THE EFFECT OF REPEAT DOSING OF MOSAPRIDE ON PLASMA ALDOSTERONE IN HEALTHY JAPANESE VOLUNTEERS

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In man 5-HT_4 agonists have been shown to evoke a rise in plasma aldosterone, an effect that can be blocked with a selective 5-HT_4 receptor antagonist [1–3]. The effect on aldosterone appears to be independent of HPA axis activation, as it is not accompanied by changes in ACTH or cortisol. However, the utility of this response as a biomarker for 5-HT_4 receptor activation appears limited, as the rise in plasma aldosterone may be an acute effect, perhaps limited to a first dose, as repeated administration of cisapride at 8 h intervals failed to evoke further rises in aldosterone [4]. The objective of the current study was to investigate the effect of mosapride on plasma aldosterone and to evaluate the robustness and reproducibility of any effect.

Twelve healthy Japanese male volunteers were entered into this double-blind, placebo-controlled, 4-way crossover study and were randomly assigned to one of four treatment sequences. At each visit, volunteers were dosed orally with a single dose of either mosapride (15 mg) or a matched placebo, each treatment being administered twice with a minimum of 1 week washout between visits. Blood samples were taken at regular intervals between 1 h pre-dose to 3 h post-dose and plasma concentrations of aldosterone, ACTH, cortisol and electrolytes were determined at each time point. In addition, blood pressure and heart rate were measured. The average baseline plasma aldosterone concentration across all study periods was 112.6 pg ml^{-1} (range 57.4, 223.9). Mosapride evoked an increase in plasma aldosterone concentrations, peaking approximately 2–2.5 h post-dose, which re-occurred following repeat dosing either 1 or 3 weeks later. The average plasma aldosterone concentration 2.5 h after the first and second mosapride challenges was 224.5 pg ml^{-1} (range 75.9, 493.7) and 193.3 pg ml^{-1} (range 104.6, 312.1) respectively compared with 103.5 pg ml^{-1} (range 55.8, 199.7) and 110 pg ml^{-1} (range 59, 269) for placebo. Average plasma aldosterone concentrations after mosapride dosing were almost twice (68% greater) those seen on placebo ($P < 0.0001$). No significant changes were seen in any other parameter. In conclusion, mosapride (15 mg) can evoke a rise in plasma aldosterone that is both significantly greater than that seen in response to placebo and is repeatable when the interval between challenges is at least 1 week. The increases were independent of any apparent stimulation of the HPA axis or changes in cardiovascular parameters.

This study demonstrates the robustness and reproducibility of the aldosterone response to mosapride stimulation and suggests that this may form the basis for a biomarker of 5-HT_4 receptor activation in man.

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