PDI-C-10

ROLE OF CYP3A IN THE METABOLISM, DISPOSITION AND CLINICAL EFFECTS OF l-a-ACETYLMETHADOL (LAAM) IN HUMANS. D. Whittington, BS, P. Sheffels, BS, C. J. Hoffer, CCRC, E. D. Kharasch, MD, PhD, University of Washington, Seattle, WA.

Background: LAAM is a long-acting opioid agonist prodrug used for preventing opiate withdrawal. LAAM undergoes intestinal and hepatic CYP3A-catalyzed bioactivation via sequential *N*-demethylation to nor-LAAM and dinor-LAAM, which are more potent and longer-acting than LAAM. The role of CYP3A in LAAM disposition is unknown. We tested the hypothesis that CYP3A induction (or inhibition) would increase (decrease) LAAM metabolism and bioactivation and thus clinical effect.

Methods: Healthy volunteers (n=13) were studied in an IRB-approved, randomized, balanced crossover. They received oral LAAM after CYP3A induction (rifampin), inhibition (troleandomycin) or control. Plasma and urine LAAM, norLAAM and dinorLAAM were determined by ESI-LCMS.

Results: CYP3A induction (or inhibition) decreased (or increased) plasma LAAM (mean AUC 9 and 594 vs 170 ng-hr/ml) and increased (or decreased) LAAM metabolism (mean [norLAAM+dinorLAAM]/LAAM ratio 10.2 and 3.8 vs 6.0). Surprisingly, however, CYP3A induction (or inhibition) decreased (or increased) plasma metabolites (norLAAM + dinorLAAM mean AUC 113 and 2170 vs 1120 ng-hr/ml). Opioid effects were greater with CYP3A inhibition.

Discussion: CYP3A mediated human LAAM metabolism. CYP3A induction (or inhibition) increased (or decreased) LAAM metabolism but bioactivation and thus clinical effect were oppositely affected. This suggests another, CYP3A pathway, leading to drug inactivation.

PIII-1

EFFECTS OF ARGATROBAN ALONE OR IN COMBINATION WITH PHEN-PROCOUMON OR ACENOCOUMAROL ON PT, APTT AND ECARIN CLOTTING TIME. U. Klinkhardt, MD, J. Graff, MD, H. Breddin, MD, S. Harder, MD, University Hospital Frankfurt am Main, Frankfurt am Main, Germany.

After i.v. therapy with the thrombin inhibitor argatroban (ARG), many patients continue oral anticoagulation (OAC). Phenprocoumon (PH) and Acenocoumarol (AC) are commonly used in Europe.

In an interaction study (N=36 subjects) ARG plasma levels and effects on aPTT, INR, and Ecarin Clotting Time (ECT) alone and during combined treatment with PH or AC were investigated. Subjects received a 5h-infusion of 1.0, 2.0 or 3.0 μg/kg/min ARG at four days before and during initation of OAC.

The PK of ARG was not influenced by OAC. aPTT was prolonged by ARG alone, and further prolonged by 10-30 sec. during OAC. The PK-PD relationship between aPTT and ARG was altered when OAC was initiated, whereas the relationship between ARG and ECT was not affected. A linear relationship was observed between the INR's measured "on" and "off" ARG, and a factor X [INR = X * INR(+ARG)] was obtained by regression analysis. The factor varies with the ISI of the thromboplastin reagent and the ARG-dose (e.g. for PC and ISI 1.02: ARG 1.0, X=0.8; ARG 2.0, X=0.77; ARG 3.0, X=0.66. ISI 2.13: ARG 1.0, X=0.63; ARG 2.0, X=0.56; ARG 3.0, X=0.41). Similar values were found for AC.

A simple rule is proposed for the calculation of the "true" INR during the transition period between ARG and OAC: ARG can be discontinued after initation of OAC when the INR reaches 3.0 to 4.0, resulting in the therapeutic range of INR between 2 and 3. ECT can be used to monitor ARG alone and during oral anticoagulation.

PIII-2

INTERACTION OF THE GLYCOPROTEIN IIB/IIIA-INHIBITOR YM337 WITH UNFRACTIONATED HEPARIN AND ASPIRIN IN HUMANS. J. Graff, MD, U. Klinkhardt, MD, D. Westrup, PhD, H. Breddin, MD, S. Harder, MD, Inst. Clin. Pharm, University Hospital Frankfurt, Inst. Clin. Pharm, University Hospital, Frankfurt am Main, Germany.

In a randomized, placebo-controlled study the pharmacodynamic interaction of unfractionated heparin (UFH) and acetylic salicylic acid (ASA) on YM 337, a monoclonal humanized antibody of the platelet GPIIb/IIIa-receptor, was investigated in 3 treatment groups with each 6 healthy volunteers. Group 1: ASA (3days)+UHF+YM (placebo) Group 2: ASA (placebo)+UFH (placebo)+YM337, group 3: ASA+UFH +YM337. Assessments were made over 24h and included bleeding time (BT), PAC1- and CD62-expression, ADP (20μM)-and collagen-(5μg/ml)-induced platelet aggregation.

Results: In group 3 BT was prolonged to 30 min after UFH administration, increasing to 43±5 min after YM337-infusion (6h). BT remained elevated to 28±15 min at 24 h, while group 1+2 returned to normal values. Collagen-induced aggregation was reduced to 74% under YM337 alone and decreased in group 3 to 24%. In both groups receiving active YM337, PAC1-expression showed a reduction to <20% after 6 hours of infusion. CD62-expression was not significantly affected by any treatment.

Conclusion: UFH and YM337 have strong synergistic effects on BT, while coadministration of ASA strongly augments inhibitory effects of YM337 on collagen induced platelet aggregation.

PIII-3

DIFFERENCES BETWEEN BETA-BLOCKING EFFECTS OF METOPROLOL, BISOPROLOL AND CARVEDILOL. G. Koshucharova, MD, K. Stoschitzky, MD, W. Klein, MD, Division of Cardiology, Universitätsklinik Graz, Graz, Austria.

Purpose: Beta-blockers are effective in the treatment of heart failure. However, metoprolol and bisoprolol decreased mortality by 34%, whereas carvedilol did so by 65%.

Methods: We compared the effects of 50, 100 and 200mg metoprolol, 2.5, 5 and 10mg bisoprolol, and 25, 50 and 100mg carvedilol to those of placebo in a randomized, double-blind, placebo-controlled, cross-over study in 12 healthy males. Two hours after oral administration heart rate was measured at rest and exercise.

Results: At rest, increasing doses of metoprolol and bisoprolol caused increasing effects on heart rate (-13%, -15% and -18% in both cases), whereas increasing doses of carvedilol had decreasing effects (-13%, -7% and -3%). Both 200mg metoprolol and 10mg bisoprolol were more effective than 100mg carvedilol. During exercise, heart rate was decreased by metoprolol (-21%, -22% and -24%), bisoprolol (-17%, -21% and -25%) and carvedilol (-16%, -16% and -18%) to a similar extent.

Conclusion: Carvedilol appears to cause clinically relevant beta-blockade in healthy subjects during exercise but not at rest. This might be a result of reflex sympathetic stimulation caused by a decrease in blood pressure resulting from alpha-blockade. These data might explain why carvedilol, in contrast to metoprolol and bisoprolol, may fail to cause up-regulation of beta-adrenoceptor density and to decrease nocturnal melatonin release. They might possibly be helpful to interpret the results of the forthcoming COMET study.