ORIGINAL

Comparison of incidence of hyponatremia between intranasal and oral desmopressin in patients with central diabetes insipidus

Yuko Kataoka¹⁾, Sachi Nishida¹⁾, Akihiro Hirakawa²⁾, Yutaka Oiso¹⁾ and Hiroshi Arima¹⁾

¹⁾ Department of Endocrinology and Diabetes, Field of Internal Medicine, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan

²⁾ Biostatistics and Bioinformatics Section, Center for Advanced Medicine and Clinical Research, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan

Abstract. Central diabetes insipidus (CDI), which is characterized by polyuria and polydipsia, is caused by a deficiency of the antidiuretic hormone arginine vasopressin (AVP). While CDI is treated with desmopressin, an analogue of AVP, the intranasal formulation is inconvenient and CDI patients reportedly prefer the oral formulation to the intranasal one. In Japan, intranasal desmopressin had been the only formulation for the treatment of CDI until 2012, when the desmopressin orally disintegrating tablet (ODT) was approved for treatment. In this study we analyzed 26 patients with CDI in whom intranasal desmopressin was switched to desmopressin ODT. The mean daily dose of intranasal desmopressin was 10 ± 8 $\mu\text{g/day}$, and that of desmopressin ODT was 142 ± 59 $\mu\text{g/day}$. The mean serum sodium levels were 140 ± 5 mmol/L and 140 ± 3 mmol/L with intranasal desmopressin and desmopressin ODT, respectively, and there were no significant differences between these values. The frequency of hyponatremia (<135 mmol/L) with intranasal desmopressin was 11.7% and that with desmopressin ODT was 7.6%, while the frequency of hyponatremia (<130 mmol/L) with intranasal desmopressin was 4.2% and that with desmopressin ODT was 1.3%. Statistical analyses revealed that incidence of hyponatremia was significantly decreased after the switch to desmopressin ODT. Thus, it is suggested that water balance is better controlled with desmopressin ODT than with intranasal desmopressin in patients with CDI.

Key words: Desmopressin, Central diabetes insipidus, Hyponatremia, Vasopressin

ARGININE VASOPRESSIN (AVP) is the antidiuretic hormone which is synthesized in the magnocellular neurons in the supraoptic and paraventricular nuclei [1, 2]. AVP is axonally transported to the posterior pituitary, released into the systemic circulation, and acts through V2 receptor in the kidney in order to promote reabsorption of free water [1, 2]. The osmoregulation of AVP release is so precise that increases in plasma osmolality of only 1-2% lead to increases in plasma AVP [1, 3, 4]. As a result, plasma osmolality in most cases is controlled at levels of around 280 mOsm/kg, which is the threshold of AVP release [1, 3, 4].

The deficiency of AVP causes a disorder called cen-

tral diabetes insipidus (CDI), which is characterized by polyuria accompanied by thirst and polydipsia [5, 6]. Patients with CDI are treated with desmopressin, an analogue of AVP, which is usually given twice or three times per day [7]. The concentration of desmopressin in blood reaches a peak soon after administration, and the antidiuretic action remains maximal for several hours [8-11]. Due to the pharmacokinetics/pharmacodynamics of desmopressin, its most frequent side effect in the treatment of CDI is hyponatremia [12, 13].

In Japan, intranasal desmopressin had been the only formulation for the treatment of CDI until 2012, when desmopressin orally disintegrating tablet (ODT) was approved for treatment. Because the efficiency and safety of desmopressin ODT have been demonstrated [13, 14], and oral formulations are preferred for their ease of administration [15, 16], it is predicted that desmopressin ODT will be the first-line treatment for CDI in Japan as it was reported previously in Denmark [17].

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Correspondence to: Hiroshi Arima, Department of Endocrinology and Diabetes, Field of Internal Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. E-mail: arima105@med.nagoya-u.ac.jp

However, it is unclear whether or not the frequency of hyponatremia will differ between the two formulations.

In the current study, we analyzed the incidence of hyponatremia in patients with CDI in whom intranasal desmopressin was switched to desmopressin ODT.

Materials and Methods

Patients

Using databases of the electronic medical recording systems, 32 patients (15 males and 17 females) with CDI in whom intranasal desmopressin was switched to desmopressin ODT were reviewed in May 2014 at Nagoya University Hospital. Five patients were excluded from the study because the duration of desmopressin ODT treatment was less than 4 months, and 1 was excluded because she had adipsia. As a result, a total of 26 patients were subjected to the analysis. The protocol of study was approved by the institutional review board of Nagoya University Hospital, and the study adhered to the principles of the Declaration of Helsinki.

Diagnosis of CDI

The diagnosis of CDI was based on a history of polyuria and polydipsia that had been controlled by intranasal desmopressin. In addition, pituitary MRI was examined in all 26 patients, and the bright spot in the posterior pituitary on midsagittal T1-weighted MRI of the brain was absent in all of them (3-tesla MRI; 13 subjects, 1.5-tesla MRI; 13 subjects). In 10 patients, a deficiency in plasma AVP responses to osmotic stimulation with hypertonic saline was also confirmed.

Anterior pituitary function

The diagnosis of anterior pituitary dysfunction was based on the basal levels of plasma anterior pituitary hormones or the responses of ACTH, GH, TSH/PRL and LH/FSH to CRH, GRH, TRH and GnRH, respectively. The substitution of hormones including steroid hormones and thyroxine was investigated on the medical records.

Switch from intranasal desmopressin to desmopressin ODT

Twenty patients were admitted to the Nagoya University Hospital for the switch from intranasal desmopressin to desmopressin ODT. These patients started the treatment with 60 µg desmopressin ODT mostly at night, and dose titration was performed based

on urine volume and urine osmolality. For 6 patients, intranasal desmopressin was switched to desmopressin ODT without admitting them to the hospital. They started treatment with 60 µg desmopressin ODT twice daily and dose titration was performed.

Serum sodium levels

Serum sodium levels measured before and after the switch to desmopressin ODT were subjected to the analysis of incidence of hyponatremia (<135, <130 mmol/L) and hypernatremia (≥ 150 mmol/L). By setting the maximum duration of intranasal desmopressin treatment in the analysis to 18 months, the total numbers of measurements of serum sodium levels were similar between the formulations (intranasal desmopressin: 264, desmopressin ODT: 238), and there were no significant differences in the number of measurements in each patient between intranasal desmopressin (10 ± 9) and desmopressin ODT (9 ± 6). The mean duration of intranasal desmopressin treatment for the analysis of serum sodium levels was 15 ± 3 months (range, 4 to 18 months), and that of desmopressin ODT was 8 ± 2 months (range, 4 to 12 months).

Statistical analyses

We evaluated the impact of switching to desmopressin ODT on the risk of hyponatremia (<135 mmol/L and <130 mmol/L) by using a Generalized Estimating Equations (GEE) model that is a well-known statistical method for longitudinal data. The GEE model included the variables for the switch to desmopressin ODT, time, age and gender. A two-sided *p* value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using the SAS software package (version 9.3; SAS Institute Inc., Cary, NC, USA). The data are demonstrated as mean $\pm$ SD.

Results

Background of the patients

The etiology in the 26 CDI patients is shown in Table 1. The mean ages at diagnosis of CDI and switch of intranasal desmopressin to desmopressin ODT were 38 ± 20 years (range, 3 to 74 years) and 54 ± 17 years (range, 16 to 77 years), respectively. Thirteen patients had anterior pituitary dysfunction and were substituted with both steroid hormones and thyroxine.

Table 1 Background of patients with CDI in whom intranasal desmopressin was switched to desmopressin ODT

Number of patients with CDI (male/female)	26 (13/13)
Etiology	
Idiopathic	11
Craniopharyngioma	5
Neurosurgery	4
Inflammation	2
Germ cell tumor of CNS	1
Pituitary adenoma	1
Empty sella	1
Sarcoidosis	1
Age of CDI diagnosis (mean $\pm$ SD)	38 $\pm$ 20 yr
Age of desmopressin switch (mean $\pm$ SD)	52 $\pm$ 17 yr
Anterior pituitary dysfunction (Yes/No)	13/13

CDI, central diabetes insipidus; CNS, central nervous system.

"Inflammation" includes lymphocytic infundibuloneurohypophysitis and IgG4-related diseases.

Fig. 1 Doses of intranasal desmopressin and desmopressin ODT. There was no significant correlation between the doses of intranasal desmopressin and desmopressin ODT. The number of patients in each closed circle is 1 unless indicated in parentheses.**Table 2** Results of the GEE analysis

Variables		Hyponatremia with <135 mmol/L (N = 26)			Hyponatremia with <130 mmol/L (N = 26)		
		Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Switch	Intranasal	1		0.0165	1		0.0001
	Oral	0.44	0.22 0.86		0.31	0.17 0.57	
Time, days	Ten days' increase	1.00	1.00 1.00	0.0836	1.00	1.00 1.00	0.6311
Age, years	One year increase	1.04	1.01 1.08	0.0121	1.08	1.02 1.14	0.0044
Gender	Female	1			1		
	Male	0.79	0.19 3.36	0.7494	0.17	0.02 1.45	0.1058

Dose and administration frequency of intranasal and oral DDAVP

The mean daily dose of intranasal desmopressin was 10 ± 8 μ g, and that of desmopressin ODT was 142 ± 59 μ g. The ratio of the mean daily dose of intranasal desmopressin to desmopressin ODT was approximately 1:14. However, there was a wide range of dose ratios across individuals, and there were no significant correlations between the doses of intranasal desmopressin and desmopressin ODT (Fig. 1). The mean daily administration frequency of intranasal desmopressin was 2 ± 1 , and that of desmopressin ODT was 2 ± 1 .

Serum sodium levels

The mean serum sodium levels with intranasal desmopressin were 140 ± 5 mmol/L, and those with desmopressin ODT was 140 ± 3 mmol/L. The statistical analysis did not show any significant differ-

ence in these values. Hyponatremia (<135 mmol/L) was found in 31 measurements (11.7%) with intranasal desmopressin (range, 117 to 134 mmol/L) and 18 measurements (7.6%) with desmopressin ODT (range, 125 to 134 mmol/L). The serum levels of total protein and triglyceride during hyponatremia ranged from 5.6 to 7.7 g/dL and from 38 to 294 mg/dL, respectively, indicating that pseudohyponatremia was not involved in the measurements [18]. Furthermore, blood glucose levels during hyponatremia ranged from 72 to 158 mg/dL, indicating that hyponatremia was also not due to high glucose levels [19]. Table 2 shows the impact of switching to desmopressin ODT on the risk of hyponatremia (<135 mmol/L and <130 mmol/L) based on the GEE analysis. In terms of developing hyponatremia with <135 mmol/L, the odds ratio for desmopressin ODT relative to intranasal desmopressin was 0.44 ($p = 0.0165$).

Fig. 2 Serum sodium levels before and after switch from intranasal desmopressin to desmopressin ODT. Serum sodium levels with intranasal desmopressin (A; $n=264$) and desmopressin ODT (B; $n=238$). Serum sodium levels were classified into <130 , 130–134, 135–149, and ≥ 150 mmol/L.

Hyponatremia (<130 mmol/L) was found in 11 measurements (4.2%) with intranasal desmopressin (range, 117 to 129 mmol/L) and 3 measurements (1.3%) with desmopressin ODT (range, 125 to 129 mmol/L). In terms of developing hyponatremia with <130 mmol/L, the odds ratio for desmopressin ODT relative to intranasal desmopressin was 0.31 ($p=0.0001$). While there were 2 patients treated with desmopressin ODT in whom hyponatremia (<130 mmol/L) was found, they were among 4 patients who also experienced hyponatremia with intranasal desmopressin, and there were no patients in whom hyponatremia occurred only with desmopressin ODT but not with intranasal desmopressin. In addition, we observed that the risk of hyponatremia (<135 mmol/L or <130 mmol/L) was significantly increased with age (Table 2). On the other hand, hypernatremia (≥ 150 mmol/L) was found in 1 measurement (0.4%) with intranasal desmopressin (152 mmol/L), and 1 measurement (0.4%) with desmopressin ODT (151 mmol/L). Because of the rarity of hypernatremia, the GEE analysis was not applicable. Fig. 2 shows the distribution of serum sodium levels before and after the switch from intranasal desmopressin to desmopressin ODT.

Discussion

The current study clearly demonstrated that the incidence of hyponatremia decreased significantly after the switch from intranasal desmopressin to desmopressin ODT in patients with CDI, suggesting that desmopres-

sin ODT could be superior to intranasal desmopressin in controlling water balance in patients with CDI.

The mean doses of intranasal desmopressin and desmopressin ODT given to patients with CDI were 10 $\mu\text{g/day}$ and 142 $\mu\text{g/day}$, respectively, and the mean frequency of administration was around twice per day for both formulations. The antidiuretic action of desmopressin reportedly reaches maximum in many patients when the concentration in blood reaches around 2 pmol/L [20]. It has also been reported that, when 20 μg intranasal desmopressin is given to subjects, the concentration soon exceeds 2 pmol/L, and remains higher than 2 pmol/L for several hours [10]. Similar pharmacokinetics are shown when a 200 μg desmopressin tablet is given to subjects [10]. Therefore, if patients with CDI treated with desmopressin take more water than necessary, it is likely that hyponatremia will occur. There is an option to decrease the dose of desmopressin in order to decrease the frequency of hyponatremia. However, patients with CDI would suffer from polyuria accompanied by thirst and polydipsia if the dose of desmopressin is inadequate.

The current study showed that the incidence of hyponatremia (<130 mmol/L) is significantly decreased by desmopressin ODT (1.3%) compared to intranasal desmopressin (4.2%) in patients with CDI. This is consistent with postmarketing surveillance of desmopressin showing that a lower risk of hyponatremia was found with the tablet formulation compared to the intranasal one [12], while its major indications are primary nocturnal enuresis and nocturia. The decrease in the incidence

of hyponatremia shown in the present study was not due to the relatively low dose of desmopressin ODT compared to intranasal desmopressin, as the mean serum sodium levels did not differ between the two formulations. Consistent with a previous study [13], there was no significant correlation in the doses between intranasal desmopressin and desmopressin ODT. This suggests that the bioavailability of the two formulations could differ between individuals. It is possible that the absorption of intranasal desmopressin is affected by nasal hyperaemia and/or congestion as well as the intranasal maneuvers of patients, resulting in a relatively large variability in the drug absorption of this formulation [12]. The causes of hyponatremia in CDI patients treated with desmopressin could be an excess of either desmopressin or water intake. If the bioavailability of intranasal desmopressin is not constant, the dose could be increased by the doctors or even by patients in order to avoid polyuria. It is also possible that patients try to increase water intake when they feel that the antidiuretic effects of desmopressin are not adequate, and the amount of water intake might be more than necessary in some cases. By adding an extra intranasal desmopressin administration and increasing water intake, the incidence of hyponatremia could be potentially increased. Thus, the decreased incidence of hyponatremia with desmopressin ODT might be due to the fact that its bioavailability is more constant in desmopressin ODT than in intranasal desmopressin [12], and that the titration of dosing is easier with desmopressin ODT.

The osmotic demyelination syndrome, which can be lethal, occurs when serum sodium levels increase rapidly during the treatment of severe hyponatremia [21, 22]. It is also known that chronic hyponatremia, even if the decrease in serum sodium levels is mild, could lead to several disorders such as attention deficits [23] and fracture [24]. On the other hand, our previous study showed that patients with adipsic CDI, whose serum sodium levels were often higher than 150 mmol/L, were susceptible to severe inflammation, and that their risk of death was high [25]. Thus, it is both important and difficult to maintain the serum sodium levels within normal ranges in patients with CDI. As of now, the minimum dose of desmopressin ODT is 60 µg, and it is difficult to optimize the dose in some patients for whom lower doses of desmopressin are more appropriate to maintain water balance. In these patients, intranasal desmopressin would be more suitable, as the titration of dose is easier with this formulation, given

that the dose could be decreased as appropriate. In addition, when patients with CDI have gastrointestinal troubles, intranasal desmopressin is more suitable than desmopressin ODT. Thus, while our data suggest that water balance could be better maintained with desmopressin ODT, intranasal desmopressin is still required in some situations.

There are several limitations in this study. First, since most patients with hyponatremia were asymptomatic, the number of hyponatremia cases could increase if we had measured the serum sodium levels more frequently. However, the incidence of hyponatremia (<130 mmol/L) with intranasal desmopressin shown in this study (4.2%) was similar to what we reported in a previous study in which hyponatremia occurred in 154 out of 3,527 measurements (4.3%) in 126 CDI patients without adipsia treated with intranasal desmopressin [25]. Thus, the number of measurements (intranasal desmopressin: 264; desmopressin ODT: 238) in this study seems sufficient to represent the frequency of hyponatremia in each formulation. Second, the present study examined the effects of the switch from intranasal desmopressin to desmopressin ODT on the frequency of hyponatremia, but not those of the switch from desmopressin ODT to intranasal DDAVP. Such a bidirectional switch, however, is not appropriate for a clinical study, given that most CDI patients prefer desmopressin ODT. Third, while the doses and frequency of intranasal desmopressin had been fixed in most patients subjected to the analysis, those of desmopressin ODT were titrated from the small doses and frequency. While the mean serum sodium levels were similar between the two formulations as discussed above, we could not completely exclude the possibility that such a difference affected the frequency of hyponatremia. To evaluate the frequency of hyponatremia with the fixed doses and frequency of desmopressin ODT for a longer duration would be important in future study.

In conclusion, our data demonstrated that the incidence of hyponatremia is decreased in patients with CDI after the switch from intranasal desmopressin to desmopressin ODT, suggesting that water balance is better controlled with desmopressin ODT in patients with CDI.

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Disclosures

The authors have no conflicts of interest.

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