

Synthetic DDAVP for nocturnal enuresis and the risk of symptomatic hyponatremia: which treatment now? Which form?

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Question

Recently, several cases of seizure secondary to hyponatremia have been reported in children treated with intranasal DDAVP^{1), 2)}. This has rarely been reported with the oral form. Should the intranasal form be banned for the treatment of nocturnal enuresis (NE)? Or should any form of DDAVP be banned? What are the precautions to take to avoid such an event? We hereunder summarize the literature on the subject, and present the recommendations of the Swiss Group for Pediatric Nephrology and the current position of Swiss medic.

Answer

1. Introduction

NE is a fairly common benign developmental disorder, most of the time self-limited, encountered more frequently in boys than girls, with a high rate of spontaneous resolution (approximately 15% per year from the age of 6). In case of a protracted course or in particular situations (sport camp participation, sleepover), numerous approaches have been tried, with various success, such as: behavioral therapy³⁾, DDAVP analogs (**Minirin**[®], **Nocutil**[®])⁴⁾, nocturnal alarm⁵⁾ or tricyclic antidepressant⁶⁾. We here review these therapeutic modalities, their success rate and associated side effects. We also compare data available in the literature comparing the oral form with the intranasal form for Minirin[®], especially regarding the occurrence of hyponatremia.

2. Pharmacological and non-pharmacological treatment of NE

Because of its psychological repercussion, physician will often be asked to start treatment, rather than wait for spontaneous

resolution. This is especially true for sleepover or sport camp participation, in which situations nocturnal enuresis can be frustrating for the child⁷⁾. Desmopressin, also known as DDAVP, is a synthetic analogue of AVP. Desmopressin increases tubular reabsorption of water in the collecting ducts, and decreases the nocturnal urine volume. Its current indications include: NE and central diabetes insipidus. Desmopressin is commercially available as an intranasal solution (introduced 1972), an injectable solution for intravenous, subcutaneous or intramuscular use (introduced 1981), an oral tablet formulation (introduced 1987) or a rapidly acting, water-free oral lyophilisate formulation (introduced 2005). In several randomized trials, DDAVP has been shown to rapidly reduce the number of wet night per week, although there is some evidence that this was not sustained after treatment stopped⁴⁾. The different formulas share the same physiological properties, with different bioavailability, and hence different dosages (commonly 0.1 µg for the IV route (not used for NE), 10–40 µg for the nasal route, 0.1–0.4 mg for the oral route and 60–240 µg for the sublingual route. It should be noted that published pharmacological data were obtained in adults and that the doses used in children were extrapolated from these studies. Studies in healthy adults show that the antidiuretic activity of therapeutic dosage of DDAVP nasal spray and tablets last for 6 to 24 hours⁸⁾ and 6 to 8 hours⁹⁾, respectively. The slightly longer duration action of the intranasal formulation might explain the observed tendency of this particular form to induce hyponatremia.

Other pharmacological treatments of NE include tricyclic agents. Two small studies showed no superiority of imipramine¹⁰⁾ or

amitriptyline¹¹⁾ over desmopressin. Because of their very narrow therapeutic index and potential lethal adverse effects (cardiac arrhythmia)¹²⁾, we feel that tricyclic agents should not be prescribed in children with isolated NE.

Non-pharmacological treatment of NE includes behavioral therapy and nocturnal alarm. Very few studies compared desmopressin and nocturnal alarm. In a single trial, Faraj et al.¹³⁾ found desmopressin to offer better short-term results than enuresis alarm but the latter was significantly more efficient in the long term. Glazener et al., in a complete literature analysis, also found nocturnal alarm to be more effective than desmopressin or tricyclics by the end of treatment, and subsequently⁵⁾. A thorough discussion of behavioral therapy is beyond the scope of this short review.

3. Desmopressin and the risk of hyponatremia

3.1. Review of the literature

DDAVP has been used extensively, in millions of children, for more than 30 years, and has been found to have a very good safety profile. Side effects are rare. Hyponatremia is one of the most commonly reported side effect, and potentially the most severe one¹⁴⁾. Recent data suggest that there might be an increased risk of hyponatremia with the intranasal DDAVP formulation compared to the oral formulation¹⁵⁾. It is unclear at this point why patients taking the intranasal DDAVP formulation should develop more often hyponatremia than patients on the oral formulation. Robson et al.¹⁵⁾ raises interesting hypothesis such as: repeated dose if the parents felt unsure whether an adequate dose has been administered, increased bioavailability in case of nasal mucosa inflammation/rhinitis and prolonged antidiuretic activity compared to the oral form. All these factors might explain the observed increased risk of hyponatremia with the intranasal form.

Identifiable and preventable risk factors for hyponatremia, common to both the oral and the intranasal forms, are: inappropriately high fluid intake prior to DDAVP, administration of a larger than recommended dose of DDAVP, young age (less than 6 years) and concomitant administration of another medication (NSAID).

	Age (years)	Diagnosis	Symptoms	Form	Dosage	Duration of therapy	Outcome
Children	11	EN	H, V, S	N	10 µg	1 day	R
	8	EN	S	N	20 µg	3 days	R
	6	EN	S	N	20 µg	14 days	R
	12	EN	Somn.	N	40 µg	2 days	R
	7	EN	Somn., S	N	50 µg	53 days	R
	9	EN	Somn., V	N	20 µg	5 days	R
	7	EN	S, C	N	20 µg	1 day	R
	9	EN	Na, H, S	N	20 µg	1 day	R
	Age (years)	Diagnosis	Symptoms	Form	Dosage	Duration of therapy	Outcome
Adults	58	Pit. adenoma	Somn.	O	0.3 mg	unknown	R
	70	Potomania, Parkinson	Somn.	O	0.1 mg	2 days	R
	61	Pit. adenoma	Na, V, Somn.	N	10 µg	unknown	R
	63	Nycturia	Somn.	N	unknown	unknown	unknown
	83	Incontinence	Somn.	N	10 µg	3 months	R
	67	EN	V	N	40 µg	2 days	R

Table 1: summary of patients with hyponatremia reported to Swissmedic as of 02.08.2007

Legend: C: coma, EN: enuresis nocturna, H: headache, Na: nausea, N: intranasal, O: oral, Pit. adenoma: pituitary adenoma, R: recovered, S: seizures, Somn.: somnolence, V: vomiting.

When desmopressin is prescribed, the patient and the parents should be carefully instructed to avoid high fluid intake when the medication is taken (i.e., the child should have no fluid intake after the drug administration in the evening until the next morning), not to give a higher than recommended dose, and to promptly discontinue the medication and seek assessment if headache, nausea or vomiting develops.

3.2. Hyponatremia and DDAVP reported to SwissMedic

All patients with symptomatic hyponatremia reported to Swiss medic are compiled in table 1. For pediatric patients, it is remarkable to note that all the patients were quite young; all of them on the intranasal formulation, and most of them had developed hyponatremia very soon (1–2 days) after initiation of therapy. These are the known and reported risk factors for hyponatremia with DDAVP which are: young age, intranasal formulation, and recent initiation of therapy (or change in drug dosage)¹⁾. Postmarketing reports of serious hyponatremia events have so far been more frequent for the nasal forms than for the oral forms of Desmopressin. The indication enuresis nocturna has therefore been withdrawn

from the market in Switzerland for the nasal forms of Desmopressin.

One should however keep in mind that the removal of the indication for the nasal forms is based on spontaneous reports, which means that the actual number of events is an underestimate (not all events are reported) and that despite approximations from sales figures the exact exposure is also unknown. Without knowing the actual number of events and the exact exposure, it is not possible to directly compare the incidence of serious hyponatremias under the oral as compared to the nasal forms. Of note is also that the oral forms have been on the market for a shorter duration than the intranasal forms. It is therefore very important to report any hyponatremia-related adverse event that may be observed in the future with the oral forms of desmopressin.

Conclusions

1) Desmopressin (nasal or oral) and nocturnal alarm probably have the same efficacy, although nocturnal alarm might have a lower relapse rate on the long term. If parents or physician are concerned with potential drug side effect, nocturnal alarm should be the first therapeutic option.

- 2) Both the intranasal and oral desmopressin forms have been associated with severe hyponatremia secondary to water intoxication. However, the data are now suggesting that hyponatremia occurs more often with the intranasal DDAVP formulation than with the oral formulation.
- 3) Thus, the NE indication for the intranasal form was recently withdrawn from the market in Switzerland. It should be known that the intranasal form has been previously withdrawn from its NE indication in Italy, France, UK, Spain, Portugal, Austria and Greece.
- 4) If the parents and the physician opt for drug therapy, the oral DDAVP formulation (oral or sublingual) will be administered. The efficacy of the two drug formulations have been shown to be similar.
- 5) When taking DDAVP, whichever formulation, the patient and the parents should be warned of potential side effects, and instructed accordingly:
 - To strictly adhere to the dosage that has been recommended.
 - To avoid drinking after the drug administration in the evening until the next morning

- To immediately stop DDAVP administration and seek medical help should the child present any signs or symptoms suggestive of water intoxication such as: headaches, nausea, vomiting, confusion, altered consciousness or seizure.

These recommendations apply especially to the young child, in the first few weeks of treatment or after drug dosage adjustment, or in case of concomitant drug administration (NSAID) or in case of associated disorder such as cystic fibrosis^{1), 16)}.

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