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ANTIDIURESIS IN THE TREATMENT OF OVERACTIVE BLADDER SYNDROME

Hypothesis / aims of study

Overactive bladder syndrome (OAB) is a symptom complex consisting of urgency, urgency incontinence (UUI), frequency and nocturia. Lifestyle interventions and antimuscarinics have been the mainstay of medical treatment. However, the use of antimuscarinics can be limited by their side effects, especially dry mouth. OAB causes the patients to void smaller volumes, than others who do not suffer with OAB, leading to frequent voiding. Antidiuresis, using nasal desmopressin, has been shown to be effective in the treatment of daytime urinary incontinence with minimal side effects and no antimuscarinic side effects (1). Oral desmopressin, taken at night, has been shown to be effective in adult men (2) and women (3) suffering from nocturia. This study looked at whether oral desmopressin, by decreasing urine production by the kidneys, would prolong bladder filling time thereby increasing the time to reach maximum capacity, thus reducing OAB symptoms, and providing an alternative method of treatment to OAB sufferers.

Study design, materials and methods

An investigator-initiated, two-week multi-national, multi-centre, 'proof of concept', phase IIb double-blind, placebo-controlled, prospective, randomised, cross-over study of adult men and women was conducted using 0.2mg of oral desmopressin in patients suffering with idiopathic OAB. A 7-day frequency/volume chart was completed during a one-week screening period. Patients were included in the trial period if they had four or more voids in the first eight hours of the day excluding the first morning void. They were randomised into two groups. One group had desmopressin on days 1, 3, and 5 and the other group on days 8, 10, and 12, with placebo for the rest of the time in both groups. The tablets were taken after the first morning void. Throughout the trial, frequency/volume charts were used to assess OAB symptoms. Quality of life was assessed daily using the International Consultation on Incontinence Questionnaire for OAB (ICIQ-OAB). Sodium levels were checked at baseline, and at each clinic visit. The primary endpoint was evaluation of effectiveness of desmopressin in increasing the time to first unwanted micturition during the first eight hours following treatment. The secondary endpoints evaluated the effectiveness of desmopressin in decreasing the average number of micturitions, urgency and UUI episodes during the first eight hours following treatment. The drug days were compared to the placebo days. A power calculation was conducted with 80% power. McNemar test and t-test were used for statistical analysis.

Results

1000 potential patients were screened initially by searching through hospital notes or speaking to them over the telephone. 190 eligible patients (98 women; 102 men) were screened in clinic. 88 (41 women; 47 men) were finally randomised to treatment. The age range was 22 – 85 (median age = 62, mean age = 59.6).

Time to first void was eight minutes later on the drug (92 mins) than on the placebo (84 mins). This difference was not statistically significant at the 5% level ($p = 0.27$). However the drug led to one less void compared to placebo (3.2 vs 4.2) in the first eight hours following treatment and this was statistically significant ($p<0.001$). There was also a decrease in the number of urgency episodes in the drug days compared to placebo ($p<0.003$). As far as incontinence was concerned, the majority of patients (78%) did not experience any leakage in the first eight hours following treatment, so numbers are limited but no significant difference was found between drug and placebo days (8 reductions on drug vs. 4 on placebo). However if leakage is divided into severe (≥2 UUI episodes/3 days) or mild (≤1 UUI episode/3 days) then there was significantly less leakage with desmopressin in severe cases than with placebo ($p<0.01$). Following the first eight hours of taking the tablets (in the remaining hours before the next tablet is taken), there was no marked difference between drug and placebo in frequency ($p=0.37$); urgency ($p=0.76$) or UUI ($p=0.26$) episodes.

Analysis of the ICIQ-OAB showed that there was a statistically significant subjective difference between the drug days and placebo days in terms of frequency ($p<0.001$), urgency ($p=0.01$) and UUI ($p=0.07$). As far as effect on quality of life is concerned, there was a statistically significant overall improvement in symptoms ($p=0.01$) and frequency ($p=0.04$) but there was no difference on quality of life for urgency ($p=0.09$) or UUI ($p=0.48$) between drug and placebo days.

38 people reported adverse events which were all mild. The main adverse events were headache (12 subjects) and diarrhoea (5 subjects) which all resolved. Hyponatraemia was not recorded in any patient.

Interpretation of results

The first eight hours of the day are probably the most important in many respects, as this is when we go to work, do our shopping and exercise. It is also the time when access to toilets is the most difficult unless the individual is housebound. Thus a drug that helped patients during that time period would be very useful, especially if it did not cause side effects. This proof-of-concept trial showed that desmopressin, an antidiuretic, can reduce frequency, urgency and UUI episodes in patients with OAB symptoms, with an overall improvement in quality of life. The side effects proved minimal and tolerable.

It is interesting that desmopressin did not cause an increase in the time to the first frequency episode even though there was a reduction in frequency episodes compared to placebo in the first eight hours of taking the tablets. This implies that the difference between drug and placebo is probably occurring at a time later than 92 mins. We are currently looking at the difference between second and third frequency episodes, to see when the reduction occurs.

Concluding message

Antidiuresis, using oral desmopressin tablets, is a novel, feasible and safe method of treatment for adults with OAB, and could be considered in the armamentarium of drugs available for the treatment of OAB. Trials looking at daily desmopressin in OAB patients or comparing it with antimuscarinics, or even in combination with an antimuscarinic, are greatly needed.

References

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