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Bogaert G[1], Vande Walle J[2], Mattson S[3], Schurmans T[4], Hoebeke P[2], Deboe V[5], Norgaard J[6]
1. UZ Gasthuisberg, 2. Universitaire Ziekenhuis Gent, 3. University of Linkoping, 4. Hôpital Universitaire Des Enfants Reine Fabiola, 5. Vrije Universiteit, 6. Ferring Pharmaceuticals A/S

A PHARMACODYNAMIC STUDY IN CHILDREN WITH PRIMARY NOCTURNAL ENURESIS USING A NEW 'MELT' ORODISPERSIBLE FORMULATION OF DESMOPRESSIN

Hypothesis / aims of study
Evidence-based treatment of primary nocturnal enuresis (PNE) is based on the threefold pathophysiology of the problem: high urinary output, high arousal status and eventual nocturnal overactive bladder. The administration of the antidiuretic drug desmopressin is an effective treatment for PNE, being particularly beneficial for children with relative nocturnal polyuria and normal functional bladder capacity. However, the dosage of desmopressin is not standardized, and pharmacokinetic (PK) data are extremely limited in children. To determine the pharmacodynamic (PD) properties of desmopressin in children with documented PNE, we have, therefore, performed a multicentre study using a new oral lyophilisate formulation of desmopressin. In addition, this study identified dosages that provide a duration of antidiuretic action corresponding to the length of night-time sleep.

Study design, materials and methods
Children with documented PNE (n=84), aged 6–12 years, were randomized in a double-blind, placebo-controlled study comprising a no-treatment run-in period of 2 weeks, then a 1-day PD baseline evaluation followed by PD/PK measurements after a single-dose of orodispersible desmopressin (30, 60, 120, 240, 360 or 480 µg) or placebo. To suppress endogenous vasopressin production and ensure that antidiuresis was attributable to treatment, all children were overhydrated (urine production >0.13 ml/min/kg) prior to the medication. Urinary volume, osmolality and duration of urinary concentrating action were determined.

Results
Urinary output dropped markedly within the first hour in all desmopressin dosage groups (no change in the placebo group). In addition, there was an increase of mean urine osmolality over time with onset of action within the hour following orodispersible desmopressin (>800 mOsm/kg after 1 hour except for the 30 µg desmopressin group) (again there was no change following placebo dosing). The urinary concentrating capacity was assessed by the mean maximum urinary osmolality, which occurred 1–4 hours after intake and ranged from 515 to 957 mOsm/kg depending on the different desmopressin dosage groups. In the placebo group, osmolality measurements never exceeded the highest threshold (400 mOsm/kg); the intermediate 200 mOsm/kg threshold was exceeded by one patient and the lowest (125 mOsm/kg) by five patients. At the lowest threshold, mean duration of action increased as the desmopressin dose increased. For all threshold levels of osmolality the calculated duration of action is likely to be an underestimate as, for some children, urine collections were stopped before urine osmolality had fallen below threshold level. In addition, the orodispersible formulation was well tolerated and accepted by all children.

Interpretation of results
The length of time for which the antidiuretic effect of desmopressin was observed increased as the dose increased; a clear dose-response relationship for the duration of urinary concentrating action was demonstrated at all three threshold levels of osmolality (Table 1). Pharmacodynamic data suggests a constant bioavailability. After 60 minutes, a mean maximum osmolality above 800 mOsm/kg was achieved following all doses of desmopressin, with the exception of the lowest dose (30 µg). This demonstrates that the time to peak activity is very predictable, even at low doses (± 60 min). Our data suggest that a 60 µg dose may be appropriate if an effect early in the night is required, and 120 µg is preferable for bioactivity throughout the night. The apparent similarity between the three highest doses suggests a dose in excess of 360 µg desmopressin is unnecessary, reducing the risk of adverse events.

Concluding message
Desmopressin in an orodispersible form (oral lyophilisate), has been proven to cause a substantial drop in urinary output in overhydrated patients suffering from PNE. In addition, this

study has shown that the dosage of 120–360 µg is likely to continuously reduce diuresis for a period corresponding to a night's sleep (7–11 hours) in most children with PNE, an important prerequisite to remain dry for an entire night's sleep.

Table 1. Duration of action of desmopressin using three osmolality thresholds (125, 200 and 400 mOsm/kg)

Duration of Action							
	dDVAP (30 µg)	dDVAP (60 µg)	dDVAP (120 µg)	dDVAP (240 µg)	dDVAP (360 µg)	dDVAP (480 µg)	Placebo
N	12	12	11	12	13	12	12
125 mOsm/kg (hours)							
Censored* Mean (SD) Median Min – Max	3 3.6 (2.1) 3.0 0.8–9.2	2 5.8 (2.4) 5.4 2.2–10.9	4 8.1 (1.9) 8.3 4.4–10.6	7 9.7 (1.9) 10.8 6.2–11.6	10 10.2 (1.0) 10.6 8.4–11.4	7 10.6 (0.9) 10.5 8.9–12.3	2 0.6 (1.3) 0.0 0.0–4.4
200 mOsm/kg (hours)							
Censored* Mean (SD) Median Min – Max	0 2.4 (1.7) 1.9 0.0–6.3	0 5.1 (2.6) 4.6 1.8–10.9	3 7.5 (2.1) 7.6 4.4–10.6	5 9.0 (1.8) 9.8 5.6–10.8	5 9.2 (1.6) 9.3 5.3–11.1	6 9.7 (1.2) 9.6 7.7–11.3	0 0.1 (0.2) 0.0 0.0–0.7
400 mOsm/kg (hours)							
Censored* Mean (SD) Median Min – Max	0 1.3 (1.6) 1.1 0.0–4.4	0 4.0 (2.6) 3.1 1.0–9.8	2 5.9 (2.3) 6.3 1.9–10.5	3 8.2 (2.3) 9.1 4.3–10.8	4 8.4 (1.8) 8.4 4.2–10.3	4 8.6 (1.4) 8.4 6.9–11.3	1 0.0 (0.0) 0.0 0.0–0.0

* Number of patients with no 'end' of action; measurements were censored at the time the over hydration procedure was stopped

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