PIOGLIITAZONE STIMULATES RENIN AND FAVORS SODIUM RETENTION AND WEIGHT GAIN IN HEALTHY SUBJECTS

Anne Zanchi, Arnaud Chiolerio, Marc Maillard, Juerg Nussberger, Hans R Brunner, Michel Burnier. Division of Hypertension and Vascular Medicine, CHUV, Lausanne, Switzerland.

Glitazones induce peripheral edema through an unknown mechanism in up to 20% of cases. This study examines the effects of pioglitazone (PIO) on renal sodium handling and renal hemodynamics in healthy male volunteers (HV) exposed to a high (HS) and low (LS) sodium diet. The influence of PIO on plasma renin activity (PRA), aldosterone and atrial natriuretic peptide (ANP) was examined.

Nine HV aged 22-28 y were enrolled. BMI, blood pressure and glucose tolerance were normal. The study had a double-blind, randomized, placebo controlled, twofold cross-over design. Each subject received either PIO 45 mg qd or placebo qd, for 6 weeks, with 2 weeks wash-out. From weeks 1-4, subjects were on their usual diet. During weeks 5 and 6, subjects were either on a LS or a HS diet for a week which was followed by ambulatory blood pressure measurements, hormonal measurements and renal function studies. The differences between PIO and placebo effects were examined (median, range among all subjects). No subject developed edema. Insulin sensitivity, systolic and diastolic blood pressure, glomerular filtration rate, renal plasma flow or filtration fraction did not change significantly with PIO. Weight increased with PIO in 7/9 subjects while on a LS diet (0.7kg; -1.2-2.9) and in 6/9 while on a HS diet (1.1kg; -1.5-3.4). Median sodium (Na) excretion with placebo was of 21.2mmol/24h and 239.7mmol/24h respectively while on a LS and HS diet. Urinary Na excretion decreased with PIO in 6/9 subjects on a LS diet (-12.2mmol/24h; -21.8-7.8, p=0.05), and in 5/9 subjects on a HS diet (-30mmol/24h; -344-69). Na clearance decreased in 6/9 subjects on a LS diet (-0.05 ml/min; -0.11-0.05) and in 6/9 subjects on a HS diet (-0.15 mmol/ml; -2.7-0.4). Na clearance at the proximal level decreased with PIO in 8/9 subjects on a LS diet (-0.9 ml/min; -1.4-1.5, p=0.01) and in 5/9 subjects on a HS diet (-2 ml/min; -4.3-8.5). PRA increased with PIO in 8/9 subjects on a LS diet (0.16 ng/ml/h; 0.07-0.8, p=0.02) and on a HS diet (0.09 ng/ml/h; 0.1-0.21, p=0.03). Aldosterone increased in 5/9 subjects on a LS diet (6 pg/ml; -19-144) and in 6/9 subjects on a HS diet (5 pg/ml; -20-74). ANP levels did not change.

In conclusion, pioglitazone increases PRA, independently from Na intake and favors Na retention in healthy volunteers. This mechanism could contribute to the development of edema in subjects treated with glitazones.

Key Words: Proximal Sodium Reabsorption, Epidemiology, Women