Pharmacokinetic and Pharmacodynamic evaluation of administration of losartan with aspirin in healthy volunteers.

GD MENDES, PMF Ferreira, JL DONATO, T Gagliano, MF Sampaio, G DE NUCCI

INTRODUCTION: Losartan and aspirin are often used concomitantly in patients with heart failure, ischemic heart disease and hypertension.

OBJECTIVES: 1) To investigate whether aspirin co-administration affects losartan bioavailability.

2) How long platelet inhibition lasts after a single dose of 81 mg of aspirin.

METHODS: 1) Twenty-four healthy volunteers from both sexes were recruited. Volunteers received a single 50 mg losartan with or without a 81 mg aspirin tablet. Blood samples were obtained at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 min post-dosing. The concentrations of losartan were analyzed by LC-MS-MS. Clearance (Cl) and T1/2 were used to evaluate a possible drug-drug interaction. Cmax and AUC0-8 were used to evaluate whether co-administration interferes on the bioavailability process.

2) Eight healthy volunteers were recruited for the pharmacodynamic study. Ex vivo platelet aggregation induced by arachidonic acid 300 µg/mL and ADP 20 µM were performed using a Born aggregometer. Thromboxane B2 release was measured by enzyme immunoassay. In the first period, blood samples were obtained before and after 24, 72 and 168 hours of losartan 50 mg intake. In the second period, blood samples were obtained before and after 24, 72 and 168 hours losartan 50 mg + aspirin 81 mg intake.

RESULTS: From the losartan plasma concentrations vs. time curves the following pharmacokinetic parameters were obtained: ASC0-8 hours, AUCinf, Cmax, Cl, Vd, Tmax, Ke and T1/2. No significant differences were observed in T1/2 (p-value = 0.431), Cl (p-value = 0.554), AUC0-8 hours (p-value = 0.590), Cmax (p-value = 0.987) and Vd (p-value = 0.647).

2). After 24 hours of losartan + aspirin intake, all volunteers showed complete inhibition of platelet aggregation induced by arachidonic acid and thromboxane release was 70±19% reduced (p-value = 0.001). No inhibition of platelet aggregation was observed after induction by ADP but thromboxane release was 89±15% diminished (p-value = 0.017). After 72 hours, aggregation induced by arachidonic acid remained abolished in 6 out of 7 volunteers. Thromboxane release was inhibited by 70±5% and 89±14% for arachidonic acid (p-value = 0.001) and ADP (p-value = 0.004), respectively. After 168 hours, platelets took longer to aggregate after arachidonic acid induction. TXB2 release was inhibited by 28±2% and 63±42% for arachidonic acid (0.068) and ADP (0.031) respectively.

CONCLUSIONS: 1) Since there is no significant difference in losartan bioavailability and elimination when co-administered with aspirin, we conclude that there is no pharmacokinetic interaction between both drugs. 2) One administration of aspirin 81 mg every 3 days can produce substantial inhibition of platelet aggregation. Whether this can cause substantial reduction in GI symptoms, it is under current investigation.