Sublingual desmopressin is efficient and safe in the therapy of lithiasic renal colic

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Abstract

Purpose To evaluate the effects of newer sublingual desmopressin administration in lithiasic renal colic, alone or combined with a nonsteroidal anti-inflammatory drug (NSAID).

Methods Prospective single-blind study including an initial number of 249 patients with lithiasic renal colic was randomized as follows: group NSAID (71 patients) received ketorolac tromethamine (ketorolac) 30 mg im and sublingual placebo (vitamin C), groups D1 and D2 (57 and 62 patients) received sublingual desmopressin (Minirin Melt), 60 and 120 μg, respectively, whereas group C (59 patients) received a combination of 30 mg im ketorolac and 60 μg sublingual desmopressin. Pain intensity was assessed using the visual analogue scale before and thirty minutes after drug administration. Patients experiencing pain aggravation were rescued and excluded from the study.

Results Dropout incidence was higher in the NSAID group than in the groups treated with desmopressin in monotherapy or combined with ketorolac (p < 0.05). Pain intensity was diminished at least as potently by the monotherapy with desmopressin and ketorolac. The higher dose of desmopressin and the combination therapy decreased pain intensity with 56 and 59%, respectively, significantly more than the 47% decrease obtained with ketorolac alone (p < 0.05 and p < 0.001). Mean pain decrease was higher in the combination group (C) than in the NSAID or D1 groups (p < 0.001 and p < 0.05, respectively), suggesting drug additivity. Patients did not experience severe side effects.

Conclusions Sublingual desmopressin is at least as potent as NSAID in the treatment of lithiasic renal colic. The combination of sublingual desmopressin and NSAID has additive analgesic effects.

Keywords Desmopressin · Sublingual · Renal colic · Lithiasis

Introduction

Renal colic is a very frequent and severe complication of kidney stones [1]. The acute dilation and stretching caused by ureteral obstruction is accompanied by excruciating pain [2]. The increase in hydrostatic pressure in the renal pelvis triggers prostaglandin secretion, causing a raise in the renal blood flow and diuresis [2]. This phenomenon leads to further increase in ureteropelvic pressure and ureteral contractility, with an aggravation of pain in a vicious circle, until eventual stone elimination [2].
The only two medications currently used for the therapy of acute renal colic are nonsteroidal anti-inflammatory drugs (NSAIDs), which are potent inhibitors of prostaglandin synthesis, and opioids, decreasing pain via central effects [1, 3]. The analgesic efficacy of such drugs is, however, highly variable, with many individual cases resistant to therapy [4]. These drugs are, moreover, not devoid of side effects. NSAIDs may aggravate renal insufficiency, cause gastroduodenal ulcerations and increase the risk of stroke, whereas opioids are addictive and may cause nausea, vomiting, respiratory distress, drowsiness or impaired consciousness [5, 6]. Therapeutic alternatives to the existent drugs are therefore needed.

Arginine vasopressin (AVP) or antidiuretic hormone is known as a major regulator of water balance by stimulating water reabsorption at the level of distal and collecting tubes [7]. Beside their direct effects, prostaglandins also antagonize the renal action of AVP, by interfering with cyclic adenosine monophosphate-mediated signals, thereby further increasing diuresis and pain [7–10]. Therapy with prostaglandin synthesis inhibitors seems, moreover, to be more efficient in reducing the pain of renal colic in patients having higher levels of circulating AVP; in experimental models of acute obstruction, desmopressin reduces ureteral pressure and pain [11]. Desmopressin also exerts direct myorelaxant effects on the smooth muscles of rabbit renal pelvis [12]. The central V1a receptor for AVP may, moreover, be involved in the perception of pain [13]. All these data support the idea to use AVP analogues in the therapy of lithiasic renal colic [9, 14].

1-Desamino-8-arginine vasopressin (desmopressin) is a synthetic structural analogue of AVP with potent, long-lasting antidiuretic effect, but reduced vasopressor activity. The intranasal form of administration was tested in the therapy of renal colic, with variable results [9, 14–20]. Intranasal desmopressin was proposed by certain authors as an efficient analgesic in monotherapy or as an adjuvant for NSAIDs [9, 14–18], whereas others did not find any significant beneficial effects of intranasal desmopressin in monotherapy [19] or in combination with NSAIDs or opioids [19, 20]. The sublingual administration form of desmopressin was recently used in renal colic, but only in combination with morphine, and not in monotherapy or combined with NSAIDs [21]. Desmopressin is not licensed for use in renal colic, nor included in treatment guidelines; it is often used off-label in clinical practice for pain relief in renal colic, alone or as adjuvant therapy [22]. The aim of our study was therefore to test the efficacy of sublingual desmopressin (Minirin Melt) in the therapy of renal colic, alone or in combination with a NSAID.

Patients and methods

We wanted to evaluate the therapeutic efficacy and safety of recent onset renal colic with sublingual desmopressin. In order to evaluate therapeutic efficacy, we decided to compare the effects of desmopressin administration with those of ketorolac, a classical nonsteroidal anti-inflammatory drug routinely used in renal colic. We equally aimed to check therapeutic safety by following parameters described by others to be influenced by desmopressin, such as modifications in blood pressure or natremia [23].

We performed a single-blind randomized prospective multicentric study, enrolling patients in the emergency units of two Romanian University hospitals (Iaşi and Târgu Mureş) during a period of 2 years. The study was performed according to the Declaration of Helsinki (revised, Edinburgh, 2000). All applicable regulatory requirements and local independent Ethics Committee approvals of the two Universities were obtained before enrolling patients. An informed, written consent was obtained from all enrolled patients.

We recruited an initial number of 249 patients (167 males and 82 females between 18 and 82 years, mean age of 42.6 ± 13.5 years) with renal colic of lithiasis etiology and who did not receive any medication previously. Exclusion criteria consisted in the presence of fever, renal insufficiency, hyponatremia, congenital hydronephrosis, renal tumors, pregnancy, endourologic emergencies (e.g., obstructive anuria), active peptic ulcer disease, severe cardiovascular ischemic disease, hemorrhagic diathesis. The presence of kidney stones was confirmed by radiological and ultrasound investigation. After signing the informed consent, the patients were randomly assigned to four groups. Group NSAID (71 patients) received ketorolac tromethamine (ketorolac) 30 mg intramuscularly (im) and tromethamine (ketorolac) 30 mg intramuscularly (im) and sublingual (sl) placebo (vitamin C), groups D1 and D2 (57 and 62 patients, respectively) received 60 or 120 µg sublingual (sl) desmopressin (Minirin Melt), and group C (59 patients) received a combination of 60 µg sl desmopressin and 30 mg im ketorolac. Randomization was made successively in the four groups in the rigorous order of addressability to the two emergency units, until reaching a total number of 50 volunteers experiencing a decrease in the VAS in each group 30 min after therapy administration. The intensity of pain was assessed by the patients with a visual analogue scale (VAS) ranging from 0 (“no pain”) to 10 (“unbearable pain”) at admission and 30 min after therapy administration [24]. When pain intensity increased despite therapy, becoming unbearable or remaining at initial, unbearable levels, patients were rescued with opioid administration (tramadol) and/or emergency urological intervention (insertion of a JJ ureteral probe for facilitating the drainage) and were dropped out from the study. Patients were monitored for therapy-related side effects. Blood pressure was measured in all volunteers before and 30 min after therapy administration. Serum osmolality and creatinine were assessed in all patients receiving desmopressin.
before and 30 min after drug administration. The characteristics of study groups and the number of aggravated patients dropped out from the study are shown in Table 1. Blood pressure values, serum sodium and creatinine before and 30 min after therapy are shown in Table 2, expressed as mean ± standard deviation.

**Statistical analysis**

The sample size was calculated to be at least 40 in each group for $\alpha = 0.05$, $\beta = 0.2$, power = 80%, and the final differences between the groups of at least two scores on VAS. Continuous variables were summarized as mean ± standard error of the mean and categorical ones as ratios. Two-tailed independent Student’s $t$ test and Mann–Whitney $U$ test were performed to compare quantitative variables with normal distribution and Chi-square test for comparing qualitative variables. Differences were considered significant at $p < 0.05$.

**Results**

Mean age and sex distribution were not significantly different in the four treatment groups (Table 1). The incidence of dropouts (patients with aggravating pain despite therapy) was significantly higher in the NSAID group receiving ketorolac and sublingual placebo than in all the other groups that received sublingual desmopressin either alone or in combination with ketorolac (Fig. 1). Two patients treated with ketorolac in monotherapy and one patient treated with combination therapy, but no patients treated with desmopressin in monotherapy experienced mild epigastric discomfort, possibly related to NSAID administration. Mean blood pressure of all patients was of 131/78 mmHg at admission and 126/74 mmHg at thirty minutes after therapy administration, without significant differences among groups (Table 2). All volunteers enrolled in the study and receiving sublingual desmopressin had normal serum sodium and creatinine 30 min after drug administration, irrespective of their age or sex, with unmodified mean values. The normality of these parameters 30 min after drug administration suggested therapeutic safety of sublingual desmopressin given once for renal colic (Table 2).

**Table 1** Characteristics of study groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Therapy</th>
<th>Mean age ± standard deviation</th>
<th>Number of Dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>NSAID</td>
<td>Ketorolac 30 mg im</td>
<td>42.5 ± 13.4</td>
<td>24</td>
</tr>
<tr>
<td>D1</td>
<td>Minirin Melt 60 μg sl</td>
<td>41.8 ± 11</td>
<td>19</td>
</tr>
<tr>
<td>D2</td>
<td>Minirin Melt 120 μg sl</td>
<td>43.1 ± 14.1</td>
<td>21</td>
</tr>
<tr>
<td>C</td>
<td>Minirin Melt 60 μg + Ketorolac</td>
<td>42.7 ± 14.6</td>
<td>18</td>
</tr>
</tbody>
</table>

**Table 2** Biological parameters before and 30 min after therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood pressure (mm Hg)</th>
<th>Serum Na (mEq/L)</th>
<th>Serum creatinine (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>0'</td>
</tr>
<tr>
<td>NSAID</td>
<td>130 ± 17</td>
<td>126 ± 18</td>
<td>77 ± 12</td>
</tr>
<tr>
<td>D1</td>
<td>129 ± 19</td>
<td>127 ± 16</td>
<td>79 ± 11</td>
</tr>
<tr>
<td>D2</td>
<td>130 ± 22</td>
<td>125 ± 20</td>
<td>76 ± 11</td>
</tr>
<tr>
<td>C</td>
<td>132 ± 23</td>
<td>127 ± 18</td>
<td>80 ± 9</td>
</tr>
<tr>
<td>All</td>
<td>131 ± 18</td>
<td>126 ± 16</td>
<td>78 ± 9</td>
</tr>
</tbody>
</table>

Fig. 1 Number of dropouts due to pain aggravation (see text). Black bars number of drop outs, white bars number of patients responsive to therapy kept in the study. *$p < 0.01$, **$p < 0.001$ compared to the NSAID group (Chi-square test)
homogeneity (Fig. 2). All therapies significantly decreased pain intensity after 30 min (Fig. 2). The higher dose of desmopressin (group D2) decreased absolute pain intensity significantly more than ketorolac alone (group NSAID, Fig. 2, left). The combination of 60 μg sl desmopressin and ketorolac (group C) was significantly more efficient in decreasing absolute pain intensity than any of the two drugs in monotherapy (groups NSAID and D1, Fig. 2, right). Correspondingly, combination therapy of 60 μg sl desmopressin and ketorolac (group C) caused a significantly higher relative reduction in the VAS (percentage from initial) than any of the two drugs in monotherapy (groups NSAID and D1, Fig. 3).

Discussion

Kidney stone-induced renal colic is one of the most severe pain conditions, with few therapeutic alternatives [3]. Local prostaglandin secretion increases renal blood flow and antagonizes AVP-mediated water reabsorption, thereby further increasing urinary flow and augmenting pain [9, 15]. Desmopressin is known as a potent AVP analogue, currently used for the therapy of the polyuric-polydipsic syndrome of neurogenic diabetes insipidus, but also having other potential clinical applications [13]. Desmopressin potently reduces urinary flow and may therefore have, by this mechanism of action, a therapeutic impact on renal colic [11]. Because of this line of evidence, desmopressin in its intranasal form of administration was already tested for the therapy of lithiasic renal colic in various clinical studies [9, 14–21]. Several authors observed certain beneficial effects of desmopressin on pain reduction in renal colic, either in monotherapy [9, 14, 15] or in combination with NSAIDs [15, 17, 18], whereas others did not observe any significant additive
benefit of combinations between intranasal desmopressin and NSAIDs [19], or opioids [20].

Our clinical study is one of the first aiming to follow the effects of sublingual desmopressin in lithiasic renal colic. The two chosen doses of sublingual desmopressin were in the range of the intranasal administration doses used in previous studies. Evaluation endpoint was located at 30 min after therapy administration, in line with other clinical studies [9–11, 14–21]. We decided to include only two VAS evaluations for simplifying the protocol and increasing volunteer adherence. Compared to other reports, our investigation conferred several advantages and novelties. First of all, the number of enrolled patients was larger. Secondly, the study included a control group, treated with a NSAID, and groups treated with sublingual desmopressin in monotherapy or in combination with a NSAID. The study design allowed therefore a head-to-head comparison of the therapeutic efficacy of two different drugs in monotherapy or in combination.

Intranasal desmopressin given in monotherapy has somehow limited analgesic effects in renal colic [9, 14], being considered less efficient than NSAIDs or opioids and merely playing an adjuvant role [15, 19, 20]. In contrast, we found sublingual desmopressin (Minirin Melt) at least or even more efficient than a classical NSAID (ketorolac) in treating lithiasic renal colic. The number of therapeutic failures was significantly higher in the NSAID-treated group than in the groups treated with sublingual desmopressin, irrespective of dosage (Fig. 1). Moreover, sublingual desmopressin decreased pain intensity evaluated by the VAS in the responsive patients to a level comparable to that attained by the therapy with a NSAID, either in absolute values (Fig. 2) or as percentage from the initial pain score (Fig. 3), with the higher dose of 120 μg Minirin Melt being more efficient than ketorolac 30 mg im. The far greater number of patient dropouts before 30 min in the group treated with ketorolac alone and the exclusion of dropouts from the study suggests an even more important difference in therapeutic efficacy in favor of desmopressin.

It is not immediately clear why desmopressin was more efficient for treating renal colic in our study compared to others, but the difference seems to reside in the way of administration. Therapeutic intervention was generally prompt after the onset of renal colic and sublingual desmopressin is known to be more readily available in the general circulation than other forms of administration [25]. Our data are also more consistent than previous clinical studies, taking into consideration the higher number of enrolled patients. Importantly, although epidemiological reports suggest a risk of hyponatremia and water intoxication associated with chronic desmopressin use [22, 23], one dose of sublingual desmopressin was not accompanied by the above-mentioned side effects in our study (Table 2). We did not observe any clinical signs of hyponatremia in our volunteers, and serum sodium evaluated at the end of the follow-up was unmodified in patients receiving one dose of sublingual desmopressin, including the nine volunteers of over 70 years of age. NSAID administration caused gastric discomfort in a few patients. Furthermore, therapy with sublingual desmopressin did not imply supplementary water ingestion, such as for oral NSAID therapy, decreasing the risk of further basinetal distension or drug elimination through vomiting.

We further wanted to check whether patients with lithiasic renal colic may benefit from a combination therapy between a NSAID and sublingual desmopressin. This type of combination seems logical, since the two drugs act on renal hydrodynamics through different mechanisms of action. Desmopressin lowers ureteral pressure by increasing water reabsorption [11], whereas NSAIDs inhibit local prostaglandin secretion, thereby decreasing local blood flow and ureteral contractility [26, 27]. The inhibition of prostaglandins may also increase desmopressin efficacy by increasing local cAMP production [8, 9, 14, 15]. Another argument in favor of the administration of drug combination is that higher AVP levels seem to increase the sensitivity of renal colic to NSAID therapy [10]. Other authors already tested the efficacy of combination therapy between intranasal desmopressin and a NSAID in renal colic. Certain authors observed additive effects [15, 17, 18], whereas others did not notice any benefit of combination therapy [19].

Our study showed mild but statistically significant additive analgesic effects after 30 min of follow-up when the lower dose of desmopressin (60 μg Minirin Melt) was added to ketorolac (group C, Figs. 2, 3), suggesting possible supplementary beneficial effects of this drug combination. The benefit of combination therapy seems, however, to be limited to a difference of 1.5 points in the VAS (Fig. 1). Further studies with a longer follow-up period may be more informative regarding therapeutic efficacy.

Sublingual desmopressin was recently used in the therapy of lithiasic renal colic in combination with morphine [21]. The authors suggested that desmopressin is not beneficial in this combination and may even decrease the central analgesic effects of opioids. The presence of arginine vasopressin receptors in brain is abundant [13], and this type of interference with opioid central effects may be possible [28], although further studies are needed, especially since it is known that desmopressin does not pass through blood–brain barrier [29]. The study did not include, however, a group treated with sublingual desmopressin in monotherapy. The absence of initial evaluation of pain intensity before therapy administration is another major drawback of this study.
Conclusions

This is the first study suggesting that sublingual desmopressin is efficient and safe in treating acute crisis of renal colic. This form of therapy is easy to be administered and was devoid of toxic side effects in our study even in patients older than 70. Certain supplementary follow-up precautions such as sodium and blood pressure assessment should be, however, taken into consideration. Sublingual desmopressin was at least as efficient as classical NSAIDs in treating lithiasis crisis. An association between sublingual desmopressin and NSAIDs conferred mild but significant additive analgesic effects in lithiasic renal colic. Based on these findings, sublingual desmopressin may find immediate application as first-line therapy for lithiasic renal colic, alone or in combination with NSAIDs. Further studies are, however, needed in order to check whether sublingual desmopressin is still efficient in treating renal colic at a later time point from pain onset.

Compliance with ethical standards

Conflict of interest All authors (Cătălin Pricop, Dumitru D. Brănișteanu, Martha Orsolya, Dragoș Puia, Anca Matei and Ionel Alexandru Checheriță) declare that they have no conflict of interest.

Human and animal rights All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional committees of the two involved universities and with the 1964 Declaration of Helsinki and its later amendments. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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