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Abstracts of papers, Ninety-eighth Annual Meeting, The Town and Country Hotel San Diego, California, March 5–8, 1997**

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PI-1

ALTERED CYTOKINE PRODUCTION INDUCED BY SULFAMETHOXAZOLE HYDROXYLAMINE. D.A. Hess BSc*, W.Y. Almawi*, R. Puvanesasingham*, M.J. Rieder. Depts. of Peds., Pharm./Tox., Children's Hosp. of Western Ont., Univ of Western Ont., London, Canada.

Sulfamethoxazole hydroxylamine (SMX-HA) has been implicated in sulfonamide hypersensitivity reactions. SMX-HA also inhibits mitogen-stimulated T-lymphocyte proliferation and antibody production *in vitro*. Given the importance of cytokines in the immune response, we investigated the effects of SMX-HA on cytokine transcription and translation. The production of Th1-type (IL-2, IFNγ, TNFα) and Th2-type (IL-4, IL-12) cytokines were measured to explore SMX-HA interference in cell-mediated immunity and antibody production. SMX-HA treated (0-100μM) human peripheral blood mononuclear cells were incubated for 18 hours with PMA and PHA to stimulate cytokine mRNA production. Reverse transcription polymerase chain reaction and agarose gel electrophoresis were used to detect specific cytokine mRNA transcripts. Cytokine protein was quantified by enzyme linked immunoabsorbent assay. SMX-HA (0-50μM) had no effect on Th1-type cytokine production. However IL-4 transcription and translation were significantly reduced in SMX-HA treated cells. This suggests the mechanism of SMX-HA induced inhibition is not due to decreased Th1 cytokine transcription, and thus differs from commonly used immunosuppressives cyclosporin A and FK-506. IL-4 stimulates humoural immune responses, and the decrease in antibody production observed with SMX-HA *in vitro* may be a direct result of decreased Th2 cytokine elaboration.

PI-2

DOSE-RESPONSE OF ADVERSE EVENTS (AE) IN TITRATION STUDIES OF TERAZOSIN IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA (BPH). C. Maurath,MS,T. Lin,PhD, B.Hosmane,PhD, D.Jordan,PhD, R.J. Padley,Abbott Labs, IL.

Dose-response evaluations of drugs that must be titrated are complicated due to confounding dose escalation and exposure time effects. The dose-response over time of hypotension AEs in placebo (P) controlled BPH studies of Terazosin (T) was evaluated by (1) time-to-first event using Cox proportional hazards model with time dependent covariates and (2) logistic regression with generalized estimating equations allowing for multiple events. Doses were assigned to P patients according to the titration scheme in the respective study. 6 combined studies (360 P, 636 T patients) had a difference ($p = 0.001$) in AE rates between P (5.6%) and T (14.5%) without a dose dependence, (treatment by dose interaction $p = 0.50$ by (1) and $p = 0.63$ by (2)0. Applying (1) and (2) to HYCAT (Roehrborn, J. Urol, 1996) and VA 359 (Lepor, NEJM, 1996) studies (1335 P, 1358 T totals) with AE rates of 7.9% (P) and 18.9%(T) produced congruent results. Across studies a treatment-time, not dose, effect of T for these AEs was found. We propose 2 methods to assess AEs over time for titrated drugs.

*Nonmember of the Society.

**Abstracts appear in presenting order. The first author is the presenter. PI, PII, PIII, and PIV designate Poster Sessions I, II, III, and IV; OI, OII, and OIII designate the first, second, and third oral presentation sessions.

PIV-42

GENDER AFFECTS THE RATE-DEPENDENT PROLONGATION OF CARDIAC REPOLARIZATION BY D-SOTALOL X.K., Liu*, MD, W.X., Wang*, MD, R.L. Woosley, MD, PhD, Dept. of Pharmacol., Georgetown Univ. Medical Ctr., Washington DC

Torsades de pointes (TdP) is frequently associated with the use of drugs such as d-sotalol or quinidine that prolong cardiac repolarization. Females are at a higher risk of developing drug-induced TdP. Therefore we examined possible gender differences in the effect of d-sotalol on cardiac repolarization. Hearts from female and male rabbits were perfused utilizing the Langendorff method and paced at 0.4, 0.8 and 1.2 sec intervals to study rate-dependent changes of QT interval. ECGs from three orthogonal leads were recorded and QT intervals before and after addition of 1, 10 and 100 μM d-sotalol were measured. Results: 1). At slower pacing (1.2 sec), females are more sensitive to QT prolongation by d-sotalol; 2). D-sotalol showed marked reverse rate-dependency in females but not in males at 1 and 10 μM d-sotalol concentrations. Conclusions: 1). Female rabbit hearts are more sensitive to QT prolongation by d-sotalol at slower pacing rates, and this may contribute to the higher risk of TdP in females; 2). At clinically relevant concentrations, reverse rate-dependency of d-sotalol is gender-dependent; 3). The finding that reverse rate-dependency mainly occurred at pacing intervals of 0.4 and 0.8 sec is consistent with Ik_s accumulation at faster pacing rates but does not exclude involvement of other currents.

PIV-43

PLATELET ALPHA2-ADRENOCEPTORS DENSITY IN HYPERCHOLESTEROLEMIA. RELATIONSHIP WITH PLATELET SENSITIVITY TO EPINEPHRINE. C.R. Sirtori MD,PhD; D. Baldassarre PhD, *N. Mores, MD; S. Colli PhD, E. Tremoli PhD and P. Preziosi MD. E. Grossi Paoletti Ctr., Inst. of Pharmacol. Sci., University of Milan, Italy and *Inst. of Pharmacol., Catholic University of Sacred Heart, Rome, Italy.

Aim of the study was to assess whether platelet hyperaggregation to epinephrine, frequently observed in hypercholesterolemia is associated with an increase of α_2-adrenoceptor density and/or affinity for epimephrine. Thus, platelet aggregation and binding studies, using [^{3}H]yohimbine as ligand, were performed on platelets isolated from 30 type IIa hypercholesterolemic patients (HC) and 23 controls. Platelet aggregation to epinephrine, evaluated as AC_{50}, was significantly higher in HC than in controls (0.9±1vs 0.4±0.3 μg/ml $p<0.01$). A significant increase of α_2-adrenoceptor density (Bmax) was observed in a subgroup of 13 HC patients, compared to 13 sex and age matched controls (280±61 and 230±49 fmol/mg prot., respectively, $p<0.03$). In addition, in this subgroup, an inverse correlation between platelet aggregation and plasma total ($r=-0.39$, $p<0.05$) and LDL-cholesterol levels was found ($r=-0.38$, $p<0.05$), concomitantly with a direct correlation between platelet receptor density and total and low density lipoprotein cholesterol ($r=0.54$; $p<0.01$ and $r=0.44$; $p<0.05$). In conclusion our results indicate that platelet α_2-receptor density is increased in hypercholesterolemia and that plasma and LDL-cholesterol levels significantly correlate with platelet α_2-receptor density. These findings explain, at least in part, the enhanced platelet response to epinephrine observed in hypercholesterolemia.

PIV-44

SYMPATHETIC ACTIVATION IN THE ELDERLY: IS IT DUE TO IMPAIRED ALPHA$_2$ ADRENERGIC FEEDBACK SYMPATHOINHIBITION? C.C. Lang MD, C.M. Stein MD, *F.J. Belas PhD, *I.A. Blair PhD, *M Wood MD, A.J.J. Wood, MD. Vanderbilt University, Nashville,TN.

Progressive sympathetic activation occurs with aging. To determine the role of diminished sensitivity to central α_2 adrenergic sympathoinhibition in the enhanced sympathetic activation seen in the elderly, we compared the effects of cumulative doses of clonidine (1,2, and 3 μg/kg *i.v.*) on blood pressure and sympathetic activity in 7 healthy elderly (mean age 73±6 (SD) years) and 9 healthy young volunteers (28±9 years). Sympathetic activity was determined by measurement of norepinephrine spillover using the radioisotope dilution method. Basal plasma norepinephrine was significantly higher in elderly (276±93 pg/ml) than in young subjects (155±37 pg/ml, $P<0.01$). Compared to young subjects, basal norepinephrine spillover tended to be higher (0.85±0.26 vs 0.68±0.35 ng/min) and norepinephrine clearance tended to be lower (3.2±1.0 vs 4.4±1.7 L/min) in the elderly. After clonidine, both plasma norepinephrine and norepinephrine spillover decreased significantly in both elderly and in young subjects ($P<0.0001$) with no significant difference between the groups. The decrease in blood pressure following clonidine was also similar in elderly and young subjects. Plasma levels of clonidine did not differ significantly between the elderly and young. These findings suggest that increased sympathetic activation seen in the elderly is not due to an altered sympathoinhibitory response to α_2 adrenergic stimulation.

PIV-45

SUPINE MEAN ARTERIAL BLOOD PRESSURE (MAP) LOWERING AND ORAL TOLERANCE OF BMS-186716, A NEW DUAL METALLOPROTEASE INHIBITOR OF ANGIOTENSIN CONVERTING ENZYME (ACE) AND NEUTRAL ENDOPEPTIDASE (NEP), IN HEALTHY MALE SUBJECTS. W. Liao MD PhD, C. Delaney MS, R. Smith PhD, S. Lubin RN, S. McNulty RD, K. Davis MS, A. Meier MS, H. Uderman MD, Bristol-Myers Pharmaceutical Research Institute and Medical Center at Princeton, Princeton, NJ

The MAP lowering effect of BMS-186716 was examined in a double blind, placebo controlled, ascending oral single dose tolerance study. Nine (9) healthy male subjects were randomized with placebo or active (3:6) in each of 7 doses from 2.5 to 500 mg. MAP and safety parameters were monitored over 2 days post-dose. Fixed salt diet was provided before and after dosing. **MAP**: Mean change (SD) from baseline was detected, e.g. a peak effect (occurred 3-6 hr postdose), -5.5±6.7, -8.0±7.7, -19.0±3.5, -13.4±8.7 mmHg and a 24-hr effect 0.9±5.2, -4.6±7.1, -10.0±3.3, -10.8±6.7 mmHg for placebo(n=21), 2.5(n=6), 50(n=6), and 500 mg(n=6), respectively. **Safety:** No serious AEs or withdrawals were reported. No supine tachycardia was found. Key minor AEs associated with active were: headache (x8), facial flushing (x7, most in 250-500 mg), warmth sensation (x5) and nausea (x4) were found. **Conclusions:** BMS186716 showed a sustained effect of lowering MAP over 24 hours. It had an excellent oral single dose safety profile up to 125 mg. These results would also support once-a-day dosing consideration for BMS-186716.