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ANTIDIURETIC EFFECT OF FEDOVAPAGON IN OLDER MALES WITH BENIGN PROSTATIC HYPERPLASIA AND NOCTURIA

Hypothesis / aims of study

Fedovapagon (VA106483), a novel non-peptide drug, is a selective vasopressin V_2-receptor agonist in development for the treatment of nocturia. The purpose of this study was to establish the dose response relationship of fedovapagon and nocturnal urine volumes (NUV), nocturnal void frequency and time to first void in a population of males aged 65 years and over with benign prostatic hyperplasia (BPH) and nocturia.

Study design, materials and methods

Thirty subjects, mean age 69.2 years (SD 3.2) with BPH and nocturia (2 or more voids per night) were randomised in this double-blind, placebo-controlled, five-way cross-over study. Following a two day untreated run-in period, each subject received five treatment periods, each of 2 nights, comprising 0.5 mg – 1 mg – 2 mg – 4 mg fedovapagon and placebo administered in a double-blind fashion in a randomised treatment sequence, each separated by a 1 night single-blind placebo. Subjects had free access to fluid throughout the study, ensuring thirst was satisfied at all times. Subjects were dosed with Investigational Medicinal Product (IMP) at approximately 9 pm. Subjects were prompted to void 1 hour (h) post IMP (bedtime void) and again at 9 h (first morning void). Urine voided after the prompted bedtime void and up to and including the first morning void was included in the NUV. The frequency of nocturnal voids and time to first nocturnal void was also recorded.

Results

Treatment with fedovapagon was well tolerated. Fedovapagon was effective from the first night of dosing. There was no carry-over effect of fedovapagon during the single-blind placebo treatment night between the active treatment periods. There was no effect of fedovapagon treatment on the overall 24 h urine volumes.

Fedovapagon treatment reduced NUV in a dose responsive manner.

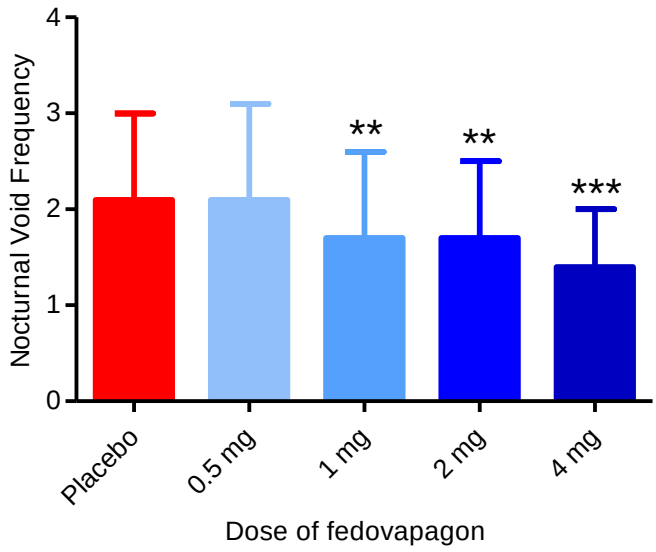
Mean nocturnal void frequencies during untreated run-in and during 4 mg treatment were 2.9 voids and 1.4 voids respectively. There was a statistically significant reduction in mean nocturnal void frequency at 1 mg, 2 mg and 4 mg doses of fedovapagon compared to placebo.

Mean times to first nocturnal void during untreated run-in and during 4 mg treatment were 2.1 h and 4.5 h respectively. There was a statistically significant increase in mean time to first nocturnal void at all doses of fedovapagon compared to placebo.

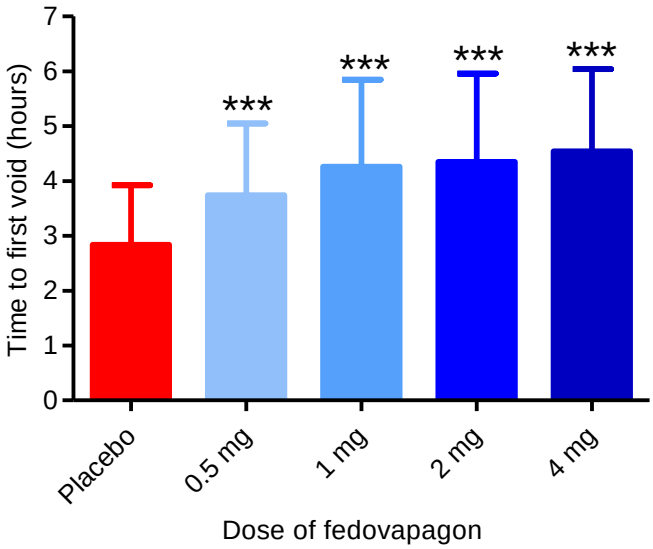
Summary of Statistical Analysis of the Effect of Fedovapagon on Nocturnal Urine Volume (mL) [Both Dosing Days Combined]

Difference in NUV (mL)	LS Means	95% confidence interval	p-value
Placebo – 0.5 mg fedovapagon	18.08	-61.60: 97.75	0.654
Placebo – 1 mg fedovapagon	150.27	70.59: 229.94	<.001
Placebo – 2 mg fedovapagon	181.69	102.02: 261.37	<.001
Placebo – 4 mg fedovapagon	303.75	224.07: 383.42	<.001

Effect of Fedovapagon on Nocturnal Void Frequency



Effect of Fedovapagon on Time to First Nocturnal Void



*Both graphs display mean (+1 SD) for the mean of both dosing days combined. Data were analysed using an ANOVA model: ** p<0.01, *** p<0.001 compared to placebo*

Interpretation of results

Administration of fedovapagon to this population resulted in a dose responsive reduction in mean nocturnal urine volume with a corresponding dose responsive reduction in nocturnal void frequency and an increase in time to first void. The absence of effect of treatment on overall 24 hour urine volume indicates a shift of urine production from the night time period to the daytime period on fedovapagon rather than a change in overall fluid balance. The absence of carry-over effect from each treatment period together with the effectiveness of fedovapagon treatment on the first night of dosing confirms the suitability of its profile as treatment for nocturia where a clear onset and offset of drug effect is required to maintain an acceptable risk:benefit profile in this indication.

Concluding message

This study confirms the dose responsive nocturnal antidiuretic effect of fedovapagon in older males with BPH and nocturia. This supports further study of fedovapagon in patients with bothersome urological symptoms who are likely to present seeking treatment for nocturia.

Disclosures

Funding: This study was sponsored by Vantia Limited **Clinical Trial:** Yes **Registration Number:** ClinicalTrials.gov identifier: NCT01330927 **RCT:** Yes **Subjects:** HUMAN **Ethics Committee:** The Ethics Committee of the Land Berlin (Working Party 6) **Helsinki:** Yes **Informed Consent:** Yes