

FOCUS ON UROLOGICAL INDICATIONS



Minirin<sup>®</sup>  
DESMOPRESSIN



# **DESMOPRESSIN**

**(MINIRIN<sup>®</sup>, DDAVP<sup>®</sup>)**

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**DESMOPRESSIN (MINIRIN<sup>®</sup>, DDAVP<sup>®</sup>)**  
**FOCUS ON UROLOGICAL INDICATIONS**

**Sponsored as a service to medicine by Ferring AB**

Published by Adis International Limited



Chowley Oak Lane  
Tattenhall  
Chester  
CH3 9GA  
England

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ISBN | 898970 67 X

FER6-099

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# SUMMARY

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Several decades of experience with desmopressin (Minirin®, DDAVP®) have confirmed its efficacy and excellent tolerability profile. Desmopressin thus remains the drug of choice in the treatment of diabetes insipidus and primary nocturnal enuresis and is a convenient and reliable method of determining renal concentrating capacity. Furthermore, patients with urinary incontinence and/or nocturia may also benefit from treatment with desmopressin, but its usefulness in these indications requires further investigation.

- Desmopressin is a synthetic analogue of vasopressin and acts as a direct agonist at renal V<sub>2</sub> receptors, regulating the volume and osmolality of the urine.
- Desmopressin is devoid of the pressor effects of vasopressin.
- Desmopressin has a longer duration of action and a more potent antidiuretic activity than vasopressin.
- Desmopressin has been the treatment of choice in patients with central diabetes insipidus for more than 20 years, being well tolerated and highly effective in long-term use.
- Desmopressin supplements the low nocturnal levels of vasopressin present in many children with primary nocturnal enuresis, thus reducing the likelihood of enuresis.
- The desmopressin renal concentrating capacity test provides an early indication of renal dysfunction and is useful in the differential diagnosis of central/ nephrogenic diabetes insipidus.
- Desmopressin is preferred over the water deprivation and Pitressin® tests for the measurement of renal concentrating capacity.
- Abnormalities of endogenous vasopressin production may be central to urinary incontinence in some patients.

# INTRODUCTION

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Desmopressin\* (Minirin®, DDAVP®) is a synthetic analogue of the naturally occurring antidiuretic hormone vasopressin. All patients with central diabetes insipidus and many patients with primary nocturnal enuresis have a deficiency of endogenous vasopressin, and the efficacy of hormone replacement therapy with desmopressin in these patients is well established. Furthermore, its renal concentrating capacity has made it a useful and convenient tool for the early diagnosis of renal dysfunction. Patients with urinary incontinence and/or nocturia may also benefit from treatment with desmopressin, but its usefulness in these indications requires further investigation.

Desmopressin has proved to be safe and well tolerated in clinical practice. A potential risk with desmopressin is fluid retention, which can, however, be avoided by controlling fluid intake.

Desmopressin has provided a major advance in the treatment of conditions attributable to a deficiency of the endogenous hormone. This monograph provides readers with a complete and up-to-date analysis of studies with desmopressin in the treatment of diabetes insipidus and primary nocturnal enuresis and in tests of renal concentrating capacity. The use of desmopressin in the treatment of urinary incontinence and/or nocturia is also evaluated. Additionally, desmopressin is used in the treatment of various bleeding disorders, such as haemophilia A and von Willebrand's disease. This therapy, which requires 10–15 times higher doses than the antidiuretic treatment, has been extensively reviewed and will not be discussed further here.<sup>[1,2]</sup>

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\* For the purposes of this monograph, all dosages of desmopressin refer to dosages of desmopressin acetate.

# PHARMACOLOGY

Desmopressin (1-deamino-8-D-arginine-vasopressin) (Minirin®, DDAVP®) is a synthetic analogue of the naturally occurring antidiuretic hormone 8-arginine vasopressin. Vasopressin acts directly on the kidney to regulate the reabsorption and excretion of water.

**Desmopressin (Minirin®, DDAVP®) has a longer duration of action than vasopressin and is without pressor effects**

Vasopressin activity is exerted through  $V_1$  and  $V_2$  receptors. The former mediates effects on smooth muscle and the latter mediates antidiuretic activity (table 1). Desmopressin has no effect on  $V_1$  receptors but has greater potency than vasopressin on renal  $V_2$  receptors.<sup>[3]</sup>

Structurally, desmopressin differs from vasopressin in two principal ways: the absence of an amino group at position 1 and the substitution of D-arginine at position 8 (fig. 1). These modifications enhance the resistance of the molecule to enzymatic breakdown,

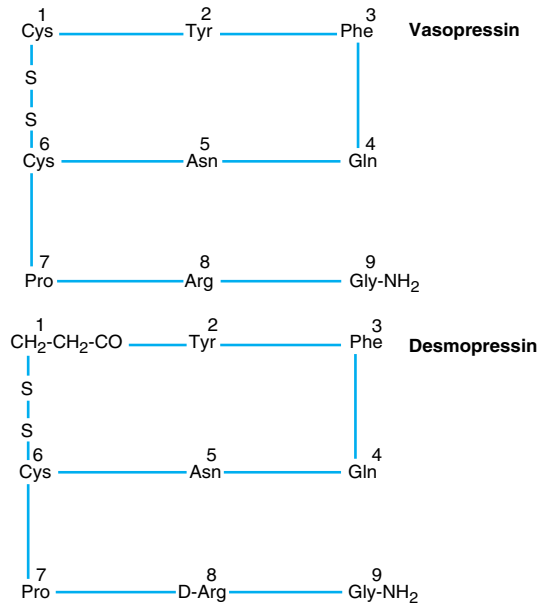


Fig. 1. Structural formulae of the naturally occurring hormone vasopressin and the synthetic analogue desmopressin.

increase the antidiuretic activity and eliminate the pressor effect.

Thus, desmopressin has a prolonged and more potent antidiuretic effect compared with

Table 1. Vasopressin receptor sites and activity

Type of receptor	Tissue	Effect of stimulation
$V_1$	Smooth muscle of blood vessels, uterus and intestine	Vasoconstriction; uterine contraction; increased intestinal peristalsis
$V_2$	Kidney, thick ascending limb of Henle's loop and collecting tubules	Antidiuretic activity

the natural hormone. Additionally, the pressor effect of vasopressin is avoided because desmopressin has no action on smooth muscle.

### Role of vasopressin in the control of water reabsorption in the kidney

Vasopressin is synthesised in the hypothalamus and stored in the posterior pituitary gland.

Secretion is regulated by changes in plasma osmolality and changes in extracellular volume.<sup>[4]</sup> Reductions in blood volume or blood pressure also stimulate vasopressin secretion. Such changes may occur during sleep: in healthy individuals there is a nocturnal increase in vasopressin that is associated with a decrease in urinary output.<sup>[5]</sup>

**Healthy individuals have an increase in nocturnal vasopressin secretion accompanied by a fall in urinary output**

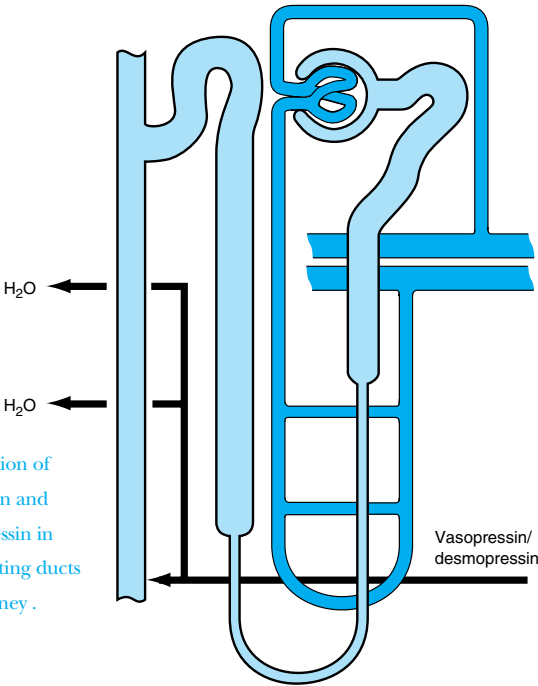


Fig. 2. Action of vasopressin and desmopressin in the collecting ducts of the kidney .

The collecting duct is the principal site of action of vasopressin (fig. 2). The presence of vasopressin, acting on V<sub>2</sub> receptors on the cells that make up the distal tubules and the collecting ducts, greatly increases the water permeability of these cells.

Flow of water from the distal tubules and collecting ducts also requires the presence of a surrounding hypertonic interstitium to create an osmotic driving force for water movement. After reaching the interstitium, water re-enters the systemic circulation via the peritubular capillary network.

## Preclinical studies

The antidiuretic activity of desmopressin (Minirin®, DDAVP®) has been investigated in numerous animal models, including hydrated rats and Brattleboro homozygous rats (a species that cannot synthesise vasopressin).

In Brattleboro rats, desmopressin (10 or 50 ng/kg) produced complete anuria for 2–4 hours; urine output returned to baseline after 10–14 hours.<sup>[6]</sup> Furthermore, in order to achieve a similar antidiuretic effect in water-loaded rats, the dose of vasopressin needs to be 500 times greater than that of desmopressin.<sup>[7]</sup>

**Oral desmopressin (Minirin®, DDAVP®) significantly enhances antidiuretic activity while oral vasopressin results in only insignificant antidiuresis in rats**

The antidiuretic potency of desmopressin after oral administration may be attributable in part to its resistance to degradation by digestive enzymes, as demonstrated by Matsui et al.<sup>[8]</sup> In this study, the antidiuretic activity of vasopressin was completely abolished following incubation with digestive enzymes. In contrast, the activity of desmopressin was either unaffected or only partially affected.

## Clinical studies

### Antidiuretic effects

The antidiuretic effect of desmopressin has been demonstrated in studies in hydrated,

healthy volunteers. In a representative study, mean urinary output was reduced from 15 ml/min to 2 ml/min 30 minutes after the administration of intranasal desmopressin 20 µg. A minimal rate of urine production of around 0.6 ml/min was seen 5 hours after treatment, while urine osmolality increased from a baseline value of 100 mOsm/kg to around 800 mOsm/kg.<sup>[9]</sup>

In a study in hydrated volunteers receiving oral desmopressin (20, 40 and 200 µg) there was a dose-dependent reduction in urine volume and a concomitant increase in urine osmolality.<sup>[10]</sup>

### Hormonal and cardiovascular responses

The hormonal, biochemical and cardiovascular responses to desmopressin have been investigated in both volunteers and patients with primary nocturnal enuresis.

Fluid-deprived adult volunteers (n=6) were treated with intravenous desmopressin 0.4 µg/kg, a dose 10-fold higher than that required for antidiuretic purposes, to determine hormonal and cardiovascular responses. Five minutes after the infusion, subjects exhibited facial flushing, a 13% decrease in mean diastolic blood pressure and an 18% increase in mean pulse rate. A significant increase in plasma renin activity and plasma cortisol levels was observed, but there were no significant changes in plasma levels of luteinising hormone, follicle-stimulating hormone, thyroid-stimulating hormone, prolactin or growth hormone.<sup>[11]</sup>

Similar haemodynamic effects were seen in the same study when intravenous desmopressin was administered to 5 patients with central diabetes insipidus.

**Desmopressin (Minirin®, DDAVP®) does not affect endogenous vasopressin secretion. Routine laboratory tests are normal after desmopressin administration**

The hormonal and biochemical effects of vasopressin were further investigated in 7 patients with primary nocturnal enuresis who were treated with intranasal desmopressin 10 µg or 20 µg for 4–24 (mean 13) months. Desmopressin had no significant effect on endogenous vasopressin secretion, and routine laboratory tests were normal in all patients. The cortisol estimations showed a normal diurnal variation in each case.<sup>[12]</sup>

# P HARMACOKINETICS

The pharmacokinetics of desmopressin (Minirin®, DDAVP®) have been investigated after oral, intranasal, intravenous and subcutaneous administration to healthy volunteers (table 2) and after oral and intranasal administration to patients with diabetes insipidus.<sup>[13,14]</sup>

## Absorption

Significant plasma concentrations of desmopressin are observed after oral administration to healthy adults. Desmopressin is detectable in plasma within 30 minutes of either intranasal or oral administration; maximal concentration and maximal response are dose-dependent and are achieved within 2 hours. Lam and colleagues investigated the pharmacokinetics of intranasal and oral desmopressin in 10 Chinese adults with

**Maximum plasma desmopressin (Minirin®, DDAVP®) concentrations are achieved within 2 hours of intranasal or oral administration**

central diabetes insipidus.<sup>[14]</sup> Following 20 µg intranasally and 200 µg orally, respective plasma desmopressin concentrations (mean ± standard error) peaked after 45.6 ± 7.3 and 93.3 ± 3.3 minutes, reaching concentrations of 24.1 ± 4.7 and 15.1 ± 3.2 pmol/L. Respective terminal half-lives were 2.2 ± 0.1 and 2.0 ± 0.1 hours. Based on the area under the concentration–time curve, the bioequivalent intranasal:oral ratio was 1:16.

Absorption of desmopressin after oral administration occurs primarily in the

**Table 2. Mean pharmacokinetic parameters of desmopressin in 8 healthy volunteers following different routes of administration (reproduced with permission)<sup>[13]</sup>**

Route	Dose (µg)	Pharmacokinetic parameter			
		AUC (pmol·L <sup>-1</sup> ·h <sup>-1</sup> )	C <sub>max</sub> (pmol/L)	T <sub>max</sub> (min)	Bioavailability <sup>a</sup>
Intravenous	2	114.4	–	–	–
Subcutaneous	2	189.4	58.3	41.4	NR
Intranasal	20	58.9	19.9	60.0	3.4%
Oral	200	23.8	12.7	71.4	0.1%

<sup>a</sup> Compared with the intravenous route.

**Abbreviations:** AUC = area under the plasma–concentration time curve; C<sub>max</sub> = peak plasma concentration; NR = not reported; T<sub>max</sub> = time to C<sub>max</sub>.

**Desmopressin (Minirin<sup>®</sup>, DDAVP<sup>®</sup>) bioavailability may be optimised by administration half an hour before or 2 hours after a meal**

duodenum and the proximal jejunum. Consequently, absorption may be reduced in conditions of rapid intestinal transport. Absorption is reduced if desmopressin is administered with food.<sup>[15]</sup> Therefore, in cases where the effect of desmopressin is less

**Desmopressin (Minirin<sup>®</sup>, DDAVP<sup>®</sup>) undergoes biphasic elimination**

than optimal, the bioavailability of orally administered desmopressin may be improved by appropriate timing of the dose (i.e. at

least half an hour before or 2 hours after a meal).

### **Distribution**

The apparent volume of distribution of desmopressin is relatively small (0.2 L), indicating that it does not enter the intracellular compartment.<sup>[16]</sup> Furthermore, results obtained in patients with communicable hydrocephalus indicate that desmopressin does not penetrate the blood–brain barrier.<sup>[17]</sup>

### **Clearance**

The elimination of desmopressin is bi-exponential, with a rapid first phase and a slower second phase, with half-life values of 8 minutes and 1–2 hours, respectively.<sup>[13,18]</sup> Urinary clearance is variable (1.19–3.83 ml·min<sup>-1</sup>·kg<sup>-1</sup>) after intravenous, intranasal or oral administration of desmopressin.<sup>[13]</sup>

# UROLOGICAL INDICATIONS

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The three main indications for desmopressin (Minirin®, DDAVP®) as an antidiuretic are:

- central (cranial) diabetes insipidus
- primary nocturnal enuresis
- renal concentrating capacity test (RCCT).

Desmopressin has also been investigated for the treatment of urinary incontinence and/or nocturia. It is approved in the UK for nocturia associated with multiple sclerosis.

## Central diabetes insipidus

Central diabetes insipidus (also known as cranial or neurogenic diabetes insipidus) arises from a deficiency in vasopressin secretion.

Symptoms include thirst, polydipsia and polyuria with nocturia. The daily water turnover is 4–20 L, depending on the severity of the vasopressin defect. A dangerous hyperosmolality or dehydration may develop within hours and consciousness may be lost. Patients with central diabetes insipidus respond to the administration of desmopressin with a prompt increase in urine osmolality. However, patients with renal (nephrogenic) diabetes insipidus show little or no response to desmopressin administration.

### *Clinical experience with desmopressin*

Previous therapies for central diabetes insipidus (posterior pituitary extracts, lysine vasopressin and non-hormonal drugs) were limited by a short duration of action, adverse effects and poor antidiuretic efficacy. The first

clinical study of desmopressin indicated a considerable improvement over vasopressin therapy in patients with diabetes insipidus.<sup>[6]</sup> Subsequent clinical trials in this indication showed desmopressin to be superior to vasopressin and other non-hormonal agents and established desmopressin as the drug of choice in central diabetes insipidus.<sup>[19,20]</sup>

**Desmopressin (Minirin®, DDAVP®) is superior to vasopressin and non-hormonal agents for the treatment of central diabetes insipidus**

### *Intranasal administration*

The intranasal dose required to control diabetes insipidus varies considerably between patients and does not appear to correlate with age, bodyweight, body surface area or the severity of polyuria.<sup>[21]</sup> The effect of intranasal desmopressin in patients with central diabetes insipidus was reported by Robinson.<sup>[22]</sup> Desmopressin was effective in all cases, the effect being noted within the first hour of administration and persisting for 8–20 hours. The effect of the drug usually ceased rather abruptly over 60–90 minutes, when an increased flow of urine was noted by the patient. The response pattern varied from case to case, though repeat administrations to a given patient yielded similar results. The crucial determinant of the frequency of administration (1, 2 or 3 times daily) necessary to control

**Individualisation of the dosage regimen is required to optimise the therapeutic response to desmopressin (Minirin®, DDAVP®) in central diabetes insipidus**

urine output was the duration of the response. No side effects, such as increased pulse rate, increased blood pressure, abdominal cramps or flushing, were noted by any patient during the initial administration of desmopressin or during 6 months' maintenance treatment, and no patient manifested changes in haemoglobin, red cell count, white cell count

or serum levels of sodium, potassium, chloride and carbon dioxide, plasma osmolality, blood urea nitrogen, creatinine, albumin, cholesterol, bilirubin, aspartate aminotransferase (GOT), alkaline phosphatase or fasting blood sugar.

In 36 children with central diabetes insipidus, intranasal desmopressin was superior to any prior treatment with respect to urine volume reduction and urine concentration maintenance in the same patients (table 3). Furthermore, the ease of administration increased patient compliance with desmopressin therapy.<sup>[21]</sup>

Clinical experience has shown that the average daily intranasal dosage for central

**Table 3. Urine volume and osmolality in 36 children with central diabetes insipidus receiving a variety of treatments (reproduced with permission of S Karger AG, Basel)<sup>[21]</sup>**

Therapy (route of administration)	No. of patients	Daily dose	Urine volume (L/24 hours)	Urinary specific gravity	Urine osmolality (mOsm/kg H <sub>2</sub> O)
Baseline	36		4.0–12	1000–1003	44–220
Pitressin® tannate in oil (IM)	18	2–5 IU	2.0–3.5	1007–1018	215–390
Pitressin® powder (IN)	14	40–80 mg	1.8–3.6	1004–1018	190–390
Lysine-8-vasopressin (IN)	3	8–20 IU	2.4–3.8	1008–1016	140–289
Chlorpropamide (oral)	2	200–400 mg	4.0–6.0	1006–1008	156–203
Desmopressin (IN)	34	2.5–30 µg	0.9–1.7	1012–1025	420–1005

**Abbreviations:** IM = intramuscularly; IN = intranasally.

diabetes insipidus is 10–20 µg once or twice daily in adults and 5–10 µg once or twice daily in children.

### Oral administration

Clinical studies have clearly demonstrated the efficacy of oral desmopressin in the treatment of diabetes insipidus.<sup>[23–25]</sup> Adverse reactions were few and similar to those reported with intranasal treatment.

As was the case with intranasal administration, oral dosage requirements were unrelated to age, severity of polyuria or bodyweight. Although it was not possible to establish a relationship between the efficacy of intranasal and oral administration that could be used to predict individual dosage requirements, it was suggested that the oral dosage needed to treat diabetes insipidus would be larger than the intranasal dosage.<sup>[25]</sup>

A 10-year follow-up was performed on 6 patients who were included in a study published in 1986.<sup>[24]</sup> The patients (now 14–27 years of age) were treated with oral desmopressin throughout this period. The total 24-hour dose was 0.2–1.6 mg, and the frequency of administration was 3 times daily in all but one case (for whom it was twice daily). All patients were well controlled, with the volume of urine ranging from 620 to 1500 ml/24 hours. The patients were also very satisfied with the efficacy and convenience of oral desmopressin therapy. A series of

clinical chemistry tests showed no significant changes that could be related to desmopressin treatment, and no adverse events were reported.<sup>[9]</sup>

As with intranasal therapy, the oral dosage required to control diuresis is highly individual. For an adult patient with diabetes insipidus, a suitable dosage is 0.1–0.2 mg two to three times daily. In rare instances, a higher dosage (0.8–1.6 mg/day) might be necessary. Patients who use intranasal desmopressin can be switched to the oral treatment overnight.

**It is possible to switch patients from intranasal to oral administration of desmopressin (Minirin®, DDAVP®) overnight**

Fjellestad-Paulsen and colleagues assessed the safety and efficacy of long-term treatment with oral desmopressin in eight patients (aged 3–21 years) with central diabetes insipidus.<sup>[26]</sup> Five normal children of both sexes (aged 4–19 years) served as controls. As expected, urine osmolality was lower and urine volumes were larger among the patients vs the controls. No differences were seen between patients and controls with respect to plasma osmolality and sodium levels. The mean concentrations of atrial natriuretic peptide and aldosterone in the plasma were somewhat lower in the patients than in the controls, although the difference was not statistically significant. In

addition, there was no significant difference in plasma renin activity between the two groups.

The efficacy of the desmopressin tablet was very similar after 1 year and after 3.5 years of treatment. The disease was well controlled in all cases, mean daily diuresis being 1.7 L, with an absence of nocturnal polyuria. There was no relationship between the oral dose required and the previous intranasal dose, or the age or weight of the patient. No adverse reactions or clinically important deviations in laboratory values were reported. No circulating antibodies to desmopressin were detectable. It was concluded that long-term treatment with oral desmopressin is safe and effective.

Lam and co-workers performed a 1-year prospective study in 10 Chinese adults with central diabetes insipidus previously controlled with intranasal desmopressin.<sup>[14]</sup> Oral desmopressin (300–600 µg/day in 2–3 doses) produced and maintained a stable and satisfactory antidiuresis, comparable to that seen with the previous intranasal therapy. The oral treatment was well tolerated, with no events warranting drug withdrawal.

#### Dose equivalence between intranasal and oral treatments

The use of oral desmopressin was investigated in 12 patients with diabetes insipidus who were previously well controlled with intranasal therapy.<sup>[27]</sup> The oral dose of desmopressin was increased until the daily urinary output volumes became equal to those produced

during intranasal therapy. The antidiuretic dose-equivalence ratio for intranasal:oral desmopressin ranged between 1:15 and 1:30 (mean ratio 1:18). This ratio is in agreement with results obtained in enuretic children by Janknegt and colleagues, who found the efficacy of a 20 µg intranasal dose to be similar to that of an oral 400 µg dose.<sup>[28]</sup>

#### Parenteral desmopressin

Desmopressin is administered parenterally in the initial treatment of early postneurosurgical central diabetes insipidus before intranasal administration is initiated. Parenteral desmopressin is initiated at relatively low doses (0.1–0.5 µg) and the antidiuretic effect usually lasts for 8–12 hours. In a study by Chanson et al., postoperative central diabetes insipidus was corrected 6 hours after initiation of a 3-day course of desmopressin 1, 2 or 4 µg intramuscularly every 12 hours.<sup>[29]</sup> The effect on diuresis and osmolality was maximal from 18 hours onwards. Tolerability was excellent: 11/15 patients (73%) had mild hyponatraemia without clinical sequelae.

#### Nocturnal enuresis

Monosymptomatic nocturnal enuresis is defined as exclusive night-time wetting in the absence of the following factors:

- daytime incontinence of any type or severity
- increased frequency of micturition (voiding  $\geq 8$  times a day) plus urgency (a sudden desire

to void that has to be obeyed immediately in order to avoid incontinence)

- voiding postponement, with infrequent voidings ( $\leq 3$  voidings per day)
- habitual holding manoeuvres such as sitting on the heel (i.e. squatting) or pinching the penis
- prolonged initiation of voiding and/or straining and/or interrupted (fractionated) voiding.

A lower age limit for the definition has not yet been set, but the usual age at which this is considered a clinical problem is around 5 years.

Monosymptomatic nocturnal enuresis has been categorised into two types:

- primary nocturnal enuresis – a disorder in children who have never been consistently dry
- secondary or onset enuresis – a disorder in those who start wetting the bed again after a significant dry period.

Monosymptomatic nocturnal enuresis is common; 20% of boys and 10% of girls are enuretic at 6 years of age. Primary nocturnal enuresis accounts for around 90% of these cases,<sup>[30]</sup> and incidence declines with age, but 2–3% of patients continue to wet the bed during their late teens and early adulthood.<sup>[31]</sup> These 2–3% will probably have a lifelong problem (fig. 3).<sup>[32]</sup>

Spontaneous resolution of nocturnal enuresis has been reported in up to 14–16% of cases annually.<sup>[30,31]</sup>

Nocturnal enuresis has been described as one of the most common of all childhood problems

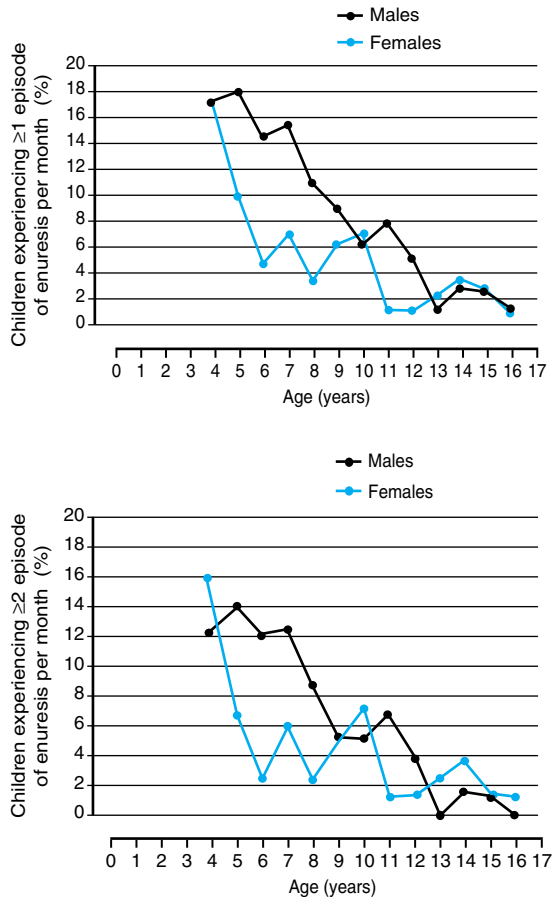


Fig. 3. Prevalence of nocturnal enuresis in a random sample of 2070 children according to age and gender.<sup>[32]</sup>

### *The impact of nocturnal enuresis*

Nocturnal enuresis often leads to considerable emotional disturbance,<sup>[30,33–36]</sup> has a deleterious impact on self-esteem,<sup>[37]</sup> and puts a significant financial burden on the child's family.<sup>[38,39]</sup>

**Nocturnal enuresis results in significant emotional disturbances and puts a significant financial burden on the child's family**

### *Pathogenesis*

The pathogenesis of nocturnal enuresis has recently been extensively reviewed by Nørgaard et al.<sup>[40]</sup>

Currently, there is a consensus among opinion leaders from all specialities worldwide that psychopathology is not a major factor in the aetiology of nocturnal enuresis. Indeed, it has been noted that the mental health of bedwetting children improves after their enuresis has been treated successfully.<sup>[37,41]</sup>

From a theoretical viewpoint, there appear to be four important factors influencing the pathogenesis of nocturnal enuresis:

- sleep pattern
- bladder behaviour and characteristics
- nocturnal diuresis
- genetic disposition.

### *Sleep pattern*

Contrary to previous views, children with nocturnal enuresis have the same sleeping patterns as non-enuretic children, and enuretic episodes are equally distributed over all stages of sleep.<sup>[42,43]</sup> However, results of a recent questionnaire-based survey of 7- to 10-year-olds indicate a significant difference in subjective arousability between enuretic and non-enuretic children, with the former group characterising themselves as very difficult or almost impossible to arouse from sleep and the latter group usually considering themselves easy or fairly easy to awaken.<sup>[44]</sup>

**Children with nocturnal enuresis have the same sleeping patterns as non-enuretic children**

### *Bladder behaviour and characteristics*

Urodynamic studies in enuretic patients have been performed with both invasive and non-invasive techniques, but these have not given any positive findings: bladder size is found to be normal even in large populations of enuretics.<sup>[45,46]</sup> Additionally, daytime bladder

**Urodynamic investigations have indicated that the cause of bedwetting in the majority of cases is not related to bladder dysfunction**

function is normal in these individuals and no correlation has been found between nocturnal instability and the time of enuresis.<sup>[43]</sup>

### Nocturnal diuresis

It has been known for many years that a substantial number of enuretic patients produce large amounts of urine during sleep. However, little attention was paid to this finding until the last 10 years, when new theories emerged concerning important factors in the pathogenesis of nocturnal enuresis.

The normal regulation of urine production leads to a significantly decreased urinary output during sleep, and the concentration of urine also becomes optimal.<sup>[47]</sup> This finding could not be reproduced in studies of patients with nocturnal enuresis, and consequently water metabolism in children became a subject for further investigation.

#### *Nocturnal secretion of vasopressin*

Normally, humans have a diurnal rhythm in the rate of urinary output that is reciprocal to urine osmolality; the secretion of endogenous vasopressin is increased at night, resulting in reduced urinary output and increased urine osmolality (fig. 4).<sup>[43,48]</sup> Patients with nocturnal enuresis have a less pronounced increase in nocturnal endogenous vasopressin or even a reversal in the diurnal rhythm. This explains the large volumes of dilute urine that are produced, which in turn lead to overfilling of the bladder and hence enuresis.<sup>[43,49]</sup>

It is important to note that bladder capacity is often normal in patients with nocturnal enuresis, which emphasises the role of vasopressin and nocturnal polyuria in the underlying aetiology.<sup>[48,50,51]</sup>

### Genetic disposition

Most evidence supports a biological aetiology and genetic predisposition for nocturnal enuresis (table 4).<sup>[52]</sup> Males are affected more than females and the risk of developing nocturnal enuresis increases if one or both parents were enuretic as children (45–75%, respectively).<sup>[52,53]</sup> A genetic locus corresponding to nocturnal enuresis has variously been identified on chromosome 12q<sup>[54]</sup> and chromosome 13q.<sup>[53]</sup> substantiating an inherited dysfunction.

### Treatment

When the child gains sufficient maturity and motivation to co-operate (usually around 7 years of age), a variety of treatments can be offered.<sup>[36]</sup> Understanding, optimism and reassurance are considered necessary elements in the initial approach to treatment of any enuretic patient. There are two main modes for the active treatment of bedwetting:

- conditioning devices (e.g. enuresis alarms)
- medical treatment.

**Patient counselling and reassurance form an integral part of the treatment of nocturnal enuresis**

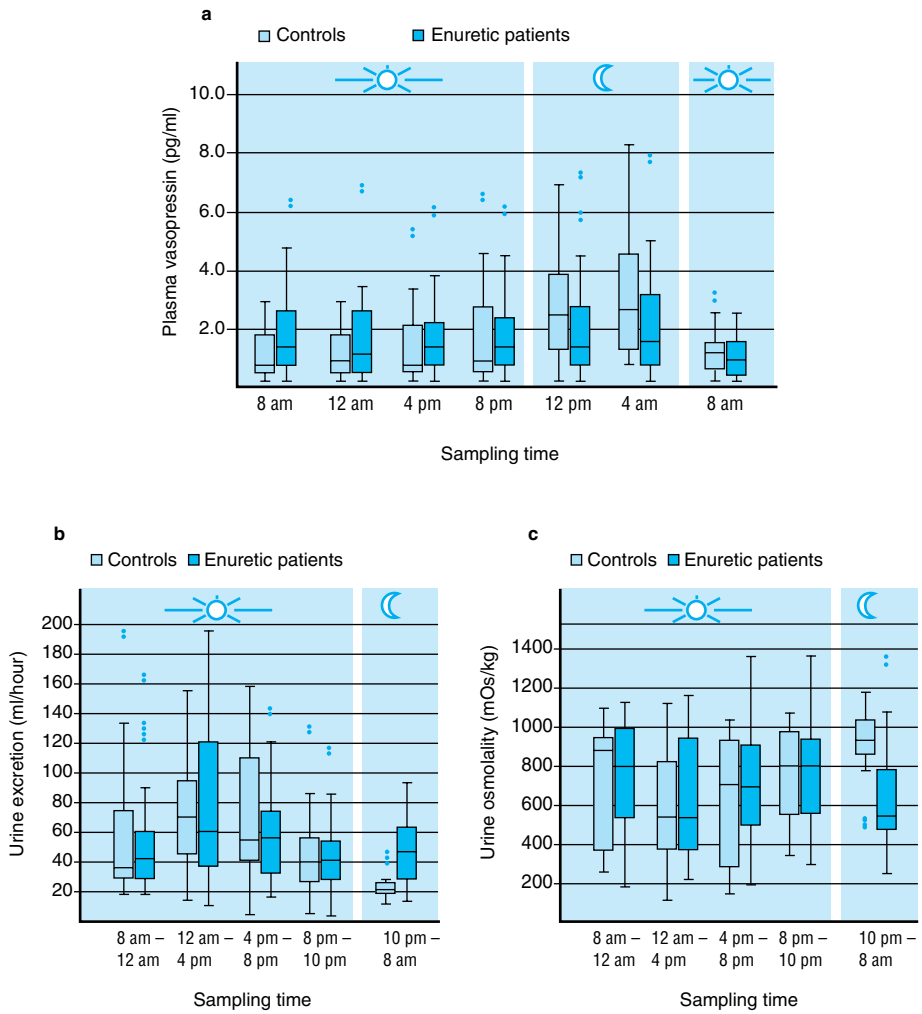


Fig. 4. Diurnal levels (total range and median value and first quartile) of plasma vasopressin (a), urine excretion rate (b) and urine osmolality (c) in 15 patients with nocturnal enuresis and 11 healthy volunteers. Dots represent extreme values exceeding the interquartile length by 1.5 times (reproduced with permission).<sup>[48]</sup>

**Table 4. Support for a biological aetiology in primary nocturnal enuresis****Hereditary**

- A clear genetic predisposition for nocturnal enuresis exists<sup>[52]</sup>

**Sleeping pattern**

- Children with primary nocturnal enuresis have the same sleeping pattern as normal children<sup>[42,43]</sup>

**Urodynamics**

- Bladder instability is not a significant factor in the pathogenesis of primary nocturnal enuresis<sup>[43]</sup>
- Small functional bladder capacity was not a requirement for the attainment of dryness in children treated with the enuresis alarm<sup>[50]</sup>

**Conditioning treatment**

Conditioning treatment with enuresis alarms is considered by many to be the first treatment choice in enuretic children. However, the initial arrest of enuresis by the alarm does not result in a permanent cure in all patients. For example, among children treated with the alarm, only 55% remained dry after 6–12 months.<sup>[50,55]</sup> Moreover, 44% of children cured by enuresis alarms had a negative opinion of this method.<sup>[56]</sup>

Heavy demands are placed on parents by alarm treatment and its use may be limited by difficulties in obtaining adequate family co-operation.<sup>[57]</sup> When these factors are taken into consideration and the family feels able to co-operate, the treatment is often successful and in many patients can result in long-term dryness. However, long-term studies are

needed to verify the exact cure rate of this treatment modality.

Medical treatment can be offered to patients unresponsive to alarm treatment or who come from families unable to support alarm treatment.

**Medical treatment**

Three types of pharmacological agents have been evaluated in studies of bedwetting:

- parasympatholytics
- tricyclic antidepressants
- the antidiuretic desmopressin (Minirin®, DDAVP®) .

*Parasympatholytics*

Oxybutynin is an antimuscarinic agent that diminishes the frequency of involuntary bladder muscle contractions and increases bladder capacity.<sup>[58]</sup> However, it is associated with antimuscarinic adverse events (e.g. dry mouth, visual impairment, constipation) that often prevent optimisation of the dosage regimen. Only one study has evaluated the efficacy of oxybutynin in paediatric nocturnal enuresis.<sup>[59]</sup> This study, which was placebo-controlled, found no significant differences

**Current evidence suggests that parasympatholytics as single therapy are not effective in nocturnal enuresis**

between oral oxybutynin 10 mg and placebo in terms of the frequency of nocturnal enuresis.

#### *Tricyclic antidepressants*

Tricyclic antidepressants have some effect on enuresis, probably arising from autonomic modulation. However, they are unsuitable for the treatment of nocturnal enuresis because of their association with serious adverse effects, including psychomotor and cognitive impairment, sedation and cardiac toxicity. Tricyclic antidepressants are therefore not recommended for the treatment of patients with nocturnal enuresis.

**Tricyclic antidepressants are not recommended in primary nocturnal enuresis**

#### *Desmopressin*

Desmopressin is effective and well tolerated in children with nocturnal enuresis.<sup>[12,60]</sup> The long-term efficacy and tolerability of desmopressin in the treatment of severe nocturnal enuresis have also been proved favourable.<sup>[61]</sup>

Studies investigating the efficacy of oral or intranasal desmopressin generally comprise an initial dosage-titration phase (around 4 weeks) to determine the optimum dosage for a given individual. The patient subsequently continues to receive this dosage during the maintenance phase of the study. A review by Houts et al. investigated the efficacy of desmopressin in

14 studies of patients with nocturnal enuresis.<sup>[62]</sup> In these studies, the number of enuretic episodes was reduced by up to 3.2 per week. Selected studies are summarised in table 5.

**Desmopressin (Minirin®, DDAVP®) has shown favourable results in terms of efficacy and tolerability in children with nocturnal enuresis**

Desmopressin is available in both intranasal and oral dosage forms for the treatment of nocturnal enuresis. Both are effective and well-tolerated in clinical use.<sup>[61,64]</sup>

*Intranasal desmopressin* The results of several studies indicate that intranasal desmopressin is the drug of choice in nocturnal enuresis.<sup>[36]</sup> Indeed, one randomised, double-blind, crossover study of 28 children and adults with nocturnal enuresis reported that the titrated effective dosage of intranasal desmopressin significantly decreased the number of wet nights per week by >90% in 68% of the patients.<sup>[69]</sup>

In another study by Terho, 52 children aged 5–13 years (most of whom were refractory to previous treatment) were randomised to four periods of 3 weeks each: two periods on placebo and two periods on intranasal desmopressin 20 µg.<sup>[67]</sup> There was a significant

**Table 5. Summary of studies of desmopressin in children with primary nocturnal enuresis**

Reference	No. of patients	Dosage regimen <sup>a</sup>	Treatment duration (weeks)	Reduction in mean number of wet nights/week (%)	Patients responding (%)	
					Full response <sup>b</sup>	Partial response <sup>c</sup>
Fjellestad-Paulsen et al. <sup>[65]</sup>	30	200 µg/day (PO) or 20 µg/day	2		31	62 (1–2 wet nights/week or an increase in dry nights by 1–2 nights/week)
Hjälmsås et al. <sup>[63]</sup>	393	20 or 40 µg/day	≤52		19	
Mathiesen et al. <sup>[64]</sup>	18	200 or 400 µg/day (PO)	6	67	0	100 (considerable improvement) <sup>d</sup>
Miller & Klauber <sup>[65]</sup>	176	20 µg/day 40 µg/day Placebo	4	21–29 34–41 13–15		
Miller et al. <sup>[66]</sup>	55	40 µg/day	≤52		51	
Terho <sup>[67]</sup>	52 47 <sup>e</sup>	20 µg/day 20, 30 or 40 µg/day	3 12	58–63	29 53 (≥5 dry nights/week)	38 19
Tuvemo <sup>[68]</sup>	18	20 µg/day	4		44 (27 or 28 dry nights/28)	44 (16–26 dry nights/28)

<sup>a</sup> Desmopressin was administered intranasally, except where indicated.

<sup>b</sup> Complete dryness unless otherwise indicated.

<sup>c</sup> >50% reduction in wet nights unless otherwise indicated.

<sup>d</sup> Mean frequency of wet nights reduced from 5.3 nights/week at baseline to 1.7 nights/week during desmopressin therapy.

<sup>e</sup> Patients who relapsed after cessation of desmopressin therapy.

Abbreviation: PO = orally.

increase ( $p < 0.01$ ) in the number of dry nights per week from 0.6 at baseline to 4.3 and 4.6 during the two 3-week periods of treatment with desmopressin. During the corresponding 3-week placebo periods, 2.1 and 2.4 dry nights per week were recorded.<sup>[67]</sup>

Miller et al. evaluated the long-term efficacy of desmopressin in 55 children who had

**Intranasal desmopressin (Minirin®, DDAVP®) has proved effective in patients refractory to previous treatments**

initially received intranasal desmopressin 40 µg per night for 2 weeks.<sup>[66]</sup> Responders continued to receive intranasal desmopressin for up to 12 months; the dosage was gradually reduced by 10 µg every 2 weeks once total dryness was achieved. In total, 28 children (51%) had a positive response to initial therapy and then progressed to total dryness with long-term therapy, while 8 children (14%) had an initial positive response but did not progress to total dryness on long-term follow-up. Complete weaning from desmopressin required >6 months in most patients, and a minimum of 3 months.<sup>[66]</sup>

Similarly, the Swedish Enuresis Trial (SWEET) assessed the long-term efficacy and tolerability of intranasal desmopressin in 393 children aged 6 to 12 years with primary nocturnal enuresis.<sup>[63]</sup> After a 6-week dose-titration phase, during which patients received

desmopressin 20 or 40 µg at bedtime, those achieving a ≥50% reduction in the frequency of wet nights ( $n=242$ ) continued open-label treatment (typically with the 40 µg dose) for up to 12 months. During dose-titration, the median weekly number of wet nights fell from 4.8 to 1.0. On completion of the trial, 133 of the 393 children (34%) had achieved a ≥90% reduction in the number of wet nights, and 75 children (19%) were completely dry at night. The majority of children who became dry reached this stage during the first 6 months of treatment.

*Oral desmopressin* It is recommended that oral desmopressin is initiated at a dosage of 200 µg/day, increasing to 400 µg/day if necessary. The antidiuretic efficacy of oral desmopressin 200 or 400 µg/day is similar to that attained with the intranasal formulation and provides a useful alternative to the intranasal route of administration.

A dose–response relationship was observed in a single-blind study of oral desmopressin administered at dosages of 50–400 µg/day in 15 children with nocturnal enuresis. The 200 µg dosage resulted in a significantly greater ( $p < 0.02$ ) number of dry nights than with 100 µg/day, but did not differ significantly from the 400 µg/day oral dosage.<sup>[25]</sup> However,

**Oral desmopressin (Minirin®, DDAVP®) therapy should be initiated at 200 µg/day and increased to 400 µg/day if necessary**

another single-blind, dose-ranging study found that a daily oral dosage of desmopressin 400 µg was generally somewhat more effective than a 200 µg dose in adolescents with severe nocturnal enuresis.<sup>[61]</sup> A subsequent 4-week, double-blind, crossover study in these patients (n=10) reported that oral desmopressin, at a dosage of 200 or 400 µg/day, produced a greater reduction in the number of wet nights (from 4.7 to 1.8 per week) than did placebo (from 4.7 to 4.1 per week).<sup>[61]</sup>

A 6-week study by Matthiesen et al. found oral desmopressin 200 or 400 µg/day to be at least as effective as the maximum effective dosage of the nasal spray in around 50% of enuretic patients.<sup>[64]</sup> In general, oral desmopressin 400 µg was more effective than the 200 µg dosage. The mean number of wet nights was reduced from 5.0 at baseline to 1.8 during oral treatment with desmopressin 200 or 400 µg/day. Three of the 18 patients who were non-responders to oral desmopressin achieved a full response with the nasal spray. There were no adverse events and no tendency towards hyponatraemia with either formulation.<sup>[64]</sup>

### *General comments on the treatment of nocturnal enuresis*

Today, more is known about nocturnal enuresis and research has established various patient subtypes. First, enuretics can be divided into monosymptomatic bedwetters and those who also have daytime incontinence. The latter group

requires a treatment directed towards their bladder dysfunction, whereas the former group will probably benefit from desmopressin treatment. Through an increased understanding of voiding dysfunction in children, a differentiated and more optimal treatment of bedwetting can be offered. Combined studies on bladder function and sleep in children suffering from bedwetting have revealed that their bladder function is normal and that enuretics have a similar sleep pattern to non-enuretics.<sup>[70]</sup>

## **Urinary incontinence and nocturia**

Urinary incontinence is a distressing and embarrassing condition that is common among the general population. There is a general increase in the prevalence of urinary incontinence with increasing age, and around 10% of the elderly population living at home are thought to be affected.<sup>[71]</sup>

Although the actual prevalence of urinary incontinence is relatively low in the elderly, up to 70% of this group have nocturia and 40% micturate more than twice nightly.<sup>[71]</sup> The need to rise in the night to micturate leads to sleep disturbances that can affect performance the following day.<sup>[72]</sup>

### *Pathogenesis*

Urinary incontinence is generally attributable to disorders of bladder storage. One of the most common causes of involuntary leakage of urine is uncontrolled spontaneous

contractions of the bladder during filling, which is known as ‘detrusor instability’. In addition to urinary incontinence, detrusor overactivity gives rise to symptoms of urgency, increased frequency of micturition and nocturia. These symptoms may have precipitating factors linked to the function of the cardiovascular, central nervous, endocrine and metabolic systems.

Patients without the need for nocturnal micturition have a daytime urinary output

**Patients with nocturia frequently have undetectable vasopressin levels**

twice as high as that at night.<sup>[73]</sup> However, in older patients with nocturia, the day:night urinary output ratio is reduced, and in such patients there is an increased frequency of nocturnal micturition. Plasma vasopressin is at undetectable levels in many such patients.<sup>[72]</sup>

From the above, it appears that abnormalities of vasopressin production may be central to urinary incontinence in some patients; desmopressin is therefore a rational therapeutic choice in patients with urinary incontinence and/or nocturia. By decreasing urinary output, desmopressin therefore allows patients to have a predictable, reliable period of hours free from nocturia and/or urinary incontinence.

### *Clinical studies*

Studies have demonstrated the favourable efficacy and tolerability of desmopressin in the treatment of urinary incontinence and/or nocturia arising in a number of patient groups. In particular, the successful treatment of urinary incontinence and/or nocturia with desmopressin in patients with multiple sclerosis (MS), 80% of whom have neurogenic bladder dysfunction, has been reported.<sup>[74–77]</sup>

### *Intranasal desmopressin*

Placebo-controlled, double-blind studies support the general efficacy and tolerability of intranasal desmopressin in nocturia<sup>[78]</sup> and urinary incontinence.<sup>[79,80]</sup> Studies in specific patient groups have demonstrated the efficacy of desmopressin administration in urinary incontinence arising as a consequence of MS (as outlined above), prostatic hyperplasia<sup>[81]</sup> and Alzheimer’s disease.<sup>[82]</sup>

A double-blind, crossover study of 33 patients with MS compared intranasal desmopressin (20 µg on retiring to bed) with placebo for the treatment of nocturia. Placebo treatment produced little change in frequency of micturition from baseline; in contrast, desmopressin produced significant reductions

**Desmopressin (Minirin®, DDAVP®) therapy is effective in the treatment of nocturia in patients with multiple sclerosis**

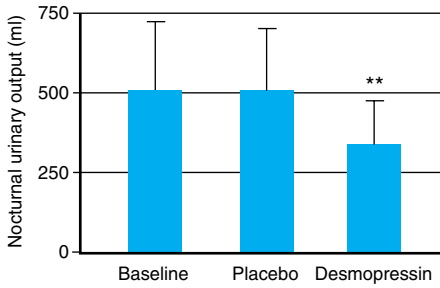


Fig 5. Effects of placebo and desmopressin 20 µg on nocturnal urinary output in a double-blind crossover study of 33 patients with nocturia as a consequence of multiple sclerosis; \*\* p<0.01 vs placebo.<sup>[75]</sup>

(p<0.01) in mean nocturnal frequency of micturition and voided volume compared with placebo (fig. 5), with little change in the daytime frequency of micturition or voided volume.<sup>[75]</sup>

Hilton and Stanton reported that desmopressin was effective in patients refractory to antispasmodic and evening fluid-

restriction interventions.<sup>[80]</sup> This 6-week, double-blind, crossover study compared desmopressin to placebo in 25 female patients with nocturia. Compared with both placebo and baseline measurements, nocturnal urinary output and frequency of micturition were both reduced during desmopressin therapy, with a slight increase in diurnal urinary output and little change in overall diurnal urinary frequency (table 6).

Another double-blind study assessed desmopressin vs placebo in 20 men with increased nocturnal frequency of micturition.

**Desmopressin (Minirin®, DDAVP®) is effective in patients with urinary incontinence who are refractory to antispasmodic therapy and evening fluid restriction**

Table 6. Mean (± SD) urinary output and frequency of micturition in a double-blind crossover study of 25 female patients with nocturia treated with desmopressin (reproduced with permission)<sup>[80]</sup>

	Baseline	Placebo	Desmopressin
Nocturnal urinary output (ml)	438 ± 183	391 ± 181	267 ± 97
Nocturnal frequency of micturition (episodes per night)	3.2 ± 1.4	2.6 ± 1.6	1.9 ± 1.2
Diurnal urinary output (ml)	789 ± 194	707 ± 399	879 ± 155
Diurnal frequency of micturition (episodes per 24 hours)	9.2 ± 3.7	10.1 ± 4.0	10.2 ± 4.3

Desmopressin therapy was found to be effective in 50% of 18 evaluable patients. However, the investigators also reported a significant drop in serum sodium concentration (141 to 137 mmol/L) and concluded that close monitoring of patients (in terms of fluid intake) and their serum sodium levels may be necessary in desmopressin-treated nocturia.<sup>[83]</sup>

#### Oral desmopressin

Oral desmopressin (200–800 µg/day) was found to be an effective, well-tolerated treatment for daytime urinary incontinence in patients with multiple sclerosis.<sup>[77]</sup>

A double-blind, crossover study of 17 elderly patients with nocturia compared desmopressin (up to 400 µg each night) and placebo.<sup>[9]</sup> After 14 days' treatment, a decrease (from baseline) in mean nocturnal urinary output was observed with desmopressin therapy compared with placebo (–0.7 and –0.1 ml/min, respectively). As expected, the duration of sleep between micturitions increased by around 2 hours during desmopressin therapy.

**IMPORTANT:** The latter conditions are not among those for which desmopressin is presently registered. Further clinical trials will reveal information about which specific patient groups are likely to benefit from antidiuretic treatment.

#### Renal concentrating capacity test (RCCT)

In a number of renal diseases, tubular function is reduced before glomerular function is

affected. A reduced tubular function is reflected by a reduced capacity of the kidney to concentrate the urine, i.e. by a reduced response to vasopressin. To this end, the water deprivation test, with or without injection of Pitressin® (vasopressin) is widely used for measuring renal concentrating capacity.<sup>[84,85]</sup> However, water deprivation for 16–24 hours is inconvenient and even harmful to already dehydrated patients. In addition, misleading results can sometimes be obtained as a result of non-compliance with test protocol, e.g. if the patient has been drinking during the test. Therefore, it is more rational to stimulate the renal V<sub>2</sub> receptors directly with an exogenous V<sub>2</sub> agonist such as desmopressin. Administration of vasopressin will stimulate renal concentrations of urine in the same manner as desmopressin, but the latter agent is preferable as it is devoid of the intestinal and vascular constricting effects of vasopressin.

This was substantiated by Aronson and Svenningsen, who introduced desmopressin for testing renal concentrating ability in children and found it advantageous in comparison with both water deprivation and Pitressin®.<sup>[86]</sup>

**Desmopressin (Minirin®, DDAVP®) followed by a test of urine osmolality is a reliable and simple method for estimating renal concentrating capacity**

There are four main indications for testing the renal capacity to concentrate urine:

- urinary tract infection
- polyuria/polydipsia
- lithium treatment
- analgesic-induced renal dysfunction.

**Application of the RCCT**

One hour after desmopressin administration, the bladder is emptied; urine osmolality is determined in two samples 3—5 h later.<sup>[87]</sup> A number of age-adjusted reference values (lowest acceptable maximum urine osmolality) have been adopted for renal concentrating capacity following the administration of desmopressin (table 7; fig. 6). In general, if the maximum osmolality is <700 mOsm/kg the renal concentrating ability is considered

**Table 7. Mean age-adjusted reference values for renal concentrating capacity following intranasal desmopressin 40 µg or subcutaneous desmopressin 4 µg**

Age (years)	Lowest acceptable maximum urine osmolality (mOsm/kg)
1	525 <sup>a</sup>
3	825 <sup>a</sup>
20	850 <sup>b</sup>
40	800 <sup>b</sup>
60	700 <sup>b</sup>
80	600 <sup>b</sup>

<sup>a</sup> Based on tests in 473 healthy volunteers.<sup>[87]</sup>  
<sup>b</sup> Based on tests in 225 healthy volunteers.<sup>[88]</sup>

abnormal.<sup>[89]</sup> Fluid restriction is not considered necessary for accurate test results, but there is a risk of water intoxication with excessive fluid intake.<sup>[90]</sup>

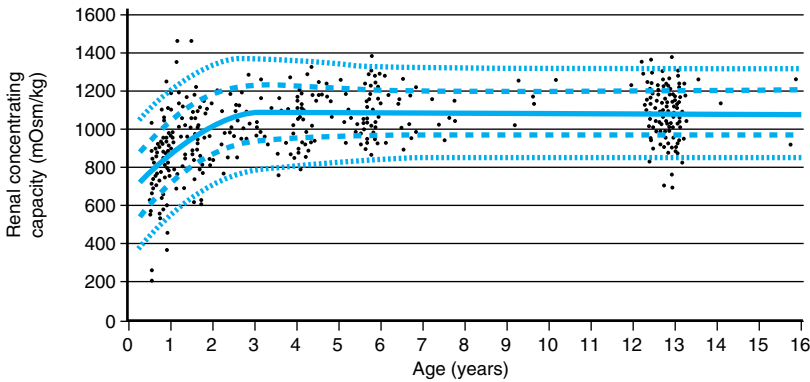


Fig.6. Reference curve for renal concentrating capacity for 0.5- to 14-year-old children as determined by the desmopressin test. Continuous lines represent mean values and broken lines represent intervals of one SD (© 1997 Springer-Verlag GmbH & Co. KG, reproduced with permission).<sup>[87]</sup>

## Indications for the RCCT

### Urinary tract infections

Concentrating capacity is the first parameter of renal function to be impaired in children with chronic pyelonephritis. Thus, the RCCT provides a simple and practical method for the estimation of renal impairment in such patients. It is also recommended in the follow-up of children with urinary tract infection.<sup>[91]</sup> In addition, desmopressin has been used for 10 years in Scandinavia to determine the extent of urinary tract infection. Normal concentrating capacity indicates that the infection is limited to the lower urinary tract, whereas a reduced concentrating capacity suggests that the kidneys are involved.

### Investigation of polydipsia/polyuria

The RCCT can be used to distinguish between psychogenic polydipsia and the two forms of diabetes insipidus. A considerable reduction in renal concentrating capacity is seen in nephrogenic diabetes insipidus, a moderate reduction indicating psychogenic polydipsia and a normal renal concentrating capacity being observed in patients with central diabetes insipidus.

### Detection of renal impairment in patients receiving lithium

In a small proportion of patients receiving long-term lithium treatment there exists a partly irreversible reduction in distal and collecting tubule function,<sup>[92]</sup> and thus a reduced capacity to concentrate urine.<sup>[93]</sup> There may also be reductions in vasopressin secretion. The desmopressin RCCT is a suitable method for testing renal concentrating capacity in lithium recipients and is as effective as fluid deprivation.<sup>[94]</sup> Tubular function of 124 lithium-treated patients, as measured with the desmopressin RCCT, was below normal in 51% of patients in a study by Bendz et al.<sup>[95]</sup> However, glomerular function was below normal in only 3% of patients, indicating that the RCCT is a more sensitive test of renal dysfunction than a test of glomerular function.

### Early detection of renal dysfunction caused by analgesics

Around 5% of patients with terminal renal insufficiency have analgesic nephropathy, and the RCCT has proved useful in the early diagnosis of renal dysfunction caused by analgesics.<sup>[96]</sup>

# CLINICAL SAFETY

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Clinical experience has shown desmopressin (Minirin®, DDAVP®) to be safe and well tolerated. During the 20 years of clinical experience with desmopressin, few adverse events have been reported when the drug is used in accordance with the manufacturer's recommendations. Besides infrequent cases of water intoxication, desmopressin is virtually free of serious adverse effects<sup>[36]</sup> and has been associated with no abnormalities in routine laboratory tests.<sup>[60,66,69]</sup> Among the non-serious adverse drug reactions experienced with desmopressin, nasal symptoms dominate. There are also occasional gastrointestinal symptoms, including nausea and abdominal pain.

**Clinical experience has shown desmopressin (Minirin®, DDAVP®) to be well tolerated**

Acute water intoxication is a rare complication of desmopressin therapy and is likely to occur only in patients who fail to reduce their water intake.<sup>[97]</sup>

**To reduce the risk of fluid retention, desmopressin (Minirin®, DDAVP®) recipients should control their fluid intake**

Although patients could be instructed to limit fluid intake to no more than 30 ml/kg for a period of 2 hours before to 12 hours after taking desmopressin,<sup>[98]</sup> a more practical recommendation might be to abstain from fluid intake for 8 hours after the medication or to take fluid only for the purpose of satisfying thirst.

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