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Is There Still a Role for Desmopressin in Children with Primary Monosymptomatic Nocturnal Enuresis?

A Focus on Safety Issues

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Abstract

It has recently became apparent that severe primary monosymptomatic nocturnal enuresis (MNE) has a worse prognosis than generally believed, and may have major consequences on the well-being of the child, thus making treatment mandatory. Desmopressin is one of the most widely prescribed medications for MNE, and in this current opinion article we discuss the safety of desmopressin in children with this condition.

Following a US FDA request in December 2007 that the prescribing information for desmopressin nasal spray be updated, desmopressin spray is no longer indicated for the treatment of MNE or for use in patients at risk for hyponatraemia.

Multiple reports of hyponatraemia in patients with nocturia (mainly the elderly) led to an increased awareness of the risks associated with desmopressin. While the pathogenesis of hyponatraemia in those over 65 years of age relates more to changing renal water and solute handling, we believe that in the young, overdosing and insufficient fluid restriction are usually the major causes.

Hyponatraemia is most frequently reported when desmopressin is administered by nasal spray compared with the tablet formulation. This may simply reflect the fact that for more than 10 years the spray was the only available mode of administration in many countries. However, it may also reflect the higher biodisponibility and/or intraindividual variability of pharmacokinetics of the spray compared with the tablet. There are few serious adverse events reported for the melt formulation (oral lyophilisate), but as it has only recently become available on the market, it would be premature to conclude that it has a better safety profile.

We believe that desmopressin in all formulations has a good safety profile in children with MNE, provided that treatment is properly prescribed and monitored; improving the training of doctors and patients in the dose-response kinetics of the drug, teaching appropriate restriction of fluid intake and by encouraging the use of desmopressin within a narrow dose range (10–20 μg spray, 120–240 μg melt and 200–400 μg tablet) when used in primary-care settings. Titrating higher doses in therapy-resistant patients should probably be carried out in a specialized enuresis centre, and only after documenting adequate morning urinary diluting capacity.

In summary, the risk of hyponatraemia is exacerbated by misuse of the drug rather than an inherent danger associated with the drug, which in our opinion should be addressed with better education rather than withdrawal of a medication that has the potential to benefit children with nocturnal enuresis.

Recent reports of hyponatraemia while using desmopressin (DDAVP; 1-desamino-8-arginine vasopressin) nasal spray in the treatment of monosymptomatic nocturnal enuresis (MNE) have put the spotlight on its continued use. In December 2007, the US FDA requested that the prescribing information for desmopressin nasal spray be updated, leading to the withdrawal by the manufacturer of desmopressin nasal spray for the treatment of MNE. We fully agree that desmopressin, like any other drug, has potential adverse effects and should therefore be used with care. However, in this current opinion article we will aim to demonstrate that the risk of adverse effects can be reduced if the treatment is properly prescribed and monitored. There is no question that some form of treatment for nocturnal enuresis in children is needed. We will discuss new evidence that suggests severe nocturnal enuresis has lower spontaneous cure rates than classically accepted, that therapy resistance to monotherapy is higher than generally thought and that enuresis is a disease with a major impact on the well-being and functioning of the child. All these make a 'wait and see' approach indefensible.

1. Do we Need to Treat Nocturnal Enuresis?

Nocturnal enuresis is a common disorder in children, with a prevalence of 5–10% in 7-year-olds.[1] While in the past it was considered to be a benign disorder with a spontaneous resolution rate of 15% per year,[1] recent evidence has seriously challenged this. It has been shown that 1% of adults still wet their beds, which means 1/10 children with nocturnal enuresis will persist with the disorder into adulthood.[1] Yeung et al.[2] demonstrated that, in particular, those with severe nocturnal enuresis (wetting 7 nights/week at the age of 5 years) have a poor prognosis, with a spontaneous cure rate of only approximately 60% before adulthood. These children suffer both directly as a result of their enuresis, and indirectly as a result of the psychological consequences, such as poor self-esteem[3-8] and parental intolerance.[9]

Recently, Yeung et al.[10] hypothesized that in nocturnal enuresis, the *primum movens,* or 'first cause', might be continuous central nervous stimulation by an overactive bladder, resulting in disrupted sleep and, consequently, attention-deficit hyperactivity disorder (ADHD) symptoms and abnormal startle reflex. This correlated with the authors' findings that in an animal model with surgically reduced bladder volume, chronic stimulation of the brain by continuous stimulation from an overactive bladder results in an exhaustion of neurotransmitters, leading to cerebral dysfunction.[11] This group further claims that in children with enuresis, light sleep causes attention problems and poorer results at school, which further worsens self-esteem and adds to the child's psychological burden. The most important observation was that successful treatment of enuresis resulted not only in normalization of sleep and startle reflex but also in a decrease in ADHD symptoms and better cognitive functioning and school results.[12]

Since the results of Yeung et al.[10] have only been published as a letter, we have to refrain from drawing premature conclusions and cannot, as yet, assert a causal relationship nor a pathogenetic cascade; however, other authors separately confirm parts of these observations,[13,14] thus bolstering their theory.

Co-morbid psychological characteristics in nocturnal enuresis have been documented,[13,15-20] especially ADHD.[21-24] Children with ADHD are more likely to experience nocturnal enuresis than their peers, and treatment duration is likely to be longer. However, these observations

regarding a role of ADHD in resistance to desmopressin treatment[24] are not in line with Crimmins et al.,[25] who found that ADHD does not interfere with response to desmopressin.

Whether there is a common pathway in pathogenesis between enuresis and ADHD is more speculative. Baeyens et al.[26] suggested a possible additional dysfunction in the cortical-striatal-pallidal pathway in enuretic children with the predominantly inattentive subtype of ADHD. This observation seems to be supported by Ornitz et al,[27] since ADHD symptoms and normalization of the startle reflex coincide with amelioration of the enuresis, although we failed to confirm this.[14] This suggests, but does not prove, a common pathogenetic cause between nocturnal enuresis, ADHD and an abnormal startle reflex.

We recently described a subgroup of children with severe enuresis and nocturnal polyuria who had disrupted sleep and periodic limb movements.[13] Our findings are in line with the hypothesis put forward by Yeung et al.,[10] although while we concentrated more on nocturnal polyuria, patients observed by Yeung et al[10] were mainly those with overactive bladder.

The Aarhus group[28] recently showed that sleep deprivation resulted in increased nocturnal diuresis; therefore, since nocturnal polyuria and an overactive bladder may lead to disrupted sleep, a vicious circle develops, whereby monotherapy is unlikely to provide a solution.

Because the data of Yeung et al.[10] are not fully published, we must remain circumspect about overemphasizing the interpretations of their letter to the editor, abstracts and different oral presentations. Nonetheless, if proved true, their new concept may change our thinking about enuresis as a whole.

2. What is the Treatment of Choice in Monosymptomatic Nocturnal Enuresis?

Only three treatments have a high level of evidence in MNE: the alarm, desmopressin and imipramine. Both the alarm and desmopressin are recommended by the International Consultation on Incontinence for the treatment of nocturnal enuresis (grade A, level 1),[21] the Hjalmas et al. study[1] and in the International Children's Continence Society (ICCS) standardization papers on the treatment of MNE.[22,29] The alarm therapy is probably the treatment of choice. Desmopressin has lower success rates in children with low voided volumes and absent nocturnal polyuria, probably because they reach already maximal urinary concentration overnight. Alarm therapy seems to be superior to desmopressin in this subgroup (in well motivated families). In contrast, data from the initial Aarhus studies[30-32] suggest that desmopressin is the treatment of choice in children with nocturnal polyuria and normal voided volumes.

Desmopressin is a synthetic analogue of AVP (vasopressin). AVP regulates serum osmolality through the control of water production by the kidneys, and exerts an antidiuretic effect mediated by renal vasopressin V_2 receptors. Desmopressin was originally introduced for the treatment of central diabetes insipidus. Currently, the main indication for treatment with desmopressin in children is nocturnal enuresis. 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, oral lyophilisate formulation (melt) to be taken without water, introduced in 2005.[33] According to Lottmann et al.,[34] the melt has similar levels of efficacy and safety at a lower dose than the tablet. Moreover, in children aged 5–11 years there was an overall preference for the melt compared with the tablet formulation.

The alarm therapy has a conditioning effect on arousal[35] and/or increases voided volumes.[36] Imipramine, a tricyclic antidepressant, is no longer recommended as a first-line treatment because of potential cardiotoxicity.[37]

3. Factors Influencing Desmopressin Response

To address the issue of whether the use of desmopressin is still warranted requires an

analysis of both the pathogenesis of enuresis and the recent literature. Desmopressin increases reabsorption of water in the distal and collecting tubules, up to maximum concentrating capacity, thereby reducing diuresis rate. An anti-enuretic effect will only be demonstrated in those who can increase their urinary osmolality; therefore, only those who do not reach maximal concentrating capacity at night without taking desmopressin will be able to respond to this agent. Two decades ago, Scandinavian groups demonstrated full desmopressin responsiveness in two-thirds of children with MNE, making it the treatment of choice for some.[30-32] They found a high percentage of patients with nocturnal polyuria, low urinary osmolality during the night and low plasma vasopressin levels. Their initial populations were clearly older and were therefore likely to be resistant to conventional therapy (in those days, imipramine and/or alarm).

These initial promising success rates of desmopressin were not confirmed in large, multicentre studies in the following years. A Cochrane review of 75 trials demonstrated (partial) success in approximately two-thirds of children with MNE; 30% responded well, 30% had a significant amelioration and 40% were desmopressin resistant.[38] Recent reports document even lower success rates,[39,40] probably indicating that patient (and centre) selection plays a major role in response rates.

There is a subpopulation of patients with MNE who have low-for-age voided volumes, low diuresis volumes overnight and high urinary osmolality. These patients cannot benefit from desmopressin and are likely to be more responsive to the alarm; however, there are some patients who have reduced voided volumes and a high nocturnal urine production who might benefit from the combination of the alarm and desmopressin. We believe that patients being enrolled in studies should be properly subtyped according to the new ICCS definitions,[22] not only excluding patients with daytime incontinence in their clinical history, but every patient with a daytime symptom suggestive for bladder dysfunction in their clinical history or bladder diary. None of the available studies has prospectively used the new ICCS criteria. The existing meta-analyses all suffer from the weakness of ill-defined patient selection and poor subtyping of the patient characteristics. It is clear that population characteristics play a major role in response rates to different treatments. Hence, in any study of enuresis, the information provided should include whether the child has mono- or non-monosymptomatic enuresis according to the new ICCS definition, a description of patient characteristics, such as bladder capacity or maximal voided volume, and nocturnal diuresis rate.

Nocturnal polyuria is thought to play a major role in the pathogenesis of nocturnal enuresis. Since there is no evidence that the alarm is superior to desmopressin in children with nocturnal polyuria, desmopressin maintains its place alongside the alarm as first-line treatment when patients have undergone only minimal screening. On the other hand, it is evident that in the presence of maximal concentrating capacity during the night, patients will have no additive anti-enuretic effect from desmopressin.

If a centre performs a more extensive diary registration of bladder and diuresis characteristics then it is reasonable to use the alarm in MNE with low nocturnal diuresis volume and high urinary osmolality. It seems likely that patients with nocturnal polyuria and low urinary osmolality overnight will benefit most from desmopressin treatment. In this subpopulation, response rates similar to those in the initial Scandinavian papers are to be expected.[30-32] There is also a possibility that desmopressin functions as a neurotransmitter in the brain and may participate in nocturnal bladder inhibition, not just in the decrease of free water excretion.[41]

4. What are the Adverse Effects?

In 2007 we reviewed the safety of desmopressin, using published data (via a MEDLINE search) and unpublished adverse reactions reported to Ferring Pharmaceuticals,[42] concluding that all desmopressin formulations have a favourable safety profile. Shortly after the submission of this paper, both the use and safety of desmopressin as a nasal spray in the treatment of

nocturnal enuresis was questioned by the FDA and European authorities, even reaching the press. In their excellent survey, Robson et al.[33] concluded that the tablets were safer than the spray, leading to withdrawal of the spray for the treatment of nocturnal enuresis in children. Multiple reports of hyponatraemia in patients with nocturia (mainly in the elderly) led to questions about the safety profile of desmopressin. These considerations, together with decreasing success rates[38,39,42] since the initial Scandinavian publications,[30-32] led some authors to question the role of desmopressin as first-line treatment for MNE.[39]

Adverse effects of desmopressin are uncommon and are generally described as mild. For the intranasal route, adverse effects include headache, abdominal pain, nausea, nasal congestion/rhinitis and epistaxis.[42] The only serious potential adverse effect is water intoxication and hyponatraemia. Symptoms include headache, nausea, vomiting, altered consciousness and seizures, and even death can occur.[33] A case report of an adolescent with desmopressin-associated hyponatraemic death stresses the importance of the role of compulsive drinking habits.[43]

There are more case reports of hyponatraemia in children treated with the intranasal formulation of desmopressin than with the oral formulation.[42] This may be due to the spray having been on the market for a much longer period of time than the tablet formulation. Both formulations have equally and increasingly been used in the past, until the request by the FDA.[33]

Robson et al.[33] have advanced several reasons as to why the intranasal formulation may be more risky. The prescription of a higher-than-recommended dose (with the intranasal formulation) increases the risk for toxicity. Doctors often mistakenly believe that a lack of an antienuretic effect suggests that the child has not reached maximal concentrating capacity, whereas the drug may not work because the child's urine is already at maximum concentration. In these circumstances, increasing the dose will not result in a higher-than-maximal concentrating capacity but will result in a prolonged duration of action. We have documented a prolonged duration of action with conventional doses of 20 μg intranasally in 17 patients.[44] Higher doses of the spray should only be used if the doctor can document that diluting capacity is restored in the morning by showing a low urine osmolarity on the second voided specimen of the morning.

The design of the spray bottle may leave patients, parents or caregivers with uncertainty as to the administered dose, therefore encouraging extra doses. This mostly occurs at the beginning of the bottle when priming is needed, and towards the end of the bottle – a frequent occurrence in clinical practice given that the spray bottles are small. Adolescents, who are averse to bed wetting, especially on sleepovers or holidays, will likely use higher doses, just to be sure nothing will happen. This is more likely to happen with the spray than with the tablet since caregivers, parents and patients, as daily clinical practice learns, consider a spray less of a drug than a tablet.

However, the major reason why the oral formulation seems to be safer than the spray is the difference in the pharmacodynamic profiles. Although the spray (2×10 μg sprays), melt (240 μg) and tablet (400 μg) are promoted to be bioequivalent in children,[45] there are no appropriate large pharmacokinetic and pharmacodynamic studies in children that confirm this. The available studies demonstrate that desmopressin is rapidly absorbed into the bloodstream regardless of the formulation. 10 μg of the intranasal formulation achieves the maximum plasma concentration within 1–2 hours of administration,[46,47] faster than the tablet (400 μg) or melt (240 μg) formulations. This is somewhat contradictory with the antidiuretic effect, observed within 30 minutes following oral administration,[48,49] compared with 1–2 hours for intranasal desmopressin.[50] The bioavailability of desmopressin in adults reaches about 2–3% after intranasal administration[46,47] and 0.08–0.16% after a desmopressin tablet.[47,51] The bioavailability of the melt formulation is approximately 60% higher than that of the tablet.[46,52]

Bioavailability of the nasal spray becomes unpredictable in the presence of a blocked nose with rhinorrhoea, where absorption may be decreased, and with nasal hyperaemia, where it may be increased.

Reports of desmopressin-induced hyponatraemia with the intranasal formulation cannot be ignored. Nonetheless, the risk seems reduced or remote when desmopressin is used in a standard dose with fluid restriction before bed. In the primary-care setting we suggest that the maximum dose in children <12 years of age, who do not auto-administer the drug, can be up to two sprays (20 μg in total). Higher doses should only be used if diluting capacity is documented in the morning – a decision best made only in a secondary- or tertiary-care setting.

5. When can we Expect Adverse Effects?

It is well known that the elderly are more at risk than children for desmopressin-induced hyponatraemia[42,53,54] but they rarely have a primary disturbance in circadian vasopressin rhythm as described in children. The risk of desmopressin-induced hyponatraemia increases with increasing age, lower serum sodium concentration at baseline, higher basal 24-hour urine volume per bodyweight, and weight gain at the time of minimum serum sodium concentration. With older age there are changes in the regulation of water and electrolyte balance, making the elderly more vulnerable to drug- and/or disease-induced hyponatraemia;[55] however, this cannot automatically be extrapolated to children. The pathophysiology of nocturia in an adult aged >60 years is totally different to that of a child with nocturnal polyuria. Adult nocturnal polyuria is a consequence of water and sodium retention during the daytime, leading to hypervolaemia overnight. Adults may also have increased sodium and water excretion during recumbency, but rarely as a result of primary disturbance in circadian vasopressin rhythm, as described in children. Incipient (subclinical) cardiac, renal, venous or lymphatic dysfunction, and decreased mobility may, in older patients, certainly result in fluid retention during the daytime, compensated by increased diuresis overnight. Desmopressin administration will initially comfort the patient during the night by reducing diuresis volume; however, these patients may not reach compensatory maximal diluting capacity during the daytime, once desmopressin activity is ended, since their primary pathophysiology will induce secondary tubular sodium and water retention during the daytime. Finally, adult patients achieve a chronic hypervolaemic state, leading to a natriuresis exceeding the diuresis during the night because desmopressin inhibits the water excretion, a status that will finally result in hyponatraemia. Desmopressin is only recommended in adults who have the ability to reach diluting capacity during the daytime. All children have this ability and most healthy subjects have a well developed osmoregulatory system to prevent hyponatraemia, resulting in less thirst and less fluid intake at low plasma sodium levels. However, children with primary polydipsia, where there is uncoupling of thirst and serum sodium levels, are prone to hyponatraemia when water excretion is inhibited. In theory, only subjects with prolonged duration of action of desmopressin and uncoupled osmoregulation are at risk of severe hyponatraemia.

The antidiuretic activity of desmopressin nasal spray and tablets lasts for 6–24 hours[50] and 6–8 hours,[47] respectively, in healthy adults, and there is a clear dose-response relationship.[48] For nocturnal enuresis, ideally the administered dose should have a duration of action that corresponds to the typical duration of sleep in a child (8–11 hours).[51] Dehoorne et al.[44] demonstrated that a dose of desmopressin 20 μg spray can last much longer than 8–11 hours, causing prolonged antidiuresis and risking hyponatraemia; however, the way to avoid this risk is to reduce the dose of desmopressin if the child does not demonstrate dilute urine in the morning. The antidiuretic effect of desmopressin will correct the nocturnal polyuria, but will result in a compensatory diuresis of dilute urine in the morning once the antidiuretic effect wears off. A 15 mL/kg drink in the morning should result in voiding before noon. Absence of a morning void on history or in the child's voiding diary is very suggestive of prolonged bioactivity of desmopressin.

6. How can we Avoid Adverse Effects?

The risk of hyponatraemia with desmopressin can be dramatically reduced by adhering to the

proper indications, dosing recommendations and precautions. Until recently, limited information existed on the pharmacodynamic response and antidiuretic effect of desmopressin in children with nocturnal enuresis. The appropriate doses used in children were inferred from studies in adults. We recently published pharmacokinetic and pharmacodynamic data in children treated with a single dose of oral lyophilisate.[48] Although we should always be circumspect about applying data from adult studies or from single-dose studies in children to our daily clinical practice, there is now enough information available for us to prescribe rationally and prevent significant adverse effects.

Before administering desmopressin, polydypsia-polyuria should be excluded by recording a fluid intake-urine output diary (using either voided volume or diaper weight). If the 24-hour diuresis volume is >1500 mL/m^2 of the body surface area (BSA), then fluid intake should be >2000 mL/m^2 BSA (since perspiration is assumed to be 500 mL/m^2 BSA). In patients with polydipsia, desmopressin should only be prescribed, when fluid intake is reduced (and documented), within a normal range (1500 mL/m^2 BSA). If there are large discrepancies between calculated fluid intake and registered 24-hour diuresis, patient compliance must be questioned. Poor compliance and motivation are not only predictive for poor response rates[56] but are also markers of an increased risk of adverse effects. In trying to decide how to manage MNE in primary care, the ICCS standardization[22] has tried to minimize what patient information should be registered. Sixty-one cases of seizure (two deaths) have been reported, leading to the withdrawal of desmopressin spray for the treatment of nocturnal enuresis in 2007, although it remains available for the indication of diabetes insipidus. We should not forget that in one fatal case, polydypsia was clearly documented.[43] No serious adverse effects have been reported in children with MNE in whom precautions (fluid restriction, avoiding overdosing) were maintained. Most reported cases, however, do lack full documentation. Recording 24 hours of fluid intake and urine production is a simple way of identifying patients with inappropriately high fluid intake, especially at night. Water intoxication can only occur if the child also has high fluid intake. Such high fluid intake remains a 'sword of Damocles', also hovering over the tablet and the melt. We cannot blame the drug alone if we have not taken reasonable measures to limit the risk.

The pharmacodynamic effect of desmopressin can be optimized by an optimal time of administration. Desmopressin has to be taken at least 1 hour before the last void before bedtime, not just before sleep time. The time taken to reach maximal antidiuretic effect for the oral lyophilisate is longer than 1 hour and may, on occasions, take up to 3 hours.[48] This time duration may be even longer for the tablet formulation, especially if administered <2 hours after the last meal. Rittig et al.[57] demonstrated reduced and delayed gastrointestinal absorption of desmopressin if administered within 90 minutes of a meal, but it did not influence the antidiuretic action of the drug, at least for the first 3 hours following desmopressin administration. For therapy-resistant children, waiting more than 2 hours after food before taking the tablet might reduce the diuresis rate early on in the night.[46] Unfortunately, for many families this is not always practical.

Optimizing the pharmacodynamic effect of desmopressin at conventional doses can be achieved by strict fluid restriction. While fluid restriction after desmopressin administration is also accepted as the way to prevent water intoxication, less attention is paid to fluid intake in the hours prior to administration of desmopressin. Fluid drunk just before desmopressin administration has not had time for absorption and renal excretion when the drug starts to exert its effect. Therefore, we suggest restricting fluid intake at least 1 hour before desmopressin administration, thus increasing both the safety and efficacy of this agent.[46] In order to ingest a sufficient amount of fluid, more daytime drinking is advised; however, more drinking during the daytime is only safe if the child is not still under the influence of the prolonged duration of the previous night's desmopressin dose.

Desmopressin, like any other drug in children, should never be prescribed by a doctor who is not

fully aware of the pharmacokinetic and pharmacodynamic properties of the drug, including the knowledge that a standard deviation of 2 hours' duration of action means a range of values of 8 hours. In patients with a duration of action of the drug of only 2–4 hours, increasing the dose is mandatory, while dose reduction would be mandatory in patients in whom bioactivity is >12 hours. The maximal dose used in primary care should be the dose where no one patient will have duration of action of the drug of >12–14 hours. We recommend starting with the lowest possible dose of desmopressin (one spray [10 μg] or one tablet [200 μg] or one melt [120 μg]). Data from the melt study[48] suggests that in up to 25% of patients this low dose might result in sufficient response. If the patient is therapy-resistant or only a partial responder, the dose can be doubled, but only if one documents the reappearance of diluting capacity and increased diuresis in the morning. De Guchtenaere et al.[46] have shown that the dose of desmopressin should not be increased at night if the morning osmolality is high and, if following a fluid load of 15 mL/kg, a morning diuresis does not ensue. One might argue that an increase in the dose is only defendable if there is therapy resistance with persistent nocturnal polyuria and low urinary osmolality overnight (insufficient concentrating capacity). However, since the pharmacodynamic studies demonstrate that up to 25% of patients will not reach maximal concentrating capacity or duration of action with low doses, the titration to higher doses remains an option. An increase in the dose of desmopressin will have only a minimal increase in response rate (±10%),[40] but entails the risk of water intoxication and hyponatraemia; hence, it is our opinion that desmopressin should only be prescribed through a specialized tertiary enuresis centre.

7. Conclusion

There has been much recent attention focussed on the safety profile of desmopressin in MNE. When MNE is considered as a benign disorder, without co-morbidity, which is enforced by the decreasing belief in its indication in MNE by some authors, then potential adverse effects of the drug are unacceptable.

In this current opinion article, we have demonstrated that severe enuresis is not a benign disorder, with an up to 30% risk for persistence into adulthood, and important psychological co-morbidities (sleep, ADHD, cognitive functions, poor self-esteem); therefore, enuresis deserves proper treatment. High doses of desmopressin should only be prescribed by a doctor with appropriate training in the treatment of enuresis, including intake, subtyping, urotherapy (fluid intake, lifestyle) and the pharmacological characteristics of desmopressin. We appeal for a strategy to define maximal doses in primary care, but leave open the possibility of uptitrating doses based on pharmacodynamic data in specialized enuresis centres.

Hyponatraemic adverse effects have primarily been reported for the spray. This is probably related to the higher biodisponibility and/or intra-individual variability of pharmacokinetics of the spray compared with the tablet or the melt. Pharmacokinetic data are only available for the melt, hence it makes sense for this to be treatment of choice, bearing in mind that it may not be inherently safer than the other preparations.

We think the evidence for serious adverse effects associated with the spray should lead us to a nuanced response on its use rather than its withdrawal. We would have preferred ongoing use of the spray in children where the tablet is not an option, but with reduced maximal doses, unless there is evidence from a pharmacodynamic test that the drug dosage may safely be increased.

In support of this we state four premises:

1. The majority of reported hyponatraemia cases with the spray are related to misuse, overdosing and excessive fluid intake, something that can just as easily happen with the other formulations.
2. If the switch from spray to the other formulations results in more adverse event reports, it may be necessary to withdraw all formulations.
3. There is evidence that the intranasal spray might be superior to the tablet in some patients.[58] No data are available for the melt and further studies are recommended.

4. Withdrawing the spray would deprive some children of the drug – some who would otherwise benefit from it. This includes young children who cannot swallow tablets or who take the tablet but do not have a time interval between meal time and desmopressin administration of >2 hours. There are countries where the melt is not available or is too expensive. Reducing the maximal dose would have been a more logical choice.

The safety of desmopressin can be improved by training doctors and educating patients about the appropriate use of the drug, fluid restriction and limiting the allowable dose in primary care (maximum 20 μg spray, 240 μg melt, 400 μg tablet). Higher doses in therapy-resistant patients should only be used after documenting persistent diluting capacity in the morning. This should probably be done in a specialized enuresis centre. Thus, the risk of hyponatraemia will be minimized. Desmopressin deserves to maintain its place in the primary treatment of MNE, together with the alarm. The risk of hyponatraemia should be addressed with better education rather than with withdrawal of a medication that benefits thousands of children.

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