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THE ANTIDIURETIC EFFECT OF FEDOVAPAGON CAN BE EFFECTIVELY CONTROLLED BY DOSE

Hypothesis / aims of study

Vasopressin V_2-receptor (V_2) agonism has been shown to be effective in nocturia. The reported risk of hyponatraemia with the peptide V_2 agonist desmopressin has been suggested to be a result of the high variability in the compound's bioavailability. This is noted both within and between subjects, especially in the elderly, and can result in a prolonged duration of action with an increased risk of water retention. Fedovapagon (VA106483), a novel non-peptide drug, is a selective V_2 agonist. The low variability of pharmacokinetic and pharmacodynamic response to fedovapagon between subjects has previously been reported [1]. The purpose of this study was to confirm that duration of action of fedovapagon within a subject can be effectively controlled by dose.

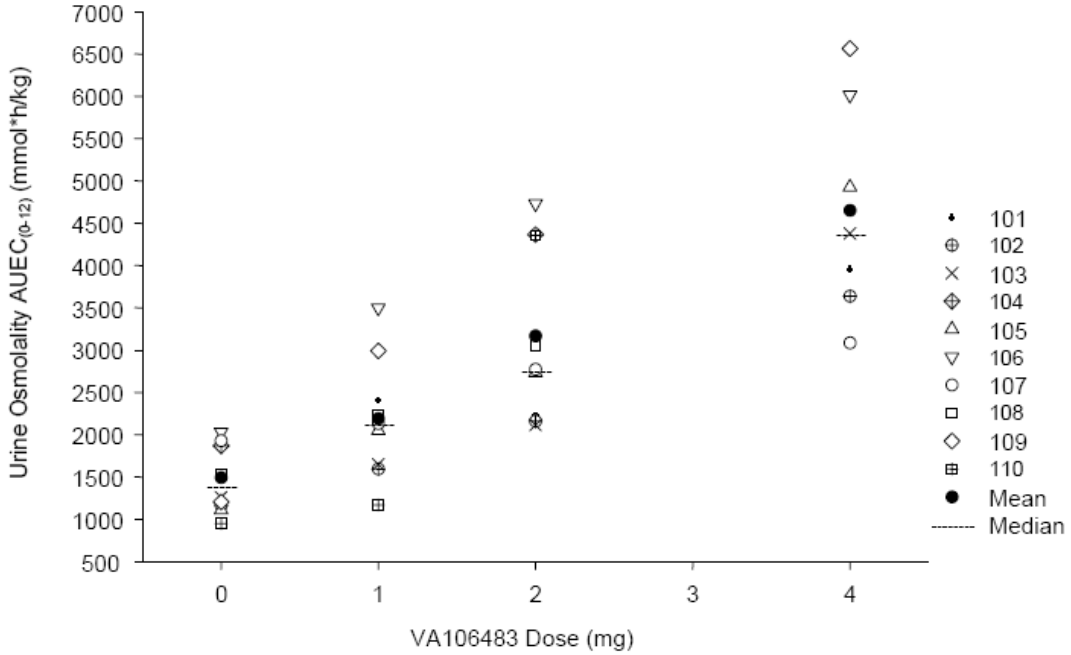
Study design, materials and methods

Ten older male subjects aged 65 years and over were enrolled in this single centre, open label, dose escalation study and received single oral doses of placebo and 1 mg – 2 mg – 4 mg fedovapagon. Each dose was separated by a 48 hour (h) period. Subjects underwent pre-treatment water loading from 2 h before dosing. A water loaded state was maintained for a total of 10 h. At designated time intervals, determination was made of urine volume, urine osmolality and safety parameters.

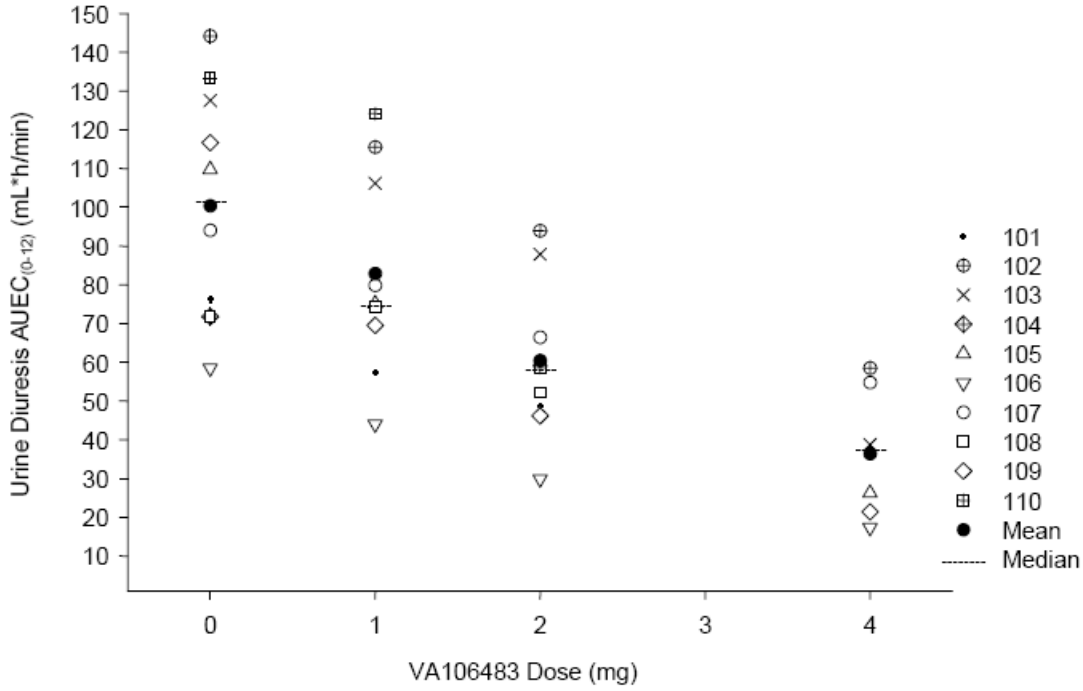
Results

The population mean age was 70 years (SD 4). Dosing of fedovapagon to the over-hydrated subjects resulted in production of lower volumes of concentrated urine and consequent reduced diuresis in all subjects. In all subjects, even at the highest dose of 4 mg, drug effect had diminished sufficiently to permit maximal water excretion by approximately 12 hours post dose. The antidiuretic effect (osmolality and diuresis), assessed by area under the effect curve (AUEC) analysis, increased with increasing dose in all subjects and was significantly correlated with increasing exposure ($p<0.0001$). In each model, placebo $AUEC_{0-12}$ was a statistically significant covariate ($p<0.03$).

Individual, Mean, and Median Urine Osmolality $AUEC_{(0-12)}$ versus Administered Dose



Individual, Mean, and Median Diuresis $AUEC_{(0-12)}$ versus Administered Dose



Interpretation of results

The data in this study show that the duration of action of fedovapagon can be controlled by dose while achieving a period of antidiuresis of sufficient duration to reduce urine production during the night time period if dosed before bedtime. This is an important property in the context of the treatment of nocturia since it avoids persistent antidiuresis which has the potential to lead to accumulation of fluid the morning after a bedtime dose and consequent electrolyte dilution.

Concluding message

This study shows that the antidiuretic effect of fedovapagon can be controlled by dose giving the potential to improve the risk:benefit profile of V_2 agonists in the treatment of nocturia.

The period of antidiuresis needed to achieve clinical efficacy in nocturia will be confirmed in further investigation.

References

1. Imnadze M, Weiss J, Yea C, Marks B, McElwaine-Johnn H, Nathadwarawala M. Novel non-peptide pharmacologic therapy for nocturia in men. J Urology 183 (Issue 4, Suppl): e590, April 2010

Disclosures

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