Desmopressin resistant monosymptomatic nocturnal enuresis: new pathophysiological and pharmacological insights.

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Introduction

Nocturnal enuresis (NE) or bedwetting is a frequently encountered problem during childhood, and may adversely affect the psychosocial well-being of both the child and their families (1). Given the significant impact of this condition, treatment is advisable to be initiated from the age of 5-6 years (2). Monosymptomatic nocturnal enuresis (MNE) is a subtype of NE, characterised by micturition during sleep in absence of lower urinary tract symptoms and/or daytime incontinence. Nocturnal polyuria (NP) is recognised as one of the major underlying causes in many children with MNE (3). Since the late eighties, medical researchers were able to explain the phenomenon of NP by a lack of nocturnal increase of arginine-vasopressin (AVP) plasma levels (4). The first-line pharmacological treatment of MNE is therefore orally administered desmopressin (dDAVP), a synthetic AVP analogue. To date, there are two oral formulations available, namely tablet and lyophilisate (where this last one is not reimbursed in Belgium for this indication). However, around 40% of the children with MNE show dDAVP resistance (3). Hypothetically, besides poor adherence to treatment or to administration recommendations, other underlying pathophysiological mechanisms might play a role in dDAVP resistant MNE. Moreover, the prescription of dDAVP in children is only based on sparse paediatric pharmacological data, and therefore deserves further exploration (5). In this PhD-dissertation, we therefore aimed to gain knowledge on underlying mechanisms explaining dDAVP resistance in children with MNE.

New pathophysiological insights in NP and the clinical relevance in dDAVP-resistant enuresis

By studying the circadian regulation of renal function in the pathophysiology of NP, we were able to demonstrate that in a subgroup of children with NE and NP, there was a diminished circadian rhythm of renal functions, such as sodium excretion and glomerular filtration (6).

It is not possible to explain this observation by an AVP disorder alone, since there is not only effect on diuresis but also on osmotic excretion. The latter suggests that alterations in physiologic mechanisms driving circadian rhythms could be involved, such as changes in hemodynamic parameters, body temperature, sleep, sodium, solute-excretion and glomerular filtration (7). Since dDAVP is an AVP-analogue mainly targeting free water excretion, it is plausible that this higher osmotic excretion can be linked with dDAVP resistant NP.

Desmopressin as an illustration of the challenges and the way forward in paediatric drug research

Both the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of dDAVP in children with MNE were studied. As a part of the SAFE-PEDRUG project (safepedrug.eu), a bottom-up approach starting from paediatric specificities was applied to unravel dDAVP resistance. In a first study, we identified that the claimed bioequivalence between the tablet (200 µg) and the lyophilisate (120 µg) in adults cannot be readily extrapolated to children (8). In a second study, we demonstrated that the two available oral formulations of dDAVP are not therapeutically equivalent in children at the currently approved dose levels (9). In a third study, we were able to demonstrate a biphasic absorption of dDAVP lyophilisate in children between the age of 6 months and 8 years, which has never been described before in adults nor in older children (10). To the best of our knowledge, this was the first time that a different absorption profile of dDAVP lyophilisate was demonstrated in children, however the clinical implications of this finding need to be further studied. This confirmed the findings of a previously developed juvenile animal model and PKPD-modelling study from our research group (9,11). In the last study, we showed that current dosing regimens using a flat dose of 120 µg dDAVP lyophilisate is not adequate for children urging the need to further study size-adapted dosing strategies, in order to improve dDAVP response (12).

The main conclusions of this PhD-dissertation regarding the pharmacological aspects of dDAVP are:

1. **Lack of therapeutic equivalence between children and adults**

This finding illustrates that PK/PD trials in children remain necessary to establish efficacy and safety of a drug, and extrapolation of findings in adults need to be done very carefully.

2. **Possible different absorption profile of dDAVP in children**

This observation inquires further research into absorption of oral drugs in children, especially of the lyophilisate formulations. If different absorption of lyophilisate formulations in children in comparison to adults is not only the case in dDAVP, the urge to change the practice of paediatric drug research only increases.

3. **dDAVP is the prototype of an off-patent drug, that is widely prescribed in children**

The existing knowledge gaps, i.e.PK/PD clinical studies, unlikely will be filled by industry-driven studies in the future. We admit that performing PK/PD-studies is ethologically and methodologically challenging in children, but appropriate juvenile animal models and population modelling can optimize the study design and reduce the amount of invasive procedures with even a better quality of the obtained data.

Practical clinical recommendations on dDAVP-resistant enuresis

The main recommendation is to administer dDAVP minimum one hour prior to bedtime, preferably without simultaneous food intake. The therapy should be re-evaluated every three months (treatment withdrawn for at

least one week) to monitor if further treatment is required (2). However, there is no evidence-based guideline, neither expert consensus statement available for a threating physician challenged with the treatment of child with MNE and no or suboptimal response to dDAVP.

The findings obtained in this PhD-dissertation add evidence to some aspects of the pre-existing practical recommendations and provide additional advice on considerations in daily clinical practice:

1. **Be aware of the shortcomings of the current clinical characterization to tackle therapy resistant enuresis**

The current therapeutic approach in clinical management of children with NE recommended by the International Children's Continence Society (ICCS) starts with the clinical characterization of children with NE into MNE and non-monosymptomatic nocturnal enuresis (NMNE)(2). It is well documented that in children with MNE, a significant subgroup exists with NP, who are likely to respond to dDAVP. Although clinical characterization seems a rational first step in the evaluation of children with NE, there is no evidence of its predictive value for treatment selection. Moreover, not all children with MNE have NP, as well as there are children without NP demonstrating a good response to dDAVP. To make it even more complicated, there are children with NMNE with a good response to dDAVP, when used as an add-on therapy or following treatment of lower urinary tract symptoms. Therefore, when dDAVP-resistance occurs, an individualized approach seems the only defendable strategy.

2. **If a child with MNE is treated with dDAVP, consider evaluating not only the anti-enuretic effect (decrease of number of wet nights), but also the antidiuretic effect (reduction of urine production).**

Antidiuretic effect can be screened by measuring the average nightly urine production during one week with and one week without administration of dDAVP, respectivily. The nightly urine production can be evaluated by calculating the sum of the wet diaper weight (minus the weight of a dry diaper) and the volume of the first morning void. Make sure that the amount of fluid intake during the evening is equal during both weeks.

3. **If dDAVP seems to have partial or no antidiuretic effect in a child with NP, consider to perform a renal concentrating capacity test.**

Children with NP and no or partial anti-diuretic effect to dDAVP can be categorised into 2 groups, depending on the presence or the absence of maximal concentrated urine during a renal concentration capacity test.

- If maximal concentrated urine (urinary osmolality > 800 – 850 mosmol/L) can be obtained during the renal concentration capacity test after dDAVP administration, the dDAVP resistance can be related to non-adherence to the dDAVP therapy and/or pathophysiological underlying mechanisms in solute-excretion and circadian rhythms**.**
- When there is no maximal concentrated urine (urinary osmolality < 800 – 850 mosmol/L) during the renal concentration capacity test, there are arguments that there is an insufficient drug response. This can be related to underlying renal concentrating disorders, e.g. partial diabetes insipidus. If these disorders are ruled out, the lack of response is most likely related to pharmacological aspects.

4. **Consider a diet with reduced osmotic load**, (especially intake of salts and proteins). Theoretically, high salt and protein intake during the evening can negatively influence the antidiuretic response to dDAVP by inducing an osmotic driven NP.
5. **Consider individualizing your prescription of dDAVP**, since dDAVP resistance could be related to unknown specific paediatric pharmacological characteristics of the drug in your specific patient.
   - Be careful with increasing the dose if there is an insufficient response, a higher dose does not necessarily result in a better effect. Moreover, there is always a risk of inducing hyponatremia if fluid is insufficiently restricted after dDAVP administration.
   - Consider to change timing of administration of dDAVP. The general recommendation is to administer dDAVP 1 hour before bedtime, but in a specific patient it is possible that the maximum effect is only reached 2 hours after administration.
   - Avoid concomitant food intake and administer dDAVP at least 1 hour after the evening meal. If it is not feasible for the child and/or parents to avoid concomitant food intake, and a child is using dDAVP tablets, consider a switch to dDAVP lyophilisate.

General conclusion

This doctoral dissertation focused on children with MNE and NP, whereby new insights in possible underlying reasons for dDAVP resistance were gained, as shown in **figure 1.** A bottom-up approach starting from the child with NP and enuresis, was the strategy used to tackle the problem of dDAVP resistance. Regarding the pathophysiological aspects, we confirmed that NP can only partially be explained by blunted circadian rhythm of AVP, and that other alterations in the renal circadian clock might play a role in dDAVP-resistance. Considering the pharmacological aspects of dDAVP, additional insights in the current knowledge gaps when prescribing dDAVP in children with MNE were identified. We could demonstrate for the first time a double peak absorption of the dDAVP lyophilisate in children, which lead to questioning the current flat dosing regimens. Further research is needed to understand the clinical importance of these findings and to develop new therapeutic strategies to tackle dDAVP resistant MNE.

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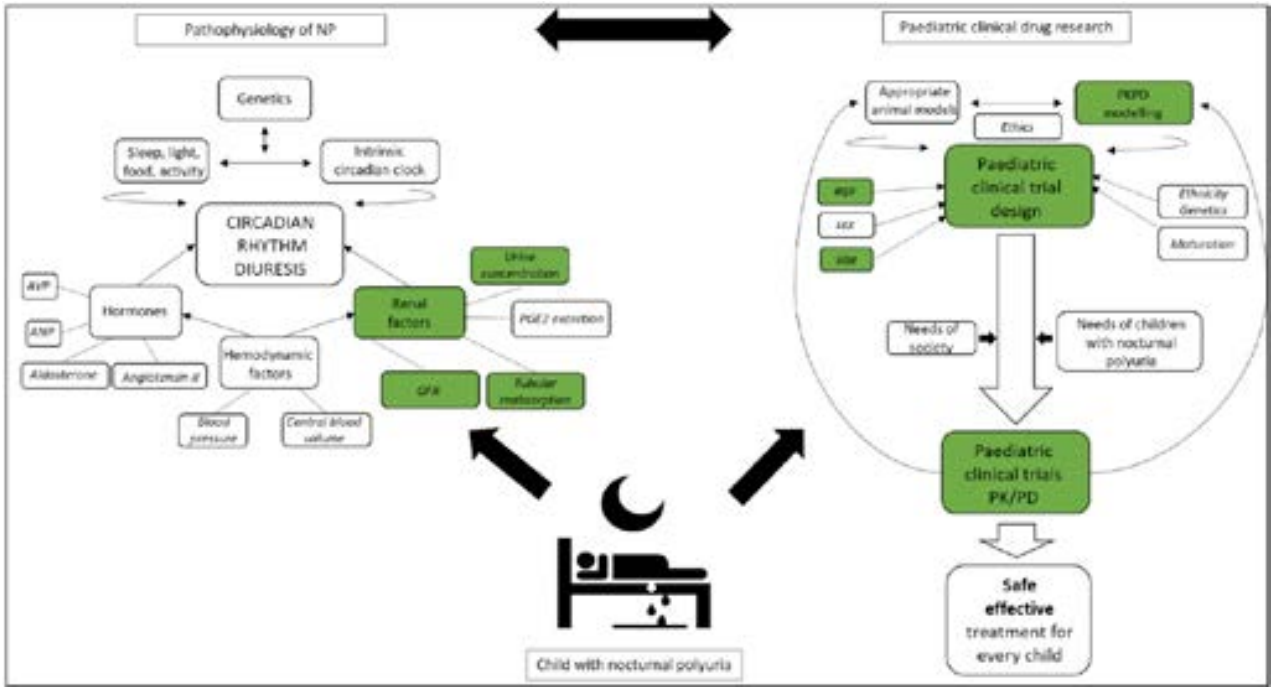
Figure 1: *Approach to a child with nocturnal polyuria (NP = nocturnal polyuria; AVP = arginine-vasopressin; ANP = atrial natriuretic peptide; GFR = glomerular filtration rate; PGE2 = prostaglandin-E2; PK = pharmacokinetics; PD = pharmacodynamics. (*) indicated in green = topics studied in this PhD-dissertation Icon "enuresis" by thenounproject.com*



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