TREATMENT OF CENTRAL DIABETES INSIPIDUS

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We owe special thanks for the work presented in this booklet to Professor Gary Robertson, Professor Yutaka Oiso and Associate Professor Hiroshi Arima: to work with some of the world’s most prominent experts in central diabetes insipidus has been a privilege.

**Abstract**

Desmopressin, a synthetic analogue of the antidiuretic hormone vasopressin, has been the treatment of choice for central diabetes insipidus (CDI) since 1972 and the quality of life of CDI patients has been greatly improved ever since its introduction. In CDI, desmopressin is given as a hormone replacement to compensate for a lack of – or at least insufficient – release of endogenous vasopressin, also called antidiuretic hormone (ADH). As with any hormone replacement therapy, the more precisely the dose can be tailored to the individual patient, the better and safer the clinical response is expected to be.

This booklet explores a number of clinical obstacles facing medical professionals who aim to tailor antidiuretic treatment to the individual CDI patient.

On a basic physiological level, the antidiuretic action of desmopressin is characterised by a considerable lag time in exerting its full effect and by large individual differences in pharmacodynamic response. Understanding these individual variations will enable more precise tailoring of the dose to patients in need of antidiuretic treatment.

In CDI specifically, in addition to these individual physiological differences in antidiuretic response to desmopressin substitution therapy, some patients maintain a small, but inadequate, endogenous production of arginine vasopressin (AVP). As a result, individual dose titration depending on the severity of CDI is required.
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CHAPTER 1

Diabetes insipidus: the water cycle in overdrive
CHAPTER 1. DIABETES INSIPIDUS: THE WATER CYCLE IN OVERDRIVE

1 CHAPTER 1. Diabetes insipidus: the water cycle in overdrive

Diabetes insipidus (DI) is a rare syndrome characterised by the excretion of abnormally large volumes of dilute urine (polyuria) and a commensurate increase in fluid intake (polydipsia). Untreated patients with this condition experience enormous difficulty with an almost constant need to make trips to the toilet and an insatiable thirst driving them to drink fluids, sometimes several times an hour. This vicious cycle continues throughout the day and the night, meaning that it is virtually impossible to complete any tasks uninterrupted, or to sleep continuously for any significant length of time.

Etymologically, diabetes (Greek: διαβαινω) means ‘to pass through’ and the first clear description of the condition was made by Aretaeus of Cappadocia, a physician of the late Hellenistic period. It wasn’t until two millennia later, in 1670, that Thomas Willis introduced a distinction between diabetes with a sweet-tasting urine (diabetes mellitus) and diabetes with polyuria without taste (diabetes insipidus, insipidus derived from Latin and meaning ‘having no flavour’).

1.1 On the DI patient’s menu: pituitaries washed down by a pitcher of water

In the early 1900s the development of a treatment for diabetes insipidus was taking its formative steps. Research was published in 1918 documenting the case of a patient who experienced a significant improvement in her condition following the consumption of two to seven fresh pituitaries from cattle each night (Figure 1). Such observations confirmed the key role of the pituitary, a gland only the size of a pea (Figure 2), in the aetiology of diabetes insipidus, and paved the way for treatment of the disease with vasopressin hormone, and later with the synthetic analogue, desmopressin.

FIGURE 1. EXTRACT FROM A REPORT IN 1918 DOCUMENTING THE ALLEVIATION OF DI SYMPTOMS WITH THE CONSUMPTION OF CATTLE PITUITARIES

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DIABETES INSIPIDUS
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One patient who has been under my care for the past two years has been very much improved by an intermittent pituitary feeding. She has taken from two to seven fresh pituitary bodies from cattle every evening. The output has hereby been checked during the night,—usually decreasing from nearly 2500 cc. to approximately 300 cc. At the same time the general state of health has improved considerably.
1.2 The many forms of diabetes insipidus

Today, diabetes insipidus is differentiated into four types based on aetiology (Table 1). Because most cases are secondary to other diseases, the incidence depends on the primary causes, as outlined below. However, whatever the cause, diabetes insipidus is very rare, with overall incidence in the general population estimated to be 3–4 in 100,000, with a slightly higher incidence among males (60% of DI patients).

**TABLE 1. THE FOUR TYPES OF DIABETES INSIPIDUS**

<table>
<thead>
<tr>
<th>Type of DI</th>
<th>Causes</th>
<th>Underlying mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrogenic diabetes insipidus</td>
<td>Acquired or genetic</td>
<td>Lack of renal sensitivity to circulating AVP</td>
</tr>
<tr>
<td>Primary polydipsia</td>
<td>Compulsive/habitual excessive intake of fluids</td>
<td>Excessive fluid intake despite normal AVP levels and sensitivity to the hormone</td>
</tr>
<tr>
<td>Gestational diabetes insipidus</td>
<td>Pregnancy</td>
<td>Lack of AVP due to increased metabolism of vasopressin by the enzyme vasopressinase, produced by the placenta</td>
</tr>
<tr>
<td>Central diabetes insipidus</td>
<td>Disease, trauma, genetic mutation</td>
<td>Lack of production of AVP</td>
</tr>
</tbody>
</table>
DI can be caused by renal insensitivity to the antidiuretic effect of vasopressin. This type is referred to as nephrogenic DI (NDI) and can be acquired or genetic. It is largely refractory to treatment with standard doses of vasopressin or desmopressin since its origin lies in a lack of sensitivity to the native hormone rather than a lack of the hormone. However, it can be ameliorated to varying degrees by thiazide diuretics resulting in a reduction of polyuria (and thus polydipsia) by up to 50% without inducing hypernatraemia. In lithium-induced nephrogenic diabetes insipidus, amiloride can substantially restore the impaired renal concentrating mechanism due to effects on renal medullary osmolytes, aquaporins, and urea transporters.

Another type of DI is caused by excessive intake of fluids and is usually referred to as primary polydipsia. In this type of DI, vasopressin or desmopressin completely correct the polyuria but have little or no effect on the polydipsia since the abnormal fluid intake is compulsive or habitual. Consequently, antidiuretic therapy almost invariably produces water intoxication with hyponatraemia and is strongly contraindicated. For this reason it is extremely important to differentiate partial DI (see below) correctly from primary polydipsia before starting antidiuretic therapy.

One very rare type of DI, referred to as gestational DI, is due to increased metabolism of vasopressin by the enzyme vasopressinase, produced by the placenta. It occurs only during pregnancy, usually in middle and late pregnancy, and is controlled much better with desmopressin than with vasopressin because the analogue is resistant to enzymatic degradation.

The final type of DI, and the main focus of this booklet, is caused by a deficiency in production of the antidiuretic hormone, arginine vasopressin, and is variously referred to as pituitary, neurohypophyseal, cranial or central DI (CDI). It can be acquired as a result of a number of diseases, trauma or genetic mutations. In all cases of this type, treatment with desmopressin completely eliminates the polyuria and polydipsia. In cases where AVP secretion is totally absent (complete DI), untreated patients are dependent entirely on water intake for maintenance of water balance, while in cases where some residual capacity to secrete AVP remains (partial DI), plasma osmolality can reach levels that allow moderate degrees of urinary concentration.

Treatment of CDI is usually lifelong because recovery from a deficiency is uncommon, even if the underlying cause is eliminated. Reversible DI is generally only seen following neurosurgery, thus there is no general evidence that treatment regimens need to be changed as patients grow older with chronic DI. Nevertheless, although spontaneous improvement or complete recovery from CDI appear to be very rare, a few cases have
been described.\textsuperscript{14} In one case of familial CDI in which the polyuria and polydipsia were severe until the age of 30 years, it was shown that, although the patient still had a severe deficiency of vasopressin after this age, his 24-hour urine osmolarity had increased to normal and spontaneous fluid intake had decreased to normal without any type of treatment or laboratory evidence of adrenal insufficiency.\textsuperscript{15} Thus, there may be some unknown age-related variable that, in some CDI patients, either enhances or substitutes for the antidiuretic effect of vasopressin, eg a change in $V_2$ receptor ($V_2R$) sensitivity or in the mobilisation and removal of aquaporin water channels after stimulation.

Compared to vasopressin, desmopressin’s ease of administration, safety and tolerability make it the first-line agent for outpatient treatment of CDI.\textsuperscript{16}

### 1.3 Desmopressin in the treatment of central diabetes insipidus

Desmopressin, being a synthetic analogue of the antidiuretic hormone vasopressin, is currently indicated for three major urological conditions, all of them characterised by polyuria (the excretion of excessive volumes of urine throughout the day and night [24 hour polyuria] or only during the night [nocturnal polyuria]): CDI, monosymptomatic nocturnal enuresis (MNE) and nocturia.

In CDI, desmopressin is given as a hormone substitute to compensate for insufficient release of endogenous vasopressin. The clinical rationale for individual up- or down-titration of desmopressin based on efficacy and safety is well documented in CDI.\textsuperscript{17} As with any other hormone replacement treatment, the more precisely the dose can be tailored to the individual patient, the better and the safer the response that can be expected. However, as outlined below, a number of clinical challenges need to be addressed to allow improved tailoring of antidiuretic treatment to the individual CDI patient.

The antidiuretic action of desmopressin (and probably vasopressin itself) is characterised by a considerable lag (around 4 hours’ delay at steady state) in exerting its full effect. In addition, large individual differences in response cannot be explained fully by differences in pharmacokinetics. It is essential to explore these individual physiological variations in order to enable more precise tailoring of dosage to patients in need of antidiuretic treatment.

In CDI, in addition to these individual differences in response to desmopressin substitution therapy, some patients maintain a small, but inadequate, endogenous production of AVP. As a result, individual dose titration depending on severity of CDI and also on the patient’s individual acceptance of the associated polydipsia/polyuria, is needed.
The expected clinical outcome of the evidence presented in this booklet is to improve the guidance for clinicians and CDI patients in order to assist in their efforts to individualise therapy according to each person’s antidiuretic response to desmopressin.
CHAPTER 2

Characteristics of desmopressin, the cornerstone of treatment for central diabetes insipidus
2.1 Antidiuretic mode of action of the native hormone, vasopressin

The antidiuretic action of vasopressin through activation of V$_2$R is caused by water reabsorption in the kidney, activated via the Gs protein/adenyl cyclases/cAMP pathway causing mobilisation of water channel aquaporin (AQP-2) to the luminal membrane of the kidney nephron’s distal convoluted tubule and the collecting duct, finally rendering the lipid bilayer of cell membranes permeable to water.\textsuperscript{18}

In mammals, including humans, a deficiency in any part of this endocrine system causes central or nephrogenic diabetes insipidus with polyuria and dilute urine.\textsuperscript{19}

2.2 Antidiuretic mode of action of desmopressin

Desmopressin (1-deamino-8-arginine vasopressin, dDAVP) was synthesised by Milan Zaoral and colleagues in Prague in 1967,\textsuperscript{20} and is a synthetic analogue of vasopressin, in which the L-arginine in position 8 has been replaced by D-arginine and the free amino group in position 1 has been removed by replacing the hemicystine component at position 1 by β-mercaptopropionic acid (Figure 4). Compared with the natural hormone, desmopressin has a longer half-life, greater antidiuretic potency and substantially reduced pressor activity.\textsuperscript{21}
2.3 Absorption, distribution, metabolism, and excretion (ADME) of desmopressin

Vasopressin and desmopressin are peptides, which are in general unsuited to oral administration due to their large molecular size, susceptibility to enzymatic degradation and short plasma half-life. However, after initial studies in rats and dogs, followed by clinical trials in healthy volunteers, and patients, it was found that although the bioavailability of orally administered desmopressin tablets was low, the drug showed a stable antidiuretic effect and a clear dose–response relationship. Since 2005 an orally disintegrating tablet (ODT) containing desmopressin (MINIRIN® Melt, Ferring Pharmaceuticals, Saint-Prex, Switzerland), which is administered sublingually without water, has been available. The absolute bioavailability is estimated to be 0.24%, 0.28%, and 0.25% after dosing with 200 µg, 400 µg, and 800 µg desmopressin Melt, respectively.

The total systemic clearance of desmopressin after intravenous administration is approximately 8 L/h (range: 4.7–10.2 L/h). The mean terminal half-life (the time required to divide the plasma concentration by two after reaching pseudo-equilibrium) is approximately 2.8 hours (range: 2.0–6.3 h) and the volume of distribution based on the terminal phase (Vz) is approximately 33 L (range: 19.6–85.3 L). In healthy volunteers, approximately 50% of an intravenous dose of desmopressin is eliminated unchanged in the urine. It has been observed that patients with moderate to severe renal impairment (creatinine clearance <30 mL/min) have a significant decrease in the renal clearance of desmopressin, and hence an increase of the terminal half-life (9.3 h vs 2.9 h in healthy volunteers). For endogenous vasopressin the half-life is so low (5–6 min) that renal impairment most likely does not affect clearance of the hormone.
2.4 Pharmacological properties of desmopressin in CDI patients

Desmopressin’s main pharmacological properties in CDI patients are illustrated in Figure 5. Following a 2-hour intravenous infusion, the average magnitude and duration of its effects on urine osmolality and urine flow are clearly reciprocal and dose dependent. Like vasopressin itself, the magnitude of the antidiuretic effect is limited by the intrinsic concentrating capacity of the human kidney, which in CDI patients is temporarily blunted owing to their prior deficiency of vasopressin. Thus, the average maximum urine osmolality achieved in the study shown was approximately 850 mOsm/kg, and was reached at an IV dose of 250 ng. This corresponded to a reduction of the rate of urine output to around 1 mL/min (1.4 L/day), which approximates to the basic rate in healthy adults. Doubling the dose of desmopressin to 500 ng did nothing further but prolonged the duration of action. As with vasopressin itself, these effects vary substantially from patient to patient, even when differences in bioavailability are not a concern due to IV administration.

(a) Adjusted diuresis

(b) Osmolality

FIGURE 5. THE PHARMACODYNAMIC PROFILE OF DESMOPRESSIN MEASURED AS (A) ADJUSTED DIURESIS (ML/KG/30 MIN) (+/-SD), AND (B) MEAN URINE OSMOLALITY (+/-SD) (BASED ON STUDY II17)

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Another advantage of desmopressin over vasopressin is the lack of effect of the analogue at V₁R. Accordingly, even high doses of desmopressin produce little or no vasoconstriction, no increase in blood pressure, and no contraction of the uterus or gastrointestinal tract, as all these effects are related to the stimulation of V₁ receptors (V₁Rs). Compared to vasopressin, desmopressin’s ease of administration, safety and tolerability make it the first-line agent for outpatient treatment of CDI.

2.5 Time delay and fluctuations in antidiuretic response to desmopressin

A study in water-loaded healthy adults given a bolus injection of 0.396 µg desmopressin indicated a time delay in reaching maximum antidiuretic response to desmopressin. However, the reason for these temporal dissociations between plasma desmopressin and changes in urine osmolality is not completely clear.

One possibility is that the delay could be due in part to the time required for newly formed urine to traverse the renal pelvis and ureters into the bladder. However, this is unlikely to be a major contributor in practice because the volume of these spaces is relatively small. Another possibility is that the concentration of desmopressin at renal V₂Rs differs from that in plasma due to the existence of some barrier that slows its diffusion into and out of its site of action. No such barrier has ever been described but its existence cannot be discounted completely.
The last and most likely explanation for the significant temporal dissociation between plasma desmopressin and urine osmolality is the time required to activate and then deactivate fully all the various cellular mechanisms that mediate or enhance the drug’s antidiuretic effect. Vasopressin and its analogue desmopressin increase urinary concentration by promoting the reabsorption of water from fluid in the collecting ducts of the kidney. This effect is achieved via binding to V₂Rs on the serosal surface of principal cells which then activate adenyl cyclase, increasing the production of cyclic AMP. The latter, in turn, phosphorylates AQP-2 water channels resulting in their insertion through the luminal surface of the principal cells, and permitting water to diffuse back into and through the cells down the osmotic gradient created by the hypertonic milieu of the renal medulla.³¹ Studies in animals indicate that the increase in AQP-2 in the membranes occurs rapidly, anywhere from 5 to 15 min after administration of AVP or desmopressin.³² This is attributed to an acute trafficking of a preformed pool of AQP-2 to the membrane, or phosphorylation of a pool of AQP-2 already present in the basolateral membrane. If these kinetics are representative of the rate of trafficking of AQP-2 in healthy humans, other explanations for the relatively long delay of around 4 h in achieving full antidiuretic effect are still needed.

However, stimulation of V₂Rs also sets in motion a number of other cellular events in cortical and medullary collecting tubules that could influence the magnitude and/or duration of the antidiuretic effect.³³–³⁹ They include increased synthesis as well as decreased endocytosis
and degradation of AQP-2, phosphorylation of many other proteins whose roles in antidiuresis are not yet known, and increased tubular reabsorption of urea and sodium – either of which could enhance antidiuresis by reducing urinary solute load and enhancing hypertonicity in the renal medulla. The kinetics of these effects, and their contribution, if any, to the observed delay in full activation and deactivation of the antidiuretic effect of desmopressin, are unknown. However, it is possible that each of these effects reaches maximum fruition at different rates, accounting not only for the delay in full effect but also the surprisingly large fluctuations in urine osmolarity within and between patients observed over time. Kidney function (glomerular filtration rate; GFR) could also play a role in variations in antidiuretic response, since desmopressin is renally excreted and is more slowly excreted in patients with poor kidney function.40 Significant variations in antidiuretic response were confirmed in Study I.30 However, the subjects included were healthy young males with normal kidney function, and as such the variations seen in this study are unlikely to be attributable to impairments in GFR.

Finally, the time delay in antidiuretic response to desmopressin could also be secondary, in part, to the continuous generation of cAMP for prolonged periods after ligand washout and receptor internalisation in the endosomes.41

2.6 Desmopressin – pros and cons of different formulations

Desmopressin can be administered as an intranasal solution (since 1972), injectable solution (since 1981), or orally as a tablet formulation (since 1987; 0.1 mg and 0.2 mg) for the treatment of CDI, MNE and nocturia. Since 2005 the ODT containing desmopressin (MINIRIN® Melt, Ferring Pharmaceuticals, Saint-Prex, Switzerland), administered sublingually without water, has been available. This formulation is associated with increased bioavailability, allowing lower dosing than with the original solid tablets.42

Desmopressin ODT offers a preferable administration method compared with desmopressin tablet,43 due to the avoidance of fluid intake with drug administration, which helps to reduce the risk of fluid overload.

In CDI there are a number of disadvantages associated with the nasal spray compared with oral formulations of desmopressin. There is greater variability in dosing using desmopressin nasal spray, and absorption may be altered in patients with nasal mucosa changes.30 However, it should be emphasised that the intranasal formulation remains of benefit in some CDI patients because the wide range of different strengths allows an individualised administration of the exact dose required to obtain control of water excretion in a given CDI patient. Also, diluted nasal preparations are sometimes used in infant CDI patients, though these require weekly reformulation due to reduced desmopressin stability upon dilution.
A dose comparison of the different formulations of desmopressin is provided in Table 2.

**TABLE 2. DOSE COMPARISON OF DIFFERENT FORMULATIONS OF DESMOPRESSIN**

<table>
<thead>
<tr>
<th></th>
<th>Melt</th>
<th>Tablet</th>
<th>Nasal spray</th>
<th>Nasal drops</th>
<th>Solution for injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 µg</td>
<td>100 µg</td>
<td>5 µg</td>
<td>5 µg</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>120 µg</td>
<td>200 µg</td>
<td>10 µg</td>
<td>10 µg</td>
<td>&lt;0.5 µg</td>
<td></td>
</tr>
<tr>
<td>240 µg</td>
<td>400 µg</td>
<td>20 µg</td>
<td>20 µg</td>
<td>&lt;1 µg</td>
<td></td>
</tr>
</tbody>
</table>

2.7 Comparing antidiuretic response to desmopressin between CDI patients and healthy volunteers

Based on PK/PD modelling from Studies I and II, the estimated concentration–osmolality relationship at steady state is compared between CDI patients and healthy volunteers in Figure 7.

In general, CDI patients had lower clearance than healthy subjects (explaining also a longer duration of high urine osmolality levels), and it is clear that the maximum potential urine osmolality was 30% lower for CDI compared to healthy subjects (p<0.001; ie CDI patients have a significantly lower ability to concentrate urine)
However, it cannot be ruled out that these population differences were confounded by sex and age (all healthy volunteers were young males, while CDI patients were predominantly females of all ages), and other study differences. Further research is needed, but this example serves to illustrate that future dose-finding studies of antidiuretic treatment in CDI patients need to be performed in the target population, not in healthy volunteers.

2.8 Tailoring desmopressin dosing to the patient’s needs

The main purpose of human fluid homeostasis is to maintain serum osmolality within a narrow and stable range (280–300 mOsm/kg). In order to compensate for loss of fluid, the kidneys have the ability to produce hypertonic urine with a urinary osmolality of up to 1200 mOsm/kg. Vasopressin is released from the pituitary gland to promote urine concentrating whenever serum osmolality increases, e.g. due to lack of fluid intake, while in contrast no vasopressin is released if excessive amounts of fluid are ingested.

Antidiuretic therapy with desmopressin in CDI can be considered a hormone replacement therapy, where the necessary V₂R stimulation is provided ‘artificially’ on top of whatever endogenous vasopressin activity the patient may have, in order to provide an appropriate duration of antidiuretic action. While this may sound relatively straightforward, clinical practice with desmopressin for over 40 years has highlighted a number of problems associated with finding the right dose for patients, for the reasons outlined in the following sections.

2.8.1 Adapting to individual variation in fluid intake

When vasopressin is substituted by desmopressin, for obvious reasons the tight regulation of fluid homeostasis is halted for the duration of antidiuretic action (6–8 h for most therapeutic doses). So a critical question in titrating the right dose of desmopressin in a patient is, how do you take the patient’s fluid intake during antidiuretic treatment into account?

The most challenging clinical situation in which this dilemma occurs is in infants with CDI. The diet of infants contains a proportionally large quantity of water, resulting in the need for a relatively larger diuresis than in older children. Therefore, fluid intake and output should be especially closely monitored and balanced, and individual desmopressin dose titration is essential in all age ranges of the paediatric population to achieve sufficient antidiuretic control while avoiding hyponatraemia.
The two major mechanisms responsible for regulating water metabolism are thirst and pituitary secretion of the hormone vasopressin.\textsuperscript{44} For larger children and adults it is normally advisable to drink according to thirst, since the osmotic threshold for vasopressin secretion is lower (by around 5–10 mOsm/kg) than for thirst.\textsuperscript{45} The potential for hyponatraemia arises with forced or habitual fluid intake, as in the most extreme cases of primary polydipsia, which is characterised by excessive intake of fluids.\textsuperscript{46} In such cases desmopressin is strongly contraindicated.

2.8.2 Adapting to differences in patients’ sensitivity to desmopressin

Any hormone needs receptors to provide a physiological reaction. Thus, the potency of a hormone depends not only on the systemic concentration of the hormone, but also on its affinity to its target receptors. Furthermore, the number of available receptors may differ between patients and within a patient over time. An obvious example of the importance of titrating to the correct dose of hormone replacement is another diabetic condition also involving polyuria: diabetes mellitus. Type 1 diabetes is characterised by complete absence of insulin (no stimulation of insulin receptors), while type 2 is characterised by decreased sensitivity of the insulin receptors, initially causing increased insulin levels, and in later stages causing decreased insulin levels.\textsuperscript{47}

In the case of vasopressin, it is well known that renal concentrating ability is impaired with ageing, which can be due either to reduced endogenous vasopressin or to an impaired renal cellular response to AVP, leading to decreased water permeability of the collecting duct.\textsuperscript{48}

The question is whether an age-related decrease in endogenous vasopressin release is followed by a compensatory upregulation of V$_2$R and AQP-2. If this is the case, then the older (partial) CDI patients would respond to lower doses of desmopressin than younger patients.

2.8.3 How to optimise the therapeutic index in CDI patients treated with desmopressin

The therapeutic index of any drug is the ratio of the dose that produces toxicity (in desmopressin’s case hyponatraemia and/or sudden drops in serum sodium) to the dose that produces a clinically desired or effective response (in desmopressin’s case, decrease in urine production during a given duration of antidiuretic action) in a population of individuals.

If sensitivity to desmopressin varies considerably between patients – and even within the same patient over time – it is clear that the dose that produces therapeutic and toxic effects will also vary considerably between patients, and the dose may therefore need to be readjusted in individual patients over time to ensure optimal efficacy and safety of the drug.
In CDI, according to the current label, dosage is individual, but the total daily sublingual dose is normally in the range of 120 µg to 720 µg desmopressin ODT. A suitable starting dose in adults and children is 60 µg three times daily (TID), administered sublingually. This dosage regimen should be adjusted in accordance with the patient’s antidiuretic response. In a previous trial of desmopressin tablets, all patients required dosing TID, and for the majority of patients, the maintenance dose for patients using the ODT is recommended as 60 µg to 120 µg sublingually TID according to the current label.

2.8.4 Clinical questions to be explored in this booklet

In summary, the overarching critical clinical questions to be investigated based on the studies presented in this booklet are:

- How can we tailor antidiuretic treatments to CDI patients’ individual needs?

- What data do we have or should we generate to enable such tailored antidiuretic treatment in the future?

- How will such individualised treatment influence the overall risk–benefit ratio of using desmopressin in CDI?

- What other factors might influence desmopressin exposure and antidiuretic action (formulation, food, interactions with concomitant drugs or other concurrent diseases) and should be taken into account when tailoring an individual dose to a patient?

- Are there as yet unknown intrinsic factors behind the large individual differences seen in the magnitude or timing of antidiuretic response to desmopressin that may involve pre-existing environmental or genetic differences in any of the cascade of cellular mechanisms that mediate vasopressin effects – and if so, how will that influence dosing of desmopressin as a synthetic analogue of vasopressin?

These are the questions to be investigated by the studies and the clinical review presented in this booklet.
CHAPTER 3

Study I. Temporal delays and individual variation in antidiuretic response to desmopressin
Temporal delays and individual variation in antidiuretic response to desmopressin

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Am J Physiol Renal Physiol 304: F268–F278, 2013. First published November 7, 2012; doi:10.1152/ajprenal.00502.2012. —This study aimed to estimate the relationship between pharmacokinetics and the antidiuretic effect of desmopressin. In the investigator-blind, randomized, parallel group study, 5 dose groups and 1 placebo group, each consisting of 12 healthy, overhydrated, nonsmoking male subjects 18–55 yr of age were infused intravenously over 2 h with placebo or 30, 60, 125, 250, and 500 ng desmopressin in 50 ml of normal saline. Plasma desmopressin and urine osmolarity rose by variable amounts during the infusions of 60, 125, 250, and 500 ng desmopressin. Plotting mean urine osmolarity against the concurrent mean plasma desmopressin yielded a temporal delay between pharmacokinetic (PK) and dynamic (PD) responses in all dose groups. Using simulation from the indirect-response model, assuming a constant (4 ng/ml) desmopressin concentration, this delay between PK and PD was estimated at 4 h (10th-90th percentile: 1.8–8.1). Within each group, however, there were large individual variations (2- to 10-fold) in the magnitude and duration of the antidiuretic effect. The antidiuretic effect of intravenous desmopressin in water-loaded healthy adults varies considerably due largely to factors other than individual differences in pharmacokinetics. The antidiuretic effect is time as well as dose dependent and may be self-amplifying. The most likely explanation for these findings is that the time required for a given level of plasma desmopressin to exert its maximum antidiuretic effect varies markedly from person to person due to individual differences in the kinetics of one or more of the intracellular mechanisms that promote the reabsorption of solute-free water by principal cells in renal collecting tubules.

Desmopressin; antidiuresis; pharmacokinetics

Desmopressin is a synthetic analog of the naturally occurring antidiuretic hormone arginine vasopressin (AVP) that is used to treat pituitary diabetes insipidus (DI) (27), monosymptomatic nocturnal enuresis (19), and nocturia (31). Like AVP itself, the antidiuretic effects of desmopressin are mediated by binding to V2 receptors (V2R) on principal cells of renal collecting tubules, thereby stimulating a cascade of biochemical events that increase urine concentration and decreases urine flow by permitting passive reabsorption of solute-free water down the osmotic gradient created by the hypertonicity in the renal medulla (21). A previous study in water-loaded healthy adults has shown that a bolus injection of a large dose of desmopressin produces a rise in urine osmolarity that reaches a maximum ~4 h after plasma desmopressin has begun to fall (7). With this kind of delay (also termed hysteresis from the Greek word meaning “coming late”), an indirect- response pharmacokinetic (PK)/pharmacodynamic (PD) model in which the agonist is assumed to inhibit elimination of the response provides a good fit to the urine osmolality data and has been used previously to characterize the PD response to desmopressin (7, 23). However, these studies did not address the cause of the delay, the effect of dose or the extent of individual differences, all of which are important for the use of desmopressin in physiological and pathophysiological research as well as clinical diagnosis and treatment. The aim of this study is to explore these questions in healthy adults who are water loaded to suppress interference in by endogenous AVP.

MATERIALS AND METHODS

Subjects

Seventy-two healthy, nonsmoking male subjects (18–55 yr of age) were recruited. The data from 12 subjects in the placebo group and from all 11 subjects in the 30-ng-dose group were analyzed but are not included in this analysis because they did not produce PK parameters and had little or no effect on urine osmolality. Two additional subjects (1 of 12 in the 500-ng group and 1 of 11 in the 125-ng group) were excluded from analysis because they developed nausea and vomiting, a potent stimulus for endogenous AVP release (25). Another subject in the 125-ng group was also excluded because of baseline hypotension, an indicator of some intrinsic abnormality in basal AVP secretion. Thus this analysis is based on the analysis of data from 43 male subjects assigned randomly to the 4 highest dose groups (Table 1). Their ages, body weights, and body mass indexes (BMI) in each group were similar both on average and in the range of individual variation (Table 1). The demographics in the placebo and 30-ng-dose group were similar.

Study Designs and Procedures

This was an investigator-blind, placebo-controlled, randomized, parallel group study. The subjects were admitted at the study center at 12 h predosing. The following morning, the subjects were requested to drink a volume of water corresponding to 1.5% of their body weight over a 30-min period. This water-loaded model is generally recognized as suitable for investigating antidiuretic response of V2R agonists. The protocol stipulated that subjects who developed nausea or vomited were excluded and replaced since nausea and vomiting increase endogenous AVP release (25). The overhydration process started 2 h before dosing. The subjects were asked to void every 15 min and instructed to drink equivalent volumes of water to maintain a constant level of slight overhydration. When the urinary output rate exceeded 10 ml/min, which usually occurred 90–120 min after the start of the water load, the subjects received either drug or placebo, administered as a constant-rate intravenous (iv) infusion of placebo or desmopressin over 2 h. Five groups received either 30, 60, 125, 250, or 500 ng of desmopressin. These doses and method of administration were chosen to simulate the pharmacokinetic patterns observed after oral administration, of 10, 20 40, 80, and 160 μg of the oral lyophilisate, the preparation and dose range most commonly used clinically for diagnosis or treatment.
The subjects were monitored for 6–12 h after the start of the infusion depending on the duration of the effect on urine osmolarity. Urine was collected every 15 min, and the volume was replaced with an equal volume of water by mouth. If the urinary output rate had not returned to baseline (12 h after the start of infusion i.e., exceeded 10 ml/min), the subject would be instructed to restrict the fluid intake and reevaluated the following morning.

Blood pressure (systolic and diastolic) and pulse rate were measured with an automatic blood pressure/pulse-measuring device (Boso Oscillomat), with the subject in a supine (during the infusion) or seated sitting position, after 3 min of rest. Preferably, the same arm was to be used throughout the study. Blood pressure and pulse were recorded in the morning of day 1, just before the start of the predosing overhydration, and hourly during the postdosing overhydration process to validate whether there was a fall in arterial blood pressure, indicating endogenous AVP release.

Serum sodium was measured before overhydration (i.e., 0–30 min prehydration), at dosing (0- to 30-min predosing) and every hour until overhydration was stopped, but for a maximum of 12 h from the start of infusion. For safety reasons, the subjects stayed at the clinic overnight. Serum sodium was measured the following morning, and the subjects were discharged, unless serum sodium (or other parameter/sign/symptom) showed a clinically relevant deviation.

The study was approved by the ethics committee, the Declaration of Helsinki was followed, and informed consent was obtained from all healthy volunteers.

Study Restrictions

The subjects were advised to avoid excessive physical activity for 7 days preceding the study and during the study. Products containing caffeine, alcohol, or grapefruit juice had to be avoided from 2 days before admission and during the study days. Three meals were served during the study day. The content of sodium was equal and standardized for all subjects.

Subjects should not have used prescribed medication or over-the-counter medication within 2 wk or five half-lives of the drug, whichever was longer, before the dosing day. No NSAIDs were allowed within 14 days before dosing. Concomitant medication was not allowed during the study days, except for paracetamol.

Study Drug

Desmopressin was obtained commercially in 1-ml single-use ampoules containing 4 μg/ml. Sterile, physiological saline (0.9% NaCl), USP for injection was used for dilution to a volume of 50 ml.

PK Blood Sampling and Laboratory Methods

Blood sampling for PK determination was performed at predose (i.e., 0–30 min predosing), and 15, 30, 45, and 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after dosing. A volume of 14 (2 × 7) ml was drawn at each time point.

Estimating Osmolality of Missed Urine Collections

The values of missed urine collections were imputed by a monotone linear function using the measured values of the collections obtained immediately before (N1) and after (N2) the missed sample collections. The calculations are based on the following assumptions.

1) Collection N1 was obtained by complete emptying of the bladder.
2) Subsequent collections were missed due to subject’s inability to void (not to loss of the collection).
3) The osmolality of each missed collection period changed by a constant amount (x) over the value of the preceding period. It increased when N2 was greater than N1 and decreased when N2 was less than N1.

### Table 1. Demographics, pharmacokinetic, pharmacodynamic, and serum sodium values of intravenous desmopressin in water-loaded adults

<table>
<thead>
<tr>
<th>Variable</th>
<th>60 ng (n = 11)</th>
<th>125 ng (n = 9)</th>
<th>250 ng (n = 12)</th>
<th>500 ng (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>41.0 ± 28.0</td>
<td>40.7 ± 27.0</td>
<td>36.1 ± 24.0</td>
<td>35.9 ± 27.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.6 ± 58.8</td>
<td>81.6 ± 68.1</td>
<td>84.2 ± 70.0</td>
<td>75.8 ± 63.9</td>
</tr>
<tr>
<td>BMI</td>
<td>24.9 ± 19.4</td>
<td>24.7 ± 20.2</td>
<td>26.1 ± 21.5</td>
<td>23.5 ± 20.4</td>
</tr>
<tr>
<td>Plasma desmopressin, pg/ml</td>
<td>1.8 ± 1.1</td>
<td>3.2 ± 2.0</td>
<td>4.4 ± 6.0</td>
<td>13.4 ± 8.4</td>
</tr>
<tr>
<td><strong>Time peaks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uosm maximum, min</td>
<td>210 ± 150</td>
<td>67 ± 0</td>
<td>80 ± 15</td>
<td>145 ± 75</td>
</tr>
<tr>
<td>Time peak Uosm to Uosm maximum, min</td>
<td>0 ± 195</td>
<td>140 ± 0</td>
<td>140 ± 30</td>
<td>290 ± 240</td>
</tr>
<tr>
<td><strong>PD/PK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pdes @Uosm, 0.8 pg/ml, min</td>
<td>260 ± 210</td>
<td>370 ± 210</td>
<td>494 ± 375</td>
<td>654 ± 585</td>
</tr>
<tr>
<td>Time from end of infusion to Uosm maximum, min</td>
<td>31 ± 205</td>
<td>102 ± 0</td>
<td>344 ± 139</td>
<td>191 ± 51</td>
</tr>
<tr>
<td><strong>Serum sodium, mmol/l</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prehydration</td>
<td>72 ± 44</td>
<td>74 ± 44</td>
<td>67 ± 38</td>
<td>72 ± 49</td>
</tr>
<tr>
<td>At 120 min, mosmol/kg H2O</td>
<td>353 ± 92</td>
<td>394 ± 125</td>
<td>623 ± 113</td>
<td>696 ± 379</td>
</tr>
<tr>
<td>Maximum, mosmol/kg H2O</td>
<td>384 ± 126</td>
<td>496 ± 125</td>
<td>787 ± 359</td>
<td>887 ± 787</td>
</tr>
<tr>
<td>Uosm maximum – Uosm @120 min</td>
<td>31 ± 0</td>
<td>102 ± 0</td>
<td>344 ± 139</td>
<td>191 ± 51</td>
</tr>
<tr>
<td><strong>Clinical observations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; AUC, area under the curve; PD, pharmacodynamic; PK, pharmacokinetic.
decreased when N2 was less than N1. Thus, when N2 was greater than N1, the first missed collection was assigned an osmolality of N1 + 2x, the second missed collection a value of N1 + 2x, and so on upward for each of the subsequent missed collections as well as for the 15-min period immediately before the time the next collection was obtained (N2). Collection N2 was obtained by complete emptying of the bladder. It included all the urine produced during the periods in which the collections were not made due to an inability to void. The measured osmolality of N2 is therefore the average of all the urine produced during the period of missed collections plus the urine produced during the 15-min period immediately before the collection.

**Indirect-Response Model**

The observed delay between desmopressin concentration and urine osmolality results in time-dependent PK/PD relationship, e.g., the relation in the initial infusion phase is different from that in the terminal phase.

To estimate a unique (time-independent) effect of a certain desmopressin concentration, the steady-state PK/PD relationship was estimated using population PK/PD modeling. An indirect response model was used assuming that the effect of desmopressin was to inhibit the “elimination” of urine osmolality according to a sigmoid $I_{max}$ function. Model fit to mean observed urine osmolality is presented in Fig. 5.

It has previously been shown that urine osmolality vs. desmopressin concentration over time is consistent with an indirect-response model (7, 23)

$$\frac{dR}{dt} = k_{in} - k_{out} \cdot (1 - I(t)) \cdot R, \quad R(0) = k_{in}/k_{out}$$

where $k_{in}$ represents the zero-order constant for production of the response, $k_{out}$ defines the first-order rate constant for elimination of response, $R$ is the response variable representing the urine osmolality, $C$ is the concentration of desmopressin in plasma, $I_{max}$ represents the maximum inhibitory effect attributed to desmopressin, $IC_{50}$ represents the concentration producing 50% of the maximum inhibition, and $n$ is a sigmoidicity factor controlling the steepness of the concentration-response curve. The assumptions for applying the indirect-response model is that the measured change in response is produced by indirect mechanisms of desmopressin action in vivo as desmopressin mediates its antidiuretic response by activation of V2Rs, and subsequent increase in water permeability in the kidneys by incorporation of aquaporins in the tubuli cells. Maximal achievable urine osmolality, $O_{max}$, was not estimable for all dose levels and was therefore assumed identical for all subjects. This was implemented using the restriction $I_{max} = 1 - k_{in}/k_{out}O_{max}$.

**PK/PD modeling** was carried out using nonlinear mixed-effects modeling software NONMEM version 7.1. A two-compartment PK model with random subject effects on primary PK parameters (clearance, intercompartmental clearance, central and peripheral volume of distribution) was used to describe the population mean and individual time-concentration profiles of desmopressin plasma concentration. Subsequently, an indirect-response model with desmopressin inhibiting osmolality decrease according to a sigmoid $E_{max}$ function and random subject effects on all primary PD parameters ($K_{on}, K_{off}, E_{max}, EC_{50},$ and sigmoidicity $\theta$) was used to describe the time-concentration-urine osmolality profile using the individual (post hoc) PK parameter estimates as fixed input to the PD model. An additive-error model was used for the PD, and a combined additive/multiplicative-error model was used for the PK model. For both PK and PD, a first-order conditional estimation algorithm was used (with interaction for the PK model).

**RESULTS**

**Plasma Desmopressin**

Plasma desmopressin rose to detectable levels in all subjects during the 2-h infusions of 60, 125, 250, and 500 ng of the peptide (Fig. 1). The extent and therefore the rate of rise were proportional to the dose (Table 1). The maximum level ($C_{max}$) occurred at or within 15 min of the end of the infusion in all subjects. Within each group, however, the individual $C_{max}$ values varied over a two- to threefold range. These variations did not correlate with the age or body weight of the subjects. When the infusions ended at 2 h, plasma desmopressin began to fall in all subjects in every dose group (Fig. 1). The time from $C_{max}$ to half-$C_{max}$ ($t_{1/2}$) averaged between 80 and 120 min in all groups with no discernible dose effect. Within each group, the individual $t_{1/2}$ varied over a twofold range, and these variations did not correlate with age, weight, or $C_{max}$. The total washout time, here defined as the time from the start of the infusion to the time that plasma desmopressin fell below the limit of detection (0.8 pg/ml) differed with the dose, ranging from an average of 4 h for the 60-ng group to 11 h for the 500-ng group (Fig. 1, Table 1). It also varied two- to threefold within each group, and the individual variations did not correlate with the subjects’ age or weight. However, they did correlate weakly with $t_{1/2}$ ($P < 0.05$) in the 60-, 125-, and 250-ng-dose groups. Similarly, the average AUC in each group correlated directly and proportionately with the dose, but individual values within each group differed by two- to threefold (Table 1). The individual differences in AUC did not correlate with individual differences in age, body weight, or BMI in any dose group except the 60-ng group, where the AUC correlated weakly and negatively with age ($P < 0.05$).

**Urine Osmolality**

After water loading of subjects, basal urine osmolality averaged ~70 mosmol/kgH2O in all groups and was <150 mosmol/kgH2O in every subject (Fig. 1). During the infusion of desmopressin, it rose in each subject. The average in each group by the end of the infusion differed with the dose, ranging

**Statistical Analysis**

The mean and range of individual plasma desmopressin and urine osmolality values at each collection period were determined and presented for each dose group up to the time that measurements were made in all subjects. The area under the curve (AUC) for each variable was determined for each subject by adding the values from time 0 until the end of the measurements in that subject. Correlations between variables were evaluated by standard least square regression analysis.

Other statistical analyses were based on population PK/PD modeling (see details below) as well as descriptive nonparametric analysis.

**Demographics**

Demographics included age, weight, and BMI. Mean plasma desmopressin (pg/ml) during and after iv infusions of 60, 125, 250, and 500 ng was plotted, as well as temporal changes in urine osmolality (mosmol/kgH2O) during and after the desmopressin iv infusions at same dose levels. For all dose levels, a two-compartment PK model was used to estimate clearance, total volume of distribution, and terminal half-life. The PK parameters were subsequently fixed and used as input to the indirect response PD model for urine osmolality.

The mean and range of serum sodium values were reported for prehydration, posthydration, at intervals during and after infusion.
from 350 mosmol/kgH2O in the 60-ng group to 700 mosmol/kgH2O in the 500-ng group (Table 1). Individual variation, however, was enormous within each group not only in the level achieved (Fig. 1, Table 1) but also in the time course profile of the rise (Fig. 2). In some subjects, particularly those receiving the two lowest doses, the rise was erratic, with intermittent peaks and valleys (Fig. 2). In some subjects in the 60-, 125-, and 250-ng-dose groups, urine osmolality did not even reach 200 mosmol/kgH2O by the end of the 120-min infusion whereas in others it rose as high as 600–1,000 mosmol/kgH2O at the same time point. These variations did not correlate with the subjects’ weight, age, baseline urine osmolality, and baseline serum sodium or plasma desmopressin at the end of the infusion.

After the infusions ended, urine osmolality continued to rise in most subjects of the 125-, 250-, and 500-ng-dose groups even though plasma desmopressin had begun to fall (Fig. 1). The magnitude of the postinfusion rise differed with the dose, averaging 31, 102, 139, and 191 mosmol/kgH2O in the 60-, 125-, 250-, and 500-ng-dose groups, respectively (Table 1). Expressed as a percentage of urine osmolality at the end of the infusion, these increments averaged 9, 26, 22, and 27% in the 60-, 125-, 250-, and 500-ng-dose groups, respectively. However, individual variation within each group was relatively large, especially among the subjects receiving the two lower doses. These variations did not relate to any other variables except the levels of osmolality at the end of the infusion in the 500-ng-dose group, and that relationship was strongly negative ($r = -0.90534$, $P < 0.001$). Thus the higher the rise during the infusion the smaller the rise in the postinfusion period, indicating that the maximum antidiuretic effect or “ceiling” was reached in most of the subjects in the 500-ng group. The duration of the postinfusion rise, calculated as the average of time elapsed from the end of the infusion to the maximum urine osmolality in each subject, also appeared to increase with the dose, ranging from 21 min in the 60-ng-dose group to 145 min in the 500-ng-dose group (Table 1). Again, however, the individual variations within each dose group were

Fig. 1. Changes in plasma desmopressin and urine osmolality during infusions of different amounts of desmopressin in healthy water-loaded adult men. Mean and range of individual values are shown respectively by heavy dark line between lighter lines above and below. A–D: plasma desmopressin (pg/ml) at 60, 125, 250, and 500 ng. E–H: urine osmolality (mosmol/kgH2O) at 60, 125, 250, and 500 ng.
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relatively large (Table 1) and unrelated to the age, body weight, basal urine osmolality, or basal serum sodium of the subjects.

After peaking, urine osmolality declined to \( \approx 200 \) mosmol/kg\( \text{H}_2\text{O} \) in all subjects in whom monitoring was continued for the full 12 h (Fig. 1). As would be expected, the time it took for urine osmolality to decrease from its peak to \( \approx 200 \) mosmol/kg\( \text{H}_2\text{O} \) also increased with the dose, ranging from an average of 66 min in the 60-ng group to 290 min in the 500-ng group (Table 1). Thus the total duration of action from the start of the infusion was also dose dependent, ranging from an average of 186 min in the 60-ng group to 410 min in the 500-ng group. Like the other pharmacodynamic properties, individual variation within each dose group was very large and these differences did not relate to the subject’s age, weight, or BMI except in the 250-ng group where they correlated weakly and negatively with weight (\( r = -0.691653, n = 11, P < 0.05 \)) and BMI (\( r = -0.6729 \)). At the end of the fall, the individual variations in plasma desmopressin did not correlate significantly with the time it took to reach this endpoint in three of the groups, but all of the relationships were negative (\( r = -0.74, -0.76, \) and \( -0.77 \) in the 60-, 250-, and 500-ng-dose groups, respectively). In other words, the longer it took for the effect of desmopressin to cease, the further plasma desmopressin had fallen. Also of particular note, although the average duration of action of desmopressin increased with the dose, individual variations were very large and they did not correlate with individual differences in the C\( _{\text{max}} \), \( t_{1/2} \), or washout time for plasma desmopressin in any of the four dose groups.

Relationship of Urine Osmolality to Plasma Desmopressin

As would be expected from the time course data (Fig. 1), the relationship between the average urine osmolality and the concurrent plasma desmopressin differed over the course of the study (Fig. 3). During the infusion, when plasma desmopressin was rising, urine osmolality also rose but the relationship between the two variables differed markedly depending on the dose. As the dose and therefore the rate of rise of plasma desmopressin increased, the relationship to urine osmolality was shifted to the right, indicating a lesser effect at any given level of the agonist. During the second phase, after the infusion ceased, the relationship in the 125-, 250-, and 500-ng-dose groups reversed direction as mean urine osmolality continued to rise while plasma desmopressin decreased (Fig. 3). The slopes of the relationship in this phase were similar in the three groups, but the positions again differed depending on the dose. A distinct second phase was not observed in the 60-ng-dose group. In the third phase, mean urine osmolality began to fall steeply in conjunction with further decreases in plasma desmopressin until both variables returned to near basal levels. At this time, the relationships between the two variables were more similar in the four groups, but they again appeared to be shifted slightly to the right at the higher doses (Fig. 3).

This shift to the right was also evident in the average level of plasma desmopressin found at both the beginning and end of the period in which urine osmolality fell from maximum to \( <200 \) mosmol/l (Table 1). At both time points, individual variations in plasma desmopressin were extremely large in all four groups, and they did not correlate with the concurrent level of urine osmolality except in the 500-ng-dose group at the beginning of the fall (\( r = 0.6729 \)). At the end of the fall, the individual variations in plasma desmopressin did correlate significantly with the time it took to reach this endpoint in three of the groups, but all of the relationships were negative (\( r = -0.74, -0.76, \) and \( -0.77 \) in the 60-, 250-, and 500-ng-dose groups, respectively). In other words, the longer it took for the effect of desmopressin to cease, the farther plasma desmopressin had fallen. Also of particular note, although the average duration of action of desmopressin increased with the dose, individual variations were very large and they did not correlate with individual differences in the C\( _{\text{max}} \), \( t_{1/2} \), or washout time for plasma desmopressin in any of the four dose groups.

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**Fig. 2. Individual urine osmolality (mosmol/kg\( \text{H}_2\text{O} \)) profiles in 4 subjects infused with different doses of desmopressin by dose.**

**Fig. 3. Antihysteresis plot of median desmopressin concentration (pg/ml) vs. urine osmolality (mosmol/kg\( \text{H}_2\text{O} \)) by dose.**
groups. The AUC for urine osmolality was closely related to the AUC for plasma desmopressin ($r = 0.83, p < 0.001$) when the individual values from all four dose groups were combined (Fig. 4). However, there was also considerable scatter around the line, and a breakdown by dose shows no significant correlation between the two values except in the 500-ng group ($r = 0.7511, p < 0.05$).

**Serum Sodium**

Two hours after the water load when urinary dilution had occurred, serum sodium averaged 137 mmol/l in all four groups (Table 1). The individual values ranged from 133 to 140 mmol/l except for one subject in the 125-ng-dose group, who had a basal level of 127 mmol/l (Table 1). This subject was excluded from the analysis because hyponatremia before desmopressin infusion suggested some intrinsic abnormality in antidiuretic function. After the infusions began and urinary concentration occurred, the average serum sodium declined gradually in all groups and the individual values remained at or below the preinfusion level in every subject, confirming continued suppression of endogenous vasopressin. There was no correlation between mean serum sodium during the study and the AUC for plasma desmopressin or urine osmolality in any dose group.

**Blood Pressure and Pulse Rate**

No abnormal findings of clinical relevance were observed for vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) during the study, and no vital signs findings were classified by investigator as adverse events.

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**PK/PD Modeling of Desmopressin and its Effect on Urine Osmolality**

**PK modeling results.** The PK of desmopressin after intravenous infusion of 60, 125, 250, and 500 ng was described for all dose levels by a two-compartment model with estimated median (10th-90th percentile) clearance: 8.9 (5.9–11.2) l/h, total volume of distribution: 12.9 (6.2–22.7) liters, and terminal half-life: 3.8 (2.8–5.7) h. Observed C$_{max}$ (maximal concentration) and AUC$_t$ (area under the concentration time curve from 0 to last observation) were approximately dose proportional with (log-log) regression slope (log-dose as covariate) equal to 0.85 (SE = 0.04) and 1.25 (SE = 0.09) for C$_{max}$ and AUC$_t$, respectively.

**Model fit.** The model fit to mean PK curves and to mean observed urine osmolality is shown in Fig. 5, both indicating a reasonable agreement between the model and observed data, which also is the case for individual curves.

**Urine osmolality modeling results.** The estimated (steady state) relationship between desmopressin concentration and urine osmolality is shown in Fig. 6, with maximal inhibition and IC$_{50}$ estimated at 0.93 (0.90–0.96) and 1.14 (0.46–2.28), respectively. Maximal achievable urine osmolality (O$_{max}$) was estimated at 947, 423 (105–970), and 117 (45–401) mosmol/kgH$_2$O for steady-state plasma desmopressin levels of 4, 2, and 1 pg/ml, respectively (Table 2).

**Delay between PK and PD.** Delay between PK and PD is illustrated in Fig. 7 and Table 2 using simulation from the indirect-response model assuming a constant (4, 2, and 1 ng/ml) desmopressin concentration. The median (10th-90th percentile) delay is estimated as time to 95% of maximum.

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![Fig. 4. Relationship of area under the curve (AUC) urine osmolality (mosmol/kgH$_2$O) to AUC for plasma desmopressin (pg/ml) in individual subjects infused with different doses of desmopressin.](http://ajprenal.physiology.org/Downloaded from)
CHAPTER 3. STUDY I. TEMPORAL DELAYS AND INDIVIDUAL VARIATION IN ANTIDIURETIC RESPONSE TO DESMOPRESSIN

The time delay in achieving the full effect cannot be determined directly from the observed results because plasma desmopressin rose and fell continuously during the study. Using simulation from the indirect-response model (Fig. 7), the equilibration delay between steady-state plasma desmopressin concentrations of 4 pg/ml and a maximum urinary osmolality of 900 mosmol/kgH2O is estimated to average 4.0 h but with considerable individual variation (1.8–8.1 h). This result agrees well with a previous study in which a moderately high dose of desmopressin was administered to healthy volunteers.

The time dependency of the full antidiuretic effect is also evident during the infusion when the relationships between mean urine osmolality and the concurrent plasma desmopressin are compared (Fig. 3). The progressive shift to the right in the relationship as the rate of infusion increased indicates that the magnitude of the effect of a given level of plasma desmopressin is not only on the level of plasma desmopressin produced but also on how fast that level is reached: the slower the rise in plasma desmopressin, the greater the effect at any given level. The length of the delay in achieving the full effect cannot be determined directly from the observed results because plasma desmopressin rose and fell continuously during the study. Using simulation from the indirect-response model (Fig. 7), the equilibration delay between steady-state plasma desmopressin concentrations of 4 pg/ml and a maximum urinary osmolality of 900 mosmol/kgH2O is estimated to average 4.0 h but with considerable individual variation (1.8–8.1 h). This result agrees well with a previous study in which a moderately high dose of desmopressin was administered to healthy volunteers.

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sin (396 ng) was given by bolus injection to water-loaded, healthy subjects (7) and is close to the average time elapsed from the start of the infusion to peak effect (265 min) in the group infused with 500 ng of desmopressin (Fig. 1, Table 1). Our data and the indirect simulation model also indicate that not only the magnitude of the maximum antidiuretic effect but also the time delay in reaching it decrease with the dose (Tables 1 and 2).

The reason(s) for the delay in producing the maximum rise in urine osmolality is not clear. It could be due in part to the time required for newly formed urine to traverse the renal pelvis and ureters into the bladder. However, this is unlikely to be a major contributor because the volume of these spaces is relatively small and more potential than actual (9). Another possibility is that the concentration of desmopressin at renal V2R differs from that in plasma due to the existence of some barrier that retards its diffusion into and out of its site of action. However, such a barrier has not been described, and its existence seems very unlikely given how quickly the response begins. The more likely explanation for the significant temporal delay in producing the full response is the time required to fully activate and then deactivate the various cellular mechanisms that mediate, enhance, or diminish the antidiuretic effect of V2R stimulation.

The antidiuretic effects of V2 agonists are mediated by promoting the readsorption of water from modified glomerular filtrate when it reaches the collecting ducts of the kidney (20, 22). This readsorption is achieved via binding of the agonist to V2R on the serosal surface of principal cells followed by activation of adenylyl cyclase, increasing the production of cAMP. The latter, in turn, stimulates phosphokinase A which phosphorylates aquaporin-2 (AQP2) water channels, increasing their association into tetramers and insertion through the luminal surface of the principal cells. This, in turn, permits water to back diffuse through the cells down the osmotic gradient created by the hypertonic milieu of the renal medulla (22). Studies in animals indicate that the increase in AQP2 in the membranes occurs rapidly, anywhere from 5 to 15 min after administration of AVP or desmopressin (18); this is attributed to acute trafficking of a preformed pool of AQP2 to the membrane, or phosphorylation of a pool of AQP2 already present in the basolateral membrane. If these kinetics are representative of the rate of trafficking of AQP2 in healthy humans, they do not explain the relatively long delay in achieving the full antidiuretic effect in the present study.

However, stimulation of V2R also sets in train a number of other cellular events in cortical and medullary collecting tubules that probably take longer and serve to enhance the magnitude and/or duration of the antidiuretic effect (2, 3, 6, 12, 24, 28, 29). They include increased synthesis as well as decreased endocytosis and degradation of AQP2 as well as increased tubular readsorption of urea and sodium (2, 11).

Table 2. Time delay to maximum antidiuretic effect obtained by simulation with indirect-response model for different steady-state levels of plasma desmopressin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Modeled Steady-State Levels of Plasma Desmopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 pg/ml</td>
</tr>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Time delay between PK and PD using simulation from the indirect-response model, h</td>
<td>0.5</td>
</tr>
<tr>
<td>Maximum antidiuretic effect, mosmol/kgH2O</td>
<td>117</td>
</tr>
</tbody>
</table>

Results are shown as median and 10th–90th percentile (80% prediction interval).
which could further increase water reabsorption by reducing the urinary solute load and increasing the hypertonicity in the renal medulla. The hypertonicity, in turn, may also feed back positively to further enhance the expression of V2R and AQP2 (14), thereby increasing even more the effectiveness of the system. In addition to phosphokinase A, V2 agonists also increase the phosphorylation of many other proteins whose role if any in antidiuresis is not yet known (13). The kinetics of these effects and their contribution, if any, to the observed delay in full activation and deactivation of the antidiuretic effect of desmopressin are unknown. However, it is conceivable if not likely that each of them is dose dependent and/or come to maximum fruition at different rates in different people. This could account not only for the delay in achieving the full effect but also the surprisingly large individual variation in the rate and/or magnitude of the response and the fluctuations in urine osmolality observed over time in some subjects given small to intermediate doses (125 ng) of desmopressin (Fig. 2).

Cellular mechanisms for deactivating or constraining the antidiuretic response to V2 agonists may also play a role in determining the duration and magnitude of the extended rise in urine osmolality. The contribution of these mechanisms to our findings cannot be determined because plasma desmopressin was continuously changing, and a method for modeling the delay in reaching steady-state effects when desmopressin falls to zero is not available. However, the V2R is subject to homologous desensitization, probably by internalization, and this desensitization may begin within 1–2 h of exposure (5). If this desensitization is dose dependent, it might contribute to the dose-related shift to the right in the relationship of urine osmolality to plasma desmopressin during the third phase of the study (Fig. 3, Table 1). The antidiuretic effect of V2 agonists may also be constrained by one or more post-receptor intracellular mechanisms. In any case, the kinetics of these desensitization or modulating processes, including the removal of AQP2 from the membrane, may be as important as PK in determining the duration of action of desmopressin and other V2R agonists.

Another issue raised by this study is whether the use of water loading to suppress endogenous vasopressin caused or increased the delay in producing the full response to desmopressin. It is known that a chronic deficiency of vasopressin due to pituitary DI or primary polydipsia diminishes the acute antidiuretic response to vasopressin (10, 32). However, a previous study showed that acute water loading to suppress endogenous vasopressin did not alter the PK or PD of a bolus injection of desmopressin (7). We also found that individual variations observed in this study did not correlate with differences in serum sodium before or after the water load. We conclude, therefore, that our findings were not appreciably influenced by the water load. Nevertheless, it would be of interest to repeat these studies in patients with severe pituitary DI, where a reduction in serum sodium by water loading is not needed to eliminate the influence of endogenous vasopressin.

This study also revealed very large individual differences in the antidiuretic response to desmopressin. These individual variations involved all facets of the response and were as evident in the results of the simulated indirect model as in the raw data itself. They could not be explained by differences in collection, corrections for missing values, fluctuations in the response curves, or the time course of the response because they were as large or even larger when the effects were expressed as the AUC for urine osmolality (Table 1). The differences seemed to be greatest among subjects receiving the intermediate or lower doses (Figs. 1 and 2, Table 1), suggesting that they may be reduced or eliminated by higher doses of desmopressin. Indeed, in the subjects given 500 ng, the individual differences in AUC for urine osmolality correlated significantly and positively with the AUC for plasma desmopressin, suggesting that exposure was the primary if not the only determinant of the variable effect in that group. However, this correlation was not observed in the other three groups, indicating that some factor(s) other than exposure to desmopressin is of greater consequence when V2R stimulation is submaximal. The variations are unlikely to be due to release of endogenous vasopressin since serum sodium remained low throughout the study, blood pressure and pulse remained stable, and other known nonosmotic stimuli for vasopressin release, such as nausea, were not observed. They did not relate to age, body weight, BMI, or the average level of plasma sodium in the subjects. Large individual differences
also were observed in another similarly designed study in patients with pituitary DI (15), indicating again that water loading and/or release of vasopressin was not responsible. Therefore, we postulate that the individual differences in the antidiuretic response to low or intermediate doses of desmopressin are due largely to genetically determined differences in the kinetics of one or more of the many cellular mechanisms that mediate the antidiuretic response to desmopressin. Although relatively small, the individual differences in PK in the present study were also surprising and difficult to explain because desmopressin was administered intravenously. These differences are not only the maximum concentration at the end of the infusion but also the AUC. Neither variable correlated with individual differences in age or body weight and, therefore, seem unlikely to be due to differences in the volume of distribution. Other possibilities include differences in desmopressin metabolism and elimination, binding to plasma proteins, and even absorption of desmopressin onto the plastic syringes utilized in the iv administration. A recent analysis of two desmopressin trials in healthy volunteers (16) demonstrated no significant age- or gender-specific differences in the PK properties of desmopressin. However, in addition to dose proportionality, they also showed an inverse proportionality to weight that was significant for $C_{\text{max}}$ and borderline significant for AUC. The reason for the discrepancy with the present study is unknown.

The findings of this study have several implications for clinical and basic investigations of antidiuretic function. One applies to the traditional use of desmopressin or vasopressin challenge tests for the differential diagnosis of DI. The previously noted difficulty in finding a level of response that reliably differentiates primary polydipsia from partial pituitary or partial nephrogenic DI (26) is now explicable by the large individual variation in the timing and magnitude of the antidiuretic response to desmopressin even when it is given by injection to healthy subjects. Fortunately, these problems in differential diagnosis can now be solved by newer more direct methods that use vasopressin assays and brain MRI or closely monitored 2-day trials of desmopressin to differentiate between the various types of DI (1). Another implication of the present study is that the PK of desmopressin do not always provide an accurate guide to the magnitude or duration of its antidiuretic effects. This may be particularly relevant to efforts to elucidate the cause of the hyponatremia that develops in a few children or elderly patients treated with desmopressin for control of enuresis or nocturia (30). In this regard, it will be of value to determine whether the large individual variations in the effect of desmopressin on urine concentration are due to differences in age, genetic, or environmental factors. The challenges for basic research will be to better define the kinetics of the various biochemical reactions that mediate, modulate, or turn off antidiuretic responses to desmopressin and to identify the genes that code for the critical components of the rate-limiting steps. In this regard, it will be important to be mindful of the influence of genetic differences, within as well as between species.

Conclusions

In summary, this study describes some important and little recognized characteristics of the antidiuretic action of desmopressin (and probably AVP itself). These characteristics might be summarized as a considerable lag or delay in exerting its full effect and large individual differences in response that cannot be explained fully by differences in PK. It may also have autocatalytic or self-enhancing effects that manifest as an apparent changing of renal “sensitivity” to the hormone. The delay is probably due to the different times required to fully activate all the various biochemical mechanisms that must contribute to achieve the maximum antidiuretic effect. The cause(s) of the relatively large individual differences in the magnitude or timing of the response is more difficult to identify but may involve preexisting environmental or genetic differences in basal plasma vasopressin or any of the cascade of cellular mechanisms that mediate its effects.

GRANTS

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DISCLOSURES

K. V. Juul and L. Erichsen are employees of Ferring.

AUTHOR CONTRIBUTIONS


REFERENCES

CHAPTER 3. STUDY I. TEMORAL DELAYS AND INDIVIDUAL VARIATION IN ANTIDIURETIC RESPONSE TO DESMOPRESSIN


F278 DESMOPRESSIN HYSTERESIS IN HEALTHY VOLUNTEERS

CHAPTER 4

Study II. Desmopressin duration of antidiuretic action in patients with central diabetes insipidus
Desmopressin duration of antidiuretic action in patients with central diabetes insipidus

Kristian Vinter Juul · Daniel G. Bichet · Jens Peter Nørgaard

Abstract The key question answered by this study is whether it is possible to deliver a pharmacokinetic and pharmacodynamic duration of antidiuretic action long enough to ensure adequate antidiuresis with two daily administrations of desmopressin in patients with central diabetes insipidus (CDI). We studied the efficacy and safety of desmopressin i.v. in 13 CDI patients using two 3-way crossover designs, in the doses 30, 60, 125 ng, and 125, 250 and 500 ng. Duration of action, minimum output rate, max osmolality and average osmolality during action (AUC osmolality) were measured every 30 min for the first 2 h during the infusion, and then every hour or every second hour until the urine output rate was greater than 2 ml/kg/30 min. The duration of antidiuretic action was 4, 8 and 11 h, respectively, for 125, 250, and 500 ng, increasing from 250 to 500 ng but for the remaining secondary dynamic efficacy parameters no difference could be detected based on descriptive statistics between the doses 250 and 500 ng, indicating that the upper plateau region of the dose–response curve had been reached. All treatment emergent adverse events were classified as unrelated or unlikely related to trial medication. No serious adverse events occurred. Data on duration of action indicates that it is possible to achieve antidiuretic control with 500 ng i.v. corresponding to 160 l orodispersible tablets twice daily in CDI patients. Today, the Minirin Melt label recommends the majority of CDI patients a dose of 60 to 120 µg t.i.d.

Keywords Desmopressin · Central diabetes insipidus · Antidiuresis · Duration of action

Introduction

Diabetes insipidus (DI) is a clinical syndrome characterised by the excretion of copious volumes of dilute urine combined with persistent intake of abnormally large quantities of fluid, usually with excessive thirst. There are three general forms of the disease: (1) Central, cranial, neurogenic or pituitary (vasopressin deficient) DI, (2) nephrogenic (vasopressin resistant) DI and (3) primary polydipsia in which vasopressin secretion is also suppressed due to excessive intake of fluids [1].

Central diabetes insipidus (CDI) is treated by desmopressin, the synthetic analogue of vasopressin, which reduces urine production and increases its osmolarity, administered sublingually or by oral tablets, by nasal inhalation, or very rarely by intramuscular, or subcutaneous injection [Company Core Data Sheet (MINIRIN Melt CCDS ver.02) issued 29 Sep 2010]. According to current label, dosage is individual in diabetes insipidus, but the total daily sublingual dose is normally in the range of 120 to 720 µg. A suitable starting dose in adults and children is 60 µg three times daily, administered sublingually. This
The pharmacodynamic and -kinetic evidence on desmopressin antidiuretic duration of action in the early CDI studies that followed the introduction of desmopressin in the 1970s [2, 4–9] was based initially on nasal and later on oral formulations that both are subject to large intra-patient variations in pharmacokinetics due to different absorption issues [9, 10]. Thus, a key question in this exploratory study was whether it is possible to deliver a pharmacodynamic and -kinetic duration of antidiuretic action in CDI patients long enough to ensure adequate 24 h coverage of antidiuresis with just 2 daily administrations, using i.v. infusion over 2 h as a pharmacological model for the preferred oral administration. While i.v. administration of desmopressin as used in our study is not appropriate in clinical practice, infusions over 2 h was chosen to mimic oral administration with Cmax achieved after 2 h and thus a Tmax similar to oral administration [4] while minimising the high intra-patient variability associated with absorption in the oral formulations. Furthermore, the dose-response relationship in terms of duration of antidiuretic action was considered independent on method of administration.

**Materials and methods**

**Study design**

The study was designed as an open-label, randomised crossover study with five low doses of desmopressin (free base) administered as a constant rate intravenous infusion over 2 h in 13 patients with pituitary diabetes insipidus. In two separate 3-way crossover parts (first the doses 30, 60, 125 ng and second 125, 250 and 500 ng) (see Table 1) were investigated with the intention to treat each patient with three dosages out of these five doses. Between doses there was a washout period of ~ 22 h.

Our dose selection was supported by population pharmacokinetic/pharmacodynamic (PK/PD) analyses of phase I to phase III studies in healthy subjects and in patients treated with desmopressin and by pharmacokinetic calculations from a similar study in healthy volunteers [Clinical Study Report: A phase I study investigating the antidiuretic effect and pharmacokinetics of five low doses of desmopressin and placebo administered as a constant rate intravenous infusion in over-hydrated healthy non-smoking male volunteers. FE992026 CS011]: The EC50 value of desmopressin for antidiuresis in the healthy volunteers was calculated as 1.7 pg/ml based on urinary osmolality, and in order to simulate the bioavailability of an oral dose, aiming at maximum plasma concentrations in the CDI patients in the clinical relevant range of 0.8–13 pg/ml, we calculated that an intravenous infusion at a constant rate for 2 h in the doses of 30, 60, 125, 250, and 500 ng approximate the oral bioavailability of 10, 20, 40, 80 and 160 µg in the oral lyophilisate, respectively.

At screening a complete medical history and physical examination, including height, weight, vital signs and evaluation of the major organ systems was conducted. Non-postmenopausal female patients also underwent a serum pregnancy test. Biochemistry, haematology and urinalysis (osmolality) was investigated and had to be within normal limits before the patient was included in the study.

Patients were hospitalised and had their usual desmopressin treatment discontinued at least 15 h before the start of the study, which allowed them to develop a maximum water diuresis. After an overnight fast with unrestricted water intake urine volume, creatinine and osmolality was determined during at least a 1 h period of observation. After the 1 h period of observation, provided the urinary output rate exceeded 2 ml/kg/30 min (corresponding a baseline 24 h urine volume of >96 ml/kg body weight), the patient received one of five doses of desmopressin in a randomised fashion. Otherwise, administration of study drug was not performed until urinary output rate exceeded 2 ml/kg/30 min in a subsequent measurement. The drug was administered as a constant rate infusion over 2 h.

### Table 1 Patients randomised allocation to treatment in two 3-way crossover designs, (30, 60, 125 ng, and 125, 250 and 500 ng)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>01T01</td>
<td>10 250 ng 125 ng 500 ng</td>
</tr>
<tr>
<td>01T02</td>
<td>11 125 ng 500 ng 250 ng</td>
</tr>
<tr>
<td>01T03</td>
<td>7 125 ng 250 ng 500 ng</td>
</tr>
<tr>
<td>01T04</td>
<td>1 30 ng 60 ng 125 ng</td>
</tr>
<tr>
<td>01T05</td>
<td>4 60 ng 30 ng 125 ng</td>
</tr>
<tr>
<td>01T06</td>
<td>5 30 ng 125 ng 60 ng</td>
</tr>
<tr>
<td>01T07</td>
<td>3 60 ng 125 ng 30 ng</td>
</tr>
<tr>
<td>01T08</td>
<td>8 500 ng 125 ng 250 ng</td>
</tr>
<tr>
<td>01T09</td>
<td>9 250 ng 500 ng 125 ng</td>
</tr>
<tr>
<td>01T10</td>
<td>6 125 ng 60 ng 30 ng</td>
</tr>
<tr>
<td>01T11</td>
<td>2 125 ng 30 ng 60 ng</td>
</tr>
<tr>
<td>01T12</td>
<td>12 500 ng 250 ng 125 ng</td>
</tr>
<tr>
<td>01T13</td>
<td>6 125 ng 60 ng 30 ng</td>
</tr>
</tbody>
</table>
Throughout the procedure, the patients were allowed to drink water ad libitum at hourly intervals. Serum sodium was monitored every second hour and thirst (measured by a 10 cm visual analogue scale using the extremes “no thirst” at the bottom and “extremely thirsty” at the top of the scale), water intake and weight were monitored at hourly intervals starting pre-dosing at 0700 and until 1 h after the antidiuretic effect of each desmopressin dose had ceased. Additional spontaneous water intake during the hospitalisation was also registered. Vital signs were measured each day pre-dosing during the period of hospitalisation.

The following 2 days, provided urine output rate was again greater than 2 ml/kg/30 min, the patients were given the second and third dose, in a randomised fashion so that each dosage level was tested on six patients, and all measurements repeated as after the first dose. Patients were allowed to resume their normal desmopressin treatment after last dosing, 1 h after the output rate had returned to baseline (defined as a urinary flow greater than 2 ml/kg/30 min).

No post study examination was planned as desmopressin is a well-characterised substance (almost 40 years on the market) and the risk of hyponatraemia was addressed during the study (serum sodium monitored every second hour).

Subjects

To ensure a homogenous CDI population in the study and to avoid inadvertent inclusion of patients with only partial pituitary DI, primary polydipsia or nephrogenic DI, the screening phase of this study was designed to document the patients to have CDI by requesting a basal 24 h urine screening phase of this study was designed to document the<br>presence of uncorrected hypothyroidism, hypoadrenalism or hypogonadism; concurrent treatment with diuretics, chlorpropamide, tricyclic antidepressants, indomethacin, carbamazepine; hyponatraemia (S–Na < 133 mmol/l) by history or on entry; allergy that could be detrimental according to the Investigator’s judgement (including severe reaction to paracetamol); active presence or a history of alcoholism or drug addiction; participation in another drug study or donated blood within the previous 90 days before the study; patients who in the opinion of the investigator, were considered unsuitable for any other reason. Concomitant therapies were avoided, except those considered necessary for the patient’s welfare or which was required to treat adverse events.

A total of 14 DI patients entered the screening and 13 of these were randomised and received a part of the first dose of study medication. The randomisation was done using two 3-way crossover designs. Each patient was divided at random into a given treatment sequence of three dosages out of the five dosages. Twelve patients completed Day 1, eleven patients completed day 2 and ten patients completed the entire study. One patient received only part of the first infusion, and therefore a new patient was included with the same treatment sequence. For demographics of randomised patients, see Table 2. Medical history was obtained from all patients, including time of onset for CDI that varied from 7 to 43 years. Desmopressin treatment was discontinued at Day-1 at least 15 h before the start of the study. If patients were treated with chlorpropamide or carbamazepine, these drugs were discontinued at least 24 h before dosing with desmopressin. Concomitant therapies were avoided, except those considered necessary for the patient’s welfare or which was required to treat adverse events.

The study was approved by the institutional review board at Hôpital du Sacré-Cœur de Montréal from where all patients where recruited, the Declaration of Helsinki was followed, and informed consent obtained from all patients.

Sample size

No formal sample size calculation was performed based on the primary endpoint of this study. However in a two-period crossover study, six patients allows to detect a difference of 1.5–2 h in the duration of anti-diuretic action assuming an SD of difference of one to 1.5 h, a type I error of 5% and a power of 80%.

Study drug

Desmopressin was obtained commercially in 1 ml single use ampoules containing 4 μg/ml. Sterile, physiologic
saline (0.9% NaCl), USP for injection was used for dilution to a volume of 50 ml.

Desmopressin (free base) 30, 60, 125, 250, and 500 ng was administered as a constant rate intravenous infusion over 2 h.

PK blood sampling and laboratory methods

Samples for desmopressin analysis were obtained according to the following scheme:

- Treatment 1: Pre-dose
- Treatment 1–3: I. 15 min and 1, 2, 4, 8 and 1 h post-dosing; II: 30 min and 1.5, 3, 6, 12 and 24 h post-dosing.

Primary and secondary endpoints and statistical methods

The patients’ urine volume, osmolality and creatinine (taken as a measure to indicate whether samples were missing or delayed) was determined every 30 min for the first 2 h during the infusion, every hour thereafter until 24:00 and then every hour or every second hour until the urine output rate was again greater than 2 ml/kg/30 min.

Urine sediment was to be performed only if U-stix was abnormal.

Primary endpoints were duration of anti-diuretic action of all doses tested, urinary osmolality and urinary volume after dose administration. Secondary endpoints encompassed pharmacokinetics (AUC, CL, V and t1/2), changes in serum sodium, weight and thirst, and number and type of adverse events.

The duration of action was based on three different cut off levels of osmolality: 125, 200 and 400 mOsm/kg. Osmolality was also investigated using average osmolality during action (AUC osmolality) calculations and maximum values. The minimum output rate was adjusted for residual urine and was considered as an estimate of the magnitude of anti-diuretic action.

The duration of anti-diuretic action was summarised using descriptive statistics for each cut of level and for each dose level. These descriptive statistics satisfying the primary objective of the trial constituted the primary analysis of this study. The overall duration of anti-diuretic action was estimated for each dose level using the nonparametric Kaplan–Meier method. For each of the remaining pharmacodynamic parameters (minimum output rate, maximum osmolality observed post-dosing and average osmolality during action (AUC osmolality)) descriptive statistics including mean, median, (inter patient) SD, minimum and maximum was applied for each dose level.

Population kinetics analysis

Population PK analysis was performed using non-linear mixed effects modelling approach, using the Visual NONMEM program, version V, the NONMEM program, version V and the Fortran compiler Digital Visual Fortran version 6.5.

The plasma concentration time profiles were analysed using 1, 2 and 3-compartment models.

The influence of subject-specific covariates (sex, age, height and body weight) on the estimated PK parameters was examined. A covariate was not added to the model unless it improved the model at the significance level $P < 0.001$.

Results

Pharmacodynamics of desmopressin

A clear dose–response relationship with respect to all the pharmacodynamic endpoints (duration of action, maximum osmolality, average osmolality and minimum diuresis) was found. Except for the duration of action (Fig. 1), the results of the doses 250 and 500 ng were similar based on

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Demographic data (safety population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised patients</td>
<td>13</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
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<tr>
<td>Female</td>
<td>11</td>
</tr>
<tr>
<td>Male</td>
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</tr>
<tr>
<td>Age(years)</td>
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<tr>
<td>Mean(SD)</td>
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<td>40</td>
</tr>
<tr>
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<td>19–61</td>
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<tr>
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<td>Oriental</td>
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<tr>
<td>Other</td>
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<tr>
<td>Height(cm)</td>
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<tr>
<td>Mean(SD)</td>
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</tr>
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<td>Min-Max</td>
<td>157–185</td>
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<td>Weight(kg)</td>
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<td>Mean (SD)</td>
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<td>Min-Max</td>
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<tr>
<td>Body mass index</td>
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<tr>
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</tbody>
</table>
CHAPTER 4. STUDY II.17 DESMOPRESSIN DURATION OF ANTIDIURETIC ACTION IN PATIENTS WITH CENTRAL DIABETES INSIPIDUS

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Descriptive statistics. Thus, the anti-diuretic effect (Fig. 2) increased and lasted longer with increasing dose, with the one exception that 500 ng dose resulted in a longer anti-diuretic effect but to a similar level as the 250 ng dose. A lower variation was detected for the higher doses indicating more consistent results between patients. For the lowest 30 ng dose, no duration of actions could be calculated for either of the cut off levels due to limited response for most of the patients.

With 125 mOsm/kg as cut off level, several observations were censored because the osmolality did not reach below 125 mOsm/kg before data collection was stopped (Fig. 3). Using the Kaplan–Meier plot, we estimated for the higher dose levels 125, 250, and 500 ng the following clinical relevant duration of actions 3 h 53 min, 8 h 20 min, and 11 h respectively.

Pharmacokinetics of desmopressin

A one compartment model with first-order elimination was determined as the most optimal model for the description of the plasma concentration time profile in accordance with other desmopressin PK-studies [10].

The geometric mean value for AUC was 4.2 (CV = 26%), 8.4 (CV = 26%), 18.5 (CV = 21%), 40.2 (CV = 147%) and 77.4 (CV = 12%) h 9 pg/ml; the geometric mean CL was 7.2 (CV = 26%), 7.2 (CV = 26%), 6.8 (CV = 21%), 6.2 (CV = 14%) and 6.5 (CV = 12%) pg/ml; the harmonic mean value for t½ was 1.8, 1.8, 2.0, 2.2 and 2.2 h after administration of 30, 60, 125, 250 and 500 ng desmopressin, respectively, infused intravenously over 2 h.

AUC increased with increasing doses of desmopressin (Fig. 4).

Safety

Nine patients experienced a total of ten treatment emergent adverse events, including injection site haemorrhage, injection site reaction, headache and nausea. All treatment
emergent adverse events were classified as unrelated or unlikely related to trial medication. No serious adverse events occurred. All treatment emergent adverse events were mild to moderate in intensity. No relationship between dose and the intensity of the adverse events was detected.

Serum sodium and thirst
In general the serum sodium values decreased after start of dose administration. However, as the first measurement was after 2 h, the exact time for onset of decrease in sodium was not captured. In most cases, the post dose measurements remained below the baseline value. A higher and later maximum reduction in serum sodium from baseline was observed for higher doses with an average decrease of about 10 mmol/l in the two highest dose levels. Similarly, the average serum sodium reduction during action (AUC serum sodium) was seen to increase with higher dosages, except for the two highest dose levels where a similar mean reduction of 7.2 mmol/l was observed. However, as all abnormal serum sodium values were rated “not clinically significant” these two findings do not lead to any safety concerns.

Only two patients had serum sodium values outside normal range. One patient had two incidences of serum sodium values above normal range, one on 125 ng (151 mmol/l) and one on 250 ng (154 mmol/l). Another patient had four consecutive values of low serum sodium at dose 500 ng (133–134 mmol/l). All abnormal values were rated “not clinically significant”. A reduction in thirst, quantified using a standard linear-analogue scale, was observed after dose administration. For the two highest doses, a continuous decrease was seen within the first 2 h with a median reduction in thirst of −7.70 cm, ranging from 4.0 to 9.5 cm reduction at the 500 ng dose level, while for the lower doses this was not apparent. No clear doserelationship of these thirst endpoints was found, possible due to the large variations in these VASmeasures.

Discussion
Consistent with previous CDI studies [2, 4–9], the present study confirmed that desmopressin duration of action, minimum output rate, maximum and average osmolality during action are dose related. Duration of action, the primary endpoint, was still increasing from 250 to 500 ng, and it therefore remains an open question exactly in which dose range the upper plateau region of the dose response Scurve is located. However, for the remaining secondary dynamic efficacy parameters no difference could be detected based on descriptive statistics between the doses 250 and 500 ng, indicating that the upper plateau region of the dose–response S curve was reached, and that a clear dose–response relationship in patients is only of importance for doses below 250 ng i.v. In order to reach the goal is to treat the majority of CDI patients twice daily, the study indicates that this is in fact achievable, as duration of action for the 500 ng dose was found to be between 11 and 15 h for the three different cut off points. However, final confirmation of this finding awaits a phase III trial testing oral dosing, e.g., 160 μg orodispersible tablets that approximates the bioavailability of the 500 ng i.v. [Clinical Study Report: Absolute bioavailability of three different doses of desmopressin in an orodispersible tablet in healthy non-smoking male volunteers. FE992026 CS004].

Spearman correlations coefficients revealed a positive correlation between duration of action, max osmolality and average osmolality during action irrespective of the dose given: A high maximum osmolality correlates with a long duration of action; a high average osmolality during action corresponds to a long duration of action; and finally, a high average osmolality during action correspond to a high maximum osmolality. These correlations support the degradation of desmopressin as a 1-compartment model with first-order absorption and first-order elimination [10]. A high maximum osmolality is due to a high maximum concentration in the blood. It will take longer to eliminate a higher concentration of desmopressin, so the duration of action is expected to be longer and the average osmolality during antidiuretic action higher.

A high inter- and intra-individual variation in PK/PD has been seen with the sublingual administration of desmopressin [10, 11], and the intravenous infusion was chosen to minimize these variations. However, this study also showed a wide variation with the i.v. administration in duration of action, max osmolality and average osmolality during action (AUC osmolality). This finding may be related to the body weight of the patient or individual differences in receptor sensitivity. Also, differences in desmopressin metabolism and elimination may be related to the individual differences. Also, the recently reported significant gender difference of the effects of desmopressin on nocturnal urine volume that cannot be explained by pharmacokinetic differences could contributed to the variations [12], however, our sample size was too small to allow for a gender-specific subanalysis. From a theoretically point of view, decreased creatinine clearance could also be related to these individual differences. The spearman correlation’s coefficients between creatinine clearance and duration of action and between max osmolality and creatinine clearance for the dose level of 125 ng did not reveal any apparent relationship, but as patients in this study was younger (mean 39 years) with creatinine
clearance within normal range, this relationship should be tested in elderly patients with decreased creatinine clearance in order to conclude anything on this relationship. Finally, absorption of desmopressin onto the plastic syringes utilised in the administration remains an unfortunate but well-known source to variation.

In order to obtain a better estimate of the pharmacodynamic effect of desmopressin, an AUC of the osmolality measurements based on a fixed time span would have been preferable. As the sampling for patients on low doses were terminated earlier than those on high doses, it was not possible to derive such an endpoint. From a statistical point of view, sampling based on a fix time span would be advisable in future studies. The cut off level of 200 and 400 mOsm/kg chosen for the determination of duration of action appeared to be too high for the low doses since osmolality levels of patients on low doses never reached these cut off levels. On the other hand the cut off level of 125 mOsm/kg lead to several censored observations as the osmolality levels were not followed until they went below 125 mOsm/kg. It was estimated in this study that when diuresis went below 2 ml/kg/30 min osmolality of the urine would be below 125 mOsm/kg. Looking at the graph of adjusted diuresis versus osmolality (Fig. 2), it is seen that a diuresis of 2 ml/kg/30 min corresponds to an osmolality of about 100 to 150 mOsm/kg, i.e. not all patients have reached below 125 mOsm/kg with a diuresis of 2 ml/kg/30 min. If diuresis is used as surrogate determination of end of action in future studies, a cut off level of 3 ml/kg/30 min seems more appropriate. Also the cut off level for duration of action should be reconsidered (above 125 mOsm/kg, but still be below 200 mOsm/kg).

Fluid intake was reduced when the patients were under desmopressin treatment. As the patients had the possibility of drinking what they wanted, this decrease in fluid intake is considered due to a down regulation of thirst, which is logical and in accordance with well-known physiological regulation of fluid intake where increased thirst stimulated by either an increase in effective osmolality or by a decrease in fluid volume promotes fluid intake [13]. Also, maximum weight increase increased with increasing dose—except for the two highest dosages. This could suggest an accumulation of fluid in the body due to a difference in fluid intake and urine output. The registrations were stopped when the patients escaped treatment, so it is not possible to assess for how long the patients’ weight would remain at a higher level and whether the weight would reach same level for the lower doses if the registrations had not been stopped.

Due to the antidiuretic effect of desmopressin, there is a well-known risk of developing hyponatraemia during desmopressin treatment [14]. In this study, the serum sodium was monitored at least every second hour. In general, the serum sodium decreased after start of dose administration, with the higher doses showing the highest decrease. However, only for one patient did the serum sodium drop below normal range. The patient was the oldest patient (61 years). Her baseline serum sodium was 143 mmol/l which decreased to 133 mmol/l (a drop of 9 units within 12 h) during the treatment with 500 ng dose. Her data on 500 ng indicated that her fluid intake was not down regulated as much as the other patients, which by basic physiological principles is the likely cause of the very low serum sodium. For all other patients the data indicate that the patients maintained normal water balance on desmopressin and were not in risk of getting hyponatraemia. The two patients that developed hypernatraemia had slightly decreased fluid intake, but were not reported to have adipsia as medical history or during the trial so no definite explanation for this can be given. However, as all abnormal serum sodium values were rated “not clinically significant” these findings do not lead to any safety concerns.

Recommendations for future studies

It is considered an important goal is to treat DI patients twice daily. This study indicates that this is achievable, as duration of action for the 500 ng i.v. infusion over 2 h, chosen as a pharmacological model to mimic oral administration, was found to be between 11 and 15 h for the three different antidiuretic cut off points. However, these findings need to be confirmed in settings more close to clinical reality and with an oral formulation, preferable, the melt tablet in a dose corresponding to 500 ng i.v., i.e., 160 µg orodispersible tablets b.i.d. Today, the Minirin Melt Summary of Products Characteristics (SmPC) recommends the majority of CDI patients a maintenance dose of 60 to 120 µg Minirin Melt t.i.d [3].

Acknowledgements This work was supported by a grant from Ferring Pharmaceutical.

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CHAPTER 5

Study III. Efficacy and safety of desmopressin orally disintegrating tablet in patients with central diabetes insipidus: results of a multicenter open-label dose-titration study
Efficacy and safety of desmopressin orally disintegrating tablet in patients with central diabetes insipidus: results of a multicenter open-label dose-titration study

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Abstract. Central diabetes insipidus (CDI) is associated with arginine vasopressin (AVP) deficiency with resultant polyuria and polydipsia. Intranasal desmopressin provides physiological replacement but oral formulations are preferred for their ease of administration. This study aimed to demonstrate the efficacy and safety of desmopressin orally disintegrating tablet (ODT) in the treatment of Japanese patients with CDI, and confirm that antidiuresis is maintained on switching from intranasal desmopressin to desmopressin ODT. A total of 20 patients aged 6–75 years with CDI were included in this 4-week multicenter, open-label study. Following observation, patients switched from intranasal desmopressin to desmopressin ODT with titration to optimal dose over ≥5 days at the study site. Following three consecutive doses with stable patient fluid balance, patients were discharged with visits at Weeks 2 and 4. Following titration from intranasal desmopressin to ODT, the mean 24-hour urine volume was unchanged, indicating similar antidiuresis with both formulations. The proportion of patients with endpoint measurements (urine osmolality, 24-hour urine volume, hourly diuresis rate and urine-specific gravity) within normal range at Days 1–2 (intranasal desmopressin) and Week 4 (desmopressin ODT) was similar. The mean daily dose ratio of intranasal desmopressin to desmopressin ODT (Week 4) was 1:24 but a wide range was observed across individuals to maintain adequate antidiuretic effect. Hyponatremia was generally mild and managed by dose titration. Desmopressin ODT achieved sufficient antidiuretic control compared to intranasal therapy and was well tolerated over long-term treatment. The wide range of intranasal:ODT dose ratios underline the importance of individual titration.

Keywords: Diabetes insipidus, Desmopressin

CENTRAL DIABETES INSIPIDUS (CDI) is a chronic, heterogeneous condition characterised by polyuria and polydipsia due to a deficiency of arginine vasopressin (AVP) secretion [1]. The most frequent aetiology is the destruction or degeneration of the neurons that originate in the supraoptic and paraventricular nuclei of the hypothalamus [1]. Mutations in the gene that encodes AVP have also been shown to be responsible for CDI [1, 2]. However, 30–50% of cases are considered idiopathic [3]. Desmopressin is a synthetic analogue of AVP used in the treatment of CDI as a physiological replacement to maintain water balance and normal urine output. In Japan, intranasal desmopressin is currently used for the treatment of CDI. However, intranasal administration can be inconvenient or embarrassing, especially in public, and also involves uncertainty over dose level. The bioavailability of the intranasal desmopressin can be unpredictable in the presence of a blocked nose with rhinorrhea (absorption decreased) or nasal hyperaemia (absorption increased) [4, 5]. Paediatric use of this route of administration is prone to greater variability in dosing; patients and parents are more likely to be unsure of adequate dosing and try to compensate, or achieve a better response, by administering more with the intranasal formulation [4]. Desmopressin is available in oral formulations, and an orally disintegrating tablet (ODT) that avoids ingestion of extra fluids overcomes issues related to swallowing difficulty and has improved bioavailability compared with the standard tablet [6]. The pharmacokinetics, efficacy and safety of desmopressin solid tablets have been

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reported from a 5-year study in nine Japanese patients with CDI (17–36 years of age) [7]. Mean urine output and urine osmolality, following a single dose of 0.1 mg desmopressin solid tablet, showed the antidiuretic effects of oral desmopressin in this patient population. There was no change in serum sodium levels and no serious safety concerns were identified. In the subsequent 5-year continued administration, well-controlled urine output was observed in eight of the nine patients tested at daily maintenance doses of 0.2 mg to 0.6 mg, and no adverse drug reactions (ADRs) were reported. Though clinical data in Japanese patients are very limited, the dosage and administration of oral desmopressin used in the clinical study conducted by Fukuda et al. [7] were equivalent to those used in overseas studies [8, 9].

Due to their ease of administration, oral formulations are the preferred treatment route for most patients with CDI [10, 11]. Therefore, it was considered clinically important to develop desmopressin ODT as an alternative to intranasal desmopressin.

The overall purpose of the current study (ClinicalTrials.gov NCT01280188) was to demonstrate the efficacy and safety of desmopressin ODT in the treatment of Japanese patients with CDI. The secondary objective was to confirm that patients are controlled to an equivalent degree according to pharmacodynamic parameters when changing from intranasal desmopressin to desmopressin ODT. Every CDI patient requires individual dose titration, depending on the severity of their CDI and also on their individual acceptability of the associated polydipsia/polyuria; therefore this study allowed a flexible dosing regimen. A 12-month follow-up treatment period is reported, and provides valuable safety data on long-term use of desmopressin ODT in Japanese patients with CDI.

Materials and Methods

Patients

Eligible patients were male or female aged 6–75 years with diagnosed CDI (including idiopathic, secondary or familial CDI) defined by evidence of at least two of the following four criteria: (1) Failure to increase urine osmolality above 300 mOsm/kg during a period of fluid deprivation sufficient to raise plasma osmolality and sodium above 295 mOsm/kg and 148 mmol/L, respectively; (2) complete and continuous control of CDI by intranasal desmopressin without 'breakthrough' diuretics, hypernatremia, hyponatremia, or symptoms or signs of water intoxication; (3) a deficient plasma vasopressin response to osmotic or non-osmotic stimulation; (4) absence of the posterior pituitary bright spot on midsagittal T1-weighted MRI of the brain. Other key inclusion criteria were maintenance of 24-hour urine volume, urine osmolality, urine specific gravity and serum sodium within normal levels while using desmopressin nasal administration.

Key exclusion criteria included presence or a history of nephrogenic diabetes insipidus (DI) or diabetes mellitus; presence of uncorrected hypothyroidism, hypocortisolism or hypogonadism; presence of a hypothalamus abnormality leading to thirst disorder; inability to undertake a water-intake restriction; evidence of other health problems unrelated to CDI; and treatment with another investigational product within the past 3 months.

The trial was performed in accordance with the Declaration of Helsinki and approved by the institutional review board/ethics committee for each site. All patients and the legal representative(s) of each patient (if applicable) provided written informed consent.

Study design and procedures

This was a multicenter, open-label dose-titration study. Intranasal desmopressin and desmopressin ODT were supplied by Ferrin Pharmaceuticals.

Each eligible patient was admitted to one of five study sites within 30 days of screening for desmopressin ODT dose titration. Patients self-administered intranasal desmopressin on Day 1 and the morning of Day 2. Subsequently, patients received desmopressin ODT 60 μg at noon and night-time of Day 2 and the morning of Day 3. Further dose titration (dosing time, dose to titrate, and time to titrate) to the optimal dose for each individual was in accordance with the investigator’s judgement based on urine volume and urine osmolality. Urine specific gravity (g/mL) and urine creatinine (mg/dL) were measured in all urine samples from every void. The start and end of the 24-hour urine volume collections were within 5±2 hours after desmopressin administration, and an average hourly diuresis rate (mL/h) was calculated. Patients continued on their optimal dose for the remainder of the study period, unless a need for adjustment arose.

The dose was increased if clinical symptoms such as polydipsia, polyuria or thirst were observed. Patients were encouraged to drink according to thirst with no other restrictions of water intake. The dose could be increased in increments of 60 μg, ranging from 60 μg...
CHAPTER 5. STUDY III. EFFICACY AND SAFETY OF DESMOPRESSIN ORALLY DISINTEGRATING TABLET IN PATIENTS WITH CENTRAL DIABETES INSIPIDUS: RESULTS OF A MULTICENTER OPEN-LABEL DOSE-TITRATION STUDY

to 180 µg, with an overall maximum daily dose of 720 µg (240 µg three times daily [tid]). The dose was decreased if clinical symptoms suggestive of overdose, such as body weight gain, malaise, headache, coldness and nausea/vomiting were observed. The dose was also decreased when serum sodium levels were below the lowest value of the normal range (≤136 mmol/L), which were reported as hyponatraemia in this study. The dose could be decreased by 60 µg per dose. When no dose adjustment was required over three consecutive doses, patients were considered titrated to their optimal dose and discharged from the study site for the remainder of the 4-week study period. Treatment compliance was verified at each study visit based on interviews and by review of empty blisters and unused study medication. Patients returned empty medication packages.

A 1-year long-term study extension monitored the safety and maintenance dose of desmopressin ODT, with bimonthly visits.

Endpoints
The primary endpoint was change from baseline to Week 4 in 24-hour urine volume measured 5±2 hours following the final desmopressin ODT dose. Baseline for this endpoint was defined as the mean value at Visit 1 (Day -30±3) and Visit 2 Day 1 (Day -1 to Day 1). Secondary efficacy endpoints included urine output (24-hour urine volume), urine osmolality and urine specific gravity values over time, from intranasal desmopressin treatment time-points: screening visit and Day 1-2 (Day 1 and morning of Day 2), to desmopressin ODT treatment time-point: Week 4. Hourly diuresis rate was also evaluated. Additional secondary endpoints were the percentage of patients within normal range for urine output (<300 mL/h), urine osmolality (>300 mOsm/kg), urine specific gravity (>1.01 g/mL) and 24-hour urine volume (<3000 mL/m² body surface area for individuals ≤15 years, <3000 mL for individuals >15 years) at Day 1-2 and Week 4.

Safety and tolerability
Safety and tolerability were monitored at each visit via observation and assessment of adverse events (AEs). AEs were coded by the system organ class and preferred terms using MedDRA (version 14.1), and categorised by severity, seriousness and likelihood of causal relationship to study medication as judged by the investigator. Serum sodium was measured during screening and on all study visits following treatment and prior to discharge. If serum sodium was ≤120 mmol/L the patient was asked to visit the trial site as soon as possible for further evaluation. Patients with serum sodium ≤125 mmol/L were withdrawn from the study immediately.

Additional safety measurements included a standard battery of blood and urine analyses, vital signs and physical examinations. These were conducted during screening, the inpatient dose titration period and at Week 4. All patients who received ≥1 dose of the study drug had ≥1 safety assessment were included in the safety analyses.

Statistical analysis
A total of at least 20 patients with CDI were to be enrolled at five study centres in Japan. No formal power calculation was performed to assess the sample size for this trial as the number of eligible patients is limited due to the rarity of CDI, with studies typically including 10–14 patients [7, 12, 8]. All primary and secondary endpoints were analysed based on the full analysis set (FAS), which included all exposed patients with at least one efficacy assessment after treatment. All endpoints were summarised descriptively. A stratified analysis by age group (<18, ≥18 years) was performed for each endpoint, using descriptive statistics only. The mean change from baseline to Week 4 for all endpoints was calculated using an ANCOVA analysis adjusting for the baseline value. Missing values were not imputed. A paired t-test and a non-parametric Wilcoxon signed rank sum test of the baseline (nasal desmopressin) and Week 4 (desmopressin ODT titrated to optimal dose) mean urine volume, diuresis rate, urine osmolality and specific gravity were performed post hoc.

Results
Baseline characteristics
A total of 26 eligible patients were registered in the study, but six of these discontinued before receiving desmopressin ODT due to the 2011 Japanese earthquake. Twenty patients entered into the study and received desmopressin ODT, of which 19 patients completed the 4-week treatment period (Fig. 1). One patient had less than 80% compliance and was excluded from the per protocol set. Baseline characteristics are summarised in Table 1. Patients were aged 8–71 years (mean 39.6 years), four were <18 years and 12/20 (60%) were male. The duration of diagnosed CDI was 2–24 years, and all patients had been treated with intranasal desmopressin
CHAPTER 5. STUDY III. EFFICACY AND SAFETY OF DESMOPRESSIN ORALLY DISINTEGRATING TABLET IN PATIENTS WITH CENTRAL DIABETES INSIPIDUS: RESULTS OF A MULTICENTER OPEN-LABEL DOSE-TITRATION STUDY

Fig. 1 Patient disposition

Table 1 Baseline characteristics

<table>
<thead>
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<th>Characteristic</th>
<th>Full analysis set/n=20</th>
<th>Per protocol set/n=19</th>
</tr>
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<td>Age (years)</td>
<td>39.6 (19.5)</td>
<td>39.2 (19.6)</td>
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<tr>
<td>Mean (SD)</td>
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<td>36 (6, 71)</td>
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<tr>
<td>Median (min, max)</td>
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<td></td>
</tr>
<tr>
<td>Sex, n (%)</td>
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<tr>
<td>Male</td>
<td>12 (60%)</td>
<td>12 (63.2%)</td>
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<tr>
<td>Female</td>
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<tr>
<td>Height (cm)</td>
<td>168.7 (14.1)</td>
<td>168.7 (14.1)</td>
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<td>161.1 (121.4, 170.0)</td>
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<tr>
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<td></td>
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<td>61.3 (24.8, 105.5)</td>
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<td>1 (5.3%)</td>
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<td>Rathke's cleft cyst</td>
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<td>No</td>
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<tr>
<td>Before menopause</td>
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<td>6 (32.3%)</td>
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<td>Other</td>
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</tr>
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<td>4 (20%)</td>
<td>4 (22.2%)</td>
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<td>Anterior pituitary dysfunction, n (%)</td>
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<td>No</td>
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<td>8 (42.1%)</td>
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<tr>
<td>Yes</td>
<td>12 (60%)</td>
<td>12 (57.9%)</td>
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<td>Hormone replacement, n (%)</td>
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<td>Thyroid</td>
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<td>12 (65.3%)</td>
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<td>Glucocorticoid</td>
<td>10 (50%)</td>
<td>9 (47.4%)</td>
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<tr>
<td>Growth hormone</td>
<td>6 (30%)</td>
<td>6 (31.6%)</td>
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<tr>
<td>Gonadotropin</td>
<td>3 (15%)</td>
<td>3 (15.8%)</td>
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<td>Diastolic blood pressure, mmHg</td>
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<td>Mean (SD)</td>
<td>72.2 (9.6)</td>
<td>72.3 (9.8)</td>
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<td>Median (min, max)</td>
<td>71.0 (54, 92)</td>
<td>71.0 (54, 92)</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
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<td>Mean (SD)</td>
<td>118.3 (14.0)</td>
<td>118.0 (14.3)</td>
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<td>Median (min, max)</td>
<td>124.0 (94, 149)</td>
<td>124.0 (96, 149)</td>
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<td>Pulse (beats/min)</td>
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<td>Mean (SD)</td>
<td>74.3 (13.2)</td>
<td>74.9 (12.4)</td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>72.5 (51, 101)</td>
<td>75.0 (51, 101)</td>
</tr>
</tbody>
</table>
CHAPTER 5. STUDY III. EFFICACY AND SAFETY OF DESMOPRESSIN ORALLY DISINTEGRATING TABLET IN PATIENTS WITH CENTRAL DIABETES INSIPIDUS: RESULTS OF A MULTICENTER OPEN-LABEL DOSE-TITRATION STUDY

Fig. 2 Changes in pharmacodynamic parameters over time
(A) 24-hour urine volume. (B) Hourly diuresis rate. (C) Urine specific gravity. (D) Urine osmolality. Data are mean±SEM of 19–28 patient measurements. (E) Proportion of patients within normal ranges of pharmacodynamics endpoints at Day 1–2 and Week 4, (n=19–23). (F) Mean serum sodium concentration over time.

since diagnosis. The aetiologies of CDI and the proportion of patients with anterior pituitary dysfunction are provided in Table 1. Subsets of patients received hormone replacement therapies including thyroid hormone, glucocorticoid, growth hormone and gonadotropin. All patients were being treated with intranasal desmopressin on Day 1 of the study (median daily dose: 8.5 μg, range 1.875–20 μg).

**Efficacy**
Primary endpoint: 24-hour urine volume
Fig. 2A shows changes from baseline to Week 4 for the primary efficacy endpoint (24-hour urine volume) for the total study population, as well as for those <18 years and ≥18 years of age. There was no statistical difference between Week 4 and baseline mean 24-hour urine volume (paired t-test p=0.10, Wilcoxon rank sum test p=0.14), suggesting equivalent 24-hour concentrating capacity with desmopressin ODT and intranasal therapy.

Secondary endpoints
Diuresis rate, urine specific gravity and urine osmolality are shown in Fig. 2B, 2C and 2D. There was no change in hourly diuresis rate at Week 4 compared with
baseline (paired \( t \)-test \( p=0.10 \), Wilcoxon rank sum test \( p=0.14 \)).

Urine specific gravity remained similar to baseline at Week 4 (mean change: 0.007+0.0087 g/mL; paired \( t \)-test \( p=0.12 \), Wilcoxon rank sum test \( p=0.06 \)). Urine osmolality was not significantly different at Week 4 (711.7±198.6 mOsm/kg) compared with baseline (597.2±120.0 mOsm/kg; average of values at screening visit and Day -1 to Day 1, paired \( t \)-test \( p=0.11 \), Wilcoxon rank sum test \( p=0.08 \)). The urine osmolality of one patient at Week 4 was 93 mOsm/kg, which suggests little urine concentrating activity, although baseline and Week 2 urine osmolality values were within normal ranges (562 and 641 mOsm/kg, respectively). Similar changes in secondary endpoints were seen in patients \( \geq 18 \) years compared with those \( \geq 18 \) years of age, although no formal testing was performed due to the low patient numbers.

Pharmacodynamic parameters within the normal range

The same or a greater proportion of patients were within the normal range for all pharmacodynamic parameters at Week 4 compared with Day 1–2 (Fig. 2E). The hourly diuresis rate, of all patients, was maintained within the normal range at Day 1–2 and Week 4. The endpoint with the greatest proportion of patients outside the normal range was 24-hour urine volume (684%); however, this value was unchanged from ral desmopressin to desmopressin ODT administration. All patients \( \leq 15 \) years were within the normal range of 24-hour urine volume measurement at Day 1–2 and Week 4 (data not shown).

Desmopressin dose and administration frequency

Individuals with mean and median desmopressin dose and dose frequency are shown in Table 2. A total of 20 patients received intranasal therapy at a median daily dose of 8.50 \( \mu \)g/day (range: 1.875–20 \( \mu \)g/day) on Days 1–2.

Although patients were still under dose titration up to Week 2, the majority of patients maintained the same desmopressin ODT dose between completion of on-site dose titration and Week 2. The median desmopressin ODT dose was maintained between Week 2 and Week 4, with patients receiving desmopressin ODT 120–360 \( \mu \)g/day, in either two or three doses. The ratio of mean daily dose of intranasal desmopressin (on Day 1) to desmopressin ODT (on Week 4) was approximately 1:24. However, there was a wide range of desmopressin intranasal:desmopressin ODT mean daily dose ratios across individuals, to maintain adequate antidiuresis, with ratios from 1:12 to 1:96 observed in this study (Table 2).

Safety

Overall, 11/20 patients experienced 26 AEs. Of these patients, eight were considered to have treatment-emergent AEs (n=11) that were possibly or probably related to the study drug (adverse drug reactions, ADRs; Table 3). The most commonly reported ADR was hypotension (7/20 patients, eight events), of which one patient experienced serious hypotension (124 mmol/L) that was classified as a serious AE (SAE) due to hospitalisation, and led to discontinuation. This SAE was judged by investigator and sponsor evaluation potentially to be the consequence of a relative overdose of desmopressin ODT during dose adjustment. Excessive fluid intake after Visit 2 was noted for this patient, which may have exacerbated the hypotension. The other six patients continued desmopressin ODT treatment following a reduction in dose and recovered quickly. However, one patient had a second mild hypotension event with onset after Week 4. All patients with hypotension were \( \geq 18 \) years old. The frequency of hypotension did not appear to be influenced by the dose of intranasal desmopressin; however, most hypotension events occurred following \( \geq 180 \) \( \mu \)g desmopressin ODT (6/8 patients) and in patients treated three times a day (6/8 patients). Fig. 2F shows the mean change in serum sodium concentration over time. During dose titration, a mild transient change in serum sodium concentration occurred (−2.7–0.2 mmol/L) from 140.2±2.2 mmol/L at screening. The mean serum sodium concentration nadir occurred on Day 4 of the in-hospital dose titration period (137.4 mmol/L). Overall, the mean change in serum sodium concentration from screening to Week 4 was −0.3±3.1 mmol/L, and changes in serum sodium levels during the study were not significant.

Results of 12-month follow-up safety data

All 19 patients who completed the 4-week study continued into the long-term safety study, with 19 patients completing 6-months follow-up and 17 patients completing the full 12-month extension. Two patient withdrawals, due to nasopharyngitis and rib fracture, respectively, were not considered to be related to the study drug. The overall median daily dose was constant (180 \( \mu \)g) throughout the 12-month extension study. A total of 13 patients did not change the daily dose during the study extension. Two patients increased the daily dose due to increase in urine volume and four patients decreased the daily dose due to reduction in serum sodium levels. Overall, six events of hypotena-
CHAPTER 5. STUDY III. EFFICACY AND SAFETY OF DESMOPRESSIN ORALLY DISINTEGRATING TABLET IN PATIENTS WITH CENTRAL DIABETES INSIPIDUS: RESULTS OF A MULTICENTER OPEN-LABEL DOSE-TITRATION STUDY

Table 2 Desmopressin dose and dose frequency

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Visit 2: initial oral dose titration period</th>
<th>Treatment period I</th>
<th>Treatment period II</th>
<th>Dose ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1-2&lt;sup&gt;a&lt;/sup&gt; (μg/day)</td>
<td>Day 3&lt;sup&gt;b&lt;/sup&gt; (μg)</td>
<td>Day 4&lt;sup&gt;c&lt;/sup&gt; (μg)</td>
<td>Day 5&lt;sup&gt;d&lt;/sup&gt; (μg)</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>10</td>
<td>60/60</td>
<td>60/60/80</td>
<td>120/120/120</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>7.5</td>
<td>60/60</td>
<td>60/60</td>
<td>60/60/60</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>3.75</td>
<td>60/60</td>
<td>60/60/120</td>
<td>120/120/120</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>10</td>
<td>60/60/120</td>
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<td>120/120/120</td>
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<tr>
<td>5</td>
<td>22</td>
<td>9.5</td>
<td>60/60/60/DC</td>
<td>60/60/60/DC</td>
<td>60/60/60/DC</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>5</td>
<td>60/60/60/DC</td>
<td>60/60/60/DC</td>
<td>60/60/60/DC</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>12</td>
<td>60/60/60/60</td>
<td>60/60/60/60</td>
<td>60/60/60/60</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>7.5</td>
<td>60/60</td>
<td>60/60/60/DC</td>
<td>60/60/60/DC</td>
</tr>
<tr>
<td>9</td>
<td>36</td>
<td>12.5</td>
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<td>60/60/120/120</td>
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<td>60/60</td>
<td>60/60</td>
</tr>
<tr>
<td>11</td>
<td>44</td>
<td>20</td>
<td>60/60</td>
<td>60/60/120/120</td>
<td>120/120/120/120</td>
</tr>
<tr>
<td>12</td>
<td>47</td>
<td>15</td>
<td>60/60</td>
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</tr>
<tr>
<td>13</td>
<td>48</td>
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<td>14</td>
<td>54</td>
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</tr>
<tr>
<td>15</td>
<td>61</td>
<td>10</td>
<td>60/60</td>
<td>60/60/DC</td>
<td>60/60/DC</td>
</tr>
<tr>
<td>16</td>
<td>63</td>
<td>5</td>
<td>60/60</td>
<td>60/60</td>
<td>60/60</td>
</tr>
<tr>
<td>17</td>
<td>65</td>
<td>5</td>
<td>60/60</td>
<td>60/60</td>
<td>60/60</td>
</tr>
<tr>
<td>18</td>
<td>65</td>
<td>5</td>
<td>60/60</td>
<td>60/60</td>
<td>60/60</td>
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<tr>
<td>19</td>
<td>66</td>
<td>5</td>
<td>60/60</td>
<td>60/60</td>
<td>60/60</td>
</tr>
<tr>
<td>20</td>
<td>71</td>
<td>5</td>
<td>60/60</td>
<td>60/60</td>
<td>60/60</td>
</tr>
</tbody>
</table>

Mean daily dose (All)<sup>a</sup> 8.86±4.49 21.1±8.32 0.0 24.1
Median daily dose (All) 8.50 180 21:1
Mean daily dose (<18 years) 7.81±2.95 255.0±75.5 225.0±83.5 29:1
Median daily dose (<18 years) 8.75 240 240 27:1
Mean daily dose (≥18 years) 9.12±4.84 212.0±87.4 204.0±83.2 22:1
Median daily dose (≥18 years) 8.50 180 180 21:1

<sup>a</sup> intranasal desmopressin; <sup>b</sup> oral desmopressin; <sup>c</sup> not dosed; DC, discharged; W, patient withdrawn from study

Table 3 Adverse drug reactions considered possibly or probably related to study drug

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>n</th>
<th>Percentage (%)</th>
<th>Number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8</td>
<td>49</td>
<td>11</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic function abnormal</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Thirst</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Hypoosmocrenia&lt;sup&gt;a&lt;/sup&gt; (&lt;15 mmol/L)</td>
<td>7</td>
<td>35</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>a</sup> Characteristics of individual events of hypoosmocrenia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Gender</th>
<th>Intranasal dose (μg/day)</th>
<th>Oral dose (μg/day)</th>
<th>Onset</th>
<th>Intensity</th>
<th>Symptoms</th>
<th>Serum sodium (mmol/L)</th>
<th>Duration (days)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>27</td>
<td>Male</td>
<td>5</td>
<td>180</td>
<td>Week 4</td>
<td>Mild</td>
<td>-</td>
<td>134</td>
<td>16</td>
<td>Dose adjusted</td>
</tr>
<tr>
<td>7</td>
<td>34</td>
<td>Male</td>
<td>12</td>
<td>Unknown&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Day 2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Mild</td>
<td>-</td>
<td>129</td>
<td>2</td>
<td>Dose adjusted</td>
</tr>
<tr>
<td>11</td>
<td>40</td>
<td>Female</td>
<td>10</td>
<td>360</td>
<td>Week 2</td>
<td>Mild</td>
<td>-</td>
<td>136</td>
<td>8</td>
<td>Dose adjusted</td>
</tr>
<tr>
<td>16</td>
<td>61</td>
<td>Male</td>
<td>10</td>
<td>180</td>
<td>Week 2</td>
<td>Mild</td>
<td>-</td>
<td>133</td>
<td>7</td>
<td>Dose adjusted</td>
</tr>
<tr>
<td>17</td>
<td>63</td>
<td>Male</td>
<td>5</td>
<td>180</td>
<td>Day 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Mild</td>
<td>-</td>
<td>130</td>
<td>5</td>
<td>Dose adjusted</td>
</tr>
<tr>
<td>19</td>
<td>65</td>
<td>Female</td>
<td>5</td>
<td>180</td>
<td>Week 2</td>
<td>Moderate</td>
<td>Headache, Nausea</td>
<td>131</td>
<td>&gt;7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Dose continued</td>
</tr>
<tr>
<td>20</td>
<td>71</td>
<td>Female</td>
<td>5</td>
<td>180</td>
<td>Day 4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Moderate</td>
<td>-</td>
<td>132</td>
<td>4</td>
<td>Withdrawn</td>
</tr>
</tbody>
</table>

<sup>b</sup> administered with intranasal and/or oral desmopressin; <sup>c</sup> dose adjustment; <sup>d</sup> duration unknown as AE onset occurred at end of study
emia were reported. One patient experienced hypotremia three times but all reductions in serum sodium were mild (132–133 mmol/L). In another patient the serum sodium levels decreased to 126 mmol/L, but this incident was judged to be due to the patient missing a scheduled dose of glucocorticoid hormone on that day. None of the observed reductions in serum sodium concentration were accompanied by any overt symptoms, and all were judged to be non-serious, with rapid return to normal levels with or without the need for dose modification. Overall, long-term desmopressin ODT treatment was well tolerated.

**Discussion**

Desmopressin is the therapy of choice in the treatment of CDI [5]. Desmopressin was initially introduced as parenteral and intranasal formulations, but is now available in oral formulations, including sublingually administered ODT [5, 13]. Previous studies have shown that a switch from intranasal to oral desmopressin achieves good antidiuretic control and is well tolerated in adults [5] and children [10, 11]. Large-scale or placebo-controlled clinical studies in patients with CDI are not feasible, because CDI is rare, and the use of placebo is not ethically acceptable due to the nature of the disease. This multicenter, open-label dose-titration study demonstrated that the oral hyphosphilate formulation of desmopressin, desmopressin ODT, maintains antidiuresis on switching from intranasal desmopressin in Japanese patients with CDI. Desmopressin ODT was well tolerated, with reduction in serum sodium concentration being the most frequently reported ADR, as seen in previous clinical trials with desmopressin [5]. While reductions in serum sodium concentration occurred early following switching from intranasal desmopressin to desmopressin ODT in this study, recovery was observed after dose modification or discontinuation of treatment in all cases, confirming the overall safety of desmopressin ODT in the treatment of CDI. Post-marketing data across all indications have shown a lower risk of hypotremia for oral formulations compared with the nasal formulation of desmopressin, leading to recommendation of oral formulations over the nasal formulation [13]. Large individual variation in intranasal drug absorption may explain unwanted increases in antidiuretic duration of action and thereby the slightly higher risk of hypotremia with the nasal formulation [13].

There are a number of disadvantages associated with the intranasal desmopressin compared with oral formulations of desmopressin. There is greater variability in dosing using intranasal desmopressin, and absorption may be altered in patients with nasal mucosa changes [5]. Furthermore, the intranasal formulation requires refrigeration to ensure long-term stability [5]. A pediatric study examining switching from desmopressin nasal spray to desmopressin oral tablets in patients with CDI reported that all patients preferred the tablet compared with the nasal formulation [10]. Nevertheless, the intranasal formulation remains of benefit in some patients including infants with CDI [14] because the wide range of different dose strengths allows individualised administration of the dose required to obtain control of water balance in each patient.

Previous studies suggest that a 19 times greater dose of desmopressin oral tablet compared with intranasal desmopressin is required to maintain adequate antidiuretic control [7] and that following switching patients were stable with adequate water turnover on doses of 100–400 µg desmopressin tablet tid [10]. Therefore, dose titration was initiated in this study with desmopressin ODT 60 µg tid. However, another study in patients with CDI demonstrated that the duration of antidiuretic action of desmopressin 500 ng IV, which corresponds to desmopressin ODT 160 µg, was between 11 and 15 h [15]. In this study, some younger patients, for whom it was not easy to take desmopressin ODT in the daytime at school, were administered with a relatively high dose of desmopressin ODT bid, without negative effects. These data suggest that there is a need for individual dose titration as previously reported [8].

Desmopressin ODT demonstrated the same level of antidiuretic control as intranasal desmopressin, with the same proportion of patients within the normal range for all pharmacodynamic endpoints at Week 4, following desmopressin ODT therapy compared with intranasal desmopressin therapy at Day 1–2. Although the overall patient numbers were small, desmopressin ODT was similarly efficacious to intranasal desmopressin in the younger (<18 years) and older (£18 years) groups. Nevertheless, there was wide variation of the intranasal desmopressin:ODT desmopressin ratios required to maintain similar levels of antidiuretic effect, ranging from 1:12 to 1:96. These data suggest that it is not possible to predict the required desmopressin ODT dose in a patient previously managed with intranasal desmopressin, and highlight the necessity of individ-
ual dose adjustment based on observed pharmacodynamic parameters. This is further demonstrated by the individual patient data in this study that show no direct dose correlation between the two formulations. We should be aware that some patients with CDI were well managed with a lower dose of desmopressin ODT, suggesting that the treatment should start with a minimum dose of desmopressin ODT in order to avoid hyponatraemia, particularly in outpatients. The dose may then be cautiously titrated in increments according to the clinical antidiuretic response. During the preparation of this manuscript, desmopressin ODT has been approved in Japan. It is of note that the label approved by the Pharmaceutical and Medical Devices Agency indicates that the intended level of efficacy may not be achieved with postprandial administration. Therefore it is desirable to avoid administration of desmopressin ODT immediately after eating.

While seven out of 20 patients experienced hyponatraemia in this study, the incidence of hyponatraemia during intranasal desmopressin therapy prior to the trial was not recorded. As patients with CDI are likely to be switched from intranasal to oral desmopressin, studies to examine the incidence of hyponatraemia in both formulations should be undertaken in the near future.

In conclusion, this study provides evidence of the efficacy and long-term safety of desmopressin ODT following individual dose titration from intranasal desmopressin therapy in the treatment of Japanese patients with CDI. These findings are consistent with other studies in CDI populations confirming that desmopressin in different formulations and bioequivalent strengths is an effective treatment for CDI [7, 8, 16, 17]. This study supports the introduction of desmopressin ODT as the first-line therapy for antidiuretic control in patients with CDI.

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Disclosures

Kristian Vinter Juul and Jens Peter Nørgaard are employees of Ferring Pharmaceuticals.

Hiroshi Arima and Yutaka Oiso are paid consultants of Ferring Pharmaceuticals.

References

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CHAPTER 6

Review. Treatment of neurohypophyseal diabetes insipidus
Treatment of Neurohypophyseal Diabetes Insipidus

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Context: In recent years, there have been several improvements in the treatment of neurohypophyseal diabetes insipidus (DI). They include new formulations of the vasopressin analogue, desmopressin, a better understanding of the effect of fluid intake on dosing and more information about treatments of infants, children, and pregnant women who present special challenges. This review aims to summarize past and current information relative to the safety and efficacy of treatments for the types of DI caused by a primary deficiency of vasopressin.

Evidence Acquisition: The review is based on publications identified primarily by a PubMed search of the international literature without limitations of date.

Evidence Synthesis: In acute settings where fluid intake is determined by factors other than thirst, desmopressin should be given intravenously in doses that have a short duration of action and can be adjusted quickly in accordance with changes in hydration as indicated by plasma sodium. In ambulatory patients, the oral formulations (tablet or melt) are preferred for their convenience. If fluid intake is regulated normally by the thirst mechanism, the tablets or melt can be taken safely one to three times a day in doses sufficient to completely eliminate the polyuria. However, if fluid intake consistently exceeds replacement needs as evidenced by development of hyponatremia, the dose should be reduced to allow higher than normal rates of urine output or intermittent breakthrough diuresis. This regimen is often indicated in infants or children since their rate of fluid intake tends to be greater than in adults. In all cases, the appropriate dose should be determined by titration owing to considerable inter-individual differences in bioavailability and antidiuretic effect.

Conclusions: Desmopressin can provide effective and safe therapy for all patients with neurohypophyseal or gestational DI if given in doses and by a route that takes into account the determinants of fluid intake.

Diabetes insipidus (DI) is a syndrome characterized by the excretion of abnormally large volume of dilute urine (polyuria) and a commensurate increase in fluid intake (polydipsia). It is differentiated into 4 types based on etiology and therapeutic requirements (1, 2).

One type is caused by a deficiency in production of the antidiuretic hormone (ADH), arginine vaspressin. It is variously referred to as neurohypophyseal, pituitary, cranial or central DI and can result from various diseases or genetic mutations that impair neurohypophyseal function (3, 4) (Table 1). In this type, treatment with vasopressin or an analog such as desmopressin completely eliminates the polyuria, thirst and polydipsia (2).

DI can also be caused by renal insensitivity to the an-
The diuretic effect of vasopressin. This type is referred to as nephrogenic DI and can also be acquired or genetic (4, 5).
It is refractory to treatment with standard doses of vaso-
pressin or desmopressin but will in some cases respond to
supranormal doses of either agonist. For long term man-
agement, however, the only practical way to reduce the
polyuria, thirst and polydipsia is to reduce sodium intake
and give a thiazide diuretic, amiloride or prostaglandin
synthetase inhibitors (2, 4).

A third type of DI is due to increased metabolism of
vasopressin by an enzyme produced by the placenta (6, 7,
8). It is referred to as gestational DI since it usually devel-
ops in the second or third trimester of pregnancy and re-
mits spontaneously 4 to 6 wk postpartum. However, it can
also develop immediately after delivery due to massive
release of vasopressin from an abruptio placenta (9). Ges-
tational DI is controlled much better with desmopressin
than with vasopressin because the analog is resistant to
degradation by the placenta (10).

The fourth type of DI is caused by excessive intake of
fluids and is usually referred to as primary polydipsia. In
this type, vasopressin is synthesized normally but its se-
cretion is suppressed by excessive fluid intake (11). It is
divided into 3 subtypes depending on whether the poly-
dipsia is psychogenic, (due to schizophrenia or other cog-
nitive abnormalities), dipsogenic (due to abnormal thirst) or
iatrogenic (due to efforts to treat other disorders) (Table
1). Treatment of these patients with vasopressin or des-
mopressin corrects the polyuria but has little or no effect
on the abnormal thirst and/or polydipsia. Consequently, it
rapidly and invariably produces water intoxication (hy-
ponatremia) and is strongly contraindicated in this form of
DI (12).

Given the markedly different effects of antidiuretic
therapy in the 4 types of DI, differentiation between them
is essential. This can be difficult by traditional methods
because primary deficiencies in vasopressin secretion or
action are often partial and, consequently, respond to fluid
depivation tests like patients with primary polydipsia (1).
These three types of DI can now be differentiated more
readily with new techniques that employ assay of plasma
vasopressin and/or MRI of the brain to determine the pres-
ence or absence of the posterior pituitary bright spot (4).

The primary purpose of this paper is to provide an up-
dated review of current information on the efficacy and
safety of all formulations of the native ADH, vasopressin
(Pitressin) and its analog, desmopressin (dDAVP), in the
treatment of neurohypophyseal DI. However, other forms
of therapy will also be reviewed. The structures of vaso-
pressin and desmopressin are shown in Figure 1. Both
produce antidiuresis by stimulating V2 receptors on the
principle cells of the kidney (13). High concentrations of
vasopressin also stimulate contraction of smooth muscle
in the GI tract and blood vessels via action at V1 receptors.
Desmopressin does not have this effect because it is relatively inactive at V1 receptors (14).

**Acute Management of Neurohypophysial DI**

The treatment of neurohypophysial DI in postoperative or acutely ill patients is straightforward if the patient has a normal thirst mechanism, is able to drink at will and does not receive fluids for other purposes. In that circumstance, water balance can be maintained just by giving enough antidiuretic therapy to keep urine specific gravity or osmolality near the normal basal level of about 1.015 or 450–600 mOsm/kg. However, if the patient requires intravenous (IV) fluids and/or is otherwise unable to regulate total fluid intake by the thirst mechanism, it may be necessary to continually adjust the level of antidiuresis and/or IV infusion to maintain hydration and plasma sodium within in the normal range. In this circumstance, formulations suitable for IV infusion are preferred since they permit the most rapid changes in the level of antidiuresis.

**Vasopressin injectable solution**

Vasopressin (Pitressin) has been available for many decades as an aqueous solution of 20 Units/mL in a 1 mL vial. Because of its short half-life, (approximately 20 min) some authors recommend that it be given by IV infusion when acute short term control of antidiuresis is desired (15). For this purpose, it has been suggested that the rate of infusion be started at 0.25 to 1 μU/kg/hour and increased every 30 min thereafter until a urine specific gravity reaches 1.010 to 1.020 or the rate of urine output falls to around 100 ml/hour. Generally, this level of antidiuresis is achieved at an infusion rate of 0.5–3 micro units/kg/hour. Accidental overdoses resulting from inadequate dilution of the highly concentrated stock solution typically result in severe abdominal cramping, diarrhea, vomiting and pallor due to action at V1 receptors.

**Desmopressin injectable solution**

The vasopressin analog desmopressin (dDAVP) is also available as a formulation suitable for IV or subcutaneous administration. It is supplied in single-dose 1-ml ampules and multidose 10-ml vials containing 4 μg/mL of the compound. This formulation has been studied and used extensively since the first clinical trial over 40 y ago (16). Early studies showed a definite relationship between the i.v. dose and the magnitude and duration of the antidiuretic effect (17, 18). In 10 patients with neurohypophysial DI, a “push” infusion of 1 μg iv increased urine osmolality to a maximum of 700–800 mOsm/kg (18). Further increases in dosage only prolonged the duration of action from an average of 26 h after 1 μg to 46 h after 8 μg.

Later studies in more patients revealed large interindividual variability in the magnitude and duration of the antidiuretic response to single IV doses of desmopressin given by “push” infusions (19). This variability was attributed to interindividual differences in renal concentrating capacity because it persisted even when the dose was increased to more than 2 μg (17, 20, 21).

A more recent randomized, cross-over study in 13 patients with neurohypophysial DI (22) also showed that the maximum antidiuretic effect and the duration of action tended to vary together as a function of the dose (Figure 2). When infused over 2 h, a dose of 250 ng increased urine osmolality to an average maximum of about 700 mOsm/kg and reduced urine flow to about 1 mL/min (1.4 L/day). This peak response was nearly identical to that produced by a 4-fold higher dose given by IV “push” (22) suggesting that the magnitude of the effect depends not only on the total dose but also the rate of rise in plasma desmopressin. This time dependency was also observed in a recent study in water-loaded healthy adults (23). In both settings, the maximum antidiuretic effect produced acutely by a 2 h i.v. infusion of desmopressin was considerably less than the maximum achievable in healthy adults during prolonged fluid deprivation (about 1200 mOsm/kg). This lower maximum antidiuretic effect in DI patients around 800–900 mOsm/kg was not due to inadequate levels of plasma desmopressin because doubling the dose from 250 to 500 ng did not increase the maximum antidiuretic effect (Figure 2). It only prolonged the duration of action from an average of about 8 to 11 hrs. This finding is consistent with a previous suggestion that the concentrating capacity of the human kidney decreases in the ab-

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**Figure 1.** Chemical Structure of Vasopressin and Desmopressin. The box indicates the deamidation of the amino-terminus in desmopressin vs. AVP. Chemical Structure of Vasopressin and Desmopressin. The box indicates the deamidation of the amino-terminus in desmopressin vs. vasopressin.
sence of vasopressin and seems to require more than 8 h of continued stimulation to fully recover (24). It is also clear that there are large individual variations in the magnitude and duration of the initial response to IV desmopressin not only in patients with neurohypophyseal DI (22) but also in water loaded healthy subjects (23). The cause of this variation is uncertain. It may be due in part to individual differences in the total volume of distribution of desmopressin. Absorption of desmopressin onto the plastic syringes utilized in the administration could also play a role (25). Other possibilities include individual differences in V2 receptor sensitivity or in the kinetics of the biochemical mechanisms that mediate the antidiuretic effect (23).

Recommendations/ precautions

These studies indicate that the parenteral formulation of desmopressin can also be used safely to control neurohypophyseal DI in acutely ill patients. The dose should depend on individual variations in the antidiuretic effect and other factors that determine fluid intake. If the latter is regulated completely by the patient’s thirst mechanism, a reasonable approach is to start by giving 250 to 500 ng twice daily via a 2 h i.v. infusion and adjust as needed to normalize urine output and maintain plasma sodium within the normal range. However, if the patient is obtunded or requires iv fluid for other reasons, it may be preferable to start with smaller doses of desmopressin (60 ng to 125 ng iv over 2 h) and adjust every 3 to 6 h as needed to reduce polyuria to the extent possible without producing water intoxication (hyponatremia).

Chronic Management of Neurohypophyseal DI

Once established, neurohypophyseal DI rarely remits. The goal of chronic management should be to provide complete, around the clock control of the polyuria as conveniently as possible with minimal risk of hyponatremia due to excessive water retention. This goal can usually be achieved by giving a longer acting form of antidiuretic therapy and educating the patient in the importance of strictly limiting fluid intake to the amounts required to satisfy thirst. Ingesting fluids for any other reason should be avoided because, unlike persons with normal posterior pituitary function, patients receiving long acting antidiuretic therapy cannot quickly increase their urine output to compensate for an increase of fluid intake. It is also important that the treatment be dosed so as to not reduce 24 h urine output below the normal range (15 to 30 mL/kg/day) because it is sometimes difficult to reduce total intake enough to compensate for a larger reduction in urine output (26). Finally, it is also essential to be sure that the patient does not have primary polydipsia rather than partial pituitary DI because giving ADH to the former abolishes the polyuria but not the polydipsia and invariably results in rapid onset of severe hyponatremia (12).

Pitressin Tannate in Oil

Pitressin Tannate in Oil is an injectable long-acting, depot formulation of vasopressin. It was used for many years for long term management of neurohypophyseal DI (27) but was voluntarily withdrawn from the market by the manufacturer in 1998 and is currently unavailable for this purpose.

Desmopressin nasal spray

Early studies comparing the pharmacodynamic response to IV or intranasal desmopressin in patients with neurohypophyseal DI suggested that the absorption ratio from the nasal mucosa was 10%–20% (28). The magnitude and duration of the antidiuretic effect of an intranasal dose varied appreciably between, and even within, patients irrespective of age, severity of polyuria or body-weight (29, 30). Thus, the duration of action ranged from eight to 24 h for a 20 μg dose (20, 30, 31) and from 4 to 18 h after 5 to 10 μg of intranasal desmopressin (32). Using a cut-off for urine osmolality of ≥ 400 mOsm/kg, the mean duration of action after 10 and 20 μg intranasal doses was found to be 7 to 9 h, respectively (33).

Because of its variable absorption and antidiuretic effects, the intranasal formulation has been withdrawn from several markets and in some cases replaced by the more

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Figure 2. The pharmacodynamic profile of Desmopressin, measured as mean urine osmolality (+/-SD). Based on PD data from 13 DI patients receiving desmopressin 30, 60, 125, 250 and 500 ng IV infusions over 2 h. The pharmacodynamic profile of Desmopressin, measured as mean urine osmolality (+/-SD). Based on PD data from 13 neurohypophyseal DI patients receiving desmopressin 30, 60, 125, 250 and 500 ng IV infusions over 2 h. With kind permission from Springer Science + Business Media.

Figure 2. The pharmacodynamic profile of Desmopressin, measured as mean urine osmolality (+/-SD). Based on PD data from 13 DI patients receiving desmopressin 30, 60, 125, 250 and 500 ng IV infusions over 2 h. The pharmacodynamic profile of Desmopressin, measured as mean urine osmolality (+/-SD). Based on PD data from 13 neurohypophyseal DI patients receiving desmopressin 30, 60, 125, 250 and 500 ng IV infusions over 2 h. With kind permission from Springer Science + Business Media.
recent oral formulations (34). Nonetheless, the intranasal formulation remains of benefit in many DI patients because the wide range of different strengths allows an individualized administration of the dose required to obtain control of water excretion. Intranasal preparations can be titrated and tailored to the individual need by either rhinyl tube (dose range, 1–10 μg) or by a metered dose spray (2.5 μg–10 μg per spray) (Table 2).

**Desmopressin oral formulations, tablets**

Peptides, like vasopressin and desmopressin, are in general unsuited to oral administration due to their large molecular size, susceptibility to enzymatic degradation and short plasma half-life. However, clinical trials in healthy volunteers, and patients (35) showed that orally administered desmopressin had a stable antidiuretic effect and a clear dose-response relationship even though its bioavailability was low. Thus, desmopressin is also formulated as a tablet (0.1 mg, 0.2 mg and 0.4 mg) for the treatment of neurohypophyseal DI.

Desmopressin enters plasma 15–30 min following oral administration and reaches a maximum concentration after 90 min (25). Due to degradation by gastrointestinal (GI) peptidases, its bioavailability by the oral route is low (25) (Table 2). The rate and extent of absorption after oral administration is reduced by 40% if taken with food or within 90 min of a meal. However, the antidiuretic action of the drug is not affected, at least for the first 3 h after treatment (36).

Oral administration of desmopressin in doses 10–20 times the intranasal dose provides adequate blood levels of desmopressin to control polyuria in neurohypophyseal DI (Table 2). Due to the ease of administration, oral formulations are the preferred route for the treatment of most patients (35, 37). A total daily maintenance dose of the tablet is normally about 100 μg to 200 μg three times daily but requirements vary and must be individualized to maintain normal urine output (38). Once-daily doses may be effective in small children and infants (39).

Clinical studies of the pharmacokinetics, pharmacodynamics, efficacy and safety of oral desmopressin tablets have also been conducted in Japanese and Chinese patients with neurohypophyseal DI (40, 41). Both short-term and long-term stable and satisfactory antidiuresis was achieved in most patients tested at total daily maintenance doses of 200 to 600 μg per day subdivided in two to three doses.

**Desmopressin oral formulations, Oral melt**

Recently, desmopressin has also been developed as a sublingual lyophilisate (melt) formulation containing 60, 120 and 240 μg. This formulation improves the bioavailability of desmopressin by approximately 60% compared to the tablet (42) (Table 2).

The first phase III study of Melt in neurohypophyseal DI patients was recently conducted, comparing peroral administration of different doses (60 μg, 120 μg) of desmopressin melt vs. nasal administration (2.5 μg, 10 μg) (43). In a 4-wk multicenter, open-label study, a total of 20 DI patients aged 6–75 y switched from intranasal desmopressin to desmopressin melt with titration to optimal dose over 5 days at each study site. For each patient optimal dosing in terms of dose and frequency were determined by the investigators based on symptoms such as polydipsia,

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**Table 2. Dose comparison of different formulations of Desmopressin**

<table>
<thead>
<tr>
<th>Year of Launch</th>
<th>Melt</th>
<th>Tablets</th>
<th>Spray</th>
<th>Drops</th>
<th>Solution for injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>0.25% (95% CI: 0.21% - 0.31%)</td>
<td>0.16% ± 0.17%</td>
<td>6.00% ± 2.29%</td>
<td>Similar to spray?</td>
<td>N/A</td>
</tr>
<tr>
<td>Dose comparison</td>
<td>60 μg</td>
<td>100 μg</td>
<td>2.5 μg</td>
<td>2.5 μg</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>120 μg</td>
<td>200 μg</td>
<td>5 μg</td>
<td>5 μg</td>
<td>&lt;0.5 μg</td>
</tr>
<tr>
<td></td>
<td>240 μg</td>
<td>400 μg</td>
<td>10 μg</td>
<td>10 μg</td>
<td>&lt;1 μg</td>
</tr>
</tbody>
</table>

Note: The indication of Desmopressin is varying between countries and regions, not all desmopressin formulations are approved for the treatment of Neurohypophyseal Diabetes Insipidus in all countries. Based on unpublished BA studies (CS004, RG84063–102, 45A02/48)
polyuria, thirst or clinically significant decreases in serum sodium. At week 4 of treatment, Desmopressin Melt provided the same level of antidiuretic control (24 h urine volume, osmolarity specific gravity and hourly diuresis) as intranasal desmopressin, at baseline. Desmopressin melt was as efficacious as intranasal desmopressin in both children and adults.

The mean daily dose of intranasal desmopressin given to maintain adequate antidiuresis was not a good predictor of the dose of melt required to obtain the same control (43). The dose ratio averaged 1:24 but individual variation was wide. Thus, individual dose titration is necessary when the formulation is changed. According to current label dosage should always be adjusted in accordance with the patient’s antidiuretic response (44).

Six patients, all adults, developed mild hyponatraemia during dose titration of desmopressin Melt. However, their sodium returned quickly to normal on continued treatment following a reduction in dose to levels that maintained their urine output within the normal range. One patient experienced serious hyponatraemia (124 mmol/l) that led to hospitalization and elimination from the study. This patient, a 63 y old female, also had secondary adrenal insufficiency treated with 10 mg of cortisol a day.

Other treatments
Carbamazepine, a drug used to treat neurologic disorders, also has a significant antidiuretic effect in neurohypophyseal DI (45, 46). At conventional doses of 200 to 800 mg p.o., it reduces urine volume by 30% to 90% and increases urine osmolarity proportionately. The mechanism is uncertain. Studies employing immunoassays have shown that carbamazepine reduces plasma vasopressin in healthy subjects (47, 48, 49) even though in one study (47) it impaired urinary dilution in response to a water load. Use of carbamazepine to treat neurologic disorders has also been implicated in the development of hyponatraemia with inappropriate antidiuresis (50).

Chlorpropamide, a sulfonylurea drug used to lower blood glucose in type 2 diabetes mellitus, also has a significant antidiuretic effect in neurohypophyseal DI. This effect, which was discovered accidently almost 50 y ago (51), occurs at doses similar to those used in diabetes mellitus (250 to 500 mg per os once a day), reaches a maximum within 3 to 10 d of starting treatment, reduces urine volume by an average of about 60% (range 30 to 90%) in patients with severe as well as partial deficiencies of vasopressin and is associated with a proportionate rise in urine osmolarity but no change in solute excretion or GFR (52–69). In patients who do not get satisfactory control of their DI with chlorpropamide therapy alone, the effects can be enhanced considerably by the addition of chlorothiazide (59) or carbamazepine (70). Chlorpropamide also impairs modestly the ability to dilute the urine after water loading not only in patients with neurohypophyseal DI (56, 64, 65, 66, 71) but also in most normal subjects (52, 53, 58, 60, 65).

The mechanism of the antidiuretic effect of chlorpropamide in neurohypophyseal DI probably does not involve an increase in vasopressin secretion (69) though it may have this effect in healthy adults (65). Most of the clinical evidence suggests that chlorpropamide acts by potentiating the antidiuretic effect of the very low levels of plasma vasopressin that persist even in patients with severe neurohypophyseal DI (57, 58, 63, 64, 65, 73) but a more recent study in LLC-PK cells indicates that chlorpropamide has a direct effect on the V2 receptor (74).

Clofibrate, a drug formerly used to treat certain hyperlipidemias, also has an antidiuretic effect in neurohypophyseal DI (65, 75, 76). Like the other nonpeptide oral agents, the magnitude of the effect varies considerably from patient to patient but, on average, at doses of 2 g a day, it decreases urine volume by about 50% and increases urine osmolarity proportionately. In most patients, combining clofibrate with chlorpropamide does not significantly improve the antidiuretic effect. The mechanism of action of clofibrate is less well defined. It is not associated with an increase in urinary ADH excretion (65) but that finding cannot be interpreted without reference to the change in osmotic stimulation of the hormone. Following these studies, follow-up of long-term clofibrate therapy for hyperlipidemia revealed that it was associated with several serious adverse effects including an unexplained increase in mortality and it was withdrawn in 2002.

The thiazide diuretics also have a paradoxical antidiuretic effect in patients with neurohypophyseal DI (77). Unlike the other nonpeptide oral agents, however, they have a similar antidiuretic effect in nephrogenic DI (78). In both cases, the antidiuretic effect tends to be smaller than that produced by the other nonpeptide oral agents but it is enhanced considerably by restricting sodium intake. Moreover, it potentiates the antidiuretic effect of the other agents and, therefore, is most often used in conjunction with them. Its mechanism of action is not altogether clear. It obviously does not depend on the effect of vasopressin since it works even in patients with severe renal resistance to the hormone (4, 78). The most likely mechanism is decreased reabsorption of sodium in the loop of Henle resulting in decreased dilution of urine and a reduction in ECF volume that stimulates a compensatory increase in proximal tubular reabsorption of sodium and water thereby diminishing delivery of filtrate to the distal nephron and collecting tubules where the defect in urinary
Patients, the maximum effect is not achieved for 24–48 h (variably every 12–24 h). In some previously untreated patients, the requisite dose usually ranges from 10 to 20 μg intranasally, 60 to 240 μg of Melt or 100 to 400 μg of the oral tablet. Due to the large individual variation, the dose should start at the lower end and titrated upward depending on the effect. If intranasal or oral administration is not possible, desmopressin can also be given by injection (1–2 μg subcutaneously every 12–24 h). In some previously untreated patients, the maximum effect is not achieved for 24–48 h after the first dose probably as because the concentrating capacity of the kidney is reduced temporarily by the vasopressin deficiency. It is particularly important to educate children with neurohypophyseal DI and/or their parents about the danger of excessive fluid intake during treatment and make them fully aware of the signs and symptoms of water intoxication.

Special populations

Neonates/Infants/Children

The treatment of neurohypophyseal DI in infants and children differs slightly because their diet contains a proportionally larger quantity of water. Consequently, it may be necessary to allow more urine output to prevent hypernatremia. How much more varies with age and diet and whether the child is allowed to drink water or flavored fluids ad libitum. The general rule should be to eliminate all forms of fluid intake except milk, water or a set amount of fruit juice and tailor treatment not to urine volume (which is nearly impossible to measure accurately in infants or young children) but to fluid intake and/or plasma sodium.

To achieve this goal, desmopressin can be given in different ways. In infants below 12 mo of age, the old Rhynil preparation of nasal spray can be diluted 1:10 with physiological saline (33). Oral administration of this dilution once or twice a day in amounts containing 1 to 3 μg of desmopressin provided good control of neurohypophyseal DI with improved linear growth and weight gain and no signs or symptoms of electrolyte disturbances (80). Subcutaneous injection of the parenteral formulation of desmopressin in doses ranging from 0.02 μg q.d. to 0.08 μg twice daily is sometimes preferred (81). With this method, serum sodium concentrations varied less and more remained within the normal range than with intranasal administration. Although studies are limited, case reports indicate that treatment should be initiated with 0.05 μg (0.0125 ml) and then titrated upward according to the effect on diuresis and serum sodium.

In children with neurohypophyseal DI below the age at which they begin to consume solid food and drink spontaneouly, brief hospitalization may be worthwhile to determine the dose of desmopressin required to completely eliminate polyuria (82). In these patients, the requisite dose usually ranges from 10 to 20 μg intranasally, 60 to 240 μg of Melt or 100 to 400 μg of the oral tablet. Due to the large individual variation, the dose should start at the lower end and titrated upward depending on the effect. If intranasal or oral administration is not possible, desmopressin can also be given by injection (1–2 μg subcutaneously every 12–24 h). In some previously untreated patients, the maximum effect is not achieved for 24–48 h after the first dose probably as because the concentrating capacity of the kidney is reduced temporarily by the vasopressin deficiency. It is particularly important to educate children with neurohypophyseal DI and/or their parents about the danger of excessive fluid intake during treatment and make them fully aware of the signs and symptoms of water intoxication.

Pregnancy

Women with pre-existing neurohypophyseal DI who becomes pregnant and women who develop temporary neurohypophyseal DI during pregnancy (gestational DI) usually can be treated successfully with oral desmopressin. Unlike the native hormone, the analog is resistant to degradation by leucine aminopeptidase produced by the placenta (10, 83). The doses required are similar to or slightly greater than those required in the nongravid state and, in the case of gestational DI, they can be discontinued 4 to 6 wk after delivery when the DI and blood levels of the peptide usually disappear. The only other difference in management is that, in monitoring the effect of treatment, it should be remembered that the plasma sodium concentration during pregnancy is normally about 5 mOsm/kg lower than in the nongravid state. Desmopressin can be administered postpartum to nursing mothers as very little appears in breast milk (84). Some cases of gestational DI may be resistant to treatment with desmopressin as well as vasopressin owing either to abnormally high levels of vasopressinase or some defect in the kidneys.

Elderly

Treatment of neurohypophyseal DI is usually life-long because recovery from an established vasopressin deficiency is uncommon, even if the underlying cause is eliminated (85). The management of neurohypophyseal DI in the elderly is similar to that in young adults but the risks of developing hyponatremia may be greater at least when intranasal desmopressin is used (82). The reason is unclear but may relate to increased renal sensitivity to desmopressin or, more likely, abnormalities in the osmoregulation of thirst and fluid intake which are known to occur in the elderly.

Hypodipsia with neurohypophyseal DI

A few patients with neurohypophyseal DI also have a deficiency in thirst (hypodipsia) due to a variety of disorders that damage the osmoreceptors in the anterior hypothalamus (Table 1) (86). The management of these patients is extremely challenging because they have lost both of the homeostatic mechanisms that normally regulate water balance. Consequently, they tend to suffer from wide swings in plasma sodium from hyper- to hyponatremia...
even when their DI is well controlled (86). These swings cannot be prevented by prescribing a fixed level of fluid intake because insensible and even urinary losses of water vary significantly from day to day depending on temperature, activity and diet. Consequently, it is necessary to prescribe fluid intake on a sliding scale based on daily changes in weight and/or plasma sodium (86, 87). Since the frequency and severity of the hyponatremia are increased by water loss, complete around the clock control of their DI is greater importance than in patients with a normal thirst mechanism. Such control can be achieved with desmopressin or with chlorpropamide, alone or in combination with chlorothiazide. In some respects the latter may be preferred because the level of control tends to be more stable and chlorpropamide may also stimulate thirst (88).

Summary

The treatment of choice for long term management of neurohypophyseal DI is desmopressin tablet or Melt. When dose titrated to allow for individual differences in bioavailability and renal sensitivity, either formulation completely eliminates the polyuria, thirst and polydipsia that characterize the disorder. The risk of hyponatremia during such treatment is uncertain but appears to be modest (< 5%) at least if urine volume is reduced no more than to the normal basal range and patients with primary polydipsia are accurately differentiated from those with partial pituitary DI. When started on treatment, the patient should also be educated about the need to drink no more than necessary to satisfy thirst. Compliance with this requirement can be problematic in infants, children and adolescents whose fluid intake is often motivated by factors other than thirst. Accurate data on the incidence of hypernatremia and the factors that influence it during long term therapy of neurohypophyseal DI are needed.

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CHAPTER 7
Conclusions and future perspectives
CHAPTER 7. Conclusions and future perspectives

It is said that good science raises more new questions than it answers. As highlighted in this booklet, research is ongoing to further our understanding of the optimisation of treatment for CDI patients. However, based on the results of the studies and the review included here, the following key conclusions can be drawn:

• **Study I**
  - The antidiuretic action of desmopressin (and probably vasopressin itself) is characterised by a considerable lag or delay in exerting its full effect. Large individual differences in the response cannot be explained fully by differences in pharmacokinetics. Understanding these individual variations better will enable more precise tailoring of the dose and timing of dose for patients in need of antidiuretic treatment.

• **Studies II and III**
  - In CDI, in addition to these individual differences in response to desmopressin substitution therapy, some patients maintain a small, but inadequate, endogenous production of AVP. As a result, individual dose titration depending on severity of CDI and also on the patients’ individual acceptability of the associated polydipsia/polyuria, is needed.

• **Review I**
  - In recent years there have been several improvements in the treatment of central diabetes insipidus. They include new formulations of the vasopressin analogue desmopressin, a better understanding of the effect of fluid intake on dosing, and more information about treatment of infants, children and pregnant women who present special challenges.

    - Desmopressin can provide effective and safe therapy for all patients with central or gestational DI if given in doses and by a route that takes into account the determinants of fluid intake.

    - In acute settings where fluid intake is determined by factors other than thirst, desmopressin should be given intravenously in doses that have a short duration of action and can be adjusted quickly in accordance with changes in hydration as indicated by plasma sodium.

    - In ambulatory patients, the oral formulations (tablet or melt) are preferred for their convenience.

    - If fluid intake is regulated normally by the thirst mechanism, desmopressin tablets or melt can be taken safely one to three times a day in doses sufficient to eliminate the polyuria completely.
- However, if fluid intake consistently exceeds replacement needs as evidenced by development of hyponatraemia, the dose should be reduced to allow higher than normal rates of urine output or intermittent breakthrough diuresis

  - This regimen is often indicated in infants or children since their rate of fluid intake tends to be greater than in adults

- In all cases, the appropriate dose should be determined by titration, owing to considerable inter-individual differences in bioavailability and antidiuretic effect

Our findings of a considerable lag or delay until desmopressin exerts its full effect at around 3–4 hours, and large individual differences in response that cannot be explained fully by differences in pharmacokinetics (Study I), have potential implications for the use of desmopressin in basic as well as clinical investigation, diagnosis and treatment. The relative timing or speed of each of the many different effects of a V₂ agonist is important for understanding the total response and should be estimated whenever it is possible to distinguish between these effects.

Another implication pertains to the hazards and limitations of trying to use the antidiuretic response to acute desmopressin challenge to differentiate between primary polydipsia and partial defects in vasopressin secretion or action. Our studies have illustrated that individual variation as well as timing and dose are major determinants of the response. As a consequence, there is currently no clear and satisfactory way to identify or eliminate these problems with the indirect method of differential diagnosis.

A third point to be drawn from these studies is that pharmacokinetic data are not an adequate substitute for pharmacodynamic data when attempting to determine the magnitude and duration of the antidiuretic effect of desmopressin and, probably, other V₂R agonists. This is relevant to their use in the treatment of CDI.

In CDI, despite its relative infrequency and the availability of satisfactory replacement therapy with desmopressin, as proved in both Study II and Study III, further research is needed. Several areas appear to be of particular importance:

- Studies into the natural history of DI throughout the entire lifespan are needed. Focus should be on a possible age-related compensatory change in V₂R sensitivity or in mobilisation and removal of aquaporin water channels, including also hormonal and/or genetic gender differences in V₂R sensitivity
• The development and trial of new formulations of desmopressin and other V2 agonists to facilitate more precise tailoring of the dose to the needs of individual patients, particularly infants with CDI, and potentially in new indications

• Ultimately, a search for alternatives to vasopressin replacement therapy. Gene therapy has been investigated in vitro and in animal models with some success. Using nonviral gene transfer techniques, a precursor form of vasopressin, provasopressin, was produced in nonendocrine cells transfected with the wild-type vasopressin gene. In another study, urine output and urine osmolality in Brattleboro rats were normalised for up to 4 months after injection of an adenoviral vector in the hypothalamus encoding the rat vasopressin cDNA. Though promising, these strategies have yet to be proven and are not yet feasible alternatives to traditional replacement therapy
CHAPTER 8

Abbreviations
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADME</td>
<td>Absorption, distribution, metabolism and excretion</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>AQP-2</td>
<td>Aquaporin 2</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical Classification System</td>
</tr>
<tr>
<td>AVP</td>
<td>Arginine vasopressin</td>
</tr>
<tr>
<td>BID</td>
<td>Bis in die (Latin for ‘twice a day’)</td>
</tr>
<tr>
<td>CDI</td>
<td>Central diabetes insipidus</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>dDAVP</td>
<td>1-deamino-8-D-arginine vasopressin</td>
</tr>
<tr>
<td>DOA</td>
<td>Duration of antidiurectic action</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report form</td>
</tr>
<tr>
<td>ED50</td>
<td>Effective dose, for 50% of people given it</td>
</tr>
<tr>
<td>FAS</td>
<td>Full analysis set</td>
</tr>
<tr>
<td>FDA</td>
<td>(US) Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good clinical practice</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<tr>
<td>ICS</td>
<td>International Continence Society</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent ethics committee</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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</tr>
<tr>
<td>IMP</td>
<td>Investigational medicinal product</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional review board</td>
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<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last observation carried forward</td>
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<tr>
<td>LUTS</td>
<td>Lower urinary tract symptoms</td>
</tr>
<tr>
<td>LVP</td>
<td>Lysine vasopressin</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MNE</td>
<td>Mono-symptomatic nocturnal enuresis</td>
</tr>
<tr>
<td>NDI</td>
<td>Nephrogenic diabetes insipidus</td>
</tr>
<tr>
<td>MCID</td>
<td>Minimal clinically important difference</td>
</tr>
<tr>
<td>OC</td>
<td>Observed cases</td>
</tr>
<tr>
<td>ODT</td>
<td>Oral disintegrating tablet</td>
</tr>
<tr>
<td>PK/PD</td>
<td>Pharmacokinetics/pharmacodynamics</td>
</tr>
<tr>
<td>PNE</td>
<td>Primary nocturnal enuresis</td>
</tr>
<tr>
<td>PP</td>
<td>Per protocol</td>
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<tr>
<td>PRO</td>
<td>Patient-reported outcome</td>
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<tr>
<td>PT</td>
<td>Preferred term</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised clinical trial</td>
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<tr>
<td>QoL</td>
<td>Quality of life</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SIADH</td>
<td>Syndrome of inappropriate antidiuretic hormone</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
<td>------------</td>
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<tr>
<td>S-Na</td>
<td>Serum sodium</td>
</tr>
<tr>
<td>SOC</td>
<td>System organ class</td>
</tr>
<tr>
<td>TID</td>
<td>Ter in die (Latin for ‘three times a day’)</td>
</tr>
<tr>
<td>V₁R</td>
<td>Vasopressin 1 receptor</td>
</tr>
<tr>
<td>V₂R</td>
<td>Vasopressin 2 receptor</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
CHAPTER 9

Bibliography
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