
The Comparative Safety of Oral Versus Intranasal Desmopressin for the Treatment of Children With Nocturnal Enuresis

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Purpose: Desmopressin is a well established and effective therapy for nocturnal enuresis. Water intoxication leading to hyponatremia is an infrequent but serious adverse event associated with desmopressin. We assessed the safety of desmopressin in children 18 years or younger with nocturnal enuresis with a focus on the relative safety of the oral compared with the intranasal formulation.

Materials and Methods: Published data (MEDLINE®) from December 1972 to August 2006 and post-marketing safety data from December 1972 to June 2005 were analyzed.

Results: A total of 21 clinical trials on desmopressin use in children with nocturnal enuresis were identified. There were no reports of hyponatremia. A total of 21 publications were identified that included 48 case reports of hyponatremia in children with nocturnal enuresis. In all case reports patients were treated with intranasal desmopressin. Post-marketing safety data included 151 cases of hyponatremia in children with nocturnal enuresis, of whom 145 were treated with intranasal desmopressin and 6 were treated with the tablet formulation. Prodromal symptoms of hyponatremia were identified as headache, nausea and vomiting.

Conclusions: Data suggest that there is a decreased risk of hyponatremia with oral desmopressin compared with intranasal desmopressin. Identifiable and preventable risk factors for hyponatremia are inappropriately high fluid intake, administration of a larger than recommended dose, young age (less than 6 years) and concomitant administration of another medication. When desmopressin is prescribed, patients should be instructed to avoid high fluid intake when the medication is ingested, not ingest a higher than recommended dose and promptly discontinue the medication and seek assessment if headache, nausea or vomiting develops.

Key Words: bladder, deamino arginine vasopressin, enuresis, hyponatremia, complications

Desmopressin is a well established and effective therapy for NE. In the quarter century since approval for this indication in 1980, numerous studies have demonstrated the efficacy and safety of desmopressin. The only serious adverse event associated with desmopressin is water intoxication, leading to hyponatremia.¹ There is anecdotal evidence that the tablet formulation of desmopressin is associated with a lower incidence of hyponatremia than the intranasal formulations. However, clinical studies that substantiate this suggestion are lacking.

We assessed the safety of desmopressin with a focus on the relative safety of the oral formulations, which include a tablet and a lyophilisate, compared with the intranasal formulations, which include droplets and a spray. Published data (MEDLINE) were analyzed on the safety of desmopressin prescribed for the treatment of NE as well as PMS adverse event data reported to Ferring Pharmaceuticals, which is the major manufacturer of desmopressin.

METHODS

Data were collected from 2 primary sources. A MEDLINE search of the English language literature was done to identify clinical trials and case reports that included information on the safety of desmopressin prescribed for the treatment of children with NE. When pertinent nonEnglish language articles were identified and the publication contained an English abstract with sufficient information, these articles were included in the review. The search included the years from 1972, which is the year that the intranasal formulation of desmopressin was introduced, to August 2006. The key words used for the search were safety, side effect(s), adverse event(s), hyponatraemia, hyponatremia and water intoxication, combined with bedwetting, nocturnal enuresis, primary nocturnal enuresis, secondary nocturnal enuresis, DDAVP, desmopressin and Minirin®. The articles were retrieved and analyzed.

PMS data on file with Ferring Pharmaceuticals were analyzed to identify adverse event reports of hyponatremia. Data were available for review from December 1972 to June 2005. During these years Ferring Pharmaceuticals followed the same methodical and careful procedures to identify PMS adverse event data regardless of the drug or formulation.

In addition, a search of the Cochrane Database of Systematic Reviews was done using the key word desmopressin. Retrieved articles were then searched for mention of the

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word hyponatraemia or hyponatremia to ensure that reports from clinical trials not listed on MEDLINE were not missed.

For the purposes of this survey a child was defined as an individual younger than 19 years. Short-term use was defined as treatment for 6 months or less. Long-term use was defined as treatment for more than 6 months. Symptoms of headache, nausea or vomiting were defined as prodromal for hyponatremia.

RESULTS

Published (MEDLINE) Data

A total of 21 clinical trials on the short-term or long-term use of desmopressin for the treatment of children with NE were identified, which included 3,101 patients.^{2–22} No additional clinical trials were identified from the Cochrane Database of Systematic Reviews. Eight trials (38%) were initiated independently of Ferring Pharmaceuticals,^{2,3,5,7,9,11,15,20} while 13 (62%) were supported by Ferring Pharmaceuticals. Five of the latter sponsored trials were pivotal studies performed for regulatory purposes^{6,10,12,18,21} and 8 were phase IV studies.^{4,8,13,16,17,19,22,23} Hyponatremia was not reported in any of these clinical trials.

In the clinical trials of short-term and long-term use of the intranasal or tablet formulations of desmopressin in children with NE the overall incidence of adverse events was low. Reported adverse events associated with desmopressin treatment in children with NE were described as mild and transient, including headache, abdominal pain, nausea and dyspepsia. In patients treated with the intranasal formulations reported adverse events also included nasal congestion, rhinitis and epistaxis. In 2 studies there was no significant difference between the reported incidences of adverse events in the treatment and control groups, and no association between the dose and the number of adverse events.^{10,12} Few patients withdrew from treatment due to an adverse event and no serious adverse events were reported in short-term or long-term studies of the treatment of NE with the intranasal or tablet formulations of desmopressin. No clinically significant changes in mean serum sodium were reported in long-term studies of the treatment of NE with the intranasal formulations or tablet formulation.^{9,16,17} One study described an increase in mean body weight,¹⁷ while in another mean body weight did not change throughout treatment.⁹

A total of 21 publications were identified that included 48 case reports of hyponatremia in children with NE who were treated with intranasal formulations of desmopressin (fig. 1).^{24–44} Ten publications provide data on the short-term use of desmopressin^{24–29,31,38,40,42} and 6 provide data on long-term use.^{30,33,35–37,39} Three publications describe a mixture of long-term and short-term data,^{34,41,44} while 2 do not mention the duration of desmopressin use.^{32,43} The table lists pertinent clinical information from the 48 case reports. Of these cases 36 (75%) involved seizures.

Excess fluid intake was identified as a contributing factor in at least 16 of the 48 cases (33%).^{26,27,34,35,37,38,40–43} Although in the majority of cases a conventional dose of desmopressin was prescribed, a higher than recommended dose might have been a factor in some cases.^{24,34,36,41} A weight gain of 700 and 1,500 gm was recorded in 1 patient each.^{29,38} The weight gain was believed to be a physical examination finding consistent with hyponatremia.⁴⁵ A total of 27 patients (56%)

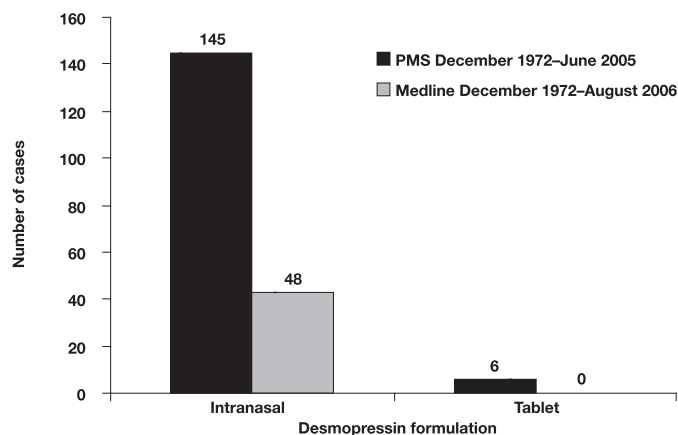


FIG. 1. Reported number of children with hyponatremia and nocturnal enuresis treated with desmopressin. PMS data included 145 children treated with intranasal formulation, of whom 21 were included in publications identified in MEDLINE search, and 6 treated with tablet formulation. MEDLINE search included 48 cases associated with intranasal formulation.

had nausea, vomiting or headache before the onset of a seizure or an altered level of consciousness.^{24–26,28,29,32,33,35–37,39–42,44}

The MEDLINE search did not reveal any case reports of hyponatremia in children with NE treated with the oral formulations (fig. 1).

PMS Data

Analysis of PMS data revealed 145 cases of hyponatremia associated with the use of intranasal formulations for the treatment of NE in children (fig. 1).⁴⁶ Of these 145 cases 21 were in the MEDLINE database. Seizures associated with hyponatremia were reported in 115 cases (80%). A total of 129 patients, representing 97% of those on whom data were available, recovered from hyponatremia. Three patients (2%) had not recovered at the time of the report and 1 (1%) died. A 9-year-old girl experienced hyponatremia with seizures following strenuous exertion during warm weather. Information on the dose of desmopressin, fluid intake and medical history was not available. Fluid intake was documented as increased or excessive during or before treatment with desmopressin in 38 cases (26%). Of the patients 105 (72%) ingested the recommended dose, 17 (12%) ingested a higher than recommended dose and in 23 (16%) the dose was not reported. A total of 41 patients (28%) were 5 to 6 years old. The drug was administered to 14 children (10%) younger than 5 years. Five patients (4%) who experienced hyponatremic seizures received imipramine in combination with desmopressin.

Analysis of PMS data revealed hyponatremia in 6 children with NE who were treated with the tablet formulation (fig. 1).⁴⁶ Four of the 6 children (67%) experienced a seizure. In 1 child a larger than recommended dose was suspected. Potential risk factors were identified in 3 of the 6 cases. One child had suspected psychogenic polydipsia and was also administered a higher than recommended dose. Two children had a tendency to drink a lot of fluids and they were concomitantly administered oxybutynin. All 6 patients recovered fully.

In the short time that the new oral lyophilisate has been marketed there have been no reports of hyponatremia associated with the formulation.

<i>Case reports of hyponatremia in children with NE treated with intranasal desmopressin</i>						
Reference	Age (yrs)—Sex	Dose (μ g)	Indication	Seizure	Sodium (mmol/l)	Treatment Duration
Simmonds et al ⁴⁰	13—F	10–20	PNE	Yes	120	4 days
Bamford and Cruickshank ²⁵	6—M	20	PNE	Yes	122	8 days
Blanchard and Brossier ²⁷	5—M	20	NE	Yes	117	5 wks
Beach et al ²⁶	10—M	20	PNE	Yes	118	3 days
Muglia et al ³⁵	15—M	80	PNE	No	124	7 mos
Yaouyanc et al ⁴²	2—M	20	PNE	Yes	118	6 wks
Hamed et al ³⁰	10—M	40	PNE	Yes	113	7 mos
Kallio et al ³³	8—F	40	PNE	No	120	2+ yrs
Kallio et al ³³	11—M	20	PNE	Yes	123	2 yrs, 2 mos, break, 1 day
Hourthane and Salisbury ³¹	8—F	40	NE	Yes	119	2 days
Guillaud et al ²⁹	4—M	20	SNE	Yes	122	8 days
Schwab et al ³⁸	6—M	10	NE	Yes	125	3 days
Robson et al ³⁷	16—F	40	NE	Yes	128	9 mos
Jensen and Hansen ³²	NM	40–50	NE	Yes	125	NM
Segal-Kuperschmit et al ³⁹	15—M	NM	PNE	Yes	NM	1 yr
Donoghue et al ²⁸	10—M	40	PNE	Yes	134	3 wks
Apakama and Bleetman ²⁴	6—M	10	NE	Yes	119	1 wks
Lebl et al ³⁴	10—M	7	NE	No	125	3 mos
Lebl et al ³⁴	5—M	7	NE	Yes	125	3 mos
Lebl et al ³⁴	7—F	21	PNE	No	125	1 yrs
Lebl et al ³⁴	6—F	7	PNE	No	120	2 yrs
Lebl et al ³⁴	9—M	7	PNE	Yes	123	Few days
Lebl et al ³⁴	10—F	7	SNE	Yes	113	2 wks
Lebl et al ³⁴	11—M	7	SNE	Yes	127	1 day
Ragoschke-Schumm et al ³⁶	16—M	20	NE	Yes	120	2+ yrs
Thumfart et al ⁴¹	5—M	30	SNE	Yes	122	1 wk
Thumfart et al ⁴¹	6—M	10	PNE	Yes	119	8 wks
Thumfart et al ⁴¹	6—M	10	PNE	Yes	112	4 wks
Thumfart et al ⁴¹	6—M	10	PNE	No	127	1 day
Thumfart et al ⁴¹	6—M	20	PNE	Yes	129	1 day
Thumfart et al ⁴¹	6—M	20	PNE	No	118	1 wk
Thumfart et al ⁴¹	8—M	20	PNE	Yes	121	2 yrs
Thumfart et al ⁴¹	8—M	20	PNE	Yes	122	2 wks
Thumfart et al ⁴¹	5—F	10	PNE	Yes	126	2 wks
Thumfart et al ⁴¹	6—F	10	PNE	Yes	120	1 day
Thumfart et al ⁴¹	6—F	40	PNE	Yes	116	3 wks
Thumfart et al ⁴¹	8—F	30	PNE	Yes	125	8 wks
Thumfart et al ⁴¹	9—F	20	PNE	Yes	126	26 wks
Dehoorne et al ⁴³	NM	NM	PNE	Yes	NM	NM
Dehoorne et al ⁴³	NM	NM	PNE	Yes	NM	NM
Dehoorne et al ⁴³	NM	NM	PNE	Yes	NM	NM
Dehoorne et al ⁴³	NM	NM	PNE	No	NM	NM
Dehoorne et al ⁴³	NM	NM	PNE	No	NM	NM
Ecoffey et al ⁴⁴	7—F	30	NE	Yes	117	7 wks
Ecoffey et al ⁴⁴	8—M	40	NE	No	127	6 wks
Ecoffey et al ⁴⁴	12—M	40	NE	No	116	4 days
Ecoffey et al ⁴⁴	5—M	20	NE	Yes	115	1 wk
Ecoffey et al ⁴⁴	9—F	10–40	NE	No	121	1 yr (occasional)

DISCUSSION

Desmopressin, also known as Minirin or DDAVP (1-deamino-8-arginine vasopressin), is a synthetic analogue of AVP. AVP regulates serum osmolality through the control of water production by the kidney and it exerts an antidiuretic effect mediated by renal V_2 -receptors. AVP also has a powerful vasopressor effect mediated by vascular V_1 -receptor. Desmopressin is a selective V_2 -receptor agonist and it has no effect on V_1 -receptors. As such, desmopressin retains the antidiuretic properties of AVP but it avoids unwanted vasopressor effects.⁴⁷ In collecting duct cells V_2 -receptors stimulated by desmopressin increase water reabsorption directly via the insertion of aquaporin-2 type water channels into the apical cell membrane of collecting duct epithelial cells.⁴⁸ Activated renal V_2 -receptors also increase sodium reabsorption, which increases medullary tonicity and enhances water reabsorption.⁴⁸

Desmopressin was originally introduced for the treatment of central diabetes insipidus. The major current indication for treatment with desmopressin is NE in children. Desmopressin is commercially available in various formulations, including an intranasal solution introduced in 1972,

an injectable solution for intravenous, subcutaneous or intramuscular use introduced in 1981, an oral tablet formulation introduced in 1987 and a rapidly acting, water-free oral lyophilisate formulation introduced in 2005. Desmopressin has a level 1, grade A recommendation from the International Consultation on Incontinence for the treatment of NE.⁴⁹

The only serious potential adverse event that has been reported in children with NE who were treated with desmopressin is hyponatremia. Symptoms of hyponatremia include headache, nausea, vomiting, altered consciousness and seizure.⁴¹

Although data obtained from published clinical trials on the safety of desmopressin did not suggest any difference in overall safety between the intranasal formulations and the oral formulations of desmopressin, and did not reveal any cases of hyponatremia associated with any oral formulations, there were 48 case reports in the literature of this adverse event with the intranasal formulations. All patients recovered completely.

PMS data included hyponatremia in 145 children with NE who were treated with intranasal desmopressin, of whom 21 were included in the publications identified in the

MEDLINE search. Analysis of PMS data also showed 6 case reports of hyponatremia in children with NE treated with the tablet formulation.

Based on sales figures up to November 2005 approximately 10 million children have been treated with desmopressin and it is estimated that 5 million have been exposed to the intranasal and oral formulations, respectively.⁴⁶ Although the oral formulations have been available for a much shorter time, exposure to intranasal and oral formulations is similar. This is probably because the oral formulations have been marketed more extensively, especially in the United States, and the international market for desmopressin increased substantially after the introduction of the tablet formulation. Although a similar number of children have been treated with each formulation, we identified 172 case reports (145 in PMS data plus 27 additional cases in the MEDLINE literature) of hyponatremia associated with the intranasal formulations in children younger than 19 years treated for NE and only 6 case reports of the tablet formulation. As such, the risks associated with the intranasal formulations would appear to be much higher. A possibility to account for the smaller number of case reports with the tablet formulation is that the medical community has presumed that the medical literature contains a sufficient number of case reports of hyponatremia associated with desmopressin treatment per se and the occurrence with an oral formulation is no longer reportable. Another possibility is that the tablet formulation has been available for a shorter period. Notwithstanding these possibilities, we believe that there is a decreased risk with the oral (tablet and lyophilisate) formulations.

There are several reasons that might explain an increased risk with the intranasal formulations. Ingestion of a higher than recommended dose is more likely with an intranasal formulation. Some patients, parents or caregivers might feel unsure whether an adequate dose has been administered with an intranasal formulation and they might increase the dose to compensate for this uncertainty. Another possible reason for this increased risk could be differences in pharmacodynamic profiles between the intranasal and oral formulations. Desmopressin is rapidly absorbed into the bloodstream regardless of the formulation. Ten μg of the intranasal formulation achieves the maximum plasma concentration within 1 hour of administration,⁵⁰ while 400 μg of the tablet and 240 μg of the lyophilisate attain a maximum dose dependent plasma concentration within 2 hours.⁴⁶ However, desmopressin tablets and the lyophilisate have a rapid onset of antidiuretic action with a decrease in urine production that is observed within 30 minutes following oral administration⁵¹ compared with 1 to 2 hours for intranasal desmopressin.⁴⁷ The bioavailability of desmopressin in adults is approximately 3% after intranasal administration⁵⁰ and 0.08% to 0.16% after a desmopressin tablet.^{50,52} The lyophilisate formulation has an average bioavailability that is approximately 60% higher than that of the tablet, that is the amount that reaches the circulation is approximately the same after the administration of 120 μg lyophilisate as after the administration of a 200 μg tablet.⁴⁶

Until recently limited information existed on the pharmacodynamic response to desmopressin in children with NE relative to the dose required to produce a useful antidiuretic effect. The doses used in children were extrapolated from studies in healthy adults. Studies in healthy adults show that the

antidiuretic activity of therapeutic doses of desmopressin nasal spray and tablets lasts for 6 to 24⁴⁷ and 6 to 8⁵⁰ hours, respectively. A pharmacodynamic study was performed in children with primary NE treated with the oral lyophilisate formulation.¹⁸ This study revealed that the duration of antidiuretic action increases with each increase in dose (fig. 2). For NE the most appropriate dose has a duration of action that corresponds to the typical duration of sleep in a child. The typical duration of sleep for children between ages 6 and 18 years is 11 and 8 hours, respectively.⁵³ A dose of desmopressin that provides a longer duration of action would be likely to increase the risk of prolonged antidiuresis and the risk of hyponatremia. When antidiuresis extends into the following day, water is accumulated and not excreted before the next dose is taken.¹⁸ In support of this proposed mechanism for hyponatremia Dehoorne et al reported a prolonged duration of antidiuretic action in 18 children treated for NE with intranasal desmopressin in whom prodromal symptoms or hyponatremia developed.⁴³ The investigators noted a significantly prolonged maximal urinary concentration period and delayed restoration of daytime diluting capacity in this population of children compared with those in a control group of 50 children with NE who were treated with the same desmopressin regimen ($p < 0.01$). The physiological mechanism is not known to explain why these 18 children had a prolonged duration of antidiuretic action but the other 50 did not.

For the lyophilisate formulation the pharmacodynamic study revealed that doses in the range of 120 to 360 μg provide a duration of antidiuretic action of up to 10.2 hours.¹⁸ Since the lyophilisate formulation has approximately 60% higher bioavailability than the tablet, an estimate of a corresponding dose for a tablet might be 200 to 600 μg . This is in the range suggested by pharmacodynamic studies on tablets in adults, which revealed a duration of antidiuretic action of 6 to 8 hours.⁵⁰ However, to our knowledge such data are not available for the intranasal formula-

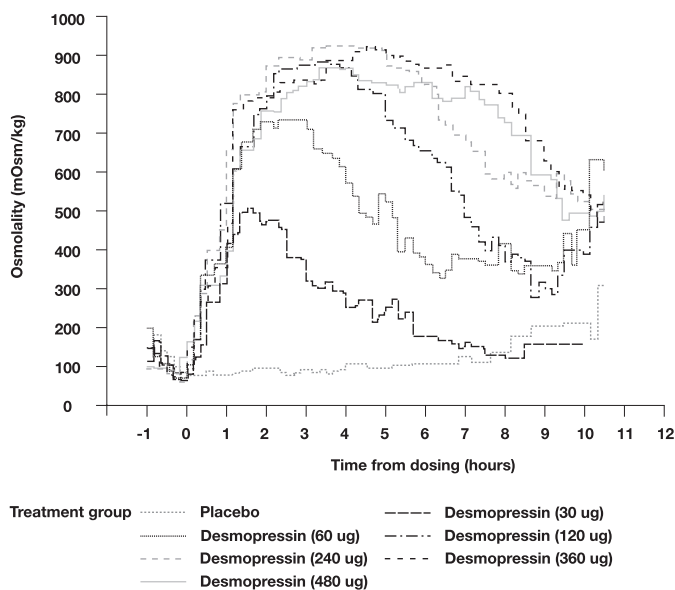


FIG. 2. Mean osmolality with time after administration of different doses of lyophilisate formulation of desmopressin in children with NE. Results revealed that duration of antidiuretic action increases with each increase in dose. Reproduced with permission from Blackwell Publishing.¹⁸

tions and the most appropriate dose for the desired duration of antidiuresis with this formulation is unclear. The bioavailability of intranasally administered desmopressin is approximately 3%.⁵⁰ Therefore, for the recommended dose range of 20 to 40 μg up to 1.2 μg of medication are available. The bioavailability of the tablet is up to 0.16% and so, for the recommended dose range of 200 to 600 μg , 0.3 to 1.0 μg of the drug is available. As mentioned, the bioavailability of the lyophilisate is about 60% higher than that of the tablet and, therefore, for the recommended dose range of 120 to 360 μg , 0.3 to 0.9 μg of the drug is available. Thus, oral formulations appear to represent a safer alternative to intranasal formulations because they have a similar onset of action, lower bioavailability of the medication for the recommended dose range, and a relatively predictable and practical duration of action that is compatible with the typical duration of sleep for children who are 6 to 18 years old.^{18,53}

Regardless of the formulation prescribed there are identifiable and preventable risk factors for hyponatremia. An inappropriately high fluid intake before desmopressin administration is a key risk factor. Excess fluid intake was identified as a contributing factor in 38 of the 145 PMS cases (26%) that we identified. Other reviews and reports confirm this risk factor. Robson et al identified an inappropriately high fluid intake in 5 of 10 cases (50%) reviewed.¹ Thumfart et al identified an inappropriately high fluid intake in 4 of 12 cases (33%) on which fluid intake data were available.⁴¹ Lebl et al attributed hyponatremia to an inappropriately high fluid intake in 2 of 7 children (29%) with NE who were treated with intranasal desmopressin.³⁴ Most recently Ecoffey et al reported inappropriately high fluid intake in 4 of the 5 cases (80%) reviewed.⁴⁴ None of the groups reported the duration of bioactivity of the administered desmopressin.

We recommend that fluid intake should be minimized on any evening that desmopressin is administered. A reasonable recommendation is to allow fluids as desired during dinner, minimize fluids to less than 240 ml (8 oz) after supper and not permit any fluids during the 2 hours preceding bedtime.¹ These restrictions require modification for children who plays sports in the evening or who reside in hot environments without air conditioning. Desmopressin should not be administered on evenings when it is not practical or possible to restrict fluid intake.

The prescription or administration of a larger than recommended dose is another key risk factor. In the cases reported by Thumfart et al 1 patient (8%) ingested a larger than recommended dose of desmopressin.⁴¹ Lebl et al speculated that hyponatremia might have been due to the ingestion of a larger than recommended dose in all 7 cases reported.²⁶ The drug should not be prescribed or taken in a higher than recommended dose. Hyponatremia might be more common early in the course of treatment with desmopressin. Thumfart et al identified the first 3 weeks of treatment as a risk factor.⁴¹ Desmopressin is not recommended or approved for the treatment of NE in children younger than 5 years. Thumfart et al identified young age as a risk factor for hyponatremia.⁴¹ Concomitant administration of another medication might be a risk factor. Robson et al identified concomitant administration of imipramine and methylphenidate in 2 of the 10 cases (20%) that they reviewed.¹ Of the 13 patients reported on by Thumfart et al 2 (15%) were on oxybutynin and 1 (8%) was on methylphenidate.⁴¹

Imipramine is known to decrease the seizure threshold.⁵⁴ The side effects of oxybutynin and methylphenidate include dry mouth, which might lead patients to consume excess fluid.²⁹ Methylphenidate influences the central nervous system, although it has no known effect on fluid homeostasis.⁵⁵ It is possible that the distractibility and lack of attention span common in some patients with ADHD who are treated with methylphenidate might make these individuals more susceptible to ingest an inappropriate amount of fluid.⁴¹

A coexistent disorder might also be a risk factor. Children with cystic fibrosis might be at increased risk, perhaps because of abnormal sweat electrolyte losses or the increased risk of inappropriate antidiuretic hormone secretion associated with the condition.⁵⁶ In addition, children with ADHD might be at risk, as noted.²⁶ Children with Prader-Willi syndrome might also be at increased risk.³⁷ These children have a voracious appetite and they often experience behavioral problems, which might predispose them to an inappropriately high fluid intake. We recommend that desmopressin should be used with caution in patients with cystic fibrosis, ADHD or Prader-Willi syndrome. The medication should not be administered during intercurrent clinical situations that might otherwise affect fluid balance or in children with severe neurological or developmental problems who might not be able to appropriately limit their evening fluid intake.

We defined headache, nausea and vomiting as prodromal symptoms. We recognize that headache, nausea and vomiting are signs of cerebral irritability and, therefore, they are symptoms of hyponatremia. We chose these definitions because from a practical clinical perspective the identification of prodromal symptoms might allow sufficient warning for a patient, caregiver or physician to discontinue desmopressin therapy and prevent a seizure or altered level of consciousness. Prodromal symptoms were common in patients in whom hyponatremia developed. Of the patients reported on by Thumfart et al 8 (62%) experienced vomiting and 2 (15%) experienced headache before the onset of hyponatremia.⁴¹ Six of the 10 patients (60%) evaluated by Robson et al had a prodromal symptom before hyponatremia.¹ Patients and their caregivers should be advised that if headache, nausea or vomiting develop, desmopressin treatment should be discontinued immediately and the child should be promptly assessed.

Finally, the completeness of PMS data should be considered. Although physicians are professionally obliged to report suspected treatment related adverse events to the relevant pharmaceutical company or health authorities, not all do so and adverse events in this respect are probably appreciably underreported. However, the comprehensiveness of the data is somewhat immaterial since PMS data collection methods were similar for the intranasal and oral formulations, and the information remains useful and relevant in terms of the proportion of adverse events associated with each formulation. Therefore, the PMS data presented are believed to reliably substantiate the published data that we reviewed. They indicate that hyponatremia in children with NE who are treated with desmopressin is more frequent with the intranasal formulations than with the tablet formulation.

CONCLUSIONS

In the clinical trial setting desmopressin has proved to be an effective and well tolerated medication for children who have NE with a low incidence of adverse events. Case reports and PMS data indicate that hyponatremia is an uncommon but serious adverse event in children with NE. The optimal dose of desmopressin for NE is one that results in antidiuresis for approximately 8 to 11 hours, which is the typical duration of sleep for a 6 to 18-year-old child. Any effect beyond this might lead to unwanted fluid retention with a risk of hyponatremia. Therefore, for optimal safety the duration of action should be limited to no more than 12 to 16 hours, giving the body 8 to 12 hours to compensate for extra fluid retained. The data suggest that the risk of hyponatremia is greater in children treated with the intranasal compared with the oral formulations, probably because in some children the duration of action of the intranasal formulation (up to 24 hours) is longer than the typical duration of sleep. We suggest that children with NE should be treated with an oral rather than intranasal formulation of desmopressin, especially since the duration of action of the oral formulations in the approved dose range is limited to approximately 10 hours. When desmopressin is prescribed, the potential side effects and associated risk factors should be clearly explained to the patient and family. They should be instructed to avoid an inappropriately high fluid intake when the medication is received, not ingest a higher than recommended dose and promptly discontinue the medication and seek assessment if headache, nausea or vomiting develops.

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Abbreviations and Acronyms

ADHD	=	attention deficit hyperactivity disorder
AVP	=	arginine vasopressin
NE	=	nocturnal enuresis
NM	=	not mentioned
PMS	=	post-marketing safety
PNE	=	primary NE
SNE	=	secondary NE

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