A Systematic Review of the Efficacy and Safety of Desmopressin for Nocturia in Adults

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Purpose: We systematically reviewed desmopressin as treatment for nocturia in generally healthy adults with a focus on benefits and harms.

Materials and Methods: After a literature search we identified 10 articles (2,191 patients) that met our inclusion criteria of parallel group design, randomized, controlled trials with information on at least 1 benefit or harm of desmopressin in patients with nocturia. We evaluated the quality of included trials based on The Cochrane Collaboration criteria, assessed heterogeneity using the I^2 statistic and performed random effects meta-analysis.

Results: Studies were generally of high quality, although 4 used an active run-in period to titrate the dose and exclude patients with adverse effects or who were nonresponders. Thus, they were at high risk for bias. Desmopressin doses of at least 25 mcg or greater decreased nocturnal voids and increased time to first void. A dose of 100 mcg provided just more than an hour of additional sleep before the first void compared with placebo as well as 0.72 fewer voids per night. Higher doses provided no significant increase in benefit. Hyponatremia (RR 5.1) and headache (RR 4.3) were the most common adverse effects. Serious adverse effects were rare.

Conclusions: Desmopressin appears to offer a modest benefit for treating nocturia in generally healthy adults with adequate safety. The initial dose should be between 50 and 100 mcg. Higher doses should only be used with caution and a lower initial dose of 25 to 50 mcg is appropriate in elderly patients. All patients should be monitored for hyponatremia. The drug should be used with caution in patients with chronic lung disease due to the rare occurrence of respiratory failure. Additional well designed, adequately powered studies 1 or more years in duration are needed.

Key Words: urinary bladder, nocturia, deamino arginine vasopressin, drug effects, review

Abbreviations and Acronyms

RCT = randomized, controlled trial

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Nocturia is defined as the need to awaken at night 1 or more times to void.[1] It affects 42% of men 60 to 69 years old and 55% of those 70 years old or older,[2] and can negatively affect quality of life.[3] Causes include prostate enlargement, decreased bladder capacity, heart failure, medication, venous insufficiency, overactive bladder, insomnia and excessive fluid intake. Current therapies such as fluid restriction, imipramine, anticholinergics, α-adrenergic receptor blockers and 5α-reductase inhibitors have limited efficacy and may have adverse effects.[4]

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Desmopressin acetate is a synthetic analogue of arginine vasopressin that is used to treat diabetes insipidus and nocturnal enuresis. Its efficacy for treating nocturia in adults has been assessed in multiple populations in short-term and long-term studies.[5] A previous meta-analysis investigated the efficacy and safety of desmopressin for nocturia[6] but since it appeared, another 5 RCTs have been published.[5,7–10] The review did not distinguish between studies at low or high risk for bias, or emphasize an evaluation of potential harm.[6]

We systematically reviewed the efficacy and safety of desmopressin for nocturia in adults, focusing on benefits and harms.

MATERIALS AND METHODS

We systematically reviewed the literature to identify randomized, placebo controlled, parallel group design trials comparing desmopressin to placebo in adults with nocturia.

Search Strategy

We searched PubMed® in April 2013 to identify RCTs of desmopressin for nocturia in adults. The initial search strategy ([desmopressin OR vasopressin OR DDAVP OR anti-diuretic OR antidiuretic] AND [prostat* OR BPH OR nocturia OR hyperplasia]) returned 277 studies. We then used the related articles feature for 1 study,[11] which identified another 157 studies. Finally, we used the clinical queries feature to search using the terms desmopressin nocturia and desmopressin prostatic, which yielded 82 and 13 studies, respectively. After eliminating duplicates we had 385 studies for review. Reference lists of included studies were searched as was a previous systematic review.[6] We updated the search in November 2013 but identified no additional studies.

Study Selection

We included randomized, placebo controlled, parallel design trials comparing desmopressin with placebo in adults with nocturia. We excluded studies in children and in specialized populations such as patients with cancer or Cushing disease.

Data Extraction and Quality Assessment

All 3 of us reviewed all abstracts returned by the initial search. Any article identified by at least one of us as possibly meeting study inclusion criteria was examined in full by all of us. A final decision regarding inclusion was made by consensus. Two of us (TR, JG) abstracted data on study design and quality, treatment outcomes and adverse events with discrepancies resolved by discussion with one of us (MHE). The quality of included studies was evaluated using The Cochrane Collaboration bias risk guidelines.[12]

Variable Definitions

We combined the outcome durations of first sleep period and time to first void into a combined outcome. Overall clinical response was defined in studies as a greater than 33% or 50% decrease in the number of voids. We combined results from studies that used either definition as a single clinical response outcome. Low and high doses were defined as less than 100 and 100 mcg or greater, respectively.

In 4 studies an active run-in period was used to titrate the dose (100 to 400 mcg) in the active treatment group.[7,13–15] Patients who experienced an adverse effect or did not respond to study drug were excluded from analysis. Only 1 of the 4 studies mentioned the number of patients receiving each drug and we used that study to estimate a mean dose of 270 mcg, and a median and modal dose of 200 mcg. Hyponatremia was not defined consistently. Three studies each defined it as serum sodium less than 135 and less than 130 mmol/l, respectively, and the remaining 4 did not clearly define it.

Statistical Analysis

We used the metan procedure in Stata®, version 13.1 to perform random effects meta-analysis. We used the weighted mean difference for the outcome of the first sleep period duration and the RR for dichotomous outcomes. The I^2 statistic was used to determine heterogeneity. We also report the number needed to treat and harm, calculated by dividing the absolute risk difference for benefit or harm into 100%.

RESULTS

Ten parallel group design RCTs in a total of 2,191 patients, including 1,410 in the desmopressin group and 781 in the placebo group, met our study inclusion criteria.[5,7–11,13–16] All included studies compared desmopressin to placebo and 1 described desmopressin and furosemide compared to placebo.[11] Four studies included men and women,[5,7,10,13] 4 included only men[8,11,15,16] and 2 included only women.[9,14] Most studies included men and/or women with at least 2 nightly voids. Mean or median age was 55 to 74 years and most studies mentioned a median or mean age of 60 to 69 years. We reviewed included studies carefully to assure that they were not duplicate reports of the same population. The supplementary table (http://jurology.com/) lists characteristics of the individual studies.

Quality of Included Studies

Eight of the 10 studies included a description of randomization, allocation concealment, blinding and followup.[5,7,9,11,13–16] In the 2 studies lacking this description[13,15] quality could still be assessed since they followed the protocol of another study that specified allocation concealment and participant blinding.[14] However, in 4 studies an active run-in period was used with patients excluded who experienced adverse events or did not respond to study drug, placing these studies at high risk for bias.[7,13–15] The Appendix shows quality assessment of the individual studies.[5,7–11,13–16]