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ORIGINAL ARTICLE

Desmopressin duration of antidiuretic action in patients with central diabetes insipidus

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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 μg 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

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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

dosage regimen should be adjusted in accordance with the patient's response. In a previous trial of Desmopressin tablets, all patients required t.i.d. dosing [2], and for the majority of patients, the maintenance dose is recommended as 60 to 120 μg sublingually three times daily according to the current label and SmPC [3].

Purpose of the study

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 dosages. 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.

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

Patient	Treatment sequence			
01T01	10	250 ng	125 ng	500 ng
01T02	11	125 ng	500 ng	250 ng
01T03	7	125 ng	250 ng	500 ng
01T04	1	30 ng	60 ng	125 ng
01T05	4	60 ng	30 ng	125 ng
01T06	5	30 ng	125 ng	60 ng
01T07	3	60 ng	125 ng	30 ng
01T08	8	500 ng	125 ng	250 ng
01T09	9	250 ng	500 ng	125 ng
01T10	6	125 ng	60 ng	30 ng
01T11	2	125 ng	30 ng	60 ng
01T12	12	500 ng	250 ng	125 ng
01T13	6	125 ng	60 ng	30 ng

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.

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 was 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 volume of >96 ml/kg body weight and urine-osmolality <200 mOsm/kg, and 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 the normal range (usually 295 mOsm/kg and 148 mEq/l, respectively).
2. Complete and continuous control of the DI by desmopressin therapy for at least 6 months without "breakthrough" diuresis, hypernatraemia, hyponatraemia, or symptoms or signs of water intoxication.
3. A deficient plasma vasopressin response to osmotic or non-osmotic stimulation (e.g. orthostatic stimuli).
4. Absence of the posterior pituitary bright spot on T-1 weighted midsaggital MRI of the brain.

Patients that met any of the following criteria was excluded from participation in this study: Presence or a history of nephrogenic diabetes insipidus, diabetes mellitus, hypertension, cardiovascular, renal or hepatic disease; presence of uncorrected hypothyroidism, hypoadrenalism or hypogonadism; concurrent treatment with diuretics, chlorpropamide, tricyclic antidepressants, indomethacine, 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

Table 2 Demographic data (safety population)

Randomised patients	13
Gender	
Female	11
Male	2
Age(years)	
Mean(SD)	39.1 (9.1)
Median	40
Min–Max	19–61
Ethnic origin	
Caucasian	13
Black	0
Oriental	0
Other	0
Height(cm)	
Mean(SD)	166.4 (7.3)
Median	165
Min–Max	157–185
Weight(kg)	
Mean (SD)	69.3 (12.7)
Median	68.0
Min–Max	52.7–93.6
Body mass index	
Mean(SD)	25.2 (5.3)
Median	23.2
Min–Max	18.2–36.6

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 t½), 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, max 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

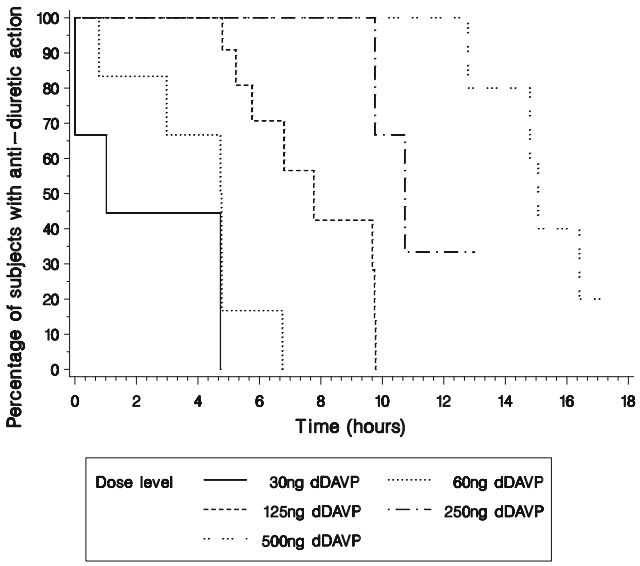

Fig. 1 Kaplan Meier plot—duration of action (Cut off at 125 mOsm/kg), PP Population

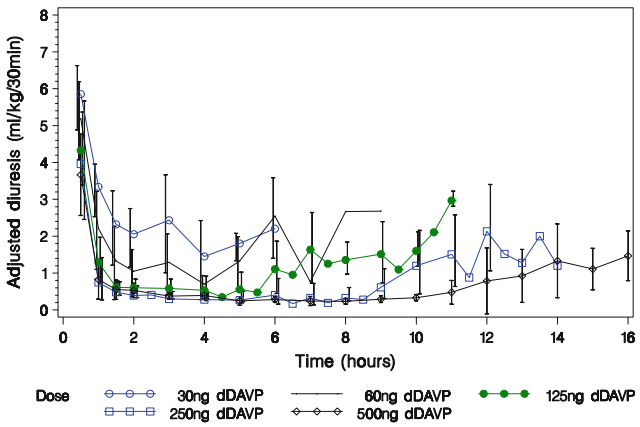

Fig. 2 Mean adjusted diuresis curve (±SD), PP population

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 doselevels 125, 250, and 500 ng the following clinical relevant duration of actions 3 h 53 min, 8 h 20 min, and 11 h respectively.

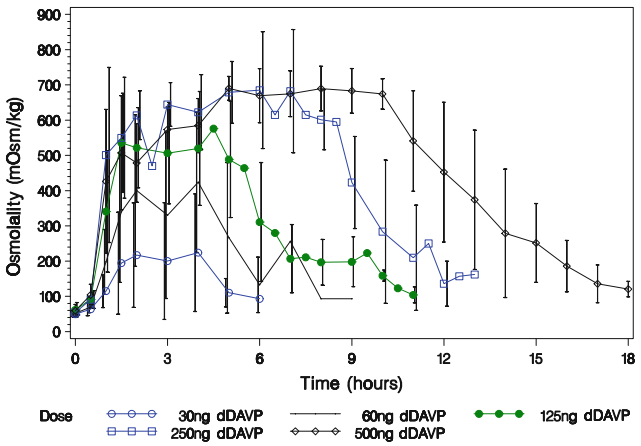

Fig. 3 Mean osmolality curves (±SD), PP population

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 × 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

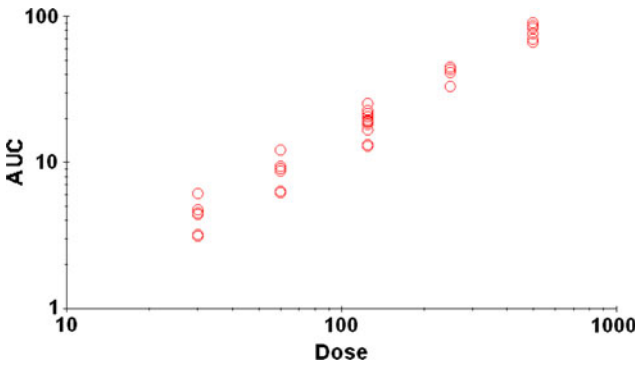

Fig. 4 AUC versus dose of desmopressin

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 dose-relationship of these thirst endpoints was found, possible due to the large variations in these VAS-measures.

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 S-curve 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 newer 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 asses 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 needs 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].

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