Desmopressin as an adjuvant to opioids or NSAIDs in treatment of renal colic: a nationwide register-based study†

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ABSTRACT

Aims Desmopressin has been reported to be effective as an adjuvant to opioids or NSAIDs in management of pain in renal colic; however real-life data are lacking on the utilisation of desmopressin in this patient segment.

Methods The Danish National Prescription Registry data-linked with Danish National Patient Registry during a 3-year period from 2009 to 2011 was used to study prescriptions for desmopressin in renal colic.

Results We identified 888 desmopressin prescriptions for renal colic, dispensed to 95 patients. The mean treatment period was 159 days, with a large variation up to a maximum of 924 days. Approximately two thirds of patients received dosing instructions to administer the drug 4 times daily to provide 24-h antidiuretic coverage. Among concomitant opioids and NSAIDs, tramadol and ibuprofen were prescribed most frequently. Antidepressants and diuretics were also widely used. A clear sex difference was seen, with female renal colic patients having three times more prescriptions overall than males, and in particular receiving more antidepressants and psychotropic drugs. A total of 4 (4.2%) of the patients experienced hospital admissions because of hyponatraemia or polydipsia during the 3-year period. We confirmed a previous case report that nephrolithiasis could be at least an occasional complication of successful therapy of Central Diabetes Insipidus (CDI) with desmopressin, identifying 12 CDI patients in total, or 2.4% of all Danish CDI patients in that period, who were also treated for renal colic.

Conclusion In summary, these real-life prescription data provide exact epidemiological measures on desmopressin utilisation in renal colic. Copyright © 2015 John Wiley & Sons, Ltd.

INTRODUCTION

Up to 12% of the general population suffer from a urinary stone (urolithiasis) sometime during their lifetime.1 If ureteral obstruction occurs, the primary symptom is renal colic, with pain presenting in waves of varying intensity, caused by spasm of the ureter around the stone, leading to obstruction and distension of the ureter, pelvicalyceal system and renal capsule.2 The pain of renal colic is mediated by prostaglandins released by the ureter in response to obstruction, sensitising nociceptors to stimuli such as bradykinins that induce pain and visceral responses (i.e. nausea, vomiting).3 Prostaglandins also cause increased renal blood flow and down-regulation of the antidiuretic hormone, arginine vasopressin (AVP), as well as the contraction of ureteral smooth muscle.4 Therefore, prostaglandin inhibitors such as indomethacin and ketorolac are considered particularly effective for renal colic patients.5 Recently, many investigators have reported the usefulness of both calcium channel blockers and α-adrenergic blockers for medical expulsive therapy on ureteral stones.6,7 α-Adrenergic blockers in particular seem to reduce the dose of NSAIDs or other analgesics that is required.8

In many cases, the natural history of uncomplicated urolithiasis supports a watchful waiting approach, for up to six or even eight weeks.9 In order to provide pain relief throughout this period, NSAIDs and opioids are commonly used,2 but may be poorly tolerated in the elderly.1 Desmopressin (a synthetic analogue of AVP) is a treatment indicated for use in nocturnal enuresis,
nocturia, central diabetes insipidus and certain bleeding disorders. It is not licensed for use in renal colic, nor included in treatment guidelines. However, since the 1990s, a number of reports have been published documenting an analgesic effect of desmopressin, either used alone or with a rescue dose of NSAID, in renal colic patients. The mechanism of pain relief with desmopressin administration is likely because of a significant reduction in intra-ureteral mean pressure within the excretory tract with the preservation of kidney blood perfusion. In addition, desmopressin counteracts the prostaglandin-mediated down-regulation of AVP, causing an antidiuretic effect mediated by stimulation of vasopressin V2-receptors in the kidney. Desmopressin has also been shown to exert an inhibitory effect on smooth muscle fibre contraction of the renal pelvis in the rabbit. Furthermore, it has been suggested that desmopressin may exert central analgesia by mediating release of β-endorphin from the hypothalamus; however this mechanism of action has not been proven, and contradictory reports exist as to whether desmopressin can cross the blood–brain barrier.

Recent studies of safety and efficacy of intranasal desmopressin combined with opioids, NSAIDs or anti-spasmodics (tramadol, pethidine, diclofenac and hyoscine N-butyl bromide) found that desmopressin could be used as an effective adjuvant in acute renal colic pain management.

Therefore, although desmopressin is not indicated for use in renal colic, there is an increasing body of literature supporting its analgesic action in these patients. The objective of the current study was to investigate whether, and to what extent, desmopressin is used off-label in clinical practice for pain relief in urolithiasis patients. To this end, we analysed retrospectively epidemiological data on all drug prescriptions of desmopressin citing renal colic as the indication which were redeemed in retail pharmacies in Denmark in a 3-year period from 2009 to 2011.

Dilutional hyponatraemia is a rare but serious safety concern associated with desmopressin and occurs rapidly after starting treatment, primarily in patients above 65 years with excessive fluid intake and thirst disorders. Because desmopressin is not indicated for renal colic, optimal doses and precautions against this electrolyte disorder are not addressed in the drug’s current label instructions or clinical guidelines. To explore this potential complication, we therefore investigated the real-life incidence of severe hyponatraemia in renal colic patients prescribed desmopressin.

MATERIAL AND METHODS

All prescriptions for desmopressin and other drugs redeemed in retail pharmacies have been recorded on an individual level since January 1994 by the Danish Medicines Agency. The data include age, sex, encrypted personal identification code, full account of the dispensed product, date of purchase, dosing instructions and indications. The Danish drug-dispensing database covers the whole nation (5,580,134 persons in December 2011) and thus represents a valid and reliable data source for pharmacoepidemiological studies. The current registry study was approved by the Danish Data Protection Agency and Danish Statistical Office (journal number 703916). Approval from an ethics board was not required according to Danish law.

We used the database to study the incidence of renal colic treated with desmopressin in Denmark during a 3-year period January 2009 to December 2011. The prescription data included date of dispensing, age and sex of the patient, number of re-dispensations, dosage and strength of medication. The frequency and distribution of prescriptions and individual users according to age, sex, dose, dosing code, concomitant medication and occurrence of hyponatremia were calculated using PROC FREQ and PROC MEANS in SAS (version 9.3, SAS Institute Inc., Cary, NC, USA).

Renal colic patients were identified and differentiated from other patient groups using desmopressin (primarily children with bedwetting, adults with central diabetes insipidus and nocturia and those with haematological conditions) according to a specific indication code provided with all prescriptions since 2004. In addition, information was obtained on prescriptions for concomitant medications, with focus on painkillers frequently recommended for renal colic patients such as opiates and NSAIDs, and on medications that may predispose elderly patients to hyponatraemia when treated with desmopressin, including loop diuretics, thiazide diuretics, angiotensin-converting-enzyme (ACE) inhibitors, cyclooxygenase inhibitors (including acetylsalicylic acid and selective COX-2 inhibitors), chlorpropamide, selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, neuroleptics and carbamazepine.

We also investigated the real-life incidence of desmopressin’s only potentially serious adverse event, severe hyponatraemia (defined as requiring hospitalisation) in renal colic patients by linking all prescription records at an individual level to national hospital admission data (Danish National Patient Registry) for...
hyponatraemia and polydipsia. It is well documented that a consistent low urine volume is a risk factor for kidney stone formation. At the same time, a decrease in urine volume is considered the most important therapeutic goal of desmopressin treatment of CDI, a condition caused by a deficiency in production of AVP. Nephrolithiasis in association with CDI has been reported as a single case, but it is not known how common this complication is at a population level. We therefore identified any patients with renal colic who were also prescribed desmopressin indicated for treatment of CDI, in order to quantify this potentially complicating factor.

In this analysis we refrained from using defined daily dosages (DDD), a widely used measure in pharmacoepidemiology, because for desmopressin they reflect recommended dosing before bedtime in approved indications and are not necessarily appropriate for an off-label condition such as renal colic where individual dose titration is needed, and in many cases 24-h drug effect is required.

Because the results represent actual values for the entire Danish population and are not estimates based on samples, all figures are presented without confidence intervals or statistical testing.

**RESULTS**

A total of 888 prescriptions for desmopressin in different formulations (nasal, oral lyophilisate or conventional tablet) were dispensed to 95 renal colic patients during the observation period. More than half of the prescriptions were for lyophilisate 120 μg. Mean age of the patients was 65.4 years ranging from 26 to 93 years. Of the patients 56.9% were female.

The mean treatment period was 159 days with a large variation from just one prescription up to a maximum of 924 days. Eighty-six percent had one to five prescriptions of desmopressin during the 3 years (Table 1). Lyophilisate, an orodispersible formulation that does not require fluid intake, was by far the most common formulation for most renal colic patients used by approximately 80% of cases (Table 1).

Approximately two thirds of patients prescribed desmopressin received dosing instructions from the prescribing physician to administer the drug four times daily (Table 2), while the remainder were instructed to use desmopressin _pro re nata_ (as needed) or had no specific dosing instructions.

In addition to desmopressin, opioids and NSAIDs were frequently used (Table 3). The most commonly used opioid was tramadol (ATC-code N02AX02), while ibuprofen (ATC-code M01AE01) was the most frequently prescribed NSAID. Antidepressants and diuretics were also widely used. A clear sex difference was seen in polypharmacy, with female renal colic patients having three times more prescriptions than males, with more NSAIDs and opioids, but also being prescribed more CNS drugs including antidepressants and psychotropic drugs.

**Safety—hospital admissions in renal colic patients because of hyponatraemia and polydipsia**

Hospital admissions because of hyponatraemia, sodium depletion and polydipsia among renal colic patients receiving desmopressin <90 days before admission occurred in three female patients and one male (Table 4) during the entire 3-year period. All 4 patients were 65 years or older and treated with desmopressin lyophilisate 60 or 120 μg. Across these three females there were >20 prescriptions of concomitant medication, most commonly buprenorphine (ATC N02AE01; 27% of the prescriptions) and citalopram (ATC N06AB04; 12%).

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**Table 1. Formulation and strength of desmopressin prescribed to colic patients 2009–11**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Strength</th>
<th># Prescriptions</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyophilisate</td>
<td>60 μg</td>
<td>234</td>
<td>26.35%</td>
</tr>
<tr>
<td></td>
<td>120 μg</td>
<td>490</td>
<td>55.18%</td>
</tr>
<tr>
<td></td>
<td>240 μg</td>
<td>55</td>
<td>6.19%</td>
</tr>
<tr>
<td>Tablet</td>
<td>0.1 mg</td>
<td>7</td>
<td>0.79%</td>
</tr>
<tr>
<td></td>
<td>0.2 mg</td>
<td>48</td>
<td>5.41%</td>
</tr>
<tr>
<td>Nasal</td>
<td>2.5 μg/dosis</td>
<td>43</td>
<td>4.84%</td>
</tr>
<tr>
<td></td>
<td>10 μg/dosis</td>
<td>9</td>
<td>1.01%</td>
</tr>
<tr>
<td></td>
<td>0.1 mg/ml</td>
<td>2</td>
<td>0.23%</td>
</tr>
</tbody>
</table>

**Table 2. Dosing codes of desmopressin prescriptions for renal colic patients 2009–2011**

<table>
<thead>
<tr>
<th>Dosing codes (where available) of desmopressin prescriptions for renal colic patient 2009–2011</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual dosing (as needed)</td>
<td>73 (29%)</td>
</tr>
<tr>
<td>2 tablets 2 times daily</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>2 tablets 4 times daily</td>
<td>170 (67%)</td>
</tr>
<tr>
<td>Other dosing codes</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Total</td>
<td>252 (100%)</td>
</tr>
</tbody>
</table>

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Central diabetes insipidus—a potentially complicating factor in renal stones?

Among the 95 renal colic patients and 499 CDI patients treated with desmopressin, 12 patients (2.4% of all CDI patients) had been prescribed desmopressin at some point for both indications. Mean age of this subset of patients was 62.6 years, ranging from 27 to 93 years of age, with 58% female patients.

DISCUSSION

The real-life data presented here confirmed that desmopressin is used in addition to opioids or NSAIDs, and in some cases as monotherapy, in renal colic patients in Denmark. A very crude estimate based upon an annual incidence of renal colic of around 0.3%, and a Danish population of approximately 5 million, would mean that there are around 45,000 new episodes per 3 years. Therefore, 888 prescriptions for desmopressin represents a small but significant proportion of instances of renal colic (approximately 2%) being treated by this method. A more conservative estimate, using the number of patients receiving desmopressin (i.e. 95) instead of the number of prescriptions, would suggest that 0.2% of renal colic episodes are treated with desmopressin; this approach takes no account of the fact that individuals may receive the drug for a number of different episodes of renal colic, rather than receiving all prescriptions for one episode, and may therefore generate an artificially low estimate. Nevertheless, given that desmopressin is not indicated for renal colic, it is interesting to see that it is employed by healthcare professionals in the clinic, even if with a relatively low frequency. Furthermore, observations reported in the literature indicate both that it can be effective in this condition and that there is a plausible mechanism of action. However, given the high rate of concomitant use of NSAIDs and opioids in this group of patients, it is impossible to establish a causal role for desmopressin in any possible analgesic benefit experienced by the renal colic patients prescribed desmopressin in this study. Further randomised studies are required, to specifically evaluate desmopressin monotherapy as a treatment for renal colic.

In this registry study, desmopressin was more frequently prescribed to women than men with renal...
colic. This is noteworthy given that urinary stone disease has a lifetime risk of about 12% in men and 6% in women.\(^ {18}\) However, even more striking was the significantly higher prescription of NSAIDs and opioids to females compared to males. These findings support a study on the influence of sex on physicians’ pain management decisions which reported that female patients were prescribed more pain medication for kidney stones than male patients.\(^ {19}\) A previous pharmacoepidemiological analysis based on Danish National Patient Registry showed that 1.5 times more women in the general population are treated with opioids than men (female/male period prevalence ratio 1.5:1), further supporting a sex difference in approach to pain treatment.\(^ {20}\)

Lyophilisate was by far the preferred formulation prescribed to most renal colic patients. Because lyophilisate can be taken without water, in contrast to tablets, this may explain why it is preferred for renal colic patients, who arguably want to avoid building up unneeded renal pressure because of urine volume—as is also the case in other conditions requiring antidiuresis, such as bedwetting.

Results of our study are in agreement with a previous report in nocturia patients of a sex difference in the small but clinically significant risk of hyponatraemia because of significantly higher desmopressin sensitivity in women.\(^ {21}\) The gene for the V2 receptor, AVPR2, has a high probability of escaping X inactivation in females\(^ {22}\) and may thereby be responsible for sex differences in renal V2R expression, leading to differences in renal sensitivity and response to any V2 receptor agonist stimulation, including desmopressin. The absolute numbers of hospital admissions because of hyponatraemia are very small in our study and prohibit strong conclusions. However, one can speculate that this genetic difference may at least partially explain the three-fold higher ratio of hospital admissions because of severe hyponatraemia in female renal colic patients compared to male. However, a high number of concomitant medications in women, including for SSRIs and other psychotropic drugs associated with hyponatraemia in particular in elderly women, may also confound the results, warranting further research.

We provided some supportive evidence to a previous case report that nephrolithiasis could be at least an occasional complication of successful therapy of CDI with desmopressin,\(^ {17}\) identifying 12 CDI patients in total, or 2.4% of all Danish CDI patients in the 3-year period, who were also treated for renal colic. This does not necessarily imply any definite causal link between desmopressin in CDI and later development of renal stones, because lifetime risk of renal stones is quite common. An alternative explanation is that physicians who already treat patients with CDI are more inclined to use desmopressin for their patients also for the treatment of incidental renal colic. Nonetheless, this finding is consistent with the clinical recommendation for treatment of CDI to allow “breakthrough diuresis”,\(^ {23}\) preferably during daytime, in order to avoid decreasing 24-hour urine production excessively, and to minimise any risk that other renal complications may arise in the long-term, because CDI is usually a chronic condition.

This study has some possible methodological limitations; the general advantages and disadvantages of using drug prescription data to determine pharmacoepidemiological measures such as incidence and period prevalence have been described in detail elsewhere.\(^ {24,25}\) In renal colic, data from the Danish National Prescription Registry and Danish National Patient Registry have the advantage of being representative real-life data and covering the entire Danish population over several years. The records of routine clinical care from these two registries make it possible to generate hypotheses on real-world utilisation patterns and complications. Nonetheless, to prove causality, different epidemiological methods are recommended.

**CONCLUSION**

In summary, the real-life prescription data presented here confirmed that, in Denmark, desmopressin is used either as an adjuvant to opioids or NSAIDs or in some cases as monotherapy in renal colic patients with a mean treatment period of roughly six months. Antidepressants and diuretics were also widely used in this patient group. A clear sex difference was seen, with female renal colic patients having three times more prescriptions for concomitant drugs than males, and in particular being prescribed more antidepressants and psychotropic drugs. A total of 4 (4.2%) of the patients experienced hospital admissions because of hyponatraemia or polydipsia during the 3-year period with females more at risk than male patients. We confirmed a previous case report that nephrolithiasis could be at least an occasional complication of successful therapy of Central Diabetes Insipidus (CDI) with desmopressin.

**CONFLICT OF INTEREST**

The study was funded by a Ph.D. grant from Ferring Pharmaceuticals. Kristian Vinter Juul and Jens Peter
Norgaard are both current employees at Ferring Pharmaceuticals. These affiliations have not affected the reporting of the results.

KEY POINTS
- The antidiuretic desmopressin has been reported to be effective as an adjuvant to opioids or NSAIDs in management of pain in renal colic but real-life data are lacking
- Using a nation-wide prescription registry data-linked with patient registry we found a mean treatment period of about \( \frac{1}{2} \) year, with two thirds of patients administering desmopressin 4 times daily to provide 24-h antidiuretic coverage.
- A clear sex difference in use of pain killers was seen, with female renal colic patients having three times more concomitant prescriptions overall than males, in particular receiving more antidepressants and psychotropic drugs.
- A total of three female and one male patients experienced hospital admissions because of hyponatraemia, a recognised adverse effect of desmopressin—even if absolute numbers were very small in our study and prohibit strong conclusions, based on literature one can speculate that genetic differences may at least partially explain the higher ratio of hospital admissions because of severe hyponatraemia in female renal colic patients compared to male.
- We suggest that kidney stone could be a complication of otherwise successful therapy of Central Diabetes Insipidus (CDI) with desmopressin reducing diuresis, identifying 12 CDI patients in total, or 2.4% of all Danish CDI patients in that period, who were also treated for renal colic.

ETHICS STATEMENT
The authors state that no ethical approval was needed.

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