

trough Cp (CLs), a trough and peak Cp (CL2s), or 3 Cp (CL3s), in 4 separate analysis, provided the test data, for which bias & precision of CL (& AUC) estimates, were computed. All selected V Cp were at or near steady state, depending on availability.

**RESULTS:** 18/41 patients had  $\geq 4$  V Cp and have been studied to date; CLgs, CLd (n = 18) & CLs (n = 18) have been computed. CL (& AUC) estimates were statistically biased ( $p < 0.05$ ; CL was over- & AUC under-estimated), but reasonably precise, for both D & S methods (e.g., M%AE, for CLd, was 22.1% and, for CLs, was 9.7%). Regression of CLd vs. CLgs resulted in CLd (mL/min) =  $0.98\text{CLgs} + 11.6$  ( $r = 0.92$ ) &, for CLs, yielded CLs =  $1.05\text{CLgs} + 3.0$  ( $r = 0.97$ ).

**CONCLUSIONS:** For V, which is cleared mainly by GFR and with only modest plasma protein binding, it appears that acceptable predictions of CL & AUC can be made based on dose, wt and CLcr, alone. We believe AUC/MIC of V to be the critical PD exposure measure, & M%AE = 22%, for AUC, is acceptable when compared to the uncertainty of the "measurement" of MIC. Even a single trough Cp measurement (possibly the least informative single sample you could obtain) can further reduce the M%AE by half. It appears reasonable to pursue a PK/PD analysis, in MRSA patients, even in those with 0 or 1 V Cp available. We are in the process of expanding the database and of evaluating the effect, on bias & precision, of having 2 or 3 Cp. If the systematic bias persists, we plan to update the Bayesian priors with our own population PK model.

### PI-102

POPULATION PHARMACOKINETICS OF BUDESONIDE IN NORMAL VOLUNTEERS AND PEDIATRIC, ADOLESCENT AND ADULT SUBJECTS WITH ASTHMA. T. Tzeng, PhD, M. Gillen, BS, B. K. Birmingham, PhD, L. Kung, MS, AstraZeneca, MegaMed, Wilmington, DE.

**AIMS:** Symbicort pMDI is a combination inhaler therapy consisting of 40-, 80-, or 160- $\mu\text{g}$  budesonide, a glucocorticosteroid, and 4.5- $\mu\text{g}$  formoterol, a  $\beta_2$ -adrenoreceptor agonist, for the treatment of asthma. In this study, retrospective population pharmacokinetic (PK) analysis was performed to assess the effects of covariates on budesonide pharmacokinetics in humans after inhalation administration.

**METHODS:** A total of 7,073 budesonide plasma values were used. Data were collected from 15 clinical trials after single/multiple inhalation administration of 40 to 1920 mg budesonide via 3 different devices, namely, Symbicort pMDI (SMDI), Pulmicort Turbuhaler (PT), and Budesonide pMDI (BMDI), to 447 pediatric, adolescent and adults with asthma, or healthy volunteers. Subject demographic covariates, creatinine clearance, patient status (asthmatic vs. healthy), dose strengths, and different devices were evaluated.

**RESULTS:** Structural PK model was a two-compartment model with linear elimination and different first-order absorption rate constants for different devices. The model parameters (typical values) from the final model were CL/F (199 L/hr),  $V_2/F$  (710 L), Q/F (47.1 L/hr),  $V_3/F$  (293 L),  $k_a$  for SMDI ( $16.5 \text{ hr}^{-1}$ ),  $k_a$  for PT ( $15.9 \text{ hr}^{-1}$ ),  $k_a$  for BMDI ( $12.0 \text{ hr}^{-1}$ ), and relative bioavailabilities of PT and BMDI to SMDI (1.03 and 1.00, respectively).

Gender and creatinine clearance had no effect on any budesonide pharmacokinetic parameters. Even though statistically significant, the following covariate effects would not cause any clinical concerns for budesonide because their targeted parameters were limited in either absorption or distribution, magnitude of effect was small, or direction of impact was irrelevant: age on CL/F and  $k_a$ , dose on  $V_2/F$  and relative bioavailability, weight on Q/F, and asthmatic state on  $k_a$ .

**CONCLUSION:** Overall, none of the significant covariate effects found in this analysis would be cause for clinical concern of budesonide in using SMDI considering the extensive safety data obtained during clinical studies and the post-marketing experience with budesonide, much of which was obtained with doses that are greater than the highest recommended dose of SMDI.

### PI-103

POPULATION PHARMACOKINETICS OF FORMOTEROL IN NORMAL VOLUNTEERS AND PEDIATRIC, ADOLESCENT AND ADULT SUBJECTS WITH ASTHMA. T. Tzeng, PhD, M. Gillen, BS, B. K. Birmingham, PhD, L. Kung, MS, AstraZeneca, MegaMed, Wilmington, DE.

**AIM:** Symbicort pMDI is a combination inhaler therapy consisting of 40-, 80-, or 160- $\mu\text{g}$  budesonide, a glucocorticosteroid, and 4.5- $\mu\text{g}$  formoterol, a  $\beta_2$ -adrenoreceptor agonist, for the treatment of asthma. In this study, retrospective population pharmacokinetic (PK) analysis was performed to assess the effects of covariates on formoterol pharmacokinetics in humans after inhalation.

**METHODS:** A total of 6,513 formoterol plasma values were used. Data were collected from 14 clinical trials after single/multiple inhalation administration of 4.5 to 56 mg formoterol via 2 different devices, namely, Symbicort pMDI (SMDI) and OXIS TBH (OTBH), to 412 pediatric, adolescent and adults with asthma, or healthy volunteers. Subject demographic covariates, creatinine clearance, patient status (asthmatic vs. healthy), dose strengths, and different devices were evaluated.

**RESULTS:** Structural PK model was a three-compartment model with linear elimination and different first-order absorption rate constants for different devices. The model parameters (typical values) from the final model were CL/F (106 L/hr),  $V_2/F$  (321 L),  $Q_3/F$  (1240 L/hr),  $V_3/F$  (947 L),  $Q_4/F$  (61.6 L/hr),  $V_4/F$  (5520 L),  $k_a$  for SMDI ( $61.5 \text{ hr}^{-1}$ ),  $k_a$  for OTBH ( $32.0 \text{ hr}^{-1}$ ), and relative bioavailability of OTBH to SMDI (1.04). Age, gender and creatinine clearance had no effect on any formoterol pharmacokinetic parameters. No covariate had impact on  $V_3/F$ ,  $V_4/F$ ,  $k_a$ , and the relative bioavailability of OTBH to SMDI. CL/F was slightly decreased with dose.  $V_2/F$  was increased with body weight. Even though statistically significant, the effects of dose and asthmatic status on  $Q_3/F$  and  $Q_4/F$ , respectively, would not cause any clinical concerns because both are the distribution parameters.

**CONCLUSION:** None of the significant covariate effects found in this analysis would be cause for clinical concern of formoterol in using SMDI considering the extensive safety data obtained during clinical studies and the post-marketing experience with formoterol, much of which was obtained with doses that are greater than the planned highest recommended dose of SMDI.

### OII-A-I

TIME COURSE OF ENZYME DE-INDUCTION OF CARBAMAZEPINE METABOLISM. J. Cloyd, PharmD, S. Marino, PhD, R. Brundage, PhD, A. K. Birnbaum, PhD, R. E. Ramsay, MD, P. Pennell, MD, J. O. Rarick, BS, U. Mishra, MS, J. R. White, MD, I. E. Leppik, MD, College of Pharmacy, University of Minnesota, College of Pharmacy, University of Florida, Dept. of Neurology, University of Miami, Dept. of Neurology, Emory University, MINCEP Epilepsy Care, Minneapolis, MN.

**BACKGROUND/AIMS:** De-induction of drug metabolizing enzymes occurs when an enzyme-inducing medication is discontinued. Response to concomitant medications affected by de-induction may change as their clearances decrease and plasma concentrations rise. Understanding the time-course of de-induction would permit better management of drug therapy. Carbamazepine (CBZ) induces its own metabolism, primarily through CYP3A pathways. This characteristic and the availability of an intravenous, stable-labeled (SL-CBZ) formulation permits a rigorous investigation of the rate and extent of de-induction during and following CBZ withdrawal.

**METHODS:** Subjects were patients with epilepsy on CBZ therapy about to discontinue the medication. CBZ pharmacokinetics (PK) were determined on four occasions: 1) while on the maintenance regimen, 2) the morning after the last dose following two weeks at the final regimen, 3) 6-8 days after the last dose, and 4) 6-8 weeks after the last dose. Subjects were admitted to a clinical research center for 24 hours to carryout the study. CBZ PK were characterized using a

single 100 mg dose of SL-CBZ. In the first study, the subject's usual morning oral dose minus 100 mg was administered immediately following the IV dose. Fourteen blood samples were obtained just prior to and up to 96 hours after the IV dose. SL CBZ and CBZ were measured in plasma using a LC-MS assay. SL-CBZ concentration-time data were analyzed using a noncompartmental model (WinNonlin vs. 5.0.1).

**RESULTS:** Seven patients (4 men, 3 women) age 21-58 have completed the study. The mean maintenance daily dose and final daily dose were  $486 \pm 195$  mg and  $143 \pm 53$  mg, respectively; with corresponding trough concentrations of  $5.9 \pm 2.2$  and  $2.3 \pm 1.4$   $\mu\text{g/mL}$ . CBZ clearance and half-life at each of the 4 studies were 42.6, 43.0, 28.3, and 24.4 mL/hr/kg and 17.3, 17.2, 23.5 and 26.3 hours, respectively. The rate of change in clearance between study 2 and 3 was equivalent to a mean 2.3 day half-life.

**CONCLUSION:** Induction of CYP3A enzymes is maintained despite low CBZ concentrations. Once CBZ is withdrawn de-induction occurs rapidly and is essentially complete within 10-12 days. Institution of monitoring strategies and adjustment in concomitant therapy affected by de-induction should be considered at the time the patient takes the last dose of CBZ.

## OII-A-II

A MODEL TO QUANTIFY AUTO-INDUCTION AND CARBAMAZEPINE CAUSED INDUCTION FOR EFAVIRENZ. M. Zhu, PhD, P. Nandy, PhD, S. Kaul, PhD, D. M. Grasela, PharmD, PhD, M. Pfister, MD, Bristol-Myers Squibb Company, Princeton, NJ.

**BACKGROUND/AIMS:** Efavirenz (EFV, anti-HIV agent) and carbamazepine (CBZ, anticonvulsant) are inducers/substrates of CYP2B6 and/or 3A4 isozymes. In certain cases there may be a medical need to provide anticonvulsant therapy in addition to the treatment of HIV infection. Therefore, interaction between EFV and CBZ is of therapeutic interest. A population drug-drug interaction (DDI) model was developed to characterize the effects of EFV auto-induction (AI) and additional enzyme induction caused by CBZ co-administration on the pharmacokinetics (PK) of EFV.

**METHODS:** EFV PK data from a single dose study (600 mg) and a multiple dose study (EFV 600 mg QD for 14 days [period A] followed by EFV 600 mg QD + CBZ 400 mg QD for 21 days [period B]) in 35 healthy subjects were modeled with NONMEM. A Well-Stirred model was used to characterize the oral clearance in term of intrinsic hepatic clearance (CL<sub>i</sub>). The CL<sub>i</sub> was modeled as an Emax function of time:

$$CL_i = CL_{i_{day1}} + [(AI_{day14} \times \text{time}) / T_{50} + \text{time}] + [(DDI_{max} \times \text{time}) / (T_{50} + \text{time})]$$

AI<sub>day14</sub> is the change of CL<sub>i</sub> from baseline (CL<sub>i<sub>day1</sub></sub>) to Day 14, T<sub>50</sub> is the time to achieve 50% of AI<sub>day14</sub>, DDI<sub>max</sub> is the maximal change of CL<sub>i</sub> from Day 14 to steady state of drug-drug interaction and T<sub>50</sub> is the time to achieve 50% of DDI<sub>max</sub>. Time was reset to 0 at the beginning of period B and expressed as time.

**RESULTS:** EFV exhibited time-dependent increase in clearance. The proposed DDI model adequately described the observed EFV concentration-time courses, and further quantified the effect of the EFV and CBZ interaction on EFV clearance. The estimated oral clearance at baseline, Day 14, Day 35 and steady-state of the interaction was 5.5, 8.6, 13.6 and 16.7 L/h, respectively, and >80% of EFV clearance at steady-state was attained after 3 weeks of CBZ co-administration. Estimated T<sub>50</sub> and T<sub>50</sub> were approximately 2 weeks for auto- and CBZ-induced enzyme induction with co-administration.

**CONCLUSIONS:** The described model permits characterization of the time course of EFV auto-induction and co-drug induced enzyme induction. A model-based approach can facilitate the evaluation of DDI related dose adjustments and the design of DDI studies.

## OII-A-III

CRANBERRY JUICE DELAYS MIDAZOLAM ABSORPTION IN HEALTHY VOLUNTEERS. N. Ngo, PharmD, E. Dees, MD, M. Paine, PhD, University of North Carolina, School of Pharmacy, University of North Carolina, School of Medicine, Chapel Hill, NC.

**BACKGROUND/AIMS:** Cranberry juice (CBJ) is growing in popularity as a natural alternative for the prevention of urinary tract infections. CBJ has also been shown to inhibit the enteric CYP3A-mediated metabolism of nifedipine *in vivo* in rats, as well as in human liver microsomes. Accordingly, the effects of CBJ on the pharmacokinetics of the CYP3A probe substrate, midazolam, were evaluated in healthy volunteers.

**METHODS:** A randomized, cross-over, open-label study was conducted at the University of North Carolina General Clinical Research Center. CBJ was prepared by diluting CBJ concentrate (R.W.Knudsen®) with water to yield 200% (double-strength) juice. Healthy volunteers (n=6) were pre-treated with 3 glasses (240 mL each) of CBJ or water, each separated by 15-minute intervals. Midazolam syrup (5 mg) was given with the third glass. Blood (10 mL) was drawn prior to dosing and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours post-dose. Plasma midazolam concentrations were measured by HPLC/MS. Midazolam pharmacokinetics were determined by non-compartmental methods using WinNonlin®.

**RESULTS:**

### PHARMACOKINETICS OF MIDAZOLAM IN HEALTHY VOLUNTEERS

Measure	Geometric Mean (CV %)		CBJ/Water Ratio [95% CI]	P-Value*
	Water	CBJ		
AUC <sub>0-∞</sub> (nmol/L*hr)	266 (33)	338 (37)	1.27 [1.02-1.58]	p = 0.08
Cl/F (L/h)	58 (33)	46 (37)	0.79 [0.63-0.98]	NS
K <sub>el</sub> (h <sup>-1</sup> )	0.18 (45)	0.18 (28)	1.00 [0.66-1.53]	NS
C <sub>max</sub> (nmol/L)	123 (32)	60 (17)	0.49 [0.36-0.66]	p < 0.05
T <sub>max</sub> (h) [median (range)]	0.5 (0.25)	3.5 (1.5-4.0)		p < 0.005**

\* Paired Student's t-test.

\*\* Wilcoxon signed-rank test.

**CONCLUSIONS:** CBJ significantly delayed the rate of absorption of midazolam, as exemplified by the 50% decrease in C<sub>max</sub> and 7-fold increase in T<sub>max</sub>. Potential mechanisms include inhibition of an uptake process in the proximal small intestine and alterations in physicochemical processes (e.g., delayed gastric emptying and increased acidity). The slight increase (30%) in AUC, representing an increase in fraction absorbed, without a change in K<sub>el</sub> in this small group of subjects suggests inhibition of enteric CYP3A as another potential mechanism underlying this drug-diet interaction.

## OII-A-IV

CORRECTING FOR INCOMPLETE AND VARIABLE GALLBLADDER CONTRACTION IMPROVES THE ESTIMATE OF BILIARY CLEARANCE OF DRUGS IN HUMANS. G. Ghibellini, PhD, L. S. Vasisht, PharmD, B. M. Johnson, PhD, W. D. Heizer, MD, R. J. Kowalsky, PharmD, K. L. Brouwer, PharmD, PhD, School of Pharmacy, University of North Carolina at Chapel Hill, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC.

**BACKGROUND/AIMS:** The anatomy of the human hepatobiliary tract, and the intermittent and incomplete expulsion of bile from the gallbladder, must be considered when quantifying biliary

clearance ( $Cl_{\text{biliary}}$ ) of drugs. We developed a clinical method that improves the recovery of biliary secretions and corrects for incomplete gallbladder contraction. A custom made oro-enteric tube and clinical protocol were used to quantitatively collect bile and determine the  $Cl_{\text{biliary}}$  of selected probes [Tc-99m mebrofenin (MEB), Tc-99m sestamibi (MIBI) and piperacillin (PIP)] that were expected to exhibit high, intermediate and low  $Cl_{\text{biliary}}$ , respectively, in healthy volunteers.

**METHODS:** Three open label studies were performed at the University of North Carolina Hospitals, General Clinical Research Center. Fourteen healthy volunteers were administered IV either 2.5 mCi MEB, 2.5 mCi MIBI, or 2 g PIP. In the case of PIP, 2.5 mCi MEB was administered IV 2 h after PIP to determine gallbladder ejection fraction. Gallbladder contraction was stimulated 2 h after administration of the Tc-99m probe with cholecystokinin-8 (CCK-8, 0.02  $\mu\text{g}/\text{kg}$ , 30-min infusion). Duodenal aspirates were collected using a custom made oro-enteric tube equipped with an occlusive balloon. The probes were quantified by gamma counting (MEB, MIBI) or LC-UV/MS analysis (PIP) in blood, bile and urine over a 3 h (MEB and MIBI) or 6 h time interval (PIP). Noncompartmental methods were used to calculate pharmacokinetic parameters. Gallbladder ejection fraction was determined by gamma scintigraphy and used as a correction factor in the calculation of  $Cl_{\text{biliary}}$ .

**RESULTS:** Gallbladder ejection fraction in response to CCK-8 was variable, ranging from 3% to 90%. The variability in  $Cl_{\text{biliary}}$  (mean  $\pm$  SD; mL/min/kg) was consistently lower upon correction of  $Cl_{\text{biliary}}$  for gallbladder ejection fraction:  $12.5 \pm 3.5$  vs.  $16.1 \pm 3.2$  for MEB,  $3.9 \pm 2.0$  vs.  $5.5 \pm 1.2$  for MIBI and  $0.012 \pm 0.011$  vs.  $0.032 \pm 0.008$  for PIP.

**CONCLUSIONS:** This clinical method is useful to determine the  $Cl_{\text{biliary}}$  of drugs in healthy humans. Correction for gallbladder ejection fraction minimizes inter-subject variability in biliary excretion of drugs by accounting for incomplete and variable gallbladder contraction.

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## PII-1

THE ITEP (INDIVIDUALIZED THERAPY EVALUATION AND PLAN): DEVELOPMENT OF A NATIONAL STANDARD FOR A THERAPEUTIC PLAN. K. L. Franson, PharmD, E. A. Dubois, PhD, A. F. Cohen, MD, PhD, Centre for Human Drug Research, Leiden University Medical Center, Leiden, The Netherlands.

**BACKGROUND:** In a 2003 study, a tool based on the Problem Oriented Medical Record was used to assess Dutch physician's ability to communicate information. At the 2004 ASCP&T Meeting we reported that more than 60% of the physicians in this study did not provide therapeutic information in their discharge letters. Thus, we decided to develop a therapeutic plan format that was consistent with Dutch practice, and which could be incorporated into pharmacotherapy education as both a teaching tool and as an assessment.

**METHODS:** We piloted the new ITEP format at our own institution in Fall 2003. The ITEP format was changed twice over the next two years based on feedback during Train the Trainers sessions with Internal Medicine groups. Subsequently, these sessions spread to the peripheral hospitals and various medical disciplines. In late 2005 we introduced a plan to the Education Committee of the Dutch Society of Clinical Pharmacology and Biopharmacy to develop a therapeutic plan format that would be used in all Dutch Medical schools. Through a special sub-committee, the ITEP has been modified to be applicable to all medical schools education programs. Pre-validation studies were performed this Summer and after some minor changes, we are now doing validation studies of the Standard in three of the nine medical schools for a full analysis.

**RESULTS:** The new 6-Step ITEP Standard:

1. Evaluate the patient's problems
2. Identify the goals of therapy
3. Consider the treatment options
4. Individualize therapy
5. Indicate the definitive plan
6. Monitor treatment plan/Follow-up

Pre-validation studies performed in students, interns and physicians indicate that using the 6-Step ITEP has limited validity as a single-use assessment instrument, but approaches significance when more than two assessments are used. In addition, the 6-Step ITEP is able to identify the group to which the tester belongs (Student, Intern, Physician), confirming the specificity of the tool. Lastly, using the tool (albeit in a controlled setting) greatly improved the physicians reporting of therapeutic information.

**CONCLUSION:** Because of the local success of the ITEP methodology to increase the quality of pharmacotherapy education, the 6-Step ITEP is on it's way to become the new national standard for therapeutic plans.

## PII-2

MODULATORY EFFECTS OF GLUCOSE CONCENTRATIONS ON CARDIAC REPOLARIZATION UNDER CONDITIONS OF DRUG-INDUCED BLOCKADE OF  $I_{\text{Kr}}$  AND/OR  $I_{\text{Ks}}$  CURRENTS IN GUINEA PIGS. R. Hreiche, PharmD, MSc, G. Ricard, J. Turgeon, BPharm, PhD, B. Drolet, BPharm., PhD, Université de Montréal, Université Laval, Montreal, PQ, Canada.

**BACKGROUND/AIMS:** Diabetes has been associated with increases of both QT interval duration and dispersion, which may trigger fatal arrhythmias. The objective of the present study was to evaluate modulation of cardiac repolarization and of potassium repolarizing currents by glucose concentrations.

**METHODS:** 1) Hearts ( $n = 48$ ) from male Hartley guinea pigs were isolated and buffer-perfused in the Langendorff mode. Hearts were paced at a basic cycle length of 250 or 150 msec, and the  $\text{MAPD}_{90}$  was measured. Three glucose concentrations (1, 5, 20 mM) were used to assess effects of glucose levels on repolarization. After a 5-min control perfusion with buffer, hearts were perfused with dofetilide 20 nM ( $I_{\text{Kr}}$  block), chromanol 293 10  $\mu\text{M}$  ( $I_{\text{Ks}}$  block) or both for 10 min. A 10-min washout period was then started to assess reversibility of drug effects. 2) Chinese Hamster Ovary (CHO) cells ( $n = 15$ ) were transfected with HERG gene, coding for  $I_{\text{Kr}}$ . Glucose effects on the  $I_{\text{Kr}}$  blockade by *d*-sotalol 25  $\mu\text{M}$  was measured by the whole cell mode of patch-clamp technique.

**RESULTS:** 1) Dofetilide 20 nM prolonged  $\text{MAPD}_{90}$  at BCL 250 msec by  $17.0 \pm 0.7$  msec at glucose 5 mM,  $25.1 \pm 2.7$  msec at 1 mM ( $p < 0.01$  vs glucose 5 mM) and  $24.2 \pm 1.3$  msec at 20 mM ( $p < 0.05$  vs glucose 5 mM). Chromanol 293 10  $\mu\text{M}$  prolonged  $\text{MAPD}_{90}$  at BCL 150 msec by  $7.4 \pm 0.2$  msec at glucose 5 mM,  $7.5 \pm 0.3$  msec at 1 mM ( $p > 0.05$  vs glucose 5 mM) and  $7.3 \pm 0.2$  msec at 20 mM ( $p > 0.05$  vs glucose 5 mM). When both drugs were used concomitantly at BCL 250 msec,  $\text{MAPD}_{90}$  was prolonged by  $35.3 \pm 0.8$  msec at glucose 5 mM,  $34.8 \pm 1.0$  msec at 1 mM ( $p > 0.05$  vs glucose 5 mM) and  $35.8 \pm 1.3$  msec at 20 mM ( $p > 0.05$  vs glucose 5 mM). 2) In patch-clamp recordings, glucose 1 and 20 mM (vs glucose 5 mM) reduced the current amplitude of  $I_{\text{Kr}}$ . Furthermore, while *d*-sotalol 25  $\mu\text{M}$  blocked  $50 \pm 4\%$  of  $I_{\text{Kr}}$  with glucose 5 mM, blockade increased to  $74 \pm 2\%$  ( $p < 0.001$ ) at 1 mM and to  $65 \pm 4\%$  ( $p < 0.05$ ) at 20 mM.

**CONCLUSION:** Low and high glucose concentrations potentiate the  $\text{MAPD}_{90}$ -prolonging effects of dofetilide and  $I_{\text{Kr}}$  blockade effects of *d*-sotalol. It does not appear to be the case when block of  $I_{\text{Ks}}$  is performed by chromanol 293, or when block of  $I_{\text{Kr}}$  and  $I_{\text{Ks}}$  is performed simultaneously. These results suggest that glycemic level