PII-12

BETA-RECEPTOR OCCUPANCY AFTER CHRONIC BISOPROLOL DOSING. C.J. Rosebraugh, MD,* J.T. Barbey, MD, C. Funck-Brentano, MD,* S.U. Yasuda, MS, PharmD, Div of Clin Pharmacol, Georgetown U Med Ctr, Washington, DC and Clin Pharmacol, Saint-Antoine Univ, Paris, France.

With evidence that β_1-adrenergic receptor blockers are an integral part of post-myocardial infarction and angina therapy, we assessed the β_1-receptor occupancy by antagonist present in plasma after chronic bisoprolol therapy. Ten patients took bisoprolol 10 mg once daily for five consecutive days. Occupancy was determined in peak and trough plasma samples in an *in vitro* receptor binding assay using rat salivary glands as a source of β_1-receptor. Percent decrease in exercise heart rate was determined as compared with control tests. A linear relationship between occupancy and percentage decrease in exercise heart rate was observed (r^2=0.56, P<0.01). Bisoprolol's low K_i (5.35×10^{-9}M) and correlations of bisoprolol plasma concentrations with percentage occupancy demonstrated that patients maintained greater than 50% receptor occupancy at trough levels. This demonstrates that bisoprolol maintains high levels of β_1-receptor occupancy at trough levels after chronic dosing.

PII-13

ADRENERGIC RESPONSES IN POST-MENOPAUSAL WOMEN: NO EVIDENCE OF MODULATION BY ESTROGEN. G.G. Sofowora, MBChB,* I. Singh, MD,* C.M. Stein, MBChB, H.B. He, PharmD,* A.J.J. Wood, MBChB, Div of Clin Pharmacol, Vanderbilt Univ Sch of Med, Nashville, TN.

Estrogen supplementation results in a decrease in cardiovascular morbidity and mortality through poorly defined mechanisms. To determine whether estrogen attenuates sympathetic response, we studied 10 healthy post menopausal women (age 54.1±10.9 years) after both a placebo patch and estrogen patch, in random order, for 36 hours. Heart rate, blood pressure, forearm blood flow and norepinephrine spillover (SO) were measured at rest, during mental stress-stroop test (ST) and during a cold pressor (CP) test. Hemodynamic responses and SO were increased during the ST and CP but short term estrogen did not affect these responses suggesting that reduction in stress response does not contribute to estrogen's beneficial cardiovascular effects.

	Pulse		MAP		FBF		NESO	
	P	E	P	E	P	E	P	E
Baseline	63	62	77	78	1.9	2.1	896	1566
	±7	±7	±6	±6	±1	±1	±764	±1291
Stroop	70	70	85	83	3.0	3.7	881	2153
	±9	±9	±8	±9	±2	±2	±610	±1787
CPT	71	69	87	85	2.3	1.9	1488	2059
	±9	±6	±8	±9	±1	±1	±1042	±1219

PII-14

LIMITED AVAILABILITY OF NO IMPAIRS HEMODYNAMIC EFFICACY OF THE NEW ORGANIC NITRATE SP/W-5186 IN MAN. D. Trenk,* PhD, M. Hinder,* MD, E. Fung,* E. Stengele,* MD, R. Bonn,* PhD, E. Jähnchen,* MD, Dept Clin Pharmacol, Herz-Zentrum, Bad Krozingen, Germany.

SP/W-5186 is a new organic nitrate, which is converted into the active metabolite by hydrolysis. The latter is in vitro (rat aortic rings) approximately 50 times more potent than Isosorbide-5-mononitrate (IS-5-MN). The time courses of effects of SP/W-5186 150 mg on established surrogate parameters for the antiischemic efficacy of NO-donors were compared with the ones observed following administration of a single dose of IS-5-MN 20 mg in 12 healthy subjects. a/b-ratio of the finger pulse curve increased to a similar extent after administration of both compounds (SP/W-5186: 0.77±0.42; IS-5-MN: 0.72±0.34) in comparison with placebo. Systolic blood pressure (RRsys) following orthostatic challenge decreased (SP/W-5186: -27.0±10.8 mmHg; IS-5-MN: -26.9±11.7 mmHg) while heart rate (HR) in orthostasis was increased (SP/W-5186: 27.3±12.3 bpm; IS-5-MN: 25.5±11.3 bpm). Calculation of the total integrated effect revealed comparable efficacy on RRsys and HR, while the effect of IS-5-MN (14.35±1.74 1·h) on a/b-ratio was more marked than the one of SP/W-5186 (13.56±1.39 1·h; p=0.0326). Thus, SP/W-5186 exerts significant effects on surrogate parameters of the antiischemic efficacy of NO-releasing drugs with single doses of SP/W-5186 150 mg being equi-effective to IS-5-MN 20 mg. Mass-balance studies indicate that approximately 60% of the dose administered were excreted in urine as metabolites with the intact NO-moiety. The attenuated hemodynamic efficacy of SP/W-5186 in man can therefore be attributed to the rapid renal elimination of the active, NO-releasing metabolites.

PII-15

CONCENTRATION-EFFECT RELATIONSHIPS OF THE NEW ORALLY ACTIVE RGD-TYPE GLYCOPROTEIN IIB/IIIA-ANTAGONIST S1197 IN MAN. D. Trenk,* PhD, E. Stengele,* MD, R. Adler,* MD, M. Just,*# MD, D. Brockmeier,*# PhD, M. Seibert-Grafe,*# MD, E. Jähnchen,* MD, Dept Clin Pharmacology, Herz-Zentrum, Bad Krozingen, and #Hoechst Marion Roussel, Frankfurt, Germany.

The blockade of the glycoprotein (GP) IIb/IIIa receptor is the most effective means of platelet inhibition. The acetate salt HR1740 and the maleate salt HMR1794 are orally active prodrugs of S1197, which is a non-peptidic RGD-type GP IIb/IIIa receptor antagonist currently under clinical investigation. The inhibitory effects of single oral doses of the acetate salt (54 and 90 mg) and the maleate salt (60, 100, 150 and 200 mg) on collagen- (1 µg/ml) and ADP- (6 and 10 µMol/L) induced platelet aggregation were determined in healthy male volunteers (n=6 per dose) up to 24 hours after administration. Pharmacokinetics of S1197 were linear with a terminal half-life of elimination of 16.8±8.5 h. A dose-dependent increase in the inhibitory effect on agonist-induced aggregation was observed with respect to the maximum effect as well as the duration of effect. Mean maximum inhibition of ADP-induced aggregation (6 µMol/L) was in the order of 70% and was still significant 24 hours after administration of the higher doses (150 and 200 mg). Plasma concentration vs effect relationships of S1197 could be established with EC_{50}-values of 9.3 ng/ml (ADP 6 µMol/L), 15.3 ng/ml (ADP 10 µMol/L) and 33.1 ng/ml (Collagen 1 µg/ml). Activated clotting time (ACT) was not changed compared to placebo. The results indicate that a continuous inhibition of platelet function can be obtained by once daily administration of this new drug.