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CONCENTRATION-EFFECT-RELATIONSHIPS OF TWO INFUSION RATES OF RILMENIDINE, FOR BLOOD PRESSURE AND SEDATION IN HEALTHY SUBJECTS. J.M.A. van Gerven, MD, PhD, M. Dubar, PharmD, N. Frey, PharmD, R.C. Schoemaker, MSc, R. Jochemsen, PhD, A.F. Cohen, MD, PhD, Centre for Human Drug Research, Leiden, The Netherlands, and Institut de Recherches Int. Servier, Courbevoie, France.

Background: The infusion rate can influence the effects of some anti-hypertensives[1] and sedatives.[2] This may be relevant for the optimal release profile of a new rilmenidine SR-tablet.

Aims: To study the effects of infusion rate on blood pressure and sedation over a wide plasma concentration of rilmenidine.

Subjects and methods: Nine healthy subjects (19-26 yrs) took part in a 3-way crossover, placebo-controlled, double-blind, double-dummy study of two *iv* infusion rates (1.8 mg in 1 hr and 2.6 mg in 5 hrs), aimed at the same peak plasma level. The effects on blood pressure (BP) and sedation (saccadic peak velocity, SPV), measured for 24 hrs, and their PK/PD-relationships were compared between the two infusion rates.

Results: The average time profiles of BP and SPV closely followed the drug levels. The average max. systolic/diastolic BP-reductions from baseline were similar with fast- (17.9/11.6 mmHg) and slow-rate infusions (18.3/13.3 mmHg), and small with placebo (3.9/2.0 mmHg). SPV decreased 95.9°/sec (-21.7%) with fast-, 112.1°/sec (-24.6%) with slow-, and 28.2°/sec (-6.3%) with placebo-infusion. PK/PD-relationships were mostly linear for BP and SPV, with no effect of infusion rates.

Conclusion: The rate of administration does not influence the effects of the centrally-acting antihypertensive rilmenidine.

Refs.: [1]CPT 1987;41:26-30, [2]CPT 1994;55:535-545

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BETA-2 ADRENERGIC RECEPTOR (BAR2) POLYMORPHISM IS NOT ASSOCIATED WITH ESSENTIAL HYPERTENSION (HT) IN AFRICAN-AMERICANS (AA) OR CAUCASIAN-AMERICANS (CA). H.G. Xie, MD, PhD, R.B. Kim, MD, C.M. Stein, MD, J.V. Gainer, MD, N.J. Brown, MD, B. Leake, MS,* and A.J.J. Wood, MD, Division of Clinical Pharmacology, Vanderbilt University Medical Center, Nashville, TN 37232-6602.

The human vascular BAR2 mediates vasodilation, with blunted vasodilator responses noted in HT. Common polymorphisms of the BAR2 (Arg16→Gly, Gln27→Glu) are associated with altered response, *in vitro* and *in vivo*. An association between the Gly16 BAR2 variant and HT was found in African Caribbeans but not in black South Africans. No relevant data are available for AA or CA. A PCR-based SSCP method with direct sequencing of the bands of interest was used for detection of the Arg16→Gly and Gln27→Glu BAR2 variants in 311 normotensive (NT) subjects (123 AA and 188 CA) and 172 HT subjects (73 AA and 99 CA). No significant association between the subjects' BAR2 alleles and HT was seen in the two ethnic populations studied (HT *vs* NT; *Gly16:* 52.1% *vs* 51.2% in AA; 56.6% *vs* 54.3% in CA; *Glu27:* 21.9% *vs* 20.7% in AA; 40.9% *vs* 34.8% in CA; all $P>0.05$). These data suggest that the common genetic polymorphisms of the human BAR2 gene do not cosegregate with the presence of HT in AA or CA.

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INTERETHNIC DIFFERENCES IN BETA-2 ADRENOCEPTOR (BAR2) POLYMORPHISMS IN AFRICAN-AMERICAN (AA), CAUCASIAN (CA), AND CHINESE (CHN) POPULATIONS. H.G. Xie, MD, PhD,[1] R.B. Kim, MD,[1] C.M. Stein, MD,[1] J.V. Gainer, MD,[1] N.J. Brown, MD,[1] B. Leake, MS,*[1] Z.S. Xiao, MD,*[2] N. He, MS,*[2] H.H. Zhou, MD,[2] and A.J.J. Wood, MD,[1] Div. Clin Pharmacol, Vanderbilt Univ. Sch. Med.,[1] Nashville, TN 37232-6602; Pharmacogenetics Res. Inst., Hunan Medical University,[2] Changsha, Hunan 410078, China.

There are marked interethnic differences in BAR2-mediated vascular response. To determine if racial differences exist in the distribution of BAR2 polymorphisms, three healthy populations consisting of 104 CHN, 123 AA, and 188 CA subjects were studied. A PCR-based SSCP method with direct sequencing of the bands of interest was used for detection of the two common BAR2 variants (Arg16→Gly and Gln27→Glu). CHN had a significantly lower frequency of the Gly16 allele (41.3%) than AA (51.2%, $P=0.04$) or CA (54.3%, $P=0.003$), a lower frequency of the Gly16 homozygotes than CA (18.3% *vs* 35.1%, $P=0.003$), and a lower frequency of the Glu27 allele (7.2%) than AA (20.7%, $P<0.0001$) or CA (34.8%, $P<0.0001$). AA had a lower frequency of the Glu27 allele (20.7% *vs* 34.8%, $P<0.0001$) and Glu27 homozygotes (4.9% *vs* 15.4%, $P=0.003$) than CA. These data suggest that responses to BAR2 stimulation in different ethnic populations may vary on the basis of genetic factors.

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STEADY-STATE PK OF OMAPATRILAT IN HEALTHY SUBJECTS. C.L. Delaney, MS, M. Jemal, PhD, F.A. Beierle, PhD, I.M. Ferreira, PhD, K.D. Davis, MS, A. Meier, BS, N.F. Ford, MD, PhD, H.D. Uderman, MD, and W. Liao, PhD, MD, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ.

Background: Omapatrilat is a vasopeptidase inhibitor acting on both neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE). The steady-state PK of omapatrilat was examined in a Phase I, ascending, multiple-dose study. **Methods:** Forty-six normotensive subjects were randomized to receive omapatrilat 10, 25, 50, 75, and 125 mg or placebo once daily for 10 days. Plasma concentrations of omapatrilat were analyzed by LC/MS/MS. C_{max} and AUC values were assessed after the first dose and at steady state. **Results:** The steady-state PK profile of omapatrilat indicated a long, effective half-life (14-19 hr) over the dosing range of 10-125 mg. Rapid absorption, indicated by a short T_{max}, was found to be between 0.5-2.0 hr at all doses. Based on C_{max} and AUC, dose linearity of absorption and exposure to omapatrilat on day 1 was confirmed in doses up to 125 mg. At steady state on day 10, C_{max} was linear for the entire dosing range, but AUC was linear up to 75-mg dose level. Omapatrilat demonstrated a pooled AUC accumulation ratio of 1.65. The steady state was reached in 3-4 days, based on long, effective half-life. **Conclusions:** Accumulation of omapatrilat demonstrated a rapid oral absorption and prolonged elimination profile in healthy subjects, providing a basis for a once-daily dosing regimen.