 3.2 fold higher than that of CYP3A4, whereas there was no difference in CL_{int} between both CYP3A isoforms for sildenafil *N*-demethylation and udenafil *N*-dealkylation. The HLMs(9) heterozygous for CYP3A5*3 allele had higher metabolite formation activity than those(6) homozygous for CYP3A5*3 (2.1 \pm 1.2 vs. 1.0 \pm 0.8 pmol/min/mg.protein for sildenafil *N*-demethylation; 9.4 \pm 4.0 vs. 4.3 \pm 3.5 pmol/min/mg.protein for vardenafil *N*-deethylation and 0.7 \pm 0.4 vs. 0.4 \pm 0.2 pmol/min/mg.protein for udenafil *N*-dealkylation).

CONCLUSION: These findings suggest that CYP3A5 as well as CYP3A4 contribute significantly on the metabolism of PDE5Is. The genetic polymorphic of CYP3A5 might confer to interindividual variability in the disposition of PDE5Is, especially for vardenafil. It needs further *in vivo* study in order to confirm the effect of CYP3A5 genotypes on the pharmacokinetics of PDE5Is.

PII-24

IDENTIFICATION OF HUMAN LIVER CYTOCHROME P450 ENZYMES INVOLVED IN THE METABOLIC PATHWAY OF CLOPIDOGREL. S. Bae, K. Kim, D. Cho, C. Yeo, K. Liu, J. Shon, J. Shin; Department of Pharmacology & Pharmacogenomics Research Center, Busan, Republic of Korea

BACKGROUND: Clopidogrel is a thienopyridine prodrug used clinically to inhibit ADP-induced platelet aggregation. The conversion of clopidogrel to its active metabolite containing thiol group has been reported to be a two sequential step by P450, formed to 2-oxoclopidogrel (intermediate metabolite), and then further oxidized into active metabolite of clopidogrel. The purpose of this study is to investigate what types of human CYP isozymes are involved in the metabolic pathway of clopidogrel and their contributions on some pathway.

METHODS: Studies using ten recombinant human CYP isoforms (i.e. CYP1A2, 2A6, 2B6, 2D6, 2E1, 2C9, 2C19, 2J2, 3A4 and 3A5) were performed to identify the cytochrome P450 (CYP) isoform(s) involved in metabolism of clopidogrel. 2-oxoclopidogrel and active metabolite containing thiol group formations from clopidogrel were measured by LC/MS/MS as metabolic products. All recombinant human CYP isoforms were incubated with reduced glutathione to measure active metabolite of clopidogrel.

RESULTS: At first, among the ten recombinant CYP enzymes studied, the degree of metabolic activity was ranked in the order of CYP2C19, 2B6, 3A4, 3A5, and 1A2, toward the 2-oxoclopidogrel formation from clopidogrel (0.1-50 μ M). Otherwise, only CYP2C19 and 2B6 were involved in the formation of active metabolite from 2-oxoclopidogrel. At higher concentration (more than 50 μ M), CYP3A4 and CYP3A5 were involved in the formation of active metabolite of clopidogrel.

CONCLUSION: Our *in vitro* experiments demonstrate that conversion of clopidogrel into active metabolite appears concentration-dependent. At plasma concentrations of clopidogrel (0.1-50 μ M) to be expected after usual dosage, only CYP2C19 and 2B6 might be involved in the formation of active metabolite from 2-oxoclopidogrel. This result implies that CYP2C19 and CYP2B6 genotype seem to contribute to interindividual differences in the inhibitory response of platelet aggregation by clopidogrel.

PII-25

LAROPIPRANT DOES NOT ALTER URINE 11-DEHYDROTHROMBOXANE B₂ LEVELS IN HEALTHY SUBJECTS IN COMBINATION WITH NIACIN. V. Dishy,¹ A. Nirula,¹ W. Luo,¹ J. Janisch,¹ O. Laterza,¹ M. Gutierrez,² J. Wagner,¹ E. Lai¹; ¹Merck Research Laboratories, Rahway, NJ, ²Comprehensive Phase One, Miramar, FL

BACKGROUND: Extended release (ER) niacin in combination with laropiprant, an antagonist of the PGD₂ receptor DP₁, is effective for the treatment of dyslipidemia. The combination is better tolerated than ER niacin alone because laropiprant reduces the flushing symptoms associated with niacin. PGD₂ has been reported to have anti-aggregatory effects on platelets *in vitro*. However, *in vivo* there are multiple regulators of platelet function, making it difficult to ascertain the clinical relevance of *in vitro* studies that examine the effects of PGD₂ and/or DP₁ antagonists in isolation. Thus it is important to assess the functional status of platelets *in vivo* in order to understand the potential impact of DP₁ antagonism. Because activated platelets produce thromboxane A₂, urine 11-dehydrothromboxane B₂ (11-dTxB₂) levels correlate with the level of *in vivo* platelet activation. Measurement of urine 11-dTxB₂ is widely considered to be the best marker of *in vivo* platelet status.

METHODS: Healthy male and female subjects (N=33, age 21-55 years) were treated in a randomized, double-blind, crossover fashion with either: Once daily doses x 7 days of ER niacin 2 g or: Once daily doses x 7 days of ER niacin 2 g/ laropiprant 40 mg. 11-dTxB₂ was measured in a 24 hr urine collection on Day 7. There was a 7-day interval between treatment periods.

RESULTS: No meaningful difference was observed in urine 11-dehydrothromboxane B₂ levels between treatments of ER niacin/ laropiprant vs ER niacin on Day 7: 525 pg/mg creatinine with ER niacin/

laropiprant vs. 501 pg/mg creatinine with ER niacin. The GMR and the corresponding 90% CI were 1.05 (0.91, 1.21).

CONCLUSION: Based on this biomarker, there is no effect of laropiprant to enhance platelet activation *in vivo* when combined with ER niacin compared to ER niacin alone.

PII-26

PHARMACOKINETIC ANALYSIS OF ERLOTINIB AND OSI-420 IN PEDIATRIC PATIENTS WITH MALIGNANT GLIOMAS. P. Schaiquevich, J. C. Panetta, S. Throm, F. Bai, A. Broniscer, C. Stewart; St. Jude Children's Research Hospital, Memphis, TN

BACKGROUND: To evaluate the population pharmacokinetics of erlotinib (ERL) and its metabolite OSI-420 in pediatric patients with malignant gliomas enrolled on a Phase I study.

METHODS: Pharmacokinetic (PK) studies were obtained in 17 consenting patients studied at dosages of 70, 90, 120 or 160 mg/m². Serial blood samples were obtained before and at 1, 2, 4, 8, 24, 30 and 48 hours after the first ERL dose and up to 24 h on day 8. Plasma ERL and OSI-420 concentrations were determined using a validated LC/MSMS method. C_{max}, AUC₀₋₂₄, AUC₀₋₄₈, and T_{max} after days 1 and 8 were calculated. The ratio of OSI-420 to ERL AUC₀₋₄₈ was calculated (REM). A population (PK) analysis was conducted to determine ERL apparent oral clearance (CL_{ERL}/F) and apparent volume of distribution (V_{ERL}/F), OSI-420 apparent elimination rate constant (ke_{OSI-420}/FF), and the absorption rate constant (ka). Inter- and intra-individual variability as well as inter-occasion variability was considered. A linear mixed effects model was implemented to explore the relationships among CYP3A4*1B, CYP3A5*3, MDR1 (exons 21 and 26) and BCRP (exons 2 and 5) SNPs and the PK parameters of ERL and OSI-420.

RESULTS: After the 1st and 8th ERL dose, the median T_{max} ranged between 2 and 4 h. Neither C_{max} nor AUC₀₋₄₈ showed a proportional increase with the actual ERL dosage administered. The REM was approximately 8% for all dosages studied. The mean population estimates were ka 0.44 h⁻¹, CL_{ERL}/F 3.5 L/h/m², V_{ERL}/F 54.2 L/m², and ke_{OSI-420}/FF 3.5 h⁻¹, respectively. Dosage was significantly related to CL_{ERL}/F (p<0.01). A significant relationship was found between ka and MDR1 exon 26 (p<0.05) and between ke_{OSI-420}/FF and CYP3A4*1A/*1B polymorphisms (p<0.05).

CONCLUSION: The results obtained at steady-state are consistent with previously published data in adults. However, no relationship was noted between ERL dosage and C_{max} or AUC.

PII-27

CYTOCHROME P450 2C9 (CYP2C9) METABOLIC CAPACITY IN PEOPLE WITH AND WITHOUT CANCER. S. S. Shord, L. H. Cavallari, M. A. Viana, K. Momary, R. E. Molokie, J. Necessas; University of Illinois at Chicago, Chicago, IL

BACKGROUND: Two recent studies indicate that some patients with cancer demonstrate substantial decline in the metabolism of drugs by CYP enzymes and discordance of the genotype and phenotype for several of these enzymes. One possible explanation for the reduced catalytic activity and poor correlation between genotype and phenotype could be elevated cytokine levels. The purpose of this study was to compare CYP2C9 activity between people with and without cancer and examine the relationship between CYP2C9 activity and serum cytokines in people with and without cancer.

METHODS: Twenty subjects were enrolled into the study: 10 subjects with cancer who were currently receiving treatment (C) and 10 subjects without cancer who were matched to the subjects with cancer based on gender and race (NC). Tolbutamide was measured in the plasma before and after 500mg of oral tolbutamide by HPLC. The urine collected from 0 to 12 h after the dose was used to measure tolbutamide and its metabolites by HPLC. CYP2C9 genotype was determined by PCR followed by pyrosequencing and cytokine values were determined by an ELISA.

RESULTS: The mean (\pm standard deviation) apparent oral clearance was higher (C, 19.5 ± 10.5 vs. NC, 15.8 ± 5.0 ml/min, $p=0.35$), whereas the mean urinary metabolic ratio from 0 to 12 h was similar (C, 838 ± 693 vs. NC, 775 ± 390 , $p=0.75$) in subjects with cancer. Neither age nor genotype statistically affected the noted differences. Mean IL-6 (C, 7.2 ± 9.4 vs. NC, 1.5 ± 1.3 pg/ml) and TNF- α (C, 26.2 ± 71.2 vs. NC, 3.6 ± 4.2 pg/ml) were 5- to 7-fold higher in subjects with cancer. No statistically significant correlation between cytokine values and clearance or urinary metabolic ratio was found.

CONCLUSION: CYP2C9 metabolic capacity and serum cytokine values appear higher in people with cancer compared to people without cancer, although no differences reached statistical significance in our study population.

P11-28

CYTOCHROME P450 (CYP) 2D6 INFLUENCES CODEINE METABOLISM IN SICKLE CELL DISEASE (SCD). S. S. Shord, R. E. Molokie, L. H. Cavallari, W. Gao, H. Jeong; University of Illinois at Chicago, Chicago, IL

BACKGROUND: Codeine containing medications (CCM) are frequently prescribed to manage an acute pain crisis for patients with SCD, but interpatient variability in responses to CCM is not well-understood. The purpose of this study was to examine the relationship between two of the most common CYP2D6 alleles in Blacks and their effects on morphine concentrations and clinical outcomes in patients with SCD.

METHODS: Fifty-four adult subjects diagnosed with SCD completed one 8-h outpatient study visit. One blood sample was drawn to determine CYP2D6 genotype. Serial blood samples were drawn to measure codeine, morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in the plasma before and after oral codeine sulfate 30mg. Codeine and its metabolites were measured in plasma using LC-MS. CYP2D6 genotype was determined using PCR with RFLP or real-time bi-allelic discrimination.

RESULTS: Three single marker assays were completed for *17 (1023C>T) and *41 alleles (-1584C>G or 2988G>A). Twenty-four subjects were identified as carriers of these SNP. The median maximal morphine concentrations (C_{max}) were similar between carriers and non-carriers ($p=0.50$). However, subjects with a 1023T ($n=12$) demonstrated lower C_{max} and area under the concentration time curve for M3G and M6G and subjects with a -1584C or 2988A ($n=12$) demonstrated a longer elimination half-life and delay to the C_{max} for morphine compared to the 30 subjects identified as non-carriers. The median number of emergency room visits or hospital admissions was not statistically different between carriers and non-carriers ($p=0.40$).

CONCLUSION: CYP2D6 genotype appears to influence the metabolism of codeine to morphine and its metabolites in SCD; however, no relationship was identified between the clinical surrogate marker for response to codeine and CYP2D6 genotype in our study population.

P11-29

Withdrawn

P11-30

IN VITRO AND IN VIVO CLINICAL PHARMACOLOGY OF ABT-751, AN ORALLY BIOAVAILABLE TUBULIN INHIBITOR, IN COMBINATION WITH CAPECITABINE AND IRINOTECAN (CAPIRI) WITH OR WITHOUT BEVACIZUMAB. M. Zhao, L. Xu, R. Jin, P. He, A. Mnatsakanyan, W. A. Messersmith, M. Hidalgo, S. D. Baker, M. A. Rudek; Johns Hopkins University, Baltimore, MD

BACKGROUND: ABT-751 (A) is an orally bioavailable sulfonamide with antimetabolic properties.

METHODS: A non-randomized dose-escalation study of A in combination with CAPIRI (capecitabine (C) and irinotecan (I)) and bevacizumab (B) is being performed to define the maximum tolerated dose, dose-limiting toxicity (DLT), and pharmacokinetics (PK) in patients with advanced colorectal cancer. Patients are treated with A QD alone for 7-d and then 21-d cycles of A with C (BID) d1-14 PO, I d1 IV, and B d1 IV. Dose escalation started at dose level (DL) 1a at A 150mg, I 200mg/m², and C 1600mg/m² (total daily dose) and escalated to full dose CAPIRI (I 250mg/m², C 2000mg/m²) for DL2. B was then added as standard of care at 7.5mg/kg for DL2b (and later, DL1b). A was reduced to 125mg with full dose CAPIRI (DL1c). Blood samples were collected for steady-state PK of A and A metabolites when administered alone or in combination. Studies with cDNA-expressed human UGT enzymes were performed.

RESULTS: Eighteen patients have been treated to date. Two DLTs were observed at DL2, one patient experienced g3 transaminitis, and another febrile neutropenia. DL1c is being expanded to 6 patients. Other toxicities have included neutropenia and GI side effects. Of 18 subjects, there have been 4 PD, 7 SD, and 1 PR after 2 cycles; 1 remains on-study. The formation of A glucuronide appears to be decreased during combination therapy (see table). A is glucuronidated by UGT1A8 and 1A4 and to a lesser extent by 1A1, 1A7, and 2B7.

	A C _{max} (μM)	A glucuronide C _{max} (μM)	A sulfate C _{max} (μM)	A AUC _{0-8h} (μM ^h)	A glucuronide AUC _{0-8h} (μM ^h)	A sulfate AUC _{0-8h} (μM ^h)	A T _{1/2} (h)	A glucuronide T _{1/2} (h)	A sulfate T _{1/2} (h)
Alone	22.9±6.2	8.3±3.3	11.7±3.3	72±15	51±19	68±20	5.8±2.4	9.2±3.2	9.6±2.9
Combination	22.6±7.3	7.7±2.2	13.5±3.8	87±32	43±10	74±18	5.4±2.0	8.2±3.4	8.4±2.3

Data is presented as mean±SD

CONCLUSION: Thus, we conclude that a) coadministration of CAPIRI appears to have little effect on A PK and b) A is glucuronidated by 5 UGT isozymes, 2 of which glucuronidate the I metabolite SN-38.

P11-31

PHARMACOKINETICS (PK) OF CARBOPLATIN IN TUMOR TISSUE OF HUMANS: USEFULNESS OF MICRODIALYSIS. W. J. Loos, I. R. Konings, F. K. Engels, M. H. Lam, C. van Noort, R. de Wit, S. Sleijfer, E. A. Wiemer, J. Verweij; Erasmus MC - Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

BACKGROUND: To better understand mechanisms underlying (in)sensitivity of tumors to anti-tumor agents, assessing intra-tumor drug PK could be important. PK in tumor may differ considerably from PK in normal tissue and blood due to increased tumor interstitial pressure and differences in terms of vascularity and capillary permeability. Currently, little is known about tumor PK, due to the fact that the unbound drug concentration can rarely be measured directly. Microdialysis is a novel, minimally invasive sampling method that enables direct assessment of tissue / tumor disposition and penetration of small molecules. Here we explored the feasibility of the application of microdialysis in a clinical setting, using carboplatin as model drug.

METHODS: Adult cancer patients with a (sub)cutaneous primary tumor or superficial metastatic lesion ≥ 20 mm amendable for microdialysis, and for whom carboplatin based therapy was considered appropriate treatment, were eligible for the study. Plasma and microdialysate samples from tumor tissue and adipocytic normal tissue were collected up to 47 h after dosing and analyzed for carboplatin-derived unbound platinum. Pharmacokinetic parameters were estimated using non-compartmental analysis.

RESULTS: A total of 5 patients have currently been studied. Concentration time-curves in tumor and adipocytic normal tissue follow the pattern of the curves in plasma. See Table for a summary of the exposure data.

CONCLUSION: Microdialysis can be successfully employed to study drug penetration in tumor and adipocytic normal tissue of patients. In the case of carboplatin, the drug penetrates well into tissue with, on average, equal exposures of unbound platinum in plasma, adipocytic normal tissue and tumor.

Table: Exposure measurements of carboplatin-derived unbound platinum

Patient	AUC plasma (µg ^h /mL)	AUC tumor (µg ^h /mL)	AUC normal (µg ^h /mL)	Cmax plasma (µg/mL)	Cmax tumor (µg/mL)	Cmax normal (µg/mL)	AUC ratio tumor/plasma	AUC ratio normal/plasma	
A	63.3	64.3	---	25.0	21.7	---	1.02	---	
B	57.7	62.5	83.6	21.7	21.3	25.5	1.08	1.45	
C	60.2	65.6	51.4	27.1	24.8	19.6	1.09	0.85	
D	75.4	47.7	53.4	23.8	13.9	12.5	0.63	0.71	
E	41.0	33.9	---	19.3	13.4	---	0.83	---	
							mean	0.93	1.00
							SD	0.20	0.40

PII-32

INHIBITION OF PROSTATE TUMOR GROWTH BY DIGERANYL BISPHOSPHONATE, AN INHIBITOR OF GERANYLGERANYL DIPHOSPHATE SYNTHASE. A. J. Wiemer, J. D. Neighbors, D. F. Wiemer, R. J. Hohl; University of Iowa and Terpenoid Therapeutics, Iowa City, IA

BACKGROUND: Bisphosphonates (BP) are used for treatment of osteoporosis and bone-related cancers. The clinical nitrogen-containing bisphosphonates deplete cells of both farnesyl diphosphate (FPP) and geranylgeranyl diphosphate (GGPP). We systematically developed a series of GGPP synthase inhibitors including digeranyl bisphosphonate (DGBP), which are more potent and specific for GGPP depletion than the clinical BP. The efficacy of DGBP and zoledronate to inhibit human prostate cancer (PC-3) xenografts was evaluated.

METHODS: Nude mice (n=20) were subcutaneously implanted with PC-3 cells (1.5 x 10⁶ in 100 µL). After tumor development mice were randomized into cohorts (n=5) and drugs were administered as follows: DGBP (0.10 mg/kg) and zoledronate (0.10 mg/kg) subcutaneously three times per week, and docetaxel (14 mg/kg) intraperitoneally once per week. Tumor volume was measured and normalized to baseline sizes. Tissues were harvested to assess for induced alterations in GGPP levels and GG-modified proteins.

RESULTS: Mice were followed for 32-40 days depending on treatment. Control tumors increased 8.8 +/- 3.7 fold (mean +/- SEM). DGBP-treated mice had a tumor growth rate of 1.7 +/- 0.7 fold, a significant reduction (p = 0.004, single factor ANOVA). Zoledronate-treated mice increased 5.6 +/- 1.4 fold, which was not significantly different from the control over the course of treatment (p = 0.40). Mice treated with docetaxel displayed a 0.37 +/- 0.17 fold increase, a significant reduction (p=0.0006). Analyses for tissue evidence of GGPP depletion are ongoing.

CONCLUSIONS: At comparable doses, DGBP was more effective than zoledronate at inhibition of prostate cancer xenograft growth. DGBP was found to be well-tolerated at therapeutic doses in the mouse. This data suggests that inhibition of GGPP synthase is a viable therapeutic strategy in diseases for which GG-modified proteins are relevant.

PII-33

OVARIAN TUMOUR REPOPULATION IN RESPONSE TO SUSTAINED AND INTERMITTENT PACLITAXEL THERAPY. V. Vassileva, M. Piquette-Miller; University of Toronto, Toronto, ON, Canada

BACKGROUND: Tumour repopulation between cycles of chemotherapy may negatively impact the clinical outcome of ovarian cancer patients. Thus, avoiding treatment-free periods when tumour cells proliferate by providing sustained chemotherapy regimens may improve clinical response.

METHODS: We investigated the impact of sustained versus intermittent paclitaxel (PTX) administration on tumour repopulation in ovarian cancer. Growth, clonogenic survival and apoptosis were followed in SKOV3 and A2780 cells after equivalent exposure to intermittent and sustained levels of PTX. *In vivo* tumour repopulation in response to sustained and intermittent PTX therapy was investigated in an intraperitoneal xenograft model of human ovarian cancer. Tumour growth, proliferation and apoptosis were evaluated at different intervals during and after the course of treatment using 5-bromo-2'-deoxyuridine uptake, Caspase 3 and terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling immunoassays.

RESULTS: Sustained treatment significantly reduced survival *in vitro* in both cell lines, whereas an increase in clonogenic survival was observed in the intermittent group with each treatment gap, indicating a gradual acceleration in repopulation rates. Similarly, *in vivo*, sustained therapy resulted in a significant reduction of tumour growth and proliferation. Intermittent therapy resulted in increased tumour proliferation and no efficacy. The percentage of apoptotic tumour cells significantly increased in the sustained group, whereas no significant changes were seen in the control and intermittent groups. Intermittent administration of PTX significantly augmented both *in vitro* and *in vivo* tumour repopulation rates, whereas sustained delivery inhibited tumour growth and repopulation.

CONCLUSION: Sustained administration of PTX may increase chemoresponsiveness and clinical response in ovarian cancer by attenuating tumour repopulation.

PII-34

A PHASE-I DOSE ESCALATION STUDY OF CYCLICAL WEEKLY TEMOZOLOMIDE(TMZ)COMBINED WITH WEEKLY PEGYLATED INTERFERON ALFA-2B(PEG-IFN) IN PATIENTS-(PTS)WITH REFRACTORY AND/OR ADVANCED SOLID TUMORS. U. B. Dandamudi, A. P. Beelen, N. J. Reddy, N. C. Crosby, M. S. Ernstoff, L. D. Lewis; Dartmouth Hitchcock Medical Center, Lebanon, NH

BACKGROUND: TMZ, an oral prodrug alkylating agent, is used to treat astrocytomas and some activity in melanoma. IFN-2b, an immunomodulator, is effective in treating melanoma. We therefore undertook a phase-I study of the combination.

METHODS: This was an open-label dose-escalation study in patients with advanced solid tumors. The primary study objective was to define the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of TMZ given on days 1-7 and days 15-22 in combination with subcutaneous (SC) PEG-IFN given weekly, in 28-day cycles, with clinical and laboratory monitoring. Angiogenesis factors (AFs), bFGF, VEGF and endostatin, and PEG-IFN plasma concentrations were measured using enzyme linked immunoabsorbent and electrochemiluminescence assays respectively.

RESULTS: We treated 19 pts (10F : 9M) median age 58 yrs (range 41-79). Tumor types were; 3 pts with melanoma or colon, 2 pts with pancreas, thyroid or renal cell, 1 pt each with head and neck, sarcoma, bladder, meningioma, glioma, adrenal, and penis. Two pts received PEG-IFN 3 mcg/kg/week plus TMZ 100mg/m², each had a DLT (grade IV fatigue or confusion). 9/10 pts tolerated 1.5mcg/kg/week of PEG-IFN and TMZ 100mg/m² days 1-7 and 15-22 in 28 day cycle; 1/10 pts developed grade IV fatigue. Seven pts were treated with PEG-IFN 1.5mcg/kg/week and TMZ 125 mg/m² daily. 2/7 pts had DLT's of grade III headaches, weakness, myalgias and fatigue and 5/7 withdrew consent prior to completing two cycles. The PEG-IFN pharmacokinetic parameters (PK) were median (range) Cmax-1122 ng/ml (579-1414), Tmax-24 h (21.2-48) and T½-54.9 h (49.6-88.8). There was no consistent treatment effect on the AFs studied. Of 9 pts evaluable for anti-tumor effects, 1/9 had stable disease (colon), 8/9 had progressive disease.

CONCLUSION: The MTD of cyclical oral TMZ (days 1-7 and 15-22) was 100 mg/m² when combined with weekly SC PEG-IFN 1.5 mcg/kg/week in 28-day cycles. The PK of PEG-IFN were consistent with those reported for monotherapy.

PII-35

CONTRIBUTION OF CYP3A5 TO VINORELBINE METABOLISM: INCONSISTENCIES BETWEEN *IN VITRO* MODELS. A. Topletz, J. B. Dennison, S. D. Hall, J. L. Renbarger; Indiana University School of Medicine, Indianapolis, IN

BACKGROUND/AIMS: Vinorelbine is a semi-synthetic vinca alkaloid used in the treatment of advanced breast and non-small cell lung cancers. The metabolism of vincristine and vinblastine, related vinca alkaloids, is highly selective for CYP3A5 relative to CYP3A4 but the contribution of CYP3A5 to vinorelbine metabolism has not been previously studied.

METHODS: Rate of metabolism was determined by quantitation of substrate depletion rates. We quantified the contribution of CYP3A4 and 5 to vinorelbine metabolism using cDNA-expressed CYP3A enzymes, selective inhibitors and human liver microsomes (HLM) of known CYP3A4 and CYP3A5 phenotype. Incubations with radiolabeled vinorelbine were used to determine metabolite fingerprints for CYP3A4 and CYP3A5.

RESULTS: A panel of cDNA-expressed enzymes, incubated with vinorelbine, indicated that metabolism was catalyzed only by CYP3A4 and CYP3A5. The Michaelis-Menten constant of vinorelbine was approximately 2.0 μ M for CYP3A4 and CYP3A5 and maximal rates of metabolism were similar. There was no statistical difference in vinorelbine metabolism between HLMs expressing CYP3A5 to those expressing only CYP3A4 at comparable levels. There was no selective inhibition of vinorelbine metabolism by the CYP3A4 selective inhibitor, cyclosporine. There were clear qualitative differences in metabolite formation fingerprints between CYP3A4 and CYP3A5.

CONCLUSION: The results of this study conclude that although CYP3A5 metabolizes vinorelbine in the recombinant system. HLM data suggests little contribution of CYP3A5 to the overall metabolism of vinorelbine *in vivo*.

PII-36

EFFECT OF AXITINIB (AG-013736) CONCENTRATION ON QT INTERVAL AFTER ADMINISTRATION ALONE AND IN COMBINATION WITH KETOCONAZOLE IN HEALTHY VOLUNTEERS. B. E. Houk,¹ N. Sarapa,² Y. K. Pithavala¹; ¹Pfizer Global Research and Development, La Jolla, CA, ²CPCS Pharma Consulting, Morristown, NJ

BACKGROUND: Axitinib (AG-013736, AG), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptors 1, 2, 3, is currently in phase III clinical development as an anti-cancer agent. The effect of single-dose AG (half-life 2-5 hours), administered either alone or with ketoconazole (a potent CYP3A4 inhibitor), on heart rate corrected QT interval (QTc) was assessed in 32 healthy volunteers.

METHODS: Lead-in baseline (Day -2) and placebo (Day -1) phases preceded a 2-way crossover phase, in which subjects were randomized to receive AG 5 mg orally (PO) on Day 1, and ketoconazole (400 mg PO on days 1-7) plus AG 5 mg PO on Day 4. Crossover treatments were separated by at least 14 days. AG PK and QT interval (triplicate, time-matched with baseline) data were collected at 1, 2 and 3 hours after administration of AG alone and in combination with ketoconazole. Fridericia's, Bazett's, and a study-specific correction factor were evaluated for correction of the QT-heart rate relationship.

RESULTS: Ketoconazole increased AUC and C_{max} of AG by approximately 2- and 1.5 fold, respectively, similar to exposures expected with twice the dose (10 mg) of AG alone. Median peak concentrations occurred at 2 hours, indicating that maximal QTc effect was captured with the current design. A study-specific correction factor provided the best normalization of QT-RR relationship. Simulations with the final model parameter estimated a mean QTc change from baseline of 0.42 msec (95% prediction interval: -3.32 to 3.55) at the mean C_{max} for AG alone and 2.16 msec (0.65 to 3.44 msec) when AG was administered with ketoconazole. Additionally, the absolute QTc interval did not exceed 450 msec and the QTc change from baseline did not exceed 60 msec for any subject.

CONCLUSION: A single-dose of AG 5 mg does not cause QT prolongation in healthy volunteers. There was no clinically significant QTc prolongation at AG plasma exposures up to 2-fold greater than those expected following a 5 mg starting dose.

PII-37

A SUNITINIB EXPOSURE-EFFECT BASED META-ANALYSIS OF TREATMENT-RELATED ADVERSE EVENTS (TRAEs) IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (RCC) AND GASTROINTESTINAL STROMAL TUMOR (GIST). B. E. Houk,¹ C. Bello,¹ D. Cohen,¹ J. Kuwabara-Wagg,² B. Poland²; ¹Pfizer Global Research and Development, La Jolla, CA, ²Pharsight, Inc., Mountain View, CA

BACKGROUND: Sunitinib malate (SU) is an oral tyrosine kinase inhibitor approved for the treatment of advanced renal cell carcinoma (RCC) and imatinib-resistant or -intolerant gastrointestinal stromal tumor (GIST). The objectives of this analysis were to characterize the drug exposure-effect relationship for SU TRAEs in patients with solid tumors, RCC and GIST, and to evaluate the impact of race (Asian, others) on TRAEs.

METHODS: Data from 2 Japanese and 6 Western phase II/III clinical studies were pooled (720 SU- and 59 placebo-treated patients, 15% Asian, 37% female) in this meta-analysis. SU doses ranged from 25 to 150 mg/day or QOD on a 4-weeks on, 2-weeks off treatment cycle. Selected grade 3/4 TRAEs were evaluated in this analysis.

RESULTS: Small increases in the probabilities of NCI CTCAE grade 3/4 nausea/vomiting (<5%), neutropenia (4%; 7% in Asians), thrombocytopenia (6%; 11% in Asians) and hand-foot syndrome (1% were predicted with SU dose increases from 25 to 50 mg. The probabilities of leukopenia and lymphopenia TRAEs also increased with SU exposure (3% and 1%, respectively [5% and 6%, respectively, in Asians]); however, at a 50-mg dose, the predicted overall incidence was low (6% and 3%, respectively [12% and 22%, respectively, in Asians]). At the median exposure level for a 50-mg dose, a 30-38% absolute neutrophil count decrease (independent of race), and a 17-21% reduction in platelet counts (26-32% in Asians) was predicted. Evaluation of blood pressure changes revealed mild elevations (3-4 mmHg; Asians 1-2 mmHg higher) with SU exposure. Changes in hemoglobin, lymphocytes, and aspartate and alanine aminotransferases displayed low (<40%) correlation with SU exposure.

CONCLUSION: This analysis revealed that the predicted increase in the incidence of most commonly occurring TRAEs with SU exposure (25 to 50 mg QD) was relatively small. Therefore, starting SU dose adjustments do not appear to be warranted in the treatment of Asian and other RCC or GIST patients.

PII-38

IMPACT OF DEMOGRAPHIC AND CLINICAL FACTORS ON THE PHARMACOKINETICS (PK) OF SUNITINIB IN PATIENTS AND HEALTHY VOLUNTEERS. B. E. Houk,¹ D. Kang,² C. Bello,¹ D. Cohen,¹ B. Poland²; ¹Pfizer Global Research and Development, La Jolla, CA, ²Pharsight, Inc., Mountain View, CA

BACKGROUND: Sunitinib (SU), an oral, multitargeted tyrosine kinase inhibitor, is approved for the treatment of advanced renal cell carcinoma (RCC) and imatinib-resistant or -intolerant gastrointestinal stromal tumor (GIST). The objectives of this analysis were to describe SU and SU12662 (primary active metabolite) PKs following single and multiple dose administration and evaluate the impact of selected patient characteristics, tumor type, creatinine clearance (CrCl), and ECOG performance score on SU and total-drug (SU+SU12662) disposition.

METHODS: This was a meta-analysis of data from 12 Western and 2 Japanese studies in healthy volunteers and patients with acute myelogenous leukemia, solid malignancies, RCC and GIST (N=590).

RESULTS: The apparent clearance (CL/F), apparent volume of distribution (Vd/F) and terminal half-life of SU were estimated to be 51.8 L/hr, 2,030 L and 69 hrs, respectively. Corresponding values for

the metabolite were 29.6 L/hr, 3,080 L and 80 hrs. Tumor presence had the greatest impact on CL/F for both SU and metabolite. CL/F of SU and metabolite was lower in females and Asians, whilst females displayed lower Vd/F for the metabolite. Body weight was not correlated with CL/F of SU, but was correlated with CL/F and Vd/F of the metabolite. Vd/F of SU decreased in lower weight individuals. Performance status, age and CrCl did not impact PKs. In the Asian population, a 15% increase in area under the curve (AUC) and maximum concentration (C_{max}) was predicted for SU and total drug. Corresponding values in females were 9-10% and 17%, respectively. Changes in total-drug AUC and C_{max} were all <5% in extremely low (40 kg) and extremely high (100 kg) body weight subjects.

CONCLUSION: Individual covariate effects which were shown to increase AUC and C_{max} only ranged from 2% to 17%. Therefore, SU dose adjustments are not warranted based on this analysis of selected patient characteristics, tumor type and presence, CrCl, and ECOG performance score.

PII-39

CLINICAL IMPACT OF DRUG INTERACTIONS WITH CHEMOTHERAPY METABOLIZED BY CYP3As. E. Tonietto,¹ S. Cuerrier,¹ M. Boyer,¹ N. Letarte,¹ C. Noël,¹ V. Michaud,² J. Turgeon, PhD²; ¹Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada, ²Research Center, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada

BACKGROUND: Patients elective for chemotherapy often present with concomitant diseases requiring chronic therapies. These medications may interact with antineoplastic agents and modulate their response as well as their adverse effect profiles. The objective of our study was to evaluate the potential drug-drug interactions between substrates of high affinity for CYP3As and/or P-glycoprotein and antineoplastic agents which are substrates of these enzymes/transporters.

METHODS: A retrospective, observational, observational study was performed in 387 patients receiving highly emetogenic chemotherapy metabolized by CYP3As (regimens include etoposide, cyclophosphamide, anthracyclines, vinca alkaloids) for the treatment of lung or breast cancer. Among them, 57 were taking drugs that are substrates of high affinity for CYP3As (atorvastatin, lovastatin, simvastatin, diltiazem, verapamil, amlodipine, felodipine, nifedipine) while they were on chemotherapy. Prevalence of gastrointestinal and hematologic side effects were compared between these two groups.

RESULTS: Patients taking substrates of high affinity for CYP3As tended to have less modification of their anti-emetic therapy due to a poor control of nausea and vomiting than the control group (7.0% vs 16.4%, p=0.072). A similar tendency was observed when only women (n=38 and 290, respectively) were compared (5.1% vs 18.2%, p=0.061). Patients taking substrates of high affinity for CYP3As had significantly less neutropenia at day 1 of cycle 2 (0% vs 10.6%, p=0.005).

CONCLUSION: Our results suggest that concomitant use of high affinity substrates for CYP3As may improve the side-effect profile of antineoplastic drugs such as etoposide, cyclophosphamide, anthracyclines and vinca alkaloids. This could be explained by the modulation of influx/efflux transporter activities and drug metabolizing enzymes controlling the intracerebral and intracellular concentrations of antineoplastic agents.

PII-40

SEVERE HEPATIC IMPAIRMENT (HI) HAS NO CLINICALLY RELEVANT EFFECT ON THE PHARMACOKINETICS (PK) OF C.E.R.A. (RO0503821). A. Pannier,¹ P. Jordan,¹ F. C. Dougherty,¹ V. Kupcova,² J. Sperl,³ B. Reigner¹; ¹F. Hoffmann La Roche, Basel, Switzerland, ²III Medical Department, FNsP Bratislava, Bratislava, Slovakia, ³Hepatogastroenterologic Clinic IKEM, Praha, Czech Republic

BACKGROUND: C.E.R.A. (RO0503821, methoxy polyethylene glycol-epoetin β), a continuous erythropoietin receptor activator, provides correction of anemia and stable control of hemoglobin (Hb)

at extended dosing intervals in patients with chronic kidney disease (CKD). The study objective was to investigate the effect of severe HI on the PK of C.E.R.A. after a single intravenous (IV) dose, severe HI being a condition that may prevail in CKD patients (2 to 3 % of CKD patients).

METHODS: A non-randomized, open-label, single-dose, study was conducted in 12 patients with documented, stable, severe HI (Child Pugh Classification grade C) and 12 healthy subjects (HS) matching for age, gender and body weight. Subjects received one dose of IV C.E.R.A. (200 μg) and were followed up for 50-56 days. The primary PK parameters were area under the concentration-time curve from time of drug administration to the last measurable concentration (AUC_{last}), and maximum concentration (C_{max}).

RESULTS: PK parameters were similar in patients with HI and in HS, and there were no statistically significant differences between the two groups (Table). Mean C_{max}, mean AUC_{last} and median t_{1/2} values were similar for both groups. Median t_{max} was 0.25 hours for both groups. The ratios of the geometric least square means (and 90% CIs) for AUC_{last} and C_{max} were 0.90 (0.69, 1.17) and 0.84 (0.70, 1.01), respectively, when comparing HI to HS.

CONCLUSION: After IV injection of 200 μg C.E.R.A. in patients with severe HI and in HS, the pharmacokinetic parameters were similar in both groups. Overall, these results indicate that severe HI has no clinically relevant effect on the PK of C.E.R.A.

Geometric least squares means (LSM) of primary PK endpoints (based on analysis of variance model)

	AUC _{last} , ng*h/mL	C _{max} , ng/mL
Geometric LSM (90% CI)		
Patients with severe hepatic impairment (HI)	6044 (4892, 7467)	61.1 (52.8, 70.8)
Healthy subjects (HS)	6704 (5427, 8283)	72.8 (62.8, 84.3)
Ratio of LSM (90% CI for ratio of means)		
HI/HS	0.90 (0.69, 1.17)	0.84 (0.70, 1.01)

PII-41

POPULATION PHARMACOKINETICS OF BENDAMUSTINE AND METABOLITES IN PATIENTS WITH INDOLENT NON-HODGKIN'S LYMPHOMA (NHL). J. S. Owen,¹ M. Melhem,¹ D. D'Andrea,² M. Darwish²; ¹Cognigen Corp, Buffalo, NY, ²Cephalon, Inc., Frazer, PA

BACKGROUND: Bendamustine (BND) is a bifunctional alkylating agent in development for indolent refractory NHL as monotherapy and in combination with other agents. Separate population PK models were developed for BND and its active metabolites, gamma-OH-BND (M3) and N-desmethyl BND (M4). Covariates (demographics, laboratory values, BSA and other body size measures) of interpatient variability in BND PK parameters were explored.

METHODS: Data from a Phase 3, multicenter, open-label, single-arm trial designed to investigate the safety, efficacy, and pharmacokinetics of BND and metabolites in patients with indolent refractory NHL were modeled with NONMEM. BND HCl was administered as 120 mg/m² intravenous infusion over 1 hr in each of six 21-day cycles. Dose reductions were allowed to 90 or 60 mg/m² in subsequent cycles for drug-related AEs. Sparse PK samples were available from 78 patients in the first two cycles; a subset of 13 patients had rich PK samples following cycle 1 dosing. Data were split into index and test sets. Data were pooled for final parameter estimation. Covariate analysis used a forward selection (alpha=0.05)/backward elimination (alpha=0.001) process.

RESULTS: Plasma BND concentrations were 10-fold greater than M3, which in turn were 10-fold greater than M4. BND, M3, and M4 concentrations were adequately described using linear 3, 2, and

1-compartment open models, respectively. BND CL was 31.7 L/hr, with alpha, beta, and gamma half-lives of 17 min, 41 min, and 110 h, with the terminal phase contributing less than 1% of total exposure. No patient-related covariates, including BSA, were statistically significant.

CONCLUSION: Population pharmacokinetic models were developed for BND, M3, and M4. Linear models adequately described the PK of each analyte. Model predictions can be used for future exposure-response analysis. These findings suggest the possible use of a standard (flat) dosing regimen though this has not been tested in clinical trials.

PII-42

OPTIMIZING DOSE OF THE NOVEL THROMBIN RECEPTOR ANTAGONIST SCH 530348 BASED ON PHARMACODYNAMICS AND PHARMACOKINETICS IN HEALTHY SUBJECTS. T. Kosoglou, L. Reyderman, C. Kasserra, S. Young, J. Pei, S. E. Maxwell, J. Schiller, D. L. Cutler; Schering-Plough Research Institute, Kenilworth, NJ

BACKGROUND: SCH 530348 is an oral, potent, selective thrombin receptor antagonist under development for patients with established vascular disease. We evaluated pharmacodynamics (PD), pharmacokinetics (PK) and safety of SCH 530348 in healthy subjects in order to define the optimal dosing regimen for clinical safety and efficacy trials.

METHODS: In a randomized, open-label study, 67 men and 44 women ages 18 to 46 yr received oral SCH 530348 as a single dose of 5, 10, 20, or 40 mg or 0.5, 1, or 2.5 mg SCH 530348 QD in the AM for 28 days. TRAP-induced (15 μ M) platelet aggregation, PK, clinical and laboratory safety were assessed.

RESULTS: SCH 530348 caused dose-dependent inhibition of platelet aggregation. Single "loading" doses of SCH 530348 20 and 40-mg achieved the predefined goal of 80% platelet inhibition at 1 hr, although only 40-mg dose did so in most subjects. Of the 3 multiple "maintenance" doses, only 2.5 mg/day achieved consistent 80% platelet inhibition in most subjects as early as Day 7. Platelet function recovered after dosing cessation within days to several weeks in a dose-dependent manner. SCH 530348 was rapidly absorbed and slowly eliminated with long mean terminal-phase half-lives (t_{1/2}) of 165 to 311 hr. Steady-state was achieved within 21 days and exposure was dose-related. The most common AEs were upper respiratory tract infection, headache, and fatigue. AEs were generally mild and not dose related. There were no significant changes in lab tests, vital signs, or ECGs.

CONCLUSION: SCH 530348 produced dose-related, significant, prolonged, and reversible inhibition of TRAP-induced platelet aggregation in healthy subjects. No specific safety concern was identified. The PD/PK profile of SCH 530348 allows once-daily dosing with or without a loading dose. Dosing with 2.5 mg/day was selected for routine use to provide sustained benefit in subsequent clinical trials. In clinical situations where faster onset of action is required, a 40-mg loading dose is recommended.

PII-43

EFFECT OF LAPATINIB (LAP) ON THE METABOLISM OF INTRAVENOUS (IV) AND ORAL (PO) MIDAZOLAM (MDZ). K. M. Koch,¹ E. C. Dees,² N. J. Reddy,³ S. D. Gainer,¹ N. Arya,¹ L. Buie,² T. Shih,² L. D. Lewis,³ A. P. Beelen¹; ¹GlaxoSmithKline, Research Triangle Park, NC, ²University of North Carolina, Chapel Hill, NC, ³Dartmouth Hitchcock Medical Center, Lebanon, NH

BACKGROUND: Lapatinib (TykerbTM) is a small molecule tyrosine kinase inhibitor with activity against tumors over-expressing EGFR/HER2. It is administered orally and eliminated predominantly by CYP3A4-mediated metabolism. *In vitro* data indicate that LAP also inhibits CYP3A4. This study used MDZ as a probe substrate to characterize the potential effect of LAP on CYP3A4 activity *in vivo*.

METHODS: A partially randomized, 4-period, 4-sequence, 4-treatment, single IV and PO dose crossover study was conducted in 24 patients with advanced solid tumors. MDZ 1mg IV and 3mg

PO were each given 2 days apart in random order within each of two periods, doses in the second period occurring on the 5th and 7th days of treatment with oral LAP 1500mg given once daily. Blood was sampled for 24h after each MDZ dose to measure plasma MDZ concentrations, and prior to the 5th and 7th LAP doses to measure plasma LAP concentrations, by LC-MS/MS.

RESULTS: Geometric mean (95% confidence interval, CI) pharmacokinetic parameters for each treatment, and geometric mean ratio (90% CI) are shown below.

Parameter (units)	MDZ alone	MDZ + LAP	Ratio
AUC _{iv} (h•ng/mL)	35 (29-42)	40 (32-49)	1.14 (1.03-1.27)
AUC _{po} (h•ng/mL)	44 (33-57)	57 (45-73)	1.45 (1.33-1.57)
CL (L/h)	29 (24-35)	25 (21-31)	0.87 (0.79-0.97)
F (%)	42 (35-49)	50 (44-57)	1.23 (1.07-1.41)
F _h (%)	70 (62-78)	70 (61-79)	1.04 (0.98-1.10)
F _a •F _g (%)	59 (50-69)	72 (61-85)	1.22 (1.03-1.46)

LAP had no effect on hepatic bioavailability (F_h), but moderately increased intestinal bioavailability (F_a•F_g), apparently due to inhibition of first pass metabolism. Models used to characterize the relationship between MDZ and LAP indicated relative agreement between *in vivo* and *in vitro* inhibition constants (K_i).

CONCLUSION: LAP appears to be a weak inhibitor of hepatic CYP3A4 and a moderate inhibitor of intestinal CYP3A4.

PII-44

EFFECT OF CARBAMAZEPINE ON ASENAPINE PHARMACOKINETICS. P. Dogterom,¹ P. G. Schnabel,¹ C. Timmer,¹ R. de Greef,¹ R. Dahmen,² E. Spaans,³ P. A. Peeters¹; ¹NV Organon, Oss, The Netherlands, ²FOCUS GmbH, Neuss, Germany, ³Employee at NV Organon at the time the research was conducted, Oss, The Netherlands

BACKGROUND: Asenapine is a novel psychopharmacologic agent being developed for the treatment of schizophrenia and bipolar disorder. This high-clearance drug is predominantly eliminated by biotransformation. We performed an interaction study with carbamazepine, a known inducer of CYP3A4, to determine whether CYP3A4 induction affects the pharmacokinetics of asenapine and its metabolites, N-desmethylasenapine (desM) and N-glucuronide (N-gluc).

METHODS: 24 healthy male volunteers completed this open-label, one-sequence study, which involved multiple oral doses of carbamazepine (200 mg twice daily for 4 days, then 400 mg twice daily for 15 days). One sublingual dose of asenapine 5 mg was given before and on the last day of carbamazepine treatment. CYP3A4 activity was assessed by measuring urinary excretion of cortisol and 6 β -hydroxycortisol before and after carbamazepine treatment. Blood samples were collected for up to 72 hours after each asenapine dose. Plasma concentrations of asenapine, desM, and N-gluc were analyzed using a validated LC-MS (for asenapine and desM) or LC-MS-MS (for N-gluc) method. Pharmacokinetic parameters were calculated and drug interaction was tested on C_{max} and AUC_{0-∞} using Food and Drug Administration accepted bioequivalence criteria.

RESULTS: Compared with baseline, CYP3A4 activity increased 4-fold during carbamazepine treatment. C_{max} and AUC_{0-∞} decreased for asenapine (16%; 90% CI, 0.74-0.95 and 0.77-0.91, respectively) and desM (30%; 90% CI, 0.66-0.74 and 0.65-0.76, respectively). AUC_{0-∞} and C_{max} for N-gluc decreased by 16% (90% CI, 0.74-0.96) and 10% (90% CI, 0.82-0.99), respectively.

CONCLUSION: Carbamazepine induction of CYP3A4 decreased exposures of asenapine, desM, and N-gluc, indicating that demethylation and possible further metabolism steps are CYP3A4 mediated. However, the observed effects were not considered clinically relevant.

PII-45

LONGITUDINAL DOSE-RESPONSE ANALYSIS OF THE EFFECTS OF SIBUTRAMINE, ORLISTAT AND RIMONABANT ON BODY WEIGHT PROGRESSION IN POOLED OBESITY CLINICAL TRIALS: ILLUSTRATION OF KNOWLEDGE MANAGEMENT IN MODEL-BASED DRUG DEVELOPMENT. K. Venkatakrishnan,¹ F. Ezzet,² P. Ravva,¹ T. G. Tensfeldt,¹ V. Chow,¹ R. D. Chew,¹ T. Barbee,² R. V. Dvorak,¹ A. E. Taylor,¹ J. D. Obourn,¹ L. J. Benincosa¹; ¹Pfizer Global Research and Development, Groton, CT, ²Pharsight Corporation, Mountain View, CA

BACKGROUND: Sibutramine (S), orlistat (O) and rimonabant (R) are established (S,O) or emerging (R) pharmacotherapeutic options for obesity and have been studied in weight loss (WL) trials of up to 2 years duration. We herein describe a longitudinal mixed effects model of the WL time course and dose-effect relationships for these drugs.

METHODS: Data comprised of study-level mean body weight from 57 published clinical studies (113 arms: 51 placebo, 30 O, 24 S, 8 R). Dose ranges were 180-360 mg O, and 5-20 mg S and R. Percent weight change from baseline (PC) was described as an asymptotically decreasing hyperbolic function of time:

$$PC = -(WL_{P_{max}} + DE + \eta_1) \times \frac{Time}{Time + (ET_{50} + \eta_2)} + (\theta_{regain} \times Time) + \epsilon$$

WL_{P_{max}} is the placebo component of the asymptotic maximum PC and ET₅₀ is the time to 50% of this asymptotic maximum (η₁, η₂ are corresponding inter-trial random effects (ITV)). Drug effects (DE) were incorporated as additive components over WL_{P_{max}} as linear (O, R) or E_{max} (S) functions of dose. The θ_{regain} term described weight regain.

RESULTS: Parameter estimates (%CV) were: WL_{P_{max}}: 5.4% (3%); ET₅₀: 4 months (5%); θ_{regain}: 0.15% (3%) per month; R slope 0.37% per mg (2%); O slope 0.01% per mg (10%); ED₅₀ 38 mg (15%) and E_{max} 23% (39%) for S. Model-based estimates (90% prediction intervals incorporating ITV and parameter uncertainty) of placebo-adjusted PC at 1 year were: 5.3 (3.3, 7.0) for 20 mg S; 2.9 (2.4, 3.5) for 360 mg O; 4.9 (4.1, 6.0) for 20 mg R.

CONCLUSION: At typical clinically prescribed doses, S and R are predicted to offer ~5% WL over placebo at 1 year of treatment, whereas WL efficacy of O is ~40% lower. Literature information on WL efficacy of these drugs has been successfully integrated using a longitudinal model. This provides a realistic description of WL time course and associated uncertainty, and permits objective comparison of drug effects, illustrating a knowledge management strategy in contemporary model-based drug development.

PII-46

COMPARISON OF PHARMACOKINETICS AND PHARMACODYNAMICS OF PRASUGREL AND CLOPIDOGREL LOADING DOSES IN HEALTHY CHINESE AND CAUCASIAN SUBJECTS. D. S. Small,¹ C. D. Payne,² P. A. Kothare,¹ E. S. Yuen,² F. Natanegara,³ M. T. Loh,³ J. A. Jakubowski,¹ K. J. Winters,¹ N. A. Farid,¹ L. Ni,¹ Y. G. Li,¹ D. E. Salazar,⁴ R. P. Kelly³; ¹Eli Lilly and Company, Indianapolis, IN, ²Eli Lilly and Company, Windlesham, United Kingdom, ³Eli Lilly and Company, Singapore, Singapore, ⁴Daiichi Sankyo, Inc., Parsippany, NJ

BACKGROUND: Prasugrel (Pras), a novel thienopyridine, is a potent oral antiplatelet agent. Clopidogrel (Clop) is an approved thienopyridine antiplatelet agent used in the prevention and treatment of atherothrombotic diseases. Both Pras and Clop are prodrugs that are metabolized to active metabolites *in vivo*. This study compared prasugrel and clopidogrel pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability in healthy Chinese and Caucasian subjects.

METHODS: An open label, single center study (18 Chinese and 14 Caucasian) consisting of 1) a single Pras 30 mg dose to Caucasians and 2) single Pras 30 mg or Clop 300 mg doses to Chinese, given in a randomized cross-over design with a 10 day washout between doses.

Plasma concentrations of active metabolite and inhibition of platelet aggregation (IPA) using ADP as an agonist were determined.

RESULTS: Mean exposure to Pras's active metabolite was higher in Chinese (Table). IPA was higher in Chinese than in Caucasians at 0.5, 1, and 2 hours following Pras 30 mg (Figure). At all time points, IPA was higher in Chinese following Pras 30 mg than following Clop 300 mg. Pras was well tolerated in both groups, although there was a higher incidence of mild bleeding-related adverse events in Chinese subjects.

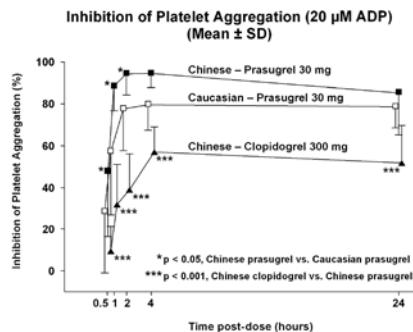
CONCLUSION: Administration of 30 mg Pras resulted in higher plasma concentrations of Pras's active metabolite in Chinese compared to Caucasians, which led to a greater IPA in Chinese. In Chinese subjects, Pras 30 mg produced greater inhibition of platelet aggregation than the approved Clop 300 mg loading dose.

Table

Pharmacokinetic parameter estimates of prasugrel's and clopidogrel's active metabolites, expressed as geometric mean (CV %) except as noted

Parameters	Chinese-Prasugrel 30 mg (n = 16)	Caucasian-Prasugrel 30 mg (n = 14)	Chinese-Clopidogrel 300 mg (n = 17)
AUC _{0-tlast} ¹ (ng•h/mL)	361 (26)	246 (29)	33.6 (61)
C _{max} ² (ng/mL)	320 (39)	192 (40)	30.7 (56)
t _{max} ³ (h)	0.50 (0.25-1.10)	0.50 (0.50-2.00)	1.00 (0.50-2.00)

¹Chinese/Caucasian geometric least square mean ratio (90% CI) = 1.47 (1.24, 1.73) ²Chinese/Caucasian geometric least square mean ratio (90% CI) = 1.67 (1.32, 2.11) ³Median (range)



PII-47

THE PHARMACOKINETICS AND PHARMACODYNAMICS OF PRASUGREL IN HEALTHY CHINESE, JAPANESE, AND KOREAN SUBJECTS COMPARED WITH HEALTHY CAUCASIAN SUBJECTS. D. S. Small,¹ P. A. Kothare,¹ E. S. Yuen,² Y. G. Li,¹ K. J. Winters,¹ N. A. Farid,¹ L. Ni,¹ D. E. Salazar,³ C. D. Payne²; ¹Eli Lilly and Company, Indianapolis, IN, ²Eli Lilly and Company, Windlesham, United Kingdom, ³Daiichi Sankyo, Inc., Parsippany, NJ

BACKGROUND: Prasugrel is a novel thienopyridine prodrug that is metabolized to an active metabolite, which binds irreversibly to the platelet P2Y₁₂ receptor and inhibits ADP-induced platelet aggregation for the life of the platelet. We compared prasugrel pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability in healthy Chinese, Japanese, Korean and Caucasian subjects.

METHODS: In an open label, single center, parallel design study, 89 healthy subjects (25 Chinese, 20 Japanese, 22 Korean, and 22 Caucasian) aged 20-65 years were given a prasugrel 60 mg loading dose

(LD) followed by daily 10 mg maintenance doses (MD) for 7 days and then 5 mg MD for 10 days. Plasma concentrations of prasugrel's active metabolite and ADP-induced inhibition of platelet aggregation (IPA) were determined.

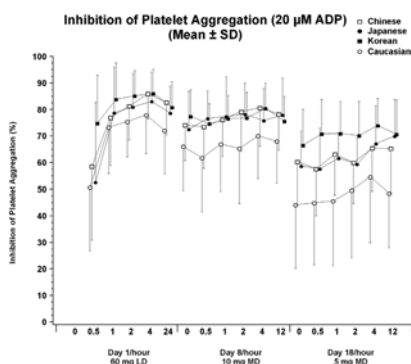
RESULTS: Mean exposure to prasugrel's active metabolite in all treatment regimens was higher in each of the Asian groups compared to Caucasians (Table), although there was considerable overlap between individual exposure estimates in Asians and Caucasians. Mean IPA was also higher in Asians compared to Caucasians following prasugrel 60 mg LD (Figure), however the difference did not consistently achieve statistical significance. Prasugrel 10 mg or 5 mg MD led to statistically significantly higher IPA in each Asian group compared to Caucasians. Prasugrel was well tolerated during LD and MD regimens by all groups.

CONCLUSION: Prasugrel produced greater exposure to the active metabolite and higher IPA in Asians than in Caucasians.

Table

Geometric mean (CV%) of prasugrel's active metabolite presented as area under the curve AUC_{0-tlast}

Parameters	Prasugrel 60 mg LD (ng•h/mL)	Prasugrel 10 mg MD (ng•h/mL)	Prasugrel 5 mg MD (ng•h/mL)
Caucasian n = 22	486 (31)	69.6 (34)	30.3 (42)
Chinese n = 25	653 (48)	94.7 (43)	42.4 (48)
Japanese n = 19	643 (27)	89.9 (26)	41.6 (29)
Korean n = 22	611 (28)	83.9 (37)	40.6 (28)



PII-48

EFFECT OF RIFAMPIN, CYP3A4 INDUCER, ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF TOLVAPTAN, A NON-PEPTIDE VASOPRESSIN ANTAGONIST. S. E. Shoaf, S. Mallikaarjun; Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, MD

BACKGROUND: Tolvaptan (TLV) is a selective vasopressin receptor (V_2) antagonist being studied for several indications. Studies with ketoconazole and grapefruit juice indicated that tolvaptan is a CYP3A4 substrate. The effect of CYP3A4 induction on TLV pharmacokinetics (PK) and pharmacodynamics (PD) needed to be characterized.

METHODS: This study was a single-center, open-label, sequential study of the effects of multiple dose rifampin 600 mg on the PK and PD of tolvaptan 240 mg in 15 healthy men and women. On Days 3 to 8 and Day 10, rifampin 600 mg was administered 1 hour prior to breakfast. TLV 240 mg was administered in the fasted state on Days 1 (alone) and 9 (with rifampin). Blood samples for PK analysis were drawn for 72 h. Urine volume and fluid intake (PD parameters) were determined for 14 intervals in the 48 hours postdose.

RESULTS: Rifampin decreased TLV plasma concentrations by ~85% and PD parameters by 75%. PD parameters following TLV + rifampin were similar to that following a single 60-mg dose of TLV. Changes in the shape of the TLV concentration-time curve appears to explain why PD effects were less than PK effects. Urine excretion following TLV alone, was at its maximum for all intervals from 0 to 24 hours postdose, and for TLV + rifampin was at its maximum from 0 to 8 hours postdose. In each treatment, 7 subjects experienced treatment-emergent adverse events. All events were mild to moderate in severity.

CONCLUSION: When co-administered with rifampin, tolvaptan concentrations were decreased ~85% and PD parameters by 75%. Tolvaptan co-administered with rifampin was safe and well tolerated.

Mean (SD) Tolvaptan Pharmacokinetic Parameters

Treatment	C _{max}	t _{max} ^a	AUC _t
240 mg TLV alone	1000 (436)	2.5 (1-12)	11600 (4060)
TLV+Rifampin	168 (73.5)	3 (1.5-6)	1470 (686)

^aValues are median (minimum-maximum). Units are ng/mL for C_{max}, h for t_{max} and ng•h/mL for AUC_t.

PII-49

EFFECT OF KETOCONAZOLE AND GRAPEFRUIT JUICE, CYP3A4 INHIBITORS, ON THE PHARMACOKINETICS OF TOLVAPTAN, A NON-PEPTIDE VASOPRESSIN ANTAGONIST. S. E. Shoaf, S. Mallikaarjun; Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, MD

BACKGROUND: Tolvaptan (TLV) is a selective vasopressin receptor (V_2) antagonist being studied for several indications. In vitro studies indicated that tolvaptan is primarily metabolized via CYP3A4. The clinical effect of potent CYP3A4 inhibition needed to be characterized.

METHODS: The effect of ketoconazole (KETO) was determined in a randomized, placebo-controlled, sequential study in 24 healthy subjects. On Day 1, subjects were given either 30 mg TLV (19) or placebo (5). Blood samples for pharmacokinetic (PK) analysis were drawn over 72 h. On Days 4 to 6, 200 mg KETO was administered. On Day 5, tolvaptan/placebo was administered with KETO and PK samples were obtained for 72 h. ¹⁴C-Erythromycin breath testing (ERBT) was performed on Day -1 and at 2 hours postdose on Days 1, 4 and 5. The area under the dpm-time curve from 0 to 1 hour was determined. The effect of grapefruit juice was determined in a separate two-period, randomized, crossover study in 20 healthy subjects. Treatments were 60 mg TLV alone or 60 mg TLV + 240 mL reconstituted grapefruit juice given on Day 1 and Day 4. Blood samples for PK analysis were drawn for 72 h.

RESULTS: CYP3A4 activity, as measured with the ERBT, was unchanged following TLV alone and was decreased by an average of 49 ± 15% and 63 ± 12% following 200 mg KETO and 200 mg KETO+TLV, respectively. See table below for a summary of TLV PK parameters from both studies. Coadministration with KETO decreases TLV clearance 83% but grapefruit juice appears to just increase the bioavailability of TLV as t_{1/2} is unchanged.

CONCLUSION: TLV is a CYP3A4 substrate with little inhibitory activity at CYP3A4.

Mean (SD) Tolvaptan Pharmacokinetic Parameters

Treatment	C _{max}	t _{max} ^a	AUC _∞	t _{1/2}	CL/F
30 mg TLV alone	174 (65)	3 (1-6)	1460 (653)	6.9 (3.3)	5.63 (2.68)
TLV+KETO	606 (141)	3 (1.5-4)	7877 (3145)	10.5 (2.7)	0.97 (0.33)
60 mg TLV alone	320 (77.5)	3 (2-4)	2540 (849)	5.5 (1.1)	6.22 (2.49)
TLV+ Grapefruit	602 (175)	3 (1-3)	4402 (1780)	5.7 (2.3)	3.69 (1.73)

^aValues are median (minimum-maximum). Units are ng/mL for C_{max}, h for t_{max} and t_{1/2}, ng•h/mL for AUC and mL/min/kg for CL/F.

PII-50

THE PHARMACOKINETICS OF FEXOFENADINE BUT NOT MIDAZOLAM ARE ALTERED IN END-STAGE RENAL DISEASE. T. D. Nolin,¹ R. F. Frye,² H. Sadr,¹ P. Le,³ J. Himmelfarb¹; ¹Maine Medical Center, Portland, ME, ²University of Florida, Gainesville, FL, ³Maine Medical Center Research Institute, Scarborough, ME

BACKGROUND: End-stage renal disease (ESRD) can result in decreased non-renal clearance of drugs, but the extent to which individual pathways of drug metabolism and transport are affected is unknown. Reduced hepatic CYP3A activity determined by erythromycin breath testing (EBT) has been reported in ESRD. However, uptake (organic anion-transporting polypeptides, OATP) and efflux (P-glycoprotein, P-gp) transporters confound EBT interpretation, and the impact of ESRD on the activity of these transporters and gastrointestinal (GI) CYP3A has not been assessed. Therefore, the aim of this study was to evaluate the effect of ESRD on drug transport and hepatic and GI CYP3A activity.

METHODS: Ten ESRD patients undergoing chronic hemodialysis and ten matched control subjects participated after providing written informed consent. Fexofenadine (FEX) 120 mg was given orally at t=0, followed by oral midazolam (MDZ) 2 mg at t=2 hrs and IV MDZ 1 mg at t=6 hrs. Blood samples were collected before and for 12 hr after dosing. Plasma FEX, MDZ, and 1'-OH-MDZ concentrations were determined by LC/MS/MS and pharmacokinetic parameters were calculated by noncompartmental methods.

RESULTS: No significant differences were noted in the oral or intravenous MDZ and 1'-OH-MDZ half-life, CL, or AUC values, suggesting that neither hepatic nor GI CYP3A activity is altered in ESRD patients. However, FEX CL/F was decreased 63% from 102.8 ± 37.9 L/hr in control subjects to 37.9 ± 19.5 L/hr (p<0.001) in ESRD, leading to a 2.4-fold increase in the FEX AUC₀₋₁₂ in ESRD (1,245.5 ± 618.8 hr-ng/mL in control subjects versus 3,035.4 ± 1,393.8 hr-ng/mL in ESRD, p=0.003). A corresponding 35% increase in FEX half-life was also observed (3.4 ± 0.9 hr in control subjects to 4.6 ± 1.3 hr in ESRD, p=0.019).

CONCLUSION: These data suggest that ESRD has no effect on hepatic and GI CYP3A activity. Conversely, ESRD significantly decreases drug transport as evidenced by altered FEX pharmacokinetics.

PII-51

EFFECT OF GINKGO BILOBA AND VALERIAN ROOT EXTRACTS ON MYCOPHENOLIC ACID GLUCURONIDE FORMATION IN HUMAN LIVER MICROSOMES. M. F. Mohamed, S. S. Harvey, R. F. Frye; University of Florida, Gainesville, FL

BACKGROUND/AIMS: Despite increasing consumption of herbal supplements, a paucity of data exists regarding their potential to modulate the metabolism of drugs by glucuronidation. Mycophenolic acid (MPA), a widely used immunosuppressant agent, is metabolized in the liver primarily by UDP-glucuronosyltransferase (UGT) enzymes. There is evidence that valerian root extract inhibits glucuronidation of some UGT substrates, while *Ginkgo biloba* extract contains glycosides that are substrates for UGTs; therefore *Ginkgo biloba* and valerian root extracts may affect MPA metabolism. The purpose of this study was to evaluate the interaction potential of *Ginkgo biloba* and valerian root extracts with MPA glucuronidation in pooled human liver microsomes.

METHODS: Pooled human liver microsomes (0.16 mg/ml) were co-incubated with mycophenolic acid (300 µM) and 5 or 10 µl of one of the following herbal extracts: *Ginkgo biloba* extract, acid-hydrolyzed *Ginkgo biloba* extract, and valerian root extract. Each sample was assayed in triplicate including positive and negative controls. After 30 minutes of incubation at 37°C, the reaction was stopped by adding ice-cold acetonitrile. MPA-glucuronide (MPAG) was measured in each of the incubation reactions using LC/MS/MS and results are expressed as a percent of control (mean ± SD).

RESULTS:

EFFECT OF HERBAL EXTRACTS ON MYCOPHENOLIC ACID GLUCURONIDE FORMATION

	<i>Ginkgo biloba</i> extract		Acid-hydrolyzed <i>Ginkgo biloba</i> extract		Valerian extract	
	10 µl	5 µl	10 µl	5 µl	10 µl	5 µl
MPAG formation - percent of control Mean (SD)	11.4 (1.2)	27.9 (0.7)	31.9 (3.3)	39.3 (6.2)	52.5 (5.6)	75.9 (9.5)

CONCLUSION: The results show that *Ginkgo biloba* and valerian extracts have a propensity to inhibit MPA glucuronidation in human liver microsomes. *Ginkgo biloba* extract exhibited a stronger inhibition compared to the acid-hydrolyzed *Ginkgo biloba* and valerian extracts. These data indicate that *Ginkgo biloba* extracts can inhibit the metabolism of MPA and could potentially increase MPA exposure in patients.

PII-52

BIOEQUIVALENCE OF SITAGLIPTIN/METFORMIN FIXED-DOSE COMBINATION TABLETS AND COADMINISTRATION OF SITAGLIPTIN AND METFORMIN. J. Miller,¹ E. M. Migoya,¹ M. Gutierrez,² W. Zheng,¹ A. O. Johnson-Levonas,¹ J. A. Wagner,¹ K. Gottesdiener¹; ¹Merck Research Laboratories, Rahway, NJ, ²Comprehensive NeuroScience, Inc, Miramar, FL

BACKGROUND/AIMS: To evaluate the bioequivalence (BE) of sitagliptin/metformin (SITA/MET) 50-mg/500-mg and 50-mg/1000-mg fixed-dose combination (FDC) tablets and coadministration of corresponding doses of sitagliptin and metformin (SITA+MET) as individual tablets.

METHODS: This open-label, 2-part, 2-period crossover study randomized healthy subjects to 1 part of the study only, with each part consisting of 2 single-dose, crossover study periods separated by a 7-day washout. Part I consisted of Treatment A (SITA 50 mg + MET 500 mg) and B (SITA/MET 50/500 mg/mg) and Part II consisted of Treatment C (SITA 50 mg + MET 1000 mg) and D (SITA/MET 50/1000 mg/mg). Blood for PK analyses was collected up to 72 hours postdose. BE was achieved if 90% CIs for the GMR of AUC_{0-∞} and C_{max} of both SITA and MET fell within pre-specified bounds of (0.80, 1.25).

RESULTS: The study enrolled 48 subjects (65% female) with a mean age, weight, and height of 35 yrs, 165 cm, 72 kg, respectively. The 90% CIs of the GMRs for AUC_{0-∞} and C_{max} of SITA and MET fell within the BE bounds of [0.80, 1.25] (Table). Single doses of SITA/MET 50-mg/500-mg and 50-mg/1000-mg and coadministration of corresponding doses of SITA and MET as individual tablets were generally well-tolerated.

CONCLUSION: SITA/MET 50-mg/500-mg and 50-mg/1000-mg FDC tablets are BE to coadministration of SITA+MET as individual tablets. The doses used in this study bracket the SITA/MET 50-mg/850-mg FDC dose strength and support BE of this intermediate dose. These results suggest that the safety/efficacy profile of SITA+MET coadministration therapy can be applied to the SITA/MET FDC tablet. The SITA/MET FDC tablet can be used as an alternative to coadministered SITA+MET for the treatment of type 2 diabetes.

Table. Geometric mean ratios (GMR)[‡] of AUC_(0-∞) and C_{max} for sitagliptin and metformin in Parts I and II of the study.

	Part I: GMR (90% CI)	Part II: GMR (90% CI)
Sitagliptin		
AUC _{0-∞}	0.98 (0.96, 1.00)	0.97 (0.95, 0.99)
C _{max}	1.00 (0.94, 1.06)	0.94 (0.88, 1.01)
Metformin		
AUC _{0-∞}	1.00 (0.95, 1.04)	1.00 (0.94, 1.07)
C _{max}	1.00 (0.94, 1.06)	1.01 (0.93, 1.10)

AUC= area under the plasma concentration curve; C_{max}= maximum plasma concentrations; CI= confidence interval

[‡] GMR= geometric least-squares mean ratio (combination tablet/co-administration) based on the least-squares mean obtained from an ANOVA model; AUC= area under the plasma concentration versus time curve; C_{max}= maximum plasma drug concentrations.

PII-53

RELATIVE BIOAVAILABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF A NEW CLOPIDOGREL FORMULATION IN HEALTHY MALE VOLUNTEERS. S. Kim, H. Lee, E. Kwan, E. Kim, Y. Yoon; Kyungpook National University Hospital, Clinical Trial Center, Daegu, Republic of Korea

BACKGROUND: Clopidogrel is a potent antiplatelet agent widely used in the treatment of coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Clopidogrel bisulfate is the conventional formulation, whereas clopidogrel besylate is a newly developed one. Drugs formed from different salts may differ in their solubility profiles and dissolution rates, which may affect their rate of absorption and thus their onset, duration, and intensity of effect. The aim of this study was to investigate the relative bioavailability, pharmacokinetics, and pharmacodynamics of two clopidogrel formulations, clopidogrel bisulfate (Plavix®) and clopidogrel besylate (Plavid®).

METHODS: This single-center, randomized, open-label, 2-period, comparative crossover study included 44 healthy male subjects. Clopidogrel bisulfate or clopidogrel besylate was initiated with a single 300mg oral loading dose, and then continued at 75mg once daily for 5 days, on 2 occasions, separated by 14-day washout period. Pharmacokinetic analysis was done after 300mg loading dose. Platelet aggregation response to 10 µM of ADP was measured by turbidometric aggregometry during multiple doses and after steady state.

RESULTS: C_{max} and AUC for clopidogrel bisulfate was 11906 ng/mL, and 5998.8 hr*ng/mL/kg, respectively, and for clopidogrel besylate was 10892 ng/mL, and 5728.8 hr*ng/mL/kg, respectively. AUEC and E_{max} for clopidogrel bisulfate was 22379 %*hr and 37.4%, respectively, and clopidogrel besylate was 22206 %*hr and 40.4%, respectively. There were no significant differences between two clopidogrel formulations.

CONCLUSION: In this study, the 2 clopidogrel formulations were pharmacokinetically and pharmacodynamically equivalent, and the newly developed formulation had a safety profile comparable to that of the conventional formulation. (This research was supported by a grant of the Korea Health 21 R&D Project, MOHW (A050584) and by the BK21 Project in 2007.)

PII-54

COMPARISON OF PHARMACOKINETICS AND PHARMACODYNAMICS OF TICLOPIDINE BETWEEN ADMINISTRATION OF COMBINED FORMULATION OF TICLOPIDINE / GINKGO EXTRACT, AND COADMINISTRATION OF TICLOPIDINE AND GINKGO EXTRACT. T. E. Kim,¹ J. W. Kim,¹ K. S. Lim,¹ J. H. Hong,¹ K. H. Lee,² Y. O. Lee,² Y. S. Kim,² K. S. Yu,¹ I. J. Jang,¹ S. G. Shin¹; ¹Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, ²Yuyu Inc., Seoul, Republic of Korea

BACKGROUND: The antiplatelet agent ticlopidine has often been used in combination with ginkgo extract. The aim of this study was to evaluate the pharmacokinetic and pharmacodynamic characteristics of ticlopidine in a ticlopidine / ginkgo extract combined formulation, compared with coadministration of a ticlopidine tablet with a ginkgo extract tablet.

METHODS: A randomized, open-label, two-treatment, two-way crossover study was conducted in 24 healthy male subjects. Subjects were evenly allocated into two sequence groups. In one period, a ticlopidine 250 mg / ginkgo extract 80 mg combined formulation was taken orally, and in the other period, ticlopidine 250 mg and ginkgo extract 80 mg were co-administered. A seven-day wash-out separated the two periods. Serial blood sampling and bleeding time measurements were performed till 48 hours after drug administration during each period. Plasma concentrations of ticlopidine were analyzed by liquid chromatography-tandem mass spectrometry. Pharmacokinetic parameters were calculated by noncompartmental methods.

RESULTS: The geometric mean ratio of ticlopidine area under the curve of combined formulation to coadministration was 1.04 (90% confidence interval 0.96-1.13) and that of peak plasma concentration

was 1.09 (0.96-1.23). The ratio of maximal change of bleeding time to baseline was 43.5 ± 44.0 % (mean \pm standard deviation) after combined formulation administration and 43.0 ± 50.0 % after coadministration. There was no statistically significant difference between two treatment groups in the ratio of maximal change of bleeding time to baseline ($P = 0.974$).

CONCLUSION: Administration of a combined formulation of ticlopidine / ginkgo extract and coadministration of ticlopidine and ginkgo extract showed similar pharmacokinetic and pharmacodynamic characteristics regarding ticlopidine.

PII-55

POPULATION PHARMACOKINETICS OF EPLERENONE IN PEDIATRIC HYPERTENSIVE SUBJECTS. R. Khosravan,¹ D. Ouellet,² R. Boyd,³ K. Kowalski,⁴ M. Huttmacher,⁵ K. Sinha,³ M. Pressler,⁴; ¹Pfizer Inc., San Diego, CA, ²GlaxoSmithKline, Research Triangle Park, NC, ³Pfizer Inc., Groton, CT, ⁴Pfizer Inc., Ann Arbor, MI, ⁵A2PG, Ann Arbor, MI

BACKGROUND/AIMS: The main objectives were to characterize population (POP) pharmacokinetics (PK) of eplerenone (EPL, Inspr®), a selective mineralocorticoid receptor antagonist, in pediatric (PED) hypertensive subjects and to evaluate the effect of important covariates on the main PK parameters.

METHODS: In a single-dose PK study (STY1), PED hypertensive subjects received a 12.5, 50, or 100 mg EPL dose according to their age. In a multiple-dose safety study (STY2), PED hypertensive subjects initially received EPL 25 mg once daily and were titrated up to 50 mg twice daily if clinically indicated. The rich sampling PK data from STY1 were combined with the sparse sampling PK data from STY2. EPL pop PK was assessed using NONMEM / SPLUS / PERL, including stepwise forward selection / backward elimination for covariate selection followed by non-parametric bootstraps.

RESULTS: Parameter POP mean estimates for the final model in PED hypertensive subjects (35 males/16 females, 4-16 y) were

PK Model (2-compartment with lag time, FOCE method)

Final Model	CL/F = 5.95 ^a L/h; $V_d/F = 30.7^{b,c} + 0.5 \cdot (BWT^{**} - 45)$ L $K_a = 1.56^c \text{ h}^{-1}$; $t_{lag} = 0.273 \text{ h}$; $V_p/F = 42.1^d \text{ L}$ $Q/F = 0.856^d \text{ L/h}$; $\sigma_{STY1} = 18\%$; $\sigma_{STY2} = 29\%$
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Final Model	CL/F = 5.95 L/h; $V_d/F = 31.2 + 0.513 \cdot (BWT - 45)$ L
Bootstraps ^c	$K_a = 1.70 \text{ h}^{-1}$; $t_{lag} = 0.247 \text{ h}$; $V_p/F = 42.1^d \text{ L}$ $Q/F = 0.856^d \text{ L/h}$; $\sigma_{STY1} = 17\%$; $\sigma_{STY2} = 30\%$

BWT: baseline total body weight in kg; σ : residual variability coefficient of variation (CV); ^a $p < 0.001$; inter-subject variability CVs were ^a74%, ^b33%, and ^c157%; ^dFIXED; ^eparameter arithmetic means.

CONCLUSIONS: A two-compartment model with lag time was successfully used to describe EPL PK data from two studies in pediatric hypertensive subjects. The covariate analysis identified total body weight for V_d/F as a statistically significant covariate. However, age and BWT did not have statistically significant effects on CL/F.

PII-56

ALISKIREN, AN ORAL DIRECT RENIN INHIBITOR, HAS NO EFFECT ON THE PHARMACOKINETICS OR PHARMACODYNAMICS OF A SINGLE DOSE OF ACENOCOUMAROL IN HEALTHY VOLUNTEERS. H. A. Huang,¹ S. Vaidyanathan,¹ C. Yeh,¹ H. A. Dieterich,² W. P. Dole,³; ¹Novartis Pharmaceuticals Corporation, East Hanover, NJ, ²Novartis Pharma AG, Basel, Switzerland, ³Novartis Institutes for Biomedical Research, Cambridge, MA

BACKGROUND: Aliskiren (ALI) is a novel oral direct renin inhibitor approved for the treatment of hypertension. This study investigated the effect of co-administration with ALI on the pharmacokinetics and pharmacodynamic effects of a single dose of the anticoagulant acenocoumarol (ACEN) in healthy subjects.

METHODS: This was a single center, two-sequence, two-period, randomized, double-blind crossover study in 18 healthy subjects (ages 18-45 yrs). Subjects received either ALI 300 mg or placebo once daily on Days 1-10 and a single dose of ACEN 10 mg on Day 8. Treatment periods were separated by a 10-day outpatient washout period. Blood samples were taken frequently for determination of steady state plasma concentrations of ALI (LC-MS/MS) and of R(+)- and S(-)- enantiomers of ACEN (HPLC-UV), prothrombin time (PT) and International Normalized Ratio (INR).

RESULTS: Co-administration with ALI had no effect on exposure to R(+)-ACEN. Ratios of geometric means of ALI to placebo co-administration for R(+)-ACEN AUC_{0-t} and C_{max} were near unity (Table). Co-administration of ALI led to small increases (<20%) in S(-)-ACEN AUC_{0-t} and C_{max} (Table). A single dose of 10 mg ACEN prolonged PT and INR with maximum effects at 24-36 hours. The pharmacodynamic response to ACEN was not affected by co-administration of ALI. Geometric mean ratios were near unity for all pharmacodynamic parameters (AUC_{PT} , PT_{max} , AUC_{INR} and INR_{max}), with 90% CI between 0.97-1.05. ALI was well tolerated when administered alone or in combination with ACEN.

CONCLUSION: ALI does not affect the pharmacokinetics or pharmacodynamics of ACEN in healthy volunteers; hence no dose adjustment should be needed when these drugs are co-administered.

Table Effect of ALI on ACEN pharmacokinetic and pharmacodynamic parameters (n = 18).

Parameter	Ratio of geometric means(A:B)	90% CI for ratio
R(+)-ACEN		
AUC_{0-t} (ng·h/mL)	1.08	(0.97, 1.21)
C_{max} (ng/mL)	1.04	(0.94, 1.15)
S(-)-ACEN		
AUC_{0-t} (ng·h/mL)	1.19	(0.92, 1.54)
C_{max} (ng/mL)	1.09	(0.88, 1.34)

Treatment A = ALI 300 mg + ACEN 10 mg; treatment B = Placebo + ACEN 10 mg

PII-57

THE PHARMACOKINETICS AND PHARMACODYNAMICS OF OXYBUTYNIN AND ITS PRIMARY ACTIVE METABOLITE, N-DESETHYLOXYBUTYNIN FOLLOWING MULTIPLE DOSE ADMINISTRATION OF TWO MODIFIED RELEASE DOSAGE FORMS. M. Hruska,¹ M. Buckwalter,¹ J. Aquilina,² M. Frustaci,³ C. Gelotte,⁴ D. Doose,¹ S. Silber,⁵ ¹Johnson & Johnson Pharmaceutical Research & Development, Fort Washington, PA, ²Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ, ³Johnson & Johnson Pharmaceutical Research & Development, Springhouse, PA, ⁴McNeil Consumer Health USA, Fort Washington, PA, ⁵Johnson & Johnson Pharmaceutical Research & Development, Titusville, NJ

BACKGROUND: Oxybutynin (OXY) and its active metabolite, N-desethylxybutynin (NDES), produce symptoms of dry mouth, with a greater degree associated with higher NDES exposure. The objective of the study was to determine if 2 different modified release (MR) formulations, a controlled-release matrix tablet (CR) and an OROS extended-release tablet (OROS), affect the time course of NDES/OXY plasma concentration exposure ratios, and subsequent saliva output.

METHODS: The study had a randomized, multiple-dose, double blind, placebo controlled, three-treatment, three-period, balanced crossover study design. During the 3 treatment periods, separated by 1-week washout, 56 subjects (25M/31F) received CR, OROS, or placebo daily for 5 days. Subjects were administered drug under fasting conditions (Days 1 through 4) and under fed conditions (Day 5). On Days 4 and 5, PK blood samples, saliva output, and 100 mm visual analogue scale (VAS) were collected over a 12-hour period.

R-/S-OXY, and R-/S-NDES were quantified using a validated LC/MS/MS method. PK parameters were calculated using noncompartmental methods and NDES/OXY AUC ratios were determined. Area under the effect curve (AUE) was calculated for saliva output and VAS score, as objective and subjective measures of dry mouth, respectively. PK ratios and AUE obtained were compared across treatments on Day 4, and within treatments on Day 5.

RESULTS: Racemic NDES/OXY AUC ratio was greater for CR vs. OROS (p<0.0001) and under fed conditions for both CR and OROS (p<0.0001). Saliva output over the 12-hour interval was greater for OROS vs. CR (p<0.0001). VAS scores were greater for CR over the 4 to 12 hour period (p<0.01).

CONCLUSION: Exposure to NDES was greater for CR, with subsequent decrease in saliva output and increase of dry mouth perception. These results suggest that different OXY MR formulations provide distinct exposure to OXY and NDES and therefore may affect associated adverse event and patient tolerability profiles.

PII-58

AN INTEGRATED POPULATION PHARMACOKINETIC ANALYSIS OF DRUG X USING DATA FROM VARIOUS PHASE I STUDIES. A. Hazra,¹ X. Gao,² ¹Pfizer Inc., New London, CT, ²Pfizer Inc., Groton, CT

BACKGROUND: This study aims at developing a population PK model of Drug X (a PPAR- α agonist for atherosclerosis) from Phase I studies in healthy volunteers (HV).

METHODS: Data were obtained from 6 Phase I studies (1739 data points in 100 subjects) where subjects received oral solution of drug X ranging from 0.1-12 mg for single dose (SD) and 0.3-6 mg QD (14 days) for multiple dose (MD) studies. Plasma PK samples were collected up to 96 hours following SD and on Days 1 to 14 during MD dosing. Different PK models were explored using non-linear mixed effect modeling (NONMEM V). Log-normal distribution in clearance (CL/F), central (Vc) and peripheral volumes (V_T) was used for inter-individual variability (IIV) and a proportional error model was used for residual variability. Efforts were made to identify significant covariates.

RESULTS: Drug X absorption was rapid with T_{max} ranging from 0.5-1 hr in all studies. A base two compartment model with zero-order absorption and 1st-order elimination adequately described Drug X PK. Fits were significantly improved by following covariates; 1) dose for duration of zero-order absorption, 2) individual creatinine clearance (CLcr) for CL/F, and 3) individual body-weight for Vc. For the final model, consistent with marked improvement in fits via visual inspection, the overall objective function value was reduced by 45, and IIVs of CL and Vc were reduced by ~2 and 3%; IIV in CL/F, Vc and V_T were 26.5, 27.9 and 40.1% respectively; precision of parameter estimates were ranged from 3.2-33.6%.

CONCLUSION: A population PK model was developed which adequately described PK of Drug X in HV using the phase I study data. The current model will allow for assessing effect of formulation changes for absorption, and evaluating dose individualization using identified three important covariates, i.e., Dose, CLcr and weight. This model is an integrated effort along with the ongoing development of a PK-PD model for selection of dosing regimen of Phase 2 and 3 studies.

PII-59

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF M118, A NOVEL, RATIONALLY ENGINEERED LOW MOLECULAR WEIGHT HEPARIN, FOLLOWING IV INJECTION IN HUMAN VOLUNTEERS. I. Fier, MBA,¹ M. E. Richey, BSc,¹ G. Morelli, MD,² M. Abu-Rashid, BPharm, MPhil,² M. K. Di Marco, MSc, PhD,² S. Boudriau, PhD,² ¹Momenta Pharmaceuticals, Inc, Cambridge, MA, ²MDS Pharma Services, St. Laurent, QC, Canada

BACKGROUND: M118 is a novel, rationally engineered LMWH designed with attributes of monitorability, reversibility and potent anti-Xa (aXa) and anti-IIa (aIIa) activities that is in development as

adjunctive pharmacotherapy for ACS patients. The aim was to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) properties of M118 following IV administration in normal volunteers.

METHODS: 36 healthy male volunteers were admitted to a Phase I clinic for 24 hours. Subjects were administered escalating IV bolus doses of M118 (6, 12.5, 25, 50, 75, 100 aXa IU/kg) in cohorts of 6 subjects, 4 active/2 placebo (saline). Blood samples for determination of ACT, aPTT, aXa and aIIa activity, and other safety labs were collected through 24h post-dose.

RESULTS: Maximal ACT change from baseline and M118 dose were highly correlated ($R^2 = .996$) and appeared to increase in a dose-proportional fashion from 25 to 100 aXa IU/kg, as were ACT and aXa levels ($R^2 = 0.873$) and aIIa levels ($R^2 = 0.881$), respectively. A_{max} values for aXa and aIIa ranged from 0.09 - 1.52 and 0.08 - 1.11 IU/mL, respectively. Doses of 75 or 100 IU aXa activity per kg body weight resulted in mean ACT values > 200 seconds (215, 238 respectively). Mean elimination half-life was rapid (range 0.83-1.27h) for both aXa and aIIa activity (12.5 - 100 aXa IU/kg), and the ratio of aXa to aIIa activity was relatively constant over time.

CONCLUSION: M118 produced rapid, measurable, dose-dependent increases in anticoagulant activity in a linear manner. M118 was also safe and well tolerated. PK parameters were highly correlated to the PD effect of M118 supporting the use of PD markers to monitor plasma levels. Furthermore, additional clinical data has demonstrated that M118 can be efficiently reversed with protamine sulfate and concomitantly administered with ASA and clopidogrel. In aggregate, these data provide a rationale for continued clinical evaluation of M118 as a procedural anticoagulant in Percutaneous Coronary Intervention.

PII-60

POPULATION PHARMACOKINETIC COMPARISON OF ENTERIC-COATED MYCOPHENOLATE SODIUM AND MYCOPHENOLATE MOFETIL IN RENAL TRANSPLANT RECIPIENTS. B. de Winter,¹ T. van Gelder,¹ K. Budde,² D. Cattaneo,³ H. Tedesco-Silva,⁴ I. Neumann,⁵ L. Hilbrands,⁶ R. van Hest,¹ M. Pescovitz,⁷ R. Mathot¹; ¹Erasmus MC, Rotterdam, The Netherlands, ²Humboldt University, Berlin, Germany, ³Mario Negri Institute for Pharmacological Research, Bergamo, Italy, ⁴Universidade Federal de Sao Paulo, Sao Paulo, Brazil, ⁵Wilhelminenspital, Vienna, Austria, ⁶St. Radboud University Hospital, Nijmegen, The Netherlands, ⁷Indiana University Medical Center, Indianapolis, IN

BACKGROUND: The population pharmacokinetics (PK) of mycophenolic acid (MPA) were compared in maintenance renal transplant patients following administration of mycophenolate mofetil (MMF) and the bioequivalent enteric-coated mycophenolate sodium (EC-MPS).

METHODS: 208 and 184 MPA concentration vs time profiles were available from EC-MPS and MMF treated patients, respectively, 4-257 months after transplantation. PK analysis was performed using NONMEM with first-order estimation. A two-compartment model with first order absorption and elimination was used to describe the data.

RESULTS: For the two formulations no differences were detected for MPA clearance, intercompartmental clearance, central and peripheral volume of distribution; respective values (+between-subject variability (BSV)) were: 16 L/hr (39%), 22 L/hr (78%), 40 L (100%) and 518 L (494%). The absorption rate was different: 3.0 and 4.1 hr⁻¹ for EC-MPS and MMF, respectively ($p < 0.001$), with equal BSV of 136%. In NONMEM it was not possible to obtain reliable estimates of the change-point parameter lag-time (Tlag) for EC-MPS; a mixture model for Tlag was used. Following the morning dose of EC-MPS Tlag was 0.95, 1.9 and 4.8 hr for 51%, 32% and 17% of the population (BSV 8%) which is significantly different from the Tlag of the evening dose of EC-MPS (9.0 hr, $p < 0.001$ (BSV 40%)) and the Tlag (morning+evening) observed after MMF administration (0.30 hr, $p < 0.001$ (BSV 11%)). Posthoc Tlag are given in fig 1.

CONCLUSION: Following EC-MPS administration absorption of MPA is slower and more delayed than following MMF administration, consistent with EC-MPS being a delayed release formulation. Further Tlag exhibits more BSV in EC-MPS treated patients. These findings indicate that determination of trough MPA concentrations in EC-MPS treated patients may not produce a reliable estimate for exposure.

PII-61

MODELING AND SIMULATION FACILITATED DESIGN OF AN ADAPTIVE PHASE 2 DOSE-FINDING STUDY FOR PD 0348292, A NOVEL FXA INHIBITOR. R. Boyd,¹ J. Mandema,² S. McBride,³ C. Spino,³ R. Abel,³ W. Gillespie,⁴ A. Hassan,³ L. DiCarlo³; ¹Pfizer, Groton, CT, ²Quantitative Solutions Inc., Menlo Park, CA, ³Pfizer, Ann Arbor, MI, ⁴Pharsight, Cary, NC

BACKGROUND: PD 0348292 (PD292) is an oral Factor Xa (FXa) inhibitor under development for prevention of venous thromboembolism (VTE) following orthopedic surgery. To design a Phase 2 study that would have a high probability of identifying a single Phase 3 dose while minimizing the risk to patients of excessive VTE or major bleeding (MB), dose-response (D-R) modeling and clinical trial simulations were used to leverage prior knowledge and evaluate alternative study designs.

METHODS: A database of study-level VTE and MB outcomes in hip and knee replacement surgery from the literature was used to characterize incidence of VTE and MB as a function of dose for 21 compounds via a logistic regression model that specified the same slope but different potencies across compounds. An in vitro biomarker assay was used to predict PD292 D-R relationships for VTE and MB via a PK/PD model that linked biomarker response to clinical outcome for 5 of these compounds. VTE and MB D-R relationships for PD292 estimated under the models were used to simulate the outcome of each trial design 1000 times. Acceptable trial performance required that a PD292 dose be identified with both VTE and MB rates similar (odds ratio ≤ 1.3) to the comparator (enoxaparin 30 mg BID) with a probability $\geq 80\%$.

RESULTS: There was considerable uncertainty in the VTE and MB D-R relationships for PD292 because no consistent biomarker scaling was found. Therefore, the recommended design was a 6-arm parallel group study (5 PD292 dose groups and 1 comparator group), with an adaptive dose range based on interim model-based D-R analyses of VTE and MB. Five initial PD292 doses (0.1 mg to 2.5 mg) were studied and 2 higher doses (4 mg and 10 mg) could be added if lower doses were pruned due to excessive VTE and/or the estimated MB rate at the higher dose was acceptable.

CONCLUSION: Modeling and simulation facilitated design of a Phase 2 study that permitted a 100-fold dose range to be safely explored and a Phase 3 dose to be selected with high precision.

PII-62

MULTIPLE-DOSE PHARMACOKINETICS OF THE DIRECT RENIN INHIBITOR ALISKIREN IN HEALTHY CHINESE SUBJECTS. M. Bartlett,¹ S. Vaidyanathan,² R. S. Karan,² P. Hu,³ D. Howard,⁴ C. M. Yeh,⁴ H. A. Dieterich,¹ S. Al-Fayoumi,⁴ V. Jarugula,⁴ W. P. Dole⁵; ¹Novartis Pharma AG, Basel, Switzerland, ²Novartis Healthcare Private Limited, Hyderabad, India, ³Peking Union Medical College Hospital, Beijing, China, ⁴Novartis Pharmaceuticals Corporation, East Hanover, NJ, ⁵Novartis Institutes for Biomedical Research Inc., Cambridge, MA

BACKGROUND: The pharmacokinetics of aliskiren (ALI), the first direct renin inhibitor approved to treat hypertension, have been extensively studied in non-Chinese subjects. However, drug disposition may vary between different ethnic groups. This single-blind study assessed the pharmacokinetics, safety and tolerability of multiple oral doses of ALI in Chinese subjects.

METHODS: Healthy Chinese subjects (ages 18-45 years) were randomized to a single 300 mg ALI dose (n=8) or placebo (n=2) on

Day 1. Subjects then received ALI 300 mg or placebo once-daily for 7 days (Days 5-11). Blood samples for determination of plasma ALI concentrations (LC-MS/MS) were taken pre-dose and at frequent intervals for 96 h post-dose (Days 1 and 11).

RESULTS: Steady-state pharmacokinetic parameters for ALI 300 mg in Chinese subjects were within the range reported in published studies in healthy non-Oriental subjects (Table). Based on trough plasma concentrations, steady state for ALI was reached after approximately 7 days and average accumulation (F) for ALI at steady state was 2-fold. Mean $t_{1/2}$ at steady state was 48.4 h. Mean $AUC_{0-\infty}$ after a single dose (1507 ng.h/mL) and AUC_{τ} at steady state (1532 ng.h/mL) were similar, suggesting that the pharmacokinetics of ALI 300 mg are time-independent in Chinese subjects. No adverse events were reported during ALI administration.

CONCLUSION: Aliskiren 300 mg exhibits similar steady-state pharmacokinetics in healthy Chinese and non-Oriental subjects.

Steady-state PK parameters following once-daily administration of aliskiren 300 mg for 7 days

Population	C_{max} (ng/mL)	t_{max} (h)	AUC_{τ} (ng.h/mL)
Chinese (n=8)	252 ± 158	1.3 (0.5-4.0)	1532 ± 592
Non-Oriental (n=112)	198-425	0.5-2.5	1110-2310

Data are shown as mean ± SD for C_{max} and AUC_{τ} , and median (minimum-maximum) for t_{max} . For non-Oriental subjects, data are shown as the range of mean or median parameters from published studies of aliskiren 300 mg at steady state.

PII-63

SINGLE-DOSE PHARMACOKINETICS OF THE DIRECT RENIN INHIBITOR ALISKIREN IN HEALTHY CHINESE SUBJECTS. M. Bartlett,¹ S. Vaidyanathan,² R. S. Karan,² P. Hu,³ D. Howard,⁴ C. M. Yeh,⁴ H. A. Dieterich,¹ S. Al-Fayoumi,⁴ V. Jarugula,⁴ W. P. Dole⁵; ¹Novartis Pharma AG, Basel, Switzerland, ²Novartis Healthcare Private Limited, Hyderabad, India, ³Peking Union Medical College Hospital, Beijing, China, ⁴Novartis Pharmaceuticals Corporation, East Hanover, NJ, ⁵Novartis Institutes for Biomedical Research Inc., Cambridge, MA

BACKGROUND: Aliskiren (ALI) is the first in a new class of orally effective direct renin inhibitors approved for the treatment of hypertension. ALI has previously been studied extensively in non-Chinese subjects. This study assessed the pharmacokinetics, safety and tolerability of single doses of ALI (75, 150, 300 and 600 mg) in healthy Chinese subjects.

METHODS: This was a randomized, single-blind, single-center, parallel-group study in 40 healthy Chinese subjects, ages 18-45 years. Subjects received a single dose of ALI (75, 150, 300 or 600 mg; n = 8 per group) or placebo (n = 2 per group). Plasma concentration measurements of ALI (LC-MS/MS) were determined before and at frequent intervals during 96 hours after dosing.

RESULTS: ALI was absorbed rapidly after administration of a single oral dose (75-600 mg); C_{max} was attained within 2 h (median t_{max} , 0.5-2.0 h). The mean elimination half-life of ALI was similar across doses (mean $t_{1/2}$, 29-39 h). Over the 75-600 mg dose range, ALI exposure ($AUC_{0-\infty}$ and C_{max}) increased more than proportionately; however, doubling the dose of ALI from 150 to 300 mg (approved therapeutic doses) increased exposure by approximately 2-fold. ALI exposure was slightly higher in Chinese subjects than in a study of predominantly Caucasian subjects (Table), but for the 150 and 300 mg doses was generally within the range observed for mean $AUC_{0-\infty}$ (388-663 and 1274-1714 ng.h/mL, respectively) and C_{max} (72-148 and 134-306 ng/mL, respectively) in published single-dose studies in Caucasians. No adverse events were reported in the present study.

CONCLUSION: Aliskiren exhibits similar single-dose pharmacokinetics within the approved therapeutic dose range (150 and 300 mg) in healthy Chinese and Caucasian subjects.

Table. Single-dose pharmacokinetics of aliskiren in Chinese and Caucasian subjects

Parameter	Chinese subjects				Caucasian subjects			
	Aliskiren 75 mg (n=8)	Aliskiren 150 mg (n=8)	Aliskiren 300 mg (n=8)	Aliskiren 600 mg (n=8)	Aliskiren 75 mg (n=30)	Aliskiren 150 mg (n=30)	Aliskiren 300 mg (n=30)	Aliskiren 600 mg (n=30)
C_{max} (ng/mL)	62 ± 42	137 ± 115	271 ± 179	699 ± 308	26 ± 31	72 ± 62	202 ± 119	420 ± 325
t_{max} (h)	0.5(0.5-4.0)	2.0(0.5-6.0)	0.8(0.5-6.0)	1.0(0.5-2.0)	1.0(1.0-8.0)	2.5(1.0-8.0)	3.0(1.0-4.1)	2.0(1.0-4.0)
$AUC_{0-\infty}$ (ng.h/mL)	291 ± 193	876 ± 488	1507 ± 840	4726 ± 1526	356 ± 217 [†]	627 ± 401 [‡]	1620 ± 895	3520 ± 2130
$t_{1/2}$ (h)	36 ± 11	39 ± 10	38 ± 8	29 ± 5	54 ± 16 [†]	41 ± 11 [‡]	37 ± 8	34 ± 7

Data are shown as mean ± SD, except for t_{max} , which are shown as median (range). $AUC_{0-\infty}$, total area under the plasma concentration time-curve; C_{max} , maximum plasma concentration; t_{max} , time to reach C_{max} ; $t_{1/2}$, elimination half-life. [†]n = 23, [‡]n = 29.

PII-64

USE OF PHARMACOKINETIC/PHARMACODYNAMIC (PKPD) MODELING FOR STARTING DOSE SELECTION IN FIRST-IN-HUMAN TRIALS WITH HIGH-RISK MONOCLONAL ANTIBODIES. B. M. Agoram, S. W. Martin, J. Davis; Pfizer, Inc., Sandwich, United Kingdom

BACKGROUND: Recent regulatory guidance documents highlight the importance of PKPD modeling in the selection of safe starting doses resulting in minimum anticipated biological effect level (MABEL) for monoclonal antibodies (mAb). However, there are limited literature examples on the use of PKPD modelling to select a MABEL dose.

Objectives:

- To demonstrate, using literature data on two mAbs, how mechanistic PKPD models can be used to calculate MABEL doses using predicted maximum receptor occupancy (mRO) as biomarker.
- To evaluate the impact of PK and in vitro affinity changes on mRO and demonstrate how this relationship can impact MABEL dose selection.

METHODS: Literature-reported PKPD parameter estimates of an IgE mAb¹, and a CD4 mAb² were gathered. These models accounted for mAb PK, antigen turnover, and antigen-mAb complex formation and turnover. Simulations were performed to characterise the dose vs mRO profiles for the two mAbs. The effect of changes in affinity and PK parameters on the dose vs mRO profile was investigated through sensitivity analyses.

RESULTS:

- Mechanistic PKPD models were useful in characterising the dose vs mRO profile and hence for the rational selection of MABEL doses.
- In both case studies, the relationship between in vitro affinity and in vivo efficacy was nonlinear - magnitude increase in affinity did not necessarily equate magnitude increase in mRO.

CONCLUSION:

- Mechanistic PKPD models are capable of accounting for competing *in vivo* interactions to accurately predict *vivo* mRO, and as such should be preferred to more empirical calculations wherever possible.
- Antigen and antigen-mAb complex dynamics result in nonlinear affinity-mRO relationships. Thus, when selecting starting doses, it is important to consider these factors as the use of simple potency estimates such as Kd may lead to overly-conservative dose selection.

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2. Ng et al. (2006) Pharm. Res. 23(1), 95-103

P11-65

A NON-PARAMETRIC METHOD TO ANALYSE EFFECT VS TIME PROFILES IN THE ABSENCE OF PHARMACOKINETIC (PK) DATA. B. M. Agoram, P. A. Milligan, P. H. van der Graaf; Pfizer, Inc., Sandwich, United Kingdom

BACKGROUND: Inhaled bronchodilators are commonly used in asthma and chronic obstructive pulmonary disease and remain attractive mechanistic approaches for improved therapy. However, the mechanisms that contribute to their different *in vivo* duration of action - lung PK and/or PD - are not fully understood. We aim to (a) illustrate a novel non-parametric method of analysing *in vivo* efficacy vs time profiles to infer differences in mechanisms of duration of action and (b) To apply this method to data gathered on inhaled bronchodilators.

METHODS: We hypothesised that for compounds that do not differ in their PK at the site of pharmacodynamic (PD) action, but differ in their *in vivo* potencies, the relationship between the area under the effect curve (AUEC) and the observed maximum effect (MAXE) at different doses is described by the same sigmoid curve. Conversely, different AUEC vs MAXE plots for compounds with potency differences would suggest differences in their PK at the site of action. We verified this hypothesis by obtaining the analytical solution and through simulations for multiple PKPD models. We applied this methodology to in-house lung resistance data obtained for 6 inhaled bronchodilators at multiple dose levels in dogs.

RESULTS: AUEC vs MAXE plots were derived from dog PD data for all compounds. Linear and curvilinear relationships were fitted to all data. All data could be described by 2 distinct sets of model parameters suggesting the existence of 2 sets of compounds with PK differences.

CONCLUSION: We have illustrated a non-parametric method of analysing effect vs time data for different compounds to infer differences in their *in vivo* mechanisms of action. We applied this method to data obtained on inhaled bronchodilator candidates to differentiate them. This method is useful in other cases where site of action PK is either not obtainable or is not sufficiently represented by blood PK - e.g. where drug is administered directly to the site of action.

P11-66

THE POPULATION PHARMACOKINETICS (PK) OF TORCE-TRAPIB (TOR) IN ADULT SUBJECTS. C. Cronenberg, K. Diring Getz, M. Riggs, T. Tensfeldt, J. Revkin, C. Shear¹; ¹Pfizer, Inc., Groton, CT, ²Metrum Research Group LLC, Tariffville, CT

BACKGROUND: The purpose of this work was to develop a population-based model to describe the PK of TOR.

METHODS: Pooled TOR plasma concentration data from 1550 adults with varying extent of cardiovascular disease, enrolled in Phase 2/3 outpatient studies, and treated with 60 mg QD TOR for up to 1 year were analyzed using a nonlinear mixed-effects modeling approach with NONMEM (version V, level 1.1). Dichotomous (sex, race, disease state: homozygous familial hypercholesterolemia, Frederickson Types IIa and IIb) and continuous (age, body weight: BW, triglyceride concentration: TRIG) covariates were added to the model simultaneously. Model performance was evaluated via diagnostic plots, a non-parametric bootstrap and a predictive check.

RESULTS: TOR PK were described by a two-compartment model (2COM) with first-order elimination and dual absorption processes (first-order and zero-order). Population parameter estimates (95% confidence interval) for a typical individual (Caucasian, male, 85.5 kg, 55 yr old, TRIG of 125 mg/dL, elevated LDL-cholesterol) were 20.4 (18.5, 22.2) L/hr for apparent oral clearance (CL/F), 120 (104, 137) L for central volume of distribution (V₂/F), 25.1 (19.4, 29.8) L/hr for inter-compartmental clearance (Q/F), and 5430 (4312, 6176) L for peripheral volume of distribution (V₃/F). Absorption rate constant, relative bioavailability, and absorption lag time parameters were fixed. Inter-individual variances were estimated for CL/F, V₂/F, Q/F and V₃/F. The residual error model consisted of one additive and two proportional variance components. Disease state contributed to variability in CL/F. CL/F increased with increasing BW and decreased with increasing age and TRIG. Q/F, V₂/F and V₃/F decreased with increasing TRIG.

CONCLUSION: A 2COM with first-order elimination and dual absorption processes describe the PK of TOR. Variability in CL/F was explained by disease state, age, BW, and TRIG, while TRIG appeared to influence V₂/F, V₃/F and Q/F.

P11-67

DUAL CONTRIBUTION OF CYTOCHROMES P450 (CYP) 2D6 AND 3A4 TO THE ORAL CLEARANCE OF AN NK1 ANTAGONIST. C. Cronenberg, K. Venkatakrishnan, R. Obach; Pfizer, Inc., Groton, CT

BACKGROUND: This work elucidates the clinical pharmacokinetic (PK) correlates of CP-122,721 (CP) metabolism by CYPs 2D6 and 3A4 using pharmacogenomic (PG) and drug-drug interaction (DDI) approaches.

METHODS: The PK of CP were characterized after single (1-500 mg) and multiple (3-100 mg BID) oral doses to CYP2D6 extensive metabolizers (EM). The contributions of CYP2D6 at 10-100 mg QD CP doses were determined in EM/poor metabolizer (PM) PK studies and a DDI study with paroxetine (PX; 20 mg/d) using a multiple ascending dose design. The effect of the CYP3A4 inhibitor, ketoconazole (KT; 400 mg/d), on CP PK was explored in EM (30 mg BID) and PM (15 mg QD).

RESULTS: Supra-proportional increases in CP exposures in EM were observed after single doses (SD) >50 mg and multiple doses (MD) >10 mg BID. Steady-state (SS) CP exposures in PM were greater than in EM at all doses (by 9-fold at 10 mg QD to 2-fold at 100 mg QD), but the estimated contribution of CYP2D6 in EM decreased with ascending dose, ranging from ~88% at 10 mg QD to ~49% at 100 mg QD. PX increased CP exposures in EM, with DDI magnitude decreasing with CP dose. KT produced a >4-fold increase in steady-state CP exposures in both EM and PM, which was much larger than expected (~1.3-fold) in EM based on the estimated contribution (~77%) of CYP2D6 at 30 mg BID. The clinical results for CP were generally consistent with *in vitro* data, which indicated a high affinity for CYP2D6 (K_M 0.24 μM) and low affinity for CYP3A4 (K_M 30 μM).

CONCLUSION: Dose-dependencies in CP PK and the PX DDI magnitude in EM, and the PM/EM exposure ratio, indicate saturation of CYP2D6. CYP3A4, probably intestinal, also appeared to play a major role in the metabolism of CP in EM and PM. This case illustrates that for drugs metabolized by both CYPs 2D6 and 3A4, the inference of a sizeable CYP2D6 contribution from clinical PG and/or DDI data does not necessarily rule out a significant interaction with CYP3A inhibitors as well, with implications for clinical DDI strategies in drug development.

P11-68

EVALUATING INFLUENCE OF HERBAL MEDICINES ON HUMAN CYTOCHROME P450 ACTIVITIES BY A COCKTAIL APPROACH: *ANGELICAE TENUISSIMA*, *ANGELICAE DAHURICAE*, *SCUTELLARIAE BAICALENSIS*. S. J. Yi, K. S. Lim, J. H. Hong, J. Y. Cho, I. J. Jang, S. G. Shin, K. S. Yu¹; ¹Seoul National University College of Medicine and Hospital, Seoul, Republic of Korea, ²Department of Pharmacology, College of Medicine, Chungnam National University, Daejeon, Republic of Korea

BACKGROUND: We investigated the effect of herbal medicines on human cytochrome P450 (CYP) activities. Three kinds of herbal medicines, *Angelicae tenuissima*, *Angelicae dahuricae* and *Scutellariae baicalensis* were evaluated, since they have been frequently used in traditional Oriental medicine.

METHODS: A total of 24 healthy male subjects were assigned to three parallel treatment groups; A. *tenuissima*, A. *dahuricae* or S. *baicalensis* were given to 8 subjects for each group. A cocktail of probe drugs for CYP enzymes was orally administered before and after herbal medicine administration three times a day for 13 days. Probe drugs used to measure activities of CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP2C9 were omeprazole 40 mg, dextromethorphan 30 mg, chlorzoxazone 400 mg, midazolam 7.5 mg and losartan 50 mg, respectively. The probe drugs and their metabolites were quantified in plasma or urine. Changes in CYP activities were evaluated by metabolic ratios of the probe drugs at reference time points following the herbal medication period, compared to the baseline values.

RESULTS: CYP activities were not meaningfully influenced by *A. tenuissima* or *A. dahuricae*. However, *S. baicalensis* showed significant decrease in CYP3A4 and CYP2C9 activities. Compared to baseline values, the metabolic activities (95% confidence intervals) were decreased to 63% (0.40 - 0.99; P=0.046) for midazolam (CYP3A4) and 71% (0.54-0.94; P=0.024) for losartan (CYP2C9). In addition, *S. baicalensis* showed a 1.28-fold (0.95 - 1.73; P=0.088) increase in chlorzoxazone metabolic activity (CYP2E1).

CONCLUSION: Herbal medicines containing *Scutellariae baicalensis* are candidates for further evaluation of clinically significant CYP-mediated herb-drug interactions in humans.

PII-69

DISPOSITION AND MASS BALANCE OF ¹⁴C-VERNAKALANT AFTER SINGLE INTRAVENOUS AND ORAL DOSES IN HEALTHY VOLUNTEERS. Z. L. Mao,¹ A. Alak,¹ J. J. Wheeler,² J. Keirns¹; ¹Astellas Pharma US, Inc., Deerfield, IL, ²Cardiome Pharma Corp., Vancouver, BC, Canada

BACKGROUND: Vernakalant hydrochloride (VNK) prolongs atrial refractoriness and rapidly converts atrial fibrillation to sinus rhythm. This study evaluated the disposition and mass balance of single intravenous (IV) and oral doses of VNK in subjects who were either extensive (EM) or poor (PM) CYP2D6 metabolizers.

METHODS: Eight healthy men (median age, 32 y) received ¹⁴C-VNK 240 mg (specific activity, 0.329 μ Ci/mg) via 10-min IV infusion on day 1 and orally on day 22 in an open-label, crossover study. Blood, urine, and fecal samples were collected for 7 d for metabolic profiling by validated LC/MS/MS and for total ¹⁴C determinations.

RESULTS: Of the 8 subjects, 5 were EMs and 2 were PMs; 1 was an intermediate metabolizer and is excluded from this analysis. The disposition and metabolic profile of VNK were qualitatively similar after IV and oral dosing and dependent on CYP2D6 genotype. C_{max} with IV VNK was unaffected by genotype due to rapid and extensive redistribution. VNK was metabolized rapidly and extensively, predominantly to a 4-O-demethylated metabolite with subsequent glucuronidation in EMs, and predominantly via direct glucuronidation in PMs. Clearance of VNK was slower in PMs than EMs (CL, 19.8 vs 64.9 L/h; t_{1/2}, 5.7 vs 2.2 h), resulting in 3- and 6-times greater AUC_{0-∞} after IV and oral dosing, respectively. Recovery of urinary metabolites supported the metabolic profile in plasma, with higher levels of unchanged VNK in PMs than EMs (IV: 22.6% vs 8.5%; oral: 21.9% vs 3.5%). Total ¹⁴C was recovered mainly in urine (IV: 92.9%; oral: 91.4% in EMs) with lower levels in feces (7.3% and 7.7%). Mass balance was achieved in EMs with mean recovery of 99.7% and 98.7% of the IV and oral dose, respectively. VNK was well tolerated.

CONCLUSION: The elimination t_{1/2} and AUC_{0-∞} of VNK depend on CYP2D6 genotype, but C_{max} is similar between EMs and PMs due to rapid and extensive redistribution. Thus, acute exposure with short-term use of IV VNK appeared unaffected by genotype in this study.

PII-70

INFLUENCE OF CYP2D6 GENOTYPE ON THE PHARMACOKINETICS OF VERNAKALANT HYDROCHLORIDE INJECTION (RSD1235), A NOVEL ATRIAL-SELECTIVE ANTIARRHYTHMIC. Z. L. Mao,¹ L. Clohs,² J. J. Wheeler,² G. N. Beach,² J. Keirns¹; ¹Astellas Pharma US, Inc., Deerfield, IL, ²Cardiome Pharma Corp., Vancouver, BC, Canada

BACKGROUND: Vernakalant hydrochloride, a novel, relatively atrial-selective antiarrhythmic, is predominantly metabolized by 4-O-demethylation via cytochrome P450 (CYP) 2D6. This study explored the influence of CYP2D6 genotype and pharmacological inhibition on vernakalant pharmacokinetics in patients with atrial fibrillation (AF) or atrial flutter (AFL) from 2 phase 3 clinical trials.

METHODS: Patients with AF or nontypical AFL (ACT I) or typical AFL (Scene 2) lasting >3 h to \leq 45 d were randomly assigned in a 2:1 ratio to vernakalant or placebo in 2 multicenter studies. Vernakalant 3 mg/kg was given via 10-min IV infusion, and if arrhythmia persisted after a 15-min observation, a second 10-min infusion of 2 mg/kg was given. Plasma concentrations of vernakalant were determined by

validated LC/MS/MS, and CYP2D6 genotype by single nucleotide polymorphism analysis by real-time PCR.

RESULTS: Most patients given vernakalant received 2 infusions [n=148 (67%) in ACT I; n=34 (87%) in Scene 2]. Others demonstrated conversion to sinus rhythm or discontinued treatment after 1 infusion. Vernakalant showed rapid redistribution following infusion. The vernakalant C_{max} was reached after the first or second infusion among patients receiving 1 or 2 infusions, respectively, with exposure over the first 90 min (AUC₀₋₉₀) generally proportional to dose. Little difference in vernakalant C_{max} and AUC₀₋₉₀ was seen between CYP2D6 poor (PMs, n=6) and extensive metabolizers (EMs, n=138) who received 2 infusions: the PM/EM ratios (95% CI) of the geometric mean C_{max} and AUC₀₋₉₀ were 98.3% (72.7-133%) and 113.5% (85.3-150.9%), respectively. Similar results were seen for comparisons between patients who did and did not receive concomitant CYP2D6 inhibitors.

CONCLUSION: Vernakalant exposure was not enhanced in PMs. This is likely due to rapid distribution and a large V_{ss}, which are independent of metabolism.

PII-71

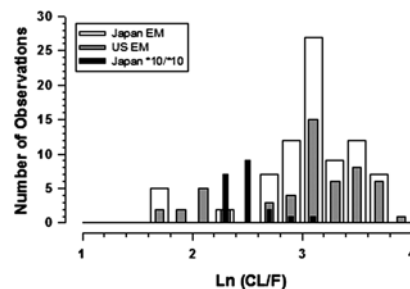
PHARMACOKINETICS OF ATOMOXETINE AND EFFECT OF CYP2D6*10/*10 GENOTYPE IN JAPANESE ADULTS. J. W. Witcher, PhD,¹ A. Long, BS,¹ J. Sauer, PhD,¹ B. P. Smith, PhD,¹ K. A. DeSante, PhD,¹ A. Matsui, PhD,² M. Takahashi, MD, PhD,² M. Nakano, MD, PhD²; ¹Eli Lilly and Company, Indianapolis, IN, ²Eli Lilly and Company, Kobe, Japan

BACKGROUND/AIMS: The major metabolic pathway for atomoxetine is CYP2D6, therefore a potential for ethnic differences due to varying CYP2D6 polymorphisms exists. This study was designed to evaluate atomoxetine pharmacokinetics, effect of intermediate metabolizer CYP2D6*10/*10 genotype (common in Japan), dose proportionality, and safety in Japanese adult subjects after single dose and steady-state. A cross-study comparison with a US study (mostly Caucasian) was performed to evaluate ethnic differences.

METHODS: Part A: single-blind, placebo-controlled, single-dose escalation from 10 to 120 mg (n=23). Part B: single-blind, placebo-controlled, multiple-dose design of 40 mg or 60 mg BID for 7 days (n=26). Noncompartmental analysis was performed. Safety assessments included AEs, pulse rate, blood pressure, orthostatic measures, and ECG. Comparisons of Japanese data to US extensive metabolizer (EM) data from a similar study design were made.

RESULTS: Dose proportionality was shown in Japanese subjects. The pharmacokinetics, distribution of clearance (CL/F) values, and urinary metabolite profile for Japanese and US subjects were similar with a slight shift toward lower CL/F values for *10/*10 subjects. While subjects with the *10/*10 genotype had a 23-30% higher C_{max} and a 62-87% higher AUC_{0-∞} on average, their plasma concentrations and CL/F values were within the overall range of Japan EM subjects. The frequency, severity, and type of AEs reported by *10/*10 subjects were indistinguishable from other subjects. Safety assessment results were similar for both studies.

CONCLUSIONS: Atomoxetine pharmacokinetics, safety, and tolerability were similar in Japanese and US subjects and showed no clinically meaningful ethnic differences. The CYP2D6*10/*10 genotype did not have a clinically meaningful effect on pharmacokinetics or safety.



PII-72

INFLUENCE OF THE BETA ADRENERGIC RECEPTOR (AR) GENETIC POLYMORPHISMS ON THE PHARMACODYNAMICS OF SEVOFLURANE. S. Jang,¹ D. Han,² K. Park¹; ¹Yonsei University College of Medicine, Seoul, Republic of Korea, ²Yongdong Severance Hospital, Seoul, Republic of Korea

BACKGROUND: To investigate whether functionally important polymorphisms of β_1 -AR and β_2 -AR gene would influence pharmacodynamics in patients after general anesthesia with sevoflurane

METHODS: Ninety ASA physical status I and II patients underwent slow inhalation induction of anesthesia, with a face mask, using sevoflurane in 100% oxygen. After the induction, anesthesia was maintained with sevoflurane and ventilation was assisted by the face mask at the end-tidal concentration of 2.5% sevoflurane to provide an adequate depth of anesthesia. Heart rate, QT intervals (QT_b, QT_h, and QT_f), and blood pressures (SBP, DBP, and MBP) were obtained as pharmacodynamic parameters of sevoflurane. Ser49Gly, Gly389Arg genotypes of β_1 -AR, and Arg16Gly, Gln27Glu, Thr164Ile genotypes of β_2 -AR were determined by polymerase chain reaction using restriction fragment length polymorphism analysis.

RESULTS: On the average, the homozygous patients for the Ser49Gly genotype showed a greater decrease of heart rate in comparison to the patients with the heterozygous genotype (13.1 vs. 5.6 beats/min, $p=0.0271$). The heterozygous patients for the Arg16Gly genotype showed a greater decrease of DBP in comparison to the patients with AA or GG genotype (15.2 vs. 19.9 mmHg, $p=0.0118$). Three genotypes (AA, GA, GG) for Arg16Gly showed a statistically significant difference in a decrease of heart rate (10.8, 13.7 and 7.1 beats/min, respectively, $p=0.0146$). No differences were found among the Gly389Arg genotypes of β_1 -AR, and the Gln27Glu of β_2 -AR. All patients had only the wild type for the Thr164Ile genotype of β_2 -AR.

CONCLUSION: This study shows that the beta adrenergic receptor genetic polymorphisms may be associated with the pharmacodynamics of sevoflurane. Individualized dosage regimen design incorporating such genetic information would help provide better clinical effects of the drug.

PII-73

HEPATIC ABC DRUG TRANSPORTERS ARE DOWNREGULATED IN AN EXPERIMENTAL RODENT MODEL OF DIABETES. G. J. Anger, L. Magomedova, M. Piquette-Miller; Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada

BACKGROUND: Recent literature suggests that diabetes is associated with an inflammatory response in humans and rodents. Inflammatory responses, characterized by elevated pro-inflammatory cytokines, have been linked to changes in hepatic drug transporter expression. Hepatobiliary drug excretion is governed largely by ATP binding-cassette (ABC) transporters such as P-glycoprotein (Mdr1a/b), breast cancer resistance protein (Bcrp) and multidrug resistance-associated proteins (Mrps). The purpose of this study was to determine if streptozotocin (STZ)-induced diabetes alters the hepatic expression of these ABC drug transporters.

METHODS: Diabetes was induced in rats by injection of STZ (45 mg/kg, sc). Control rats received vehicle alone. Blood glucose was monitored daily. Diabetic and control rats were sacrificed on day 9 and plasma and livers were collected. Real-time PCR was used to examine Bcrp, Mdr1a/b and Mrp1-3 mRNA in liver. Levels of the pro-inflammatory cytokines TNF- α and IL-6 were determined by ELISA.

RESULTS: STZ-injected rats became diabetic (>15 mmol/l) within 48 hrs. Real-time PCR results indicated that there was a significant decrease in the hepatic expression of Bcrp and Mrp2 in diabetic rats as compared to controls. A trend toward decreased expression in diabetic rats was also evident with Mdr1a mRNA. TNF- α levels were below detection in plasma for both groups while levels in liver were similar. Relative to controls, IL-6 levels in diabetic rats were elevated in plasma and liver. The IL-6 plasma difference was statistically significant while that in liver approached significance.

CONCLUSION: Experimental diabetes significantly downregulated the mRNA expression of Bcrp and Mrp2 in rat liver. This would likely translate into decreased elimination of substrates that utilize the bile route. Elevated IL-6 levels in diabetic rat plasma samples provide one possible explanation for altered expression.

PII-74

THE EFFECT OF CYP2D6 GENETIC POLYMORPHISMS ON THE DISPOSITION OF TOLTERODINE IN THE KOREAN HEALTHY SUBJECT. S. Park, C. Yeo, J. Shon, W. Kim, S. Lee, K. Liu, J. Shin; Inje University College of Medicine, Busan, Republic of Korea

BACKGROUND: CYP2D6 genetic polymorphisms are known to influence the clinical outcome as well as the disposition of CYP2D6 substrate drugs, and the composition of CYP2D6 genotype is different among ethnics. The disposition of tolterodine, a substrate of CYP2D6, was evaluated in relation to CYP2D6 genetic polymorphisms in Korean healthy subjects.

METHOD: A single oral dose of 2mg tolterodine was given to 20 Korean healthy male and 4 female subjects whose CYP2D6 genotypes were predetermined: 3 subjects with CYP2D6*1/*1, 11 with CYP2D6*1/*10B, 7 with CYP2D6*10B/*10B and 3 with CYP2D6*5/*10B, respectively. The plasma concentrations of tolterodine were monitored up to 12 hours, and pharmacokinetic parameters were estimated with using WinNonlin[®].

RESULT:

	*1/*1 (n=3)	*1/*10B (n=11)	*10B/*10B (n=7)	*5/*10B (n=3)
T _{1/2} (hr)	3.41 ± 1.68	2.63 ± 0.59	3.15 ± 0.80	4.18 ± 0.36
T _{max} (hr)	0.89 ± 0.19	1.30 ± 1.57	0.91 ± 0.50	1.50 ± 0.50
C _{max} (ng/ml)	1.37 ± 0.86	4.54 ± 4.80	7.76 ± 3.44	12.85 ± 7.35
AUC _t (hr*ng/ml)	4.05 ± 2.63	15.39 ± 18.59	29.22 ± 12.89	46.34 ± 17.52
AUC _{inf} (hr*ng/ml)	4.68 ± 2.51	16.70 ± 20.87	31.97 ± 14.03	55.16 ± 21.63

CONCLUSION: There were significant differences on the disposition of tolterodine in relation to CYP2D6 genotype, especially in subjects with CYP2D6*10B and *5 allele. The mean pharmacokinetic parameter (C_{max} and AUC_{inf}) of tolterodine were twofold and sevenfold higher ($p<0.05$) in subjects with CYP2D6*10B/*10B than those with CYP2D6*1/*10B and CYP2D6*1/*1. CYP2D6*10B allele found frequently in a Korean population showed the significant effect on the disposition of tolterodine and may influence to its clinical outcome.

PII-75

MDR1 HAPLOTYPE DEPENDENT EFFECT ON CLOXACILLIN PHARMACOKINETICS IN HUMAN SUBJECTS. O. Q. Yin, PhD,¹ B. Tomlinson, MD,² Z. Wang, MS,¹ M. S. Chow, PharmD¹; ¹School of Pharmacy, the Chinese University of Hong Kong, Shatin, Hong Kong, ²Dept. of Medicine and Therapeutics, the Chinese University of Hong Kong, Shatin, Hong Kong

BACKGROUND: The plasma cloxacillin concentrations in human subjects has shown as much as 20-fold inter-individual variation following the same oral dose. One of the contributing factors for this marked variability may be polymorphisms in the P-glycoprotein (P-gp) MDR1 gene, since recent studies appear to suggest that cloxacillin is a substrate of P-gp. The purpose of this study is to investigate the effect of MDR1 polymorphisms on cloxacillin pharmacokinetics in healthy Chinese subjects.

METHODS: A single oral 500 mg cloxacillin was administered to 18 healthy Chinese subjects under fasting conditions. Multiple blood and urine samples were collected up to 8 hours post-dose, and

cloxacillin concentrations were determined by an HPLC method. Genotyping of MDR1 exon 12 1236C>T, exon 21 2677 G>T and exon 26 3435 C>T SNPs were performed using polymerase chain reaction method.

RESULTS: Four haplotypes were identified among the study subjects, 1236C/2677G/3435C (CGC, n=4), 1236T/2677G/3435C (TGC, n=6), 1236T/2677T/3435C (TTC, n=2) and 1236T/2677T/3435T (TTT, n=6). The peak plasma concentrations (C_{max}) of cloxacillin were 6.3 ± 2.6 , 14.3 ± 5.1 , 11.4 ± 4.4 and 13.1 ± 3.4 $\mu\text{g/ml}$, and the area under the plasma concentration-time curve (AUC) were 12.8 ± 4.3 , 23.3 ± 6.3 , 18.8 ± 5.0 and 20.7 ± 6.4 $\mu\text{g}\cdot\text{hr/ml}$ respectively, for subjects with CGC, TGC, TTC and TTT haplotypes ($p=0.013$ and 0.030 respectively, for homozygous wild-type CGC haplotype compared to other haplotypes). No significant differences were observed in the elimination half-life or renal clearance of cloxacillin among the different haplotype groups.

CONCLUSION: MDR1 haplotype appears to be an important factor contributing to the inter-individual differences in cloxacillin plasma exposure by affecting the oral absorption but not renal clearance of cloxacillin in human subjects.

P11-76

LIVER X RECEPTOR- α GENE VARIABILITY AND CARDIOVASCULAR RISK IN THE INTERNATIONAL VERAPAMIL SR/TRANDOLAPRIL STUDY - GENETIC SUBSTUDY (INVEST-GENES). E. T. Price,¹ M. Martin,¹ M. Pacanowski,¹ R. M. Cooper-Dehoff,² C. J. Pepine,² J. A. Johnson,¹ I. Zineh¹; ¹University of Florida College of Pharmacy, Gainesville, FL, ²University of Florida College of Medicine, Gainesville, FL

BACKGROUND: Liver X receptor- α (LXRA) is a transcription factor that regulates genes important in cholesterol homeostasis and inflammation. A synonymous C>T single nucleotide polymorphism (SNP) in an exonic region of the LXRA gene, rs2279238, has been previously associated with metabolic phenotypes. We investigated whether rs2279238 genotype was associated with cardiovascular outcomes in people with hypertension and cardiovascular disease.

METHODS: INVEST participants were randomized to either atenolol or verapamil-SR-based treatment algorithms for blood pressure control. 1032 subjects were selected for genotyping from the INVEST-GENES case-control, comprised of 258 cases matched 3:1 with event-free controls by age, sex, and race. A composite endpoint of all-cause death, nonfatal MI, and nonfatal stroke was used to define cases. Adjusted odds ratios (OR) were calculated using logistic regression.

RESULTS: 1004 subjects were successfully genotyped. rs2279238 genotype was significantly associated with the odds of a cardiovascular event ($p=0.017$). This observation was driven by T/T carriers (OR=2.4; $p=0.005$) as C/T carriers had no increased risk (OR=1.1; $p=0.617$). The T/T genotype was also associated with variable risk of outcome based upon treatment strategy (verapamil SR vs atenolol). In the verapamil SR treatment strategy patients, the presence of the T allele was associated with increased risk for a primary event (C/T vs. C/C OR=1.89, $p=0.012$, T/T vs. C/C OR=4.1, $p=0.001$). There were no pharmacogenetic associations in the atenolol treatment strategy patients (C/T vs. C/C OR=0.688, $p=0.146$, T/T vs. C/C OR=1.6, $p=0.276$).

CONCLUSION: The T allele of rs2279238 was predictive of risk in those randomized to the verapamil SR based treatment strategy. This novel finding suggests LXRA is a genetic/pharmacogenetic target that should be further explored.

P11-77

FENOFIBRATE ATTENUATES INTERLEUKIN-1 β -STIMULATED RANTES (CCL5) PRODUCTION IN THE HUMAN ENDOTHELIUM. E. T. Price, G. Welder, I. Zineh; University of Florida College of Pharmacy, Gainesville, FL

BACKGROUND: RANTES (CCL5) is a chemokine implicated in many diseases with an inflammatory component, including cardiovascular disease. Endothelial RANTES expression is highly inducible by

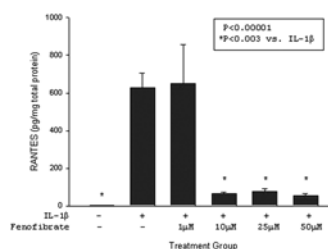
inflammatory proteins such as IL1 β . Fibrates are a class of lipid-lowering drugs with anti-inflammatory effects. Their ability to affect IL-1 β mediated endothelial RANTES expression is unknown. We examined the effects of fenofibrate on the production of this chemokine.

METHODS: Human umbilical vein endothelial cells (HUVECS) were cultured and treated with IL-1 β (2ng/mL) to induce an inflammatory response, and with fenofibrate 1-50 μM . RANTES production was measured in the cell culture supernate by cytometric immunofluorescence. ANOVA with post-hoc Tukey was performed, and significance was set at $P<0.05$.

RESULTS: As expected, RANTES production was significantly induced by IL-1 β . In cells treated with IL-1 β alone the production of RANTES was over 200 times higher than control (mean \pm SEM=2.66 \pm 0.523 pg/mg vs 628.4 \pm 75 pg/mg, $p<0.001$). Fenofibrate significantly reduced production of RANTES at concentrations 10-50 μM (Figure).

CONCLUSION: Endothelial RANTES was induced by IL-1 β , and this process was modulated by fenofibrate. The clinical significance of these findings should be further explored.

Fenofibrate attenuates IL-1 β -induced RANTES production in a dose-dependent fashion



P11-78

EFFECT OF CYTOCHROME P450 3A5*3 GENOTYPE ON THE STEREOSELECTIVE PHARMACOKINETICS OF AMLODIPINE IN HEALTHY SUBJECTS. K. Kim,¹ P. Park,² J. Park¹; ¹Dept. of Clinical Pharmacology and Toxicology, Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea, ²Dept. of Laboratory Medicine, Gil Hospital, Gachon Medical School, Incheon, Republic of Korea

BACKGROUND: Amlodipine, a dihydropyridine class calcium channel blocker, is a racemic mixture composed of S- and R-form and both form is metabolized stereoselectively. Cytochrome P450 3A (CYP3A) including CYP3A4 and CYP3A5 are involved in the metabolism of amlodipine and it was reported that polymorphic CYP3A5 genotype modulates the plasma levels of amlodipine and thus affects its pharmacokinetic characteristics. This study was conducted to find whether stereoselective pharmacokinetics of amlodipine was affected by the polymorphic CYP3A5 genotypes.

METHODS: Seventeen healthy male subjects were enrolled and genotype for CYP3A5*3 variant. After a single oral dose of 10-mg amlodipine to subjects, each enantiomers of amlodipine were analyzed using HPLC-MS/MS equipped with an AGP column.

RESULTS: Among them, seven subjects are CYP3A5*1/*3 carriers and other ten subjects are CYP3A5*3/*3 carriers. Pharmacokinetically, amlodipine showed stereoselective pharmacokinetics and S-amlodipine exhibited higher plasma levels than R-amlodipine in both genotype groups. CYP3A5*1/*3 carriers had 21% and 15% higher peak plasma concentrations of R- and S-amlodipine than CYP3A5*3/*3 carriers, respectively. CYP3A5*1/*3 carriers also have 23% and 12% higher area under the time versus concentration curve (AUC) values of R- and S-amlodipine than CYP3A5*3/*3 carriers, respectively. However, all pharmacokinetic parameters did not show any statistically significant difference.

CONCLUSION: The present study showed that despite the evidence that amlodipine is stereoselectively metabolized and CYP3A5*3 genotype affects pharmacokinetics of racemic amlodipine, CYP3A5*3 genotype did not affect stereoselective disposition of amlodipine in healthy subjects.

PII-79

A NOVEL CYP2D6 SCORING SYSTEM FOR THE PREDICTION OF CYP2D6 ACTIVITY: APPLICATION TO TAMOXIFEN METABOLISM. S. Borges, L. Li, J. Robarge, A. Nguyen, F. Azzouz, Z. Desta, T. Skaar, D. A. Flockhart; Indiana University, Indianapolis, IN

BACKGROUND: CYP2D6 is a highly polymorphic enzyme and genetic scoring systems have been developed to predict CYP2D6 activity. However, inaccurate predictions may be made if the effects of clinically used metabolic inhibitors are not considered. We tested whether the refinement of existing scoring systems by using drug interaction data improve the prediction of CYP2D6 activity as measured by the Endoxifen/N-Desmethyltamoxifen(NDM) ratio.

METHODS: From a prospective trial in 158 breast cancer patients, medication history, genotype for 29 CYP2D6 alleles and plasma concentrations of tamoxifen and its metabolites were collected 4 months after tamoxifen treatment. We assigned null, dysfunctional or fully functional alleles and duplications a score of 0, 0.5, 1 and +1, respectively. We compared our scoring system with the approaches published by Zineh et al (System 1) and Zanger et al (System 2). A mixture model was fitted into the log(Endoxifen/NDM) ratio for clustering CYP2D6 genotypes. Three new scores were developed based on this mixture model: MixScore1= (1, 2, 3); MixScore2 = (1*z1+2*z2+3*z3); and MixScore3= (mu1*z1+ mu2*z2+ mu3*z3), where (z1, z2, z3) are cluster probability assignments, and (mu1, mu2, mu3) are log(Endoxifen/NDM) in each cluster. If a subject concomitantly used a potent or weak CYP2D6 inhibitor the score was reduced by 100% and 50%, respectively.

RESULTS: All six scores with or without inhibitor input were fitted to the log(Endoxifen/NDM) in a simple linear regression. Table 1 presents the R² results.

	Proposed					
	Scoring System 1	Scoring System 2	Scoring System	MixScore1	MixScore2	MixScore3
No inh input	0.2833	0.2362	0.2948	0.2938	0.3693	0.3754
Inh input	0.4397	0.3838	0.4502	0.4576	0.5045	0.4582

CONCLUSION: When CYP2D6 inhibitors are integrated into the scoring system, both mixture model based scores and our scoring system are equally good in assessing CYP2D6 metabolic status, yielding R² as high as 45%.

PII-80

MONTELUKAST PLASMA CONCENTRATION ASSOCIATES WITH A COMMON SNP IN SLCO2B1. E. B. Mougey,¹ H. Feng,² M. Castro,³ C. Irvin,⁴ J. J. Lima¹; ¹Nemours Children's Clinic, Jacksonville, FL, ²University of Florida, Gainesville, FL, ³Washington University School of Medicine, St. Louis, MO, ⁴University of Vermont College of Medicine, Burlington, VT

BACKGROUND: Montelukast is an oral leukotriene receptor antagonist used to control asthma symptoms. High inter-individual variability in response limits the drug's effectiveness. During a large clinical trial we observed significant inter-individual variability in plasma concentrations of montelukast suggesting that at least part of the variability in response may be due to individual pharmacokinetics. We have shown that montelukast is a substrate for the organic anion transport protein OATP2B1 expressed in the intestine and the liver. The aim of the present study is to determine if common polymorphisms in SLCO2B1 that lead to nonsynonymous substitutions in OATP2B1 associate with individual plasma concentration.

METHODS: Associations were determined between the genotype of SLCO2B1 SNPs (heterozygosity ≥ 20%) and montelukast plasma concentrations for 80 adults with poorly controlled asthma who were randomized to receive 10 mg of montelukast, 300 mg of theophylline or placebo at bedtime for 6 months. Montelukast plasma concentrations were determined by HPLC.

RESULTS: Participants were middle-aged, predominantly female patients diagnosed with adult onset asthma that was poorly controlled (ACQ score of 2.3 to 2.4). Montelukast plasma concentration was measured on the morning after an evening dose and ranged from 0->1000 ng/ml. A significant association was found between rs12422149 and plasma concentration (p=0.025). For patients with the A/G genotype this represents a reduction in average plasma concentration to ≤ 30% of the plasma concentration found in patients with the G/G genotype. In contrast, no association between genotype at rs2306168 and plasma concentration was found.

CONCLUSION: SNP rs12422149 is associated with a reduction in individual montelukast plasma concentration confirming the role of OATP2B1 in absorption of montelukast and providing an explanation for individual variability in pharmacokinetics.

PII-81

TRANSPORTER MEDIATED ABSORPTION OF MONTELUKAST IN A CACO-2 MODEL SYSTEM. E. B. Mougey,¹ H. Feng,² M. Castro,³ C. Irvin,⁴ J. J. Lima¹; ¹Nemours Children's Clinic, Jacksonville, FL, ²University of Florida, Gainesville, FL, ³Washington University School of Medicine, St. Louis, MO, ⁴University of Vermont College of Medicine, Burlington, VT

BACKGROUND: Montelukast is an oral leukotriene receptor antagonist used to treat asthma, however high variability in response limits the drug's effectiveness. We have observed significant inter-individual variability in the plasma concentration of montelukast suggesting that at least part of the variability in response may be due to individual pharmacokinetics. Montelukast's physical properties predict that membrane transport proteins will be required for absorption. Individual differences in the genes for these transport proteins may be responsible for the observed variability in pharmacokinetics. The aim of the present study is to determine if the absorption of montelukast is transporter mediated using a Caco-2 model of human intestinal epithelium, and if so, identify the transport proteins involved.

METHODS: Permeability studies are conducted with Caco-2 monolayers plated on porous tissue culture inserts in HBSS buffered at the appropriate pH, using [H³]-montelukast as tracer. Times and temperatures of incubation are as indicated. In total three samples are taken for liquid scintillation counting: donor reservoir load and donor and receiver reservoir post-transport.

RESULTS: Montelukast permeability has an activation energy of 13.7±0.7 kcal/mol, consistent with transporter mediated absorption. Permeability is saturable at high concentrations of montelukast and follows Michaelis-Menten kinetics. Permeability is enhanced by progesterone (p<0.05), may be driven by the transcellular glutathione gradient (p<0.05), and is subject to competition by sulfobromophthalein, estrone 3-sulfate, pravastatin, taurocholic acid, and cholic acid (p<0.05), collectively pointing to a role for OATP2B1.

CONCLUSION: Intestinal absorption of montelukast is mediated in part by the organic anion transporter OATP2B1, suggesting that individual variability in montelukast pharmacokinetics may be mediated by genetic variability in SLCO2B1.

PII-82

IDENTIFICATION OF GENETIC VARIANTS AND GENE EXPRESSION RELATIONSHIPS ASSOCIATED WITH PHARMACOGENES IN HUMANS. R. Huang, S. Duan, E. O. Kistner, W. Zhang, N. J. Cox, M. Dolan; University of Chicago, Chicago, IL

BACKGROUND: The Very Important Pharmacogenes (VIPs) were selected by Pharmacogenetic Research Network (NIH-PGRN) due to their significant effects on drug treatment both at the pharmacokinetic and pharmacodynamic levels. Our objective was to identify single nucleotide polymorphisms (SNPs) that potentially affected the expression of these genes to improve our understanding of genetic effects on baseline expression of genes involved in the pharmacodynamics of drug therapy.

METHODS: Gene expression was evaluated in 176 International HapMap lymphoblastoid cell lines (LCLs) derived from CEU (CEPH,

Utah residents with ancestry from northern and western Europe; n=87) and YRI (Yoruba in Ibadan, Nigeria; n=89) using Affymetrix GeneChip® Human Exon 1.0 ST arrays. Genome-wide association was performed between more than 2 million publicly available HapMap SNPs and 13,314 transcript clusters representing genes.

RESULTS: The expression of two PGRN-VIPs (*GSTT1* and *GSTM1*) are significantly associated with SNPs within 2.5 Mb of the genes; while the expression of 3 and 10 PGRN-VIPs are significantly associated with distant SNPs in CEU and YRI, respectively. One SNP (rs366631) was found locally associated with *GSTM1* expression in both CEU and YRI samples. In addition, 3 and 4 PGRN-VIPs harbor SNPs that are distantly-associated with other gene expressions in CEU and YRI, respectively.

CONCLUSION: Using publicly available HapMap genetic information and our genome-wide expression data, one can identify genetic variants that are significantly associated with the expression of any set of genes of interest. In addition, SNPs that may arise from genome-wide association studies can be interrogated for potential association with gene expression.

PII-83

EFFECTS OF *CYP2D6* POLYMORPHISM ON THE PHARMACODYNAMICS OF METOPROLOL IN HEALTHY KOREAN SUBJECTS. J. Sa, J. Bae, M. Kim, C. Jang, S. Lee; College of Pharmacy, Sungkyunkwan University, Suwon, Republic of Korea

BACKGROUND: Treatment of heart failure and hypertension with metoprolol is characterised by considerable interindividual variability in pharmacokinetics, clinical efficacy and adverse effects. Genetic factors are known to contribute to individual differences in bioavailability, metabolism and drug action. In this study, the effects of polymorphisms of *CYP2D6* on the pharmacodynamics of metoprolol were evaluated.

RESULTS: At 6 hours after administration, metoprolol significantly reduced the exercise-induced increase in heart rate according to *CYP2D6* genotype, by median values of 20.3, 26.7, and 42.5 beats/min in EMs, IMs, and PMs, respectively (P<0.01). Systolic blood pressure was also significantly reduced by metoprolol according to *CYP2D6* genotype.

CONCLUSION: A linear relationship between the number of active *CYP2D6* allele and the pharmacodynamic effects of metoprolol was found. (Supported by KFDA Research Fund)

PII-84

EFFECTS OF *CYP2C9* AND *CYP2C19* POLYMORPHISMS ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF GLICLAZIDE IN HEALTHY KOREAN SUBJECTS. C. Choi, J. Bae, M. Kim, C. Jang, S. Lee; College of Pharmacy, Sungkyunkwan University, Suwon, Republic of Korea

BACKGROUND: Treatment of type 2 diabetes mellitus with oral antidiabetic drugs is characterised by considerable interindividual variability in pharmacokinetics, clinical efficacy and adverse effects. Genetic factors are known to contribute to individual differences in bioavailability, metabolism and drug action. The polymorphic enzyme *CYP2C9* and *CYP2C19* are the main enzyme catalysing the biotransformation of gliclazide. In this study, effects of *CYP2C9* and *CYP2C19* polymorphism on the pharmacokinetics (PK) and pharmacodynamics (PD) of gliclazide in healthy Korean subjects were evaluated.

METHODS: 1146 healthy Korean volunteers were recruited for genotyping of *CYP2C9* and *CYP2C19*. Genotyping for *CYP2C9* and *CYP2C19* was performed using PCR-RFLP method. Subjects with various *CYP2C9* and *CYP2C19* genotypes were selected for PK and PD study of gliclazide. A single oral dose of 5 mg gliclazide was administered to each volunteer, and plasma concentration of gliclazide was measured by HPLC. Plasma glucose levels were determined by glucose oxidase method, and plasma insulin levels by radioimmunoassay.

RESULTS: The observed frequencies of *CYP2C9* genotypes were 89.6, 9.5 and 0.8% in *CYP2C9**1/*1, *1/*3 and *1/*13, respectively. After single oral dose of gliclazide, no significant difference in any

pharmacokinetic parameters was found in *CYP2C9**1/*1, *1/*3 and *1/*13 subjects. In case of *CYP2C19*, the frequency of homozygous wild type (*CYP2C19**1/*1) was 35.6% and the frequency of heterozygous mutants (*CYP2C19**1/*2 and *1/*3) was 48.1%. There was no significant difference in pharmacokinetic parameters between the subjects with homozygous wild type and heterozygous mutants.

CONCLUSION: The defective *CYP2C9**3, *CYP2C9**13, *CYP2C19**2 and *CYP2C19**3 alleles didn't elicit the significant changes in pharmacokinetics of gliclazide. (Supported by KFDA Research Fund)

PII-85

EFFECTS OF *CYP2C19*, *CYP2D6* AND *CYP3A5* POLYMORPHISMS ON THE PHARMACOKINETICS OF CILOSTAZOL IN HEALTHY KOREAN SUBJECTS. S. Lee, J. Bae, C. Jang; College of Pharmacy, Sungkyunkwan University, Suwon, Republic of Korea

BACKGROUND: Cilostazol is a cyclic nucleotide phosphodiesterase type-3 inhibitor with antiplatelet, antithrombotic, and vasodilating properties. The hydroxylation of the quinone moiety of cilostazol to OPC-13326 is the predominant route, and the hydroxylation of the hexane moiety to OPC-13217 is the second most predominant route. The pharmacological potency of both OPC-13326 and OPC-13217 remains unclear. Cilostazol was metabolized to OPC-13326 mainly by *CYP3A4*, *CYP1B1*, and *CYP3A5* and to OPC-13217 mainly by *CYP3A5*, *CYP2C19*, *CYP3A4*, and *CYP2C8*. It has also been reported that the other CYPs *CYP1A2* and *CYP2D6* may be partially involved in the metabolism of cilostazol. In this study, the effects of polymorphisms of *CYP3A5*, *CYP2C19* and *CYP2D6* on the pharmacokinetics of cilostazol were evaluated.

METHODS: 1157 healthy Korean volunteers were recruited for genotyping of *CYP3A5*, *CYP2C19* and *CYP2D6*. Genotyping for *CYP3A5*, *CYP2C19* and *CYP2D6* was performed using PCR-RFLP and long-PCR methods. 33 subjects having different genotypes were selected for PK study of cilostazol. A single oral dose of 100 mg cilostazol was administered to each volunteer, and plasma concentration of cilostazol was measured by HPLC.

RESULTS: No significant difference in any pharmacokinetic parameters of cilostazol between the extensive metabolizers (EMs) and the poor metabolizers (PMs) of *CYP2D6* or *CYP3A5*. In case of *CYP2C19*, C_{max} was higher in PMs than in EMs, but this difference was not significant. In addition, AUC and $T_{1/2}$ was not different between two groups. Any combination of defective functional genotypes of *CYP2C19*, *CYP2D5* and *CYP3A5* also didn't affect on the pharmacokinetics of cilostazol.

CONCLUSION: The genetic polymorphisms of *CYP2C19*, *CYP2D6*, and *CYP3A5* didn't affect the pharmacokinetics of cilostazol. (Supported by KFDA Research Fund)

PII-86

*CYP2C9**3 AND *13 ALLELES SIGNIFICANTLY AFFECTED THE PHARMACOKINETICS OF GLIPIZIDE IN HEALTHY KOREAN SUBJECTS. Y. Song, N. Kim, J. Bae, M. Kim, C. Jang, S. Lee; College of Pharmacy, Sungkyunkwan University, Suwon, Republic of Korea

BACKGROUND: Treatment of type 2 diabetes mellitus with oral antidiabetic drugs is characterised by considerable interindividual variability in pharmacokinetics, clinical efficacy and adverse effects. Genetic factors are known to contribute to individual differences in bioavailability, metabolism and drug action. The polymorphic enzyme *CYP2C9* is the main enzyme catalysing the biotransformation of sulphonylureas. Glipizide is one of the antidiabetic sulphonylureas. In this study, effects of *CYP2C9* polymorphism on the pharmacokinetics (PK) and pharmacodynamics (PD) of glipizide in healthy Korean subjects were evaluated.

METHODS: Genotyping for *CYP2C9* was performed using PCR-RFLP method. Three types of *CYP2C9* (*CYP2C9**1/*1, *1/*3 and *1/*13) were detected in 340 healthy Korean volunteers. 20 subjects of them were selected for PK and PD study of glipizide. A single oral dose of 5 mg glipizide was administered to each volunteer, and plasma concentration of glipizide was measured by HPLC. Plasma glucose levels were determined by glucose oxidase method, and plasma insulin levels by radioimmunoassay.

RESULTS: Glipizide clearance values were 1.91 ± 0.51 , 1.34 ± 0.19 , and 1.15 ± 0.11 ml/hr and AUC_{inf} were 2804.5 ± 779.1 , 3790.5 ± 502.3 , 4376.7 ± 409.9 ng/ml.hr in subjects with *CYP2C9**1/*1, *1/*3, and *1/*13, respectively ($P < 0.01$). C_{max} and $T_{1/2}$ were not significantly different between subjects with three genotypes. Although *CYP2C9**3 and *CYP2C9**13 alleles significantly increased AUC_{inf} of glipizide, they didn't significantly affected the plasma glucose and insulin levels after glipizide administration.

CONCLUSION: The defective *CYP2C9**3 and *CYP2C9**13 alleles significantly affected the clearance and AUC_{inf} of glipizide, but they didn't elicit the significant changes in pharmacodynamics of glipizide. (Supported by KFDA Research Fund)

PII-87

INTERACTION OF IMATINIB WITH HUMAN ORGANIC ION CARRIERS AND ATP-BINDING CASSETTE TRANSPORTERS. S. Hu, R. Franke, K. Filipinski, C. Hu, S. Orwick, S. Baker, A. Sparreboom; St. Jude Children's Research Hospital, Memphis, TN

BACKGROUND: Imatinib is an orally administered tyrosine kinase inhibitor approved for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors. The activity of imatinib in CML has recently been linked with expression of the OCT1 gene *SLC22A1*. Here, we characterized the contribution of solute carriers and efflux transporters to imatinib transport in an effort to further understand mechanisms involved in the drug's intracellular uptake and retention (IUR).

METHODS: IUR of [³H]imatinib was studied in *Xenopus laevis* oocytes and HEK293 cells expressing OATP1A2, OATP1B1, OATP1B3, OCT1-6, OCTN1-2 or OAT1-3. Transport by ABCB1, ABCG2 or ABCC4 was assessed in transfected LLCPK1 and Saos-2 cells, respectively. Gene expression was determined in 9 leukemia cell lines using the Affymetrix U133 array.

RESULTS: Imatinib (1 μ M; 90 min) was not found to be a substrate for OCT1 in oocytes ($P = 0.21$), whereas in HEK293 cells (0.1-50 μ M; 60 min) IUR was increased by only 1.24-fold relative to control cells ($P = 0.002$). In this model, IUR was not saturable and imatinib did not inhibit OCT1-mediated transport of the known substrate TEA. Microarray analysis indicated that *SLC22A1* was interrelated with gene expression of various transporters, including ABCB1, ABCC4, ABCG2 (negative) and OATP1A2 (positive). Imatinib was confirmed to be a substrate for the 3 efflux transporters (0.1-10 μ M; 1-4 h; $P < 0.05$). Furthermore, imatinib IUR was increased by OATP1A2 (1.49-fold; $P = 0.0001$), and acidic pH stimulated OATP1A2-mediated imatinib IUR by >4-fold.

CONCLUSION: These findings indicate that imatinib is a weak substrate for OCT1, and that *SLC22A1* expression may be a composite surrogate for expression of various transporters relevant to imatinib IUR. Because of its high expression in tissues pertinent to imatinib disposition and response, such as the intestine, ciliary body, gliomas and leukemia cells, OATP1A2 may play a key role in the kinetic-dynamic profile of imatinib.

PII-88

ASSOCIATION OF *CYP2D6**10 GENOTYPE AND SMOKING STATUS WITH FLUVOXAMINE PHARMACOKINETICS IN PATIENTS WITH DEPRESSION. T. Fukuda,¹ M. Kato,² M. Wakeno,² G. Okugawa,² M. Yamashita,³ Y. Ikenaga,³ R. Kubota,³ M. Ohno,³ Y. Takekita,² T. Kinoshita,² A. A. Vinks,¹ J. Azuma³; ¹Pediatric Pharmacology Research Unit, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, ²Department of Neuropsychiatry, Kansai Medical University, Osaka, Japan, ³Clinical Pharmacology & Pharmacogenomics, Graduate School of Pharmaceutical Sciences, Osaka University, Osaka, Japan

BACKGROUND: The polymorphic cytochrome P450 (CYP) 2D6 and inducible CYP1A2 contribute to the biotransformation of fluvoxamine. The aim of the present study was to examine the potential

effects of CYP2D6 genotype, especially *CYP2D6**10, and cigarette smoking status on fluvoxamine pharmacokinetics (PK) during standard of care.

METHODS: Thirty-nine Japanese patients with depression (DSM-IV) who were on fluvoxamine 50-150 mg/day were enrolled in the study. CYP2D6 genotype was determined by a validated PCR-based method. PK samples were drawn at random times during the dosing interval at steady state. Fluvoxamine concentrations were measured by a validated LC-MS/MS assay. Smoking status was assessed by means of interview. Pharmacokinetic modeling was performed using NONMEM. The effects of CYP2D6 genotype and smoking status were explored as covariates of fluvoxamine oral clearance (CL/F).

RESULTS: Fluvoxamine data (n=51) were fitted to a one-compartment open model. In the final model, CL/F was expressed as a function of genotype and smoking status. The ratio of systemic clearance for the homozygous *CYP2D6**10 subjects relative to the *CYP2D6**1/*1 and *CYP2D6**1/*10 subjects was 0.60 (SE 0.07), and for smokers to non-smokers this ratio was 1.59 (SE 0.20), respectively. Consistent with the CL ratios, there was a significant difference in the dose-adjusted concentration of fluvoxamine measured up to at 16 hours after drug intake among patients depending on genotype and smoking status.

CONCLUSION: Our finding suggests that the CYP2D6 genotype, especially the *CYP2D6**10 allele and smoking status significantly contribute to inter-individual differences in fluvoxamine clearance and steady-state concentrations reached during treatment. To our knowledge, this is a first report to show clear pharmacogenetic and smoking effects on fluvoxamine pharmacokinetics in Asian patients with depression.

PII-89

THE EFFECT OF CYP2C19 GENOTYPE ON THE PLATELET RESPONSIVENESS TO CLOPIDOGREL IN HEALTHY KOREAN SUBJECTS. D. Cho,¹ C. Yeo,¹ M. Oh,² J. Shon,¹ E. Kim,¹ J. Shin¹; ¹Inje University College of Medicine, Busanpaik Hospital, Busan, Republic of Korea, ²Clinical Trial Center, Busanpaik Hospital, Busan, Republic of Korea

BACKGROUND: Variable inhibition of platelet aggregation in response to clopidogrel has been reported recently, but the underlying mechanisms remain unclear yet. We investigated the influence of CYP isozymes and MDR1 genetic polymorphisms on the platelet responsiveness to clopidogrel.

METHODS: 40 healthy subjects were given a single oral loading dose of 300 mg clopidogrel and followed by daily oral doses of 75 mg for 6 days. ADP-induced platelet aggregation was assessed by optical aggregometry and plasma concentrations of clopidogrel were determined using LC/MS/MS during the first 24 hours. CYP2B6, 2C19, 3A5 and MDR1 genotypes were analyzed using pyrosequencing method.

RESULTS: Baseline platelet aggregations were not significantly different between all genotype groups. At steady state, platelet aggregation was significantly influenced by the CYP2C19 genotype only. The absolute values of platelet aggregation in homozygous extensive metabolizers (*CYP2C19**1/*1), heterozygous extensive metabolizers (*CYP2C19**1/*2 and *1/*3) and poor metabolizers (*CYP2C19**2/*2, *2/*3 and *3/*3) were 31.3 % \pm 11.6 %, 33.6 % \pm 10.5 % and 56.7 % \pm 13.5 % respectively ($p < 0.0001$). In case of the other genotypes, there were no differences between groups for the platelet aggregation. Peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of clopidogrel were not associated with *MDR1* C3435T genotype.

CONCLUSION: The present study suggests that CYP2C19 poor metabolizers are associated with poor platelet response to clopidogrel, and CYP2C19 genotype seems to be a major determinant of clopidogrel resistance.

PII-90

NO EFFECT OF ABCG2 C421A SINGLE NUCLEOTIDE POLYMORPHISM ON NITROFURANTOIN PHARMACOKINETICS IN HEALTHY CHINESE SUBJECTS. K. K. Adkison,¹ S. S. Vaidya,¹ D. Y. Lee,¹ L. Li,² S. H. Koo,² A. S. Gross,³ A. Mehta,¹ J. W. Polli,¹ Y. Lou,¹ E. J. Lee²; ¹GlaxoSmithKline, Research Triangle Park, NC, ²National University of Singapore, Singapore, Singapore, ³GlaxoSmithKline, Sydney, Australia

BACKGROUND/AIMS: The efflux transporter breast cancer resistance protein (BCRP or *ABCG2*) plays an important role in the absorption and/or elimination of some drugs. Nitrofurantoin (NF) is a substrate of both hBCRP and mBcrp1 in transduced MDCKII cells and in vivo studies show that NF has a 4-fold higher AUC and 50-fold lower biliary clearance in knockout mice compared to wild-type. The objective of this study was to assess the utility of NF as a clinical probe substrate for BCRP by evaluating the impact of genetic variation on NF clinical pharmacokinetics (PK). Chinese subjects were recruited as there is a higher frequency of the *ABCG2* C421A polymorphism, which is associated with reduced BCRP transporter activity, in this population.

METHODS: The PK of a single oral NF dose (100mg) was determined in 36 healthy male subjects (age range 21-55y) with the *ABCG2* 421 CC, CA and AA genotypes (N=12 each). Plasma and urine samples were collected for 30h post-dose and NF concentrations determined by LC/MS/MS and LC/UV, respectively. ANOVA was used to compare PK parameters among genotypes. **RESULTS:** NF PK parameters (AUC, Cmax, T1/2, fe) did not differ between carriers and non-carriers of the 421A variant polymorphism

Geometric Mean (95% CI)	ABCG2 421 Genotype		
	CC	CA	AA
AUC _(0-∞) ; (µg.h/mL)	2.21 (2.00-2.45)	2.42 (2.11-2.78)	2.32 (1.99-2.70)
C _{max} ; (µg/mL)	0.875 (0.749-1.02)	0.961 (0.780-1.18)	0.963 (0.742-1.25)
T _{1/2} ; (h)	0.79 (0.59-102)	0.76 (0.64-0.89)	0.72 (0.62-0.84)
fe (% dose excreted in urine)	43 (36-52)	44 (40-49)	39 (34-45)

CONCLUSIONS: The C421A polymorphism had no effect on NF plasma and urine PK parameters, suggesting that unlike mice, BCRP may not play a major role in the elimination of NF in humans. NF has limited utility as a clinical BCRP probe.

PII-91

EVALUATION OF SULFASALAZINE AS A BCRP CLINICAL PROBE SUBSTRATE: EFFECT OF ABCG2 C421A POLYMORPHISM AND PANTOPRAZOLE ON SULFASALAZINE PHARMACOKINETICS IN HEALTHY VOLUNTEERS. K. K. Adkison,¹ S. S. Vaidya,¹ D. Y. Lee,¹ L. Li,² S. H. Koo,² A. Mehta,¹ A. S. Gross,³ J. W. Polli,¹ Y. Lou,¹ J. E. Humphreys,¹ E. J. Lee²; ¹GlaxoSmithKline, Research Triangle Park, NC, ²National University of Singapore, Singapore, Singapore, ³GlaxoSmithKline, Sydney, Australia

BACKGROUND/AIMS: Many drugs are substrates or inhibitors of the efflux transporter BCRP, which lowers systemic exposure by limiting absorption and/ increasing biliary elimination. In Bcrp-1 knockout mice, sulfasalazine (SFZ) had a 111-fold higher oral AUC and 13-fold higher iv AUC than wild-type mice. The objective of this crossover study was to evaluate SFZ as a clinical probe substrate for BCRP in carriers and non-carriers of the reduced activity *ABCG2* C421A SNP and to assess the effect of pantoprazole (PPZ), a BCRP inhibitor, on SFZ PK.

METHODS: Three cohorts of male Chinese subjects (age 21-45y; wgt 57-87kg) with CC, CA and AA genotypes (n=12 each) were enrolled. The 3 sequential treatments were SFZ 500mg single oral dose alone, with PPZ 40mg, or with famotidine 40mg (as pH control). Plasma and urine concentrations of SFZ and two metabolites SP & 5ASA were measured. PK parameters were compared to CC genotype and SFZ alone treatment by 2-way ANOVA.

RESULTS:

SFZ Alone Geometric Mean (95% CI)	ABCG2 421 Genotype		
	CC	CA	AA
SFZ AUC(0-∞); µg.h/mL	32.1 (13-78)	16.8 (7.2-40)	62.7 (33-118)
SFZ Cmax; µg/mL	4.00 (1.6-9.9)	1.70 (0.66-4.4)	6.86 (3.6-13)
SFZ T1/2; h	6.8 (6.0-7.7)	7.6 (6.8-8.5)	8.8 (7.8-9.8)
SP AUC(0-t); µg.h/mL	40.0 (29-55)	34.2 (28-42)	25.2 (15-43)

High intersubject variability was noted with no significant difference in SFZ and SP PK in AA or CA compared to CC genotype. 5ASA was not detected in most subjects. PPZ had no effect on SFZ PK based on geometric LS means ratios (SFZ+PPZ vs SFZ alone) and 90% CI of 0.97 (0.49-1.9), 1.8 (0.97-3.4), 1.0 (0.54-1.9) for SFZ AUC in CC, CA, AA cohorts. Famotidine also had no effect.

CONCLUSIONS: High PK variability, lack of C421A gene effect, and lack of pantoprazole inhibition suggest that SFZ is not a useful clinical BCRP probe drug.

PII-92

INFLUENCE OF SLCO1B1 HAPLOTYPE ON ROSIGLITAZONE PHARMACOKINETICS IN HEALTHY VOLUNTEERS. C. L. Aquilante, L. R. Bushman, S. D. Knutsen, L. E. Burt, L. Capo Rome, L. A. Kosmiski; University of Colorado at Denver and Health Sciences Center, Denver, CO

BACKGROUND: Data suggest that rosiglitazone may be a substrate for the organic anion transporting polypeptide IB1 drug transporter, which is encoded by the *SLCO1B1* gene. We sought to determine whether *SLCO1B1* variant haplotypes are associated with variability in rosiglitazone pharmacokinetics in healthy volunteers.

METHODS: Healthy Caucasian subjects (n=27) were administered a single 4 mg oral dose of rosiglitazone and blood samples were collected over a 24-hour period. Subjects were genotyped for the *SLCO1B1* -11187 G/A, -10499 A/C, 388 A/G, and 521 T/C polymorphisms. *SLCO1B1* haplotypes were computationally assigned as follows: *1A (-11187G/-10499A/388A/521T); *1B (GAGT); *5 (GAAC); *15 (GAGC); *16 (GCGC); *17 (AAGC); and *21 (AAGT). Rosiglitazone plasma concentrations were determined by HPLC and analyzed using noncompartmental methods. Rosiglitazone pharmacokinetic parameters were compared between diplotype groups using ANOVA. Linear regression was used to determine the joint effects of *SLCO1B1* diplotype, age, sex, and weight on rosiglitazone area under the plasma concentration-time curve (AUC).

RESULTS: The study population consisted of 22 women and 5 men (mean age=33.6 ± 9.9 years, mean weight=67 ± 11.7 kg). Subjects were placed in the following groups based on *SLCO1B1* diplotype: Group 1 =*1A/*1A (n=6); Group 2 =*1A/*1B or *1B/*1B (n=8); and Group 3 =subjects with at least one *5, *15, *16, or *17 haplotype (n=13). There were no significant differences in rosiglitazone AUC, C_{max}, T_{max}, t_{1/2}, oral clearance, or weight-adjusted oral clearance between the three diplotype groups. The mean AUCs in groups 1, 2, and 3 were 1569±442, 1872±632, and 1674±413 ng*h/ml, respectively (p=0.49). After controlling for covariates, the only predictor of rosiglitazone AUC was weight (p=0.013).

CONCLUSION: Our data suggest that *SLCO1B1* haplotypes do not influence interindividual variability in rosiglitazone pharmacokinetics in healthy volunteers.

P11-93

EFFECTS OF *ABCB1* GENETIC POLYMORPHISMS ON THE INTERINDIVIDUAL VARIATIONS IN SERUM HORMONE LEVELS IN WOMEN WITH NORMAL MENSTRUAL CYCLES. T. Nakamura,¹ N. Okamura,² M. Yagi,³ H. Omatsu,⁴ M. Yamamori,⁴ H. Makimoto,⁴ T. Sakaeda,⁵; ¹Section of Clinical Evaluation of Pharmacotherapy, Division of Clinical Pharmacokinetics, Department of Internal Related, Kobe University Graduate School of Medicine, Kobe, Japan, ²Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Mukogawa Women's University, Nishinomiya, Japan, ³Section of Clinical Evaluation of Pharmacotherapy, Division of Clinical Pharmacokinetics, Department of Internal Related, Kobe University Graduate School of Medicine, Kobe, Japan, ⁴Department of Pharmacy, University Hospital, School of Medicine, Kobe University, Kobe, Japan, ⁵Center for Integrative Education of Pharmacy Frontier, Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan

BACKGROUND: ABCB1/MDR1/P-glycoprotein can transport physiological hormones such as cortisol and aldosterone, and the association of *ABCB1* genetic polymorphisms with its expression and function in the body has been suggested. In the present study, we examined the effects of *ABCB1* polymorphisms on the interindividual variations of serum hormone levels in 51 women with normal menstrual cycles.

METHODS: This study enrolled 51 non-pregnant female volunteers between 21 and 24 years old. Only volunteers without hormonal therapy and without endocrinal or metabolic pathologies were included in the analysis. The menstrual cycle was divided into three phases: the premenstrual phase (days 10-1 before menstruation) (n=22), menstrual phase (n=11) and postmenstrual period (n=18). Blood sampling was performed in the evening, and the serum levels of cortisol, aldosterone, estradiol, progesterone and testosterone were measured. This study was approved by the Institutional Review Board of Kobe University Hospital, Kobe University, Japan.

RESULTS: In the postmenstrual phase, the average serum cortisol level in the subjects harboring 3435TT genotype was significantly lower than that in those harboring 3435CC genotype (5.6 ± 0.5 (mean \pm S.E.) and 9.9 ± 0.7 μ g/dL for 3435TT and 3435CC, respectively ($p < 0.05$)). The serum levels of cortisol in the menstrual and postmenstrual phases also tended to be lower in the subjects harboring 3435TT genotype, compared with those with 3435CC or 3435CT genotypes. This tendency was observed in the serum level of testosterone during the menstrual cycle, although no statistically significant difference was found among 3435C>T genotype groups. There was no significant effect of the *ABCB1* 3435C>T genotype on the serum levels of aldosterone, estradiol, and progesterone.

CONCLUSION: The *ABCB1* 3435C>T genotype may contribute to determine the basal levels of certain hormones in serum through the normal menstrual cycles.

OIII-A-1

COX INHIBITORS DOWNREGULATE PDE4D EXPRESSION IN A CLINICAL MODEL OF INFLAMMATORY PAIN. X. Wang,¹ M. Hamza,¹ S. M. Gordon,² S. M. Wahl,³ R. A. Dionne¹; ¹NIH/NINR, Bethesda, MD, ²University of Maryland, School of Dentistry, Baltimore, MD, ³NIH/NIDCR, Bethesda, MD

BACKGROUND: Pro-inflammatory mediators initiate and maintain inflammation and pain induced by tissue injury. Inhibition of cyclooxygenase (COX) enzymes is generally accepted as the mechanism of action of non-steroidal anti-inflammatory drugs, yet reports indicate other mechanisms. TNF- α plays a crucial role in inflammation and is regulated by prostaglandins and cAMP. This study evaluated the changes in TNF- α expression at the onset of clinical pain in response to administration of ketorolac or rofecoxib in a clinical model of acute inflammatory pain.

METHODS: A total of 252 oral mucosal biopsies were taken from 126 healthy volunteers undergoing the surgical extraction of

impacted third molars. Subjects randomly received either rofecoxib (50 mg, QD) or placebo orally 60 min before surgery and ketorolac (30 mg) or saline intravenously 30 min before surgery. Total RNA or protein extracted from each biopsy was used to analyze changes in gene/protein expression using microarray, qRT-PCR and Western blot.

RESULTS: Following tissue injury, TNF- α and PDE4D (encoding phosphodiesterase 4D) gene expression was significantly increased by 6-fold (n = 19) and 5-fold (n = 18) respectively in the placebo group at 3 hrs post-surgery. The increased gene expression of PDE4D in the placebo group was diminished by ketorolac and rofecoxib (1.8-fold, $p < 0.05$), whereas TNF- α gene expression was not significantly changed by ketorolac (3-fold, n = 18) and rofecoxib (3-fold, n = 9). The changes of TNF- α and PDE4D at gene expression level were in concordance with the changes in protein expression verified by Western blot and immunohistochemistry.

CONCLUSION: Our findings demonstrate that COX inhibition downregulates PDE4D expression, yet does not affect TNF- α expression in the clinical model of oral surgery, which may provide a novel molecular mechanism underlying the anti-inflammatory and analgesic effects of COX inhibitors.

OIII-A-2

PRazosin ATTENUATES SELF-REPORT EFFECTS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, 'ECSTASY') IN MALES. M. J. Baggott,¹ G. Galloway,¹ M. Jang,¹ R. Didier,² J. Mendelson¹; ¹Cal Pac Med Center Research Institute, San Francisco, CA, ²Oregon Health & Science University School of Medicine, Portland, OR

BACKGROUND: Preclinical data suggests psychostimulant effects are mediated by multiple neurotransmitter mechanisms including noradrenergic, serotonergic, and dopaminergic. MDMA (3,4-methylenedioxyamphetamine) is an illicitly used psychostimulant with putatively novel social and emotional (so-called 'entactogen') effects, such as affiliative feelings. To examine possible noradrenergic mechanisms of MDMA, we administered MDMA alone and in combination with the alpha-1 noradrenergic inverse agonist prazosin.

METHODS: 16 healthy MDMA-experienced participants (8 males and 8 females) received placebo, 1.5 mg/kg PO MDMA, 1-2 mg PO prazosin, or both drugs in a four-session randomized controlled trial in a laboratory setting. Pharmacokinetic and pharmacodynamic (physiological and self-report) measures were made and analyzed using repeated-measures ANOVA.

RESULTS: Preliminary analysis of pharmacodynamic measures from 8 male participants indicates prazosin significantly attenuated MDMA-induced increases in self-report visual analogue ratings of 'good drug effect' ($p < 0.001$), 'drug liking' ($p < 0.001$) and 'high' ($p < 0.004$) - decreasing these ratings at 1.5 hrs by a mean of 30.7% (6.3-55.95% CI) but did not attenuate increases in self-report affiliation. As expected, MDMA had significant effects on heart rate (HR) and blood pressure (BP). At 1.5 hrs, MDMA increased HR by 41.1 (26.6-55.6 95%CI) bpm and SBP/DBP by 34.8/24.9 (16.6-33.2/16.6-33.2 95%CI) mmHg. Prazosin alone did not alter supine HR or BP. Compared to MDMA alone prazosin/MDMA decreased SBP/DBP at 1.5 hrs by a mean of 8.75/9.25 mmHg (1.2-16.3/0.8-17.4 95% CI) but did not affect HR.

CONCLUSION: In males alpha-1 noradrenergic mechanisms probably mediate some vascular (BP) and pleasurable effects (drug liking, high) of MDMA but not affiliative properties. Supported by NIH DA 016776.