OII-C-3

ENHANCED GLUCURONIDE RENAL SECRETION FOLLOWING ENDOTOXIN ADMINISTRATION IN HUMANS. P. J. Van Ess, PhD, R. T. Tosheva, PhD, C. M. Charriez, PharmD, S. I. Shedlofsky, MD, R. A. Blouin, PharmD, University of Kentucky, Lexington, KY.

In man, the acute phase response (APR) and oxidative stress (OS) induced by endotoxin (LPS) administration is known to alter the pharmacokinetics (PK) of drugs. Changes in renal secretion mechanisms of glucuronide (GLUC) conjugates could potentially play a role in these altered PK. **Purpose:** To determine if the renal clearance (CL_R) of the secreted GLUC metabolite (6-hydroxychorzoxazone GLUC, 6-OH CZN-GLUC) of chlorzoxazone (CZN) is altered following LPS treatment. Further, to see if changes in CL_R following LPS treatment are related to inter-subject differences in the APR/OS as indicated by peripheral blood mononuclear (PBM) cell nuclear factor kappa-B (NF-κB) activation. **Methods:** Six healthy male volunteers in a balanced crossover design received 250 mg CZN following saline or two consecutive daily doses of LPS. Blood and urine were collected for determination of CZN, 6-OH CZN and markers of the APR and OS. **Results:** Following LPS an APR and OS was induced in all subjects as exemplified by significant ($p<0.05$) increases in C-reactive protein, cytokines, WBC counts, F_2-isoprostanes, and plasma nitrate/nitrite concentrations. A significant increase (mean=59%; $p<0.05$) in 6-OH CZN-GLUC CL_R was observed in all subjects following LPS treatment, which significantly correlated ($R=-0.902$, $p<0.05$) with changes in PBM cell NF-κB activation. **Conclusion:** These data demonstrate the potential for significant increases in the renal secretion of GLUC conjugates following an APR in man.

OII-C-4

THE PLACEBO EFFECT: ADVERSE EVENTS COMMONLY SEEN IN HEALTHY VOLUNTEER PHASE I DRUG TRIALS - AN OBSERVATION ON FINDINGS, COMPARING ACTIVE WITH PLACEBO TREATMENT. D. A. Bradford, MBBS, T. G. Mant, FRCP, D. A. Amin, MRCGP, M. P. Angell, MRCP, Quintiles GDRU, London, United Kingdom (Great Britain).

Adverse events (AEs) are any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal (investigational) product. AEs are commonly reported in placebo-treated volunteers. In this study, the AEs were reviewed retrospectively from the double-blind, placebo-controlled healthy volunteer studies performed at GDRU over a one-year time period, where the reports were generated in-house. MedRA 3.0 coding was used.

594 volunteers' data were reviewed, from 14 studies involving 11 new chemical entities. 48% of all volunteers experienced at least one AE. Surprisingly, when broken down into two discrete groups, those receiving active medication and those on placebo, this proportion of volunteers experiencing AEs was seen to be constant: active 48%, placebo 49 %. The commonest AEs seen when all volunteer data was combined were headache, flu-like symptoms, dizziness, abdominal pain and sedation. For volunteers on placebo medication, headache, dizziness and sedation were the commonest symptoms. 95% of all AEs were mild in severity. There was no clear difference in the number or nature of AEs between the two groups, even when AE severity was taken into account.

Possible trial-related and non-trial related reasons for this were discussed, along with possible methods to reduce AE incidence. The results from this study show that the 'placebo effect' may account for up to 50% of all adverse events seen in healthy volunteer Phase I trials.

PDII-A-1

LONG-TERM THERAPY WITH NEBIVOLOL DOES NOT CAUSE NITRATE TOLERANCE. G. Koshucharova, MD, K. Stoschitzky, MD, W. Klein, MD, Division of Cardiology, Universitätsklinik Graz, Graz, Austria.

Purpose: Continuous long-term therapy with nitrates may cause nitrate tolerance. Nebivolol is a highly selective beta1-adrenergic antagonist with additional NO-mediated vasodilatory effects. However, this substance never was investigated whether or not it might cause tolerance to nitrates when administered long-term.

Methods: Therefore, we performed a randomized, double-blind, placebo-controlled, cross-over study in 16 healthy males. Subjects received 5 mg Nebivolol or placebo once daily for eight days in random order divided by a drug-free interval of two weeks. Forearm blood flow (FBF) was measured by venous occlusion plethysmography three hours following oral intake of the respective last drug, then subjects received 4 mg nitroglycerin/minute/kg body weight intravenously for five minutes, and FBF was measured again.

Results: Following eight days of continuous intake of placebo, nitroglycerin increased FBF by 54 % ($p < 0.05$), whereas nitroglycerin increased FBF by 96 % ($p < 0.05$) following eight days of continuous intake of Nebivolol, with the increase following Nebivolol being significantly ($p < 0.05$) more pronounced than that following placebo.

Conclusion: These findings indicate no evidence of nitrate tolerance during long-term administration of Nebivolol. In contrary, chronic treatment with Nebivolol appears to increase rather than to decrease the vasodilating effects of nitroglycerin.

PDII-A-2

DIGOXIN-CARVEDILOL INTERACTIONS IN CHILDREN. S. Ratnapalan, MBBS, A. Costei, MD, L. Benson, MD, K. Griffith, BSc, G. Koren, MD, The Hospital for Sick Children, Toronto, Canada.

Background: Carvedilol is increasingly co-administered with digoxin in children with ventricular failure failure. Pharmacokinetic interactions were suggested in adults, but never assessed in the pediatric age group. **Objectives:** To study potential pharmacokinetic interactions between carvedilol and digoxin, which may lead to digoxin accumulation. **Methods:** Eight children, aged 2 weeks to 8 years, with moderate to severe ventricular failure who received digoxin alone and then supplemented with carvedilol. Glomerular filtration rate (GFR) and clearance of digoxin were compared before and during carvedilol therapy. **Results:** The oral clearance of digoxin tended to decrease with carvedilol (from 153.0 ± 92.3 to 80.6 ± 23.9 ml/min/1.73m2 ($p=0.056$). The ratio digoxin clearance to GFR decreased two-fold (1.81 ± 0.6 to 1.0 ± 0.24) ($p=0.002$). Two children suffered from digoxin toxicity when carvedilol was added. **Conclusions:** Carvedilol increases serum concentrations of digoxin in children, probably due to a combination of inhibition of tubular secretion and enhancement of intestinal absorption. Dosage reduction of at least 25% is recommended as is vigilance signs of digoxin toxicity.