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Antidiuretic Effect of Desmopressin Given in Hemostatic Dosages to Healthy Volunteers

Stefan Lethagen,[1]* Karin Frick,[1] and Gunnar Sterner[2]

[1]Department for Coagulation Disorders, University of Lund, University Hospital, Malmö, Sweden
[2]Department of Vascular and Renal Diseases, University of Lund, University Hospital, Malmö, Sweden

The aim of this study was to characterize the magnitude and duration of the antidiuretic effects elicited by desmopressin given in hemostatic dosage intravenously (i.v.) (0.3 μg/kg) or intranasally (i.n.) (300 μg) both as single or repeated doses (four i.n. doses with 12-hr intervals) to healthy volunteers.

Urine osmolality increased to a maximum median value of 1,087 mOsmol/kg after the single i.v. dose, 1,065 after the single i.n. dose, and 1,071 during the repeated i.n. dosing schedule, and did not differ significantly between the three dosage schedules. The increase lasted for 24 hr after single doses, and 12 hr after the last of the repeated i.n. doses.

Serum sodium did not decrease more than normal diurnal variation after single doses, but decreased marginally below the normal reference range in three volunteers after repeated doses. Lowest median serum sodium concentrations after single i.v. and i.n. doses were 140 and 141 mmol/l, respectively, and 139 after repeated i.n. doses.

Body weight changed only marginally after single doses, but increased 1.3 kg during repeated dosing.

In adult healthy volunteers, single desmopressin doses give an antidiuretic effect lasting for about 24 hr. There is no difference in magnitude or duration between i.v. or i.n. doses. The effect is prolonged as long as the doses are repeated. Serum sodium is only marginally affected by single doses, but tends to decrease after four repeated doses with 12-hr intervals. If desmopressin is repeated for a period of up to 48 hr, fluid intake should be restricted to 2 liters per day in adults. Am. J. Hematol. 57:153–159, 1998.

Key words: desmopressin; antidiuresis; hemostasis; osmolality; diurnal; hyponatremia

INTRODUCTION

Desmopressin (1-desamino-8-D-arginine vasopressin) is a synthetic analogue of the antidiuretic hormone vasopressin. Desmopressin has been used for many years for its antidiuretic properties, e.g., in patients with diabetes insipidus or nocturnal enuresis or for diagnostic purposes in dosages of 2–8 μg parenterally or 20–80 μg intranasally [1]. When given in 10–20 times higher dosage, desmopressin has hemostatic effects with large increases in plasma concentrations of coagulation factor VIII, von Willebrand factor and tissue plasminogen activator [2,3], and of platelet adhesiveness [4]. Maximal hemostatic effect is achieved with a dosage of 0.3 μg/kg intravenously [5]. Because of its hemostatic effects, desmopressin is used in a wide range of bleeding disorders, such as mild hemophilia A, von Willebrand's disease (vWD), and most forms of platelet dysfunctions, both acquired and congenital. The intravenous route (0.3 μg/kg) is used mostly in connection with surgery or large bleedings, whereas the intranasal spray (300 μg) is used for home treatment, e.g., for bleedings such as epistaxis or menorrhagia, after minor trauma, or as cover for tooth extractions or minor surgery [6–9].

Although desmopressin is a potent anti-diuretic, water retention is not a prominent clinical problem and only a

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*Correspondence to: Dr. Stefan Lethagen, Department for Coagulation Disorders, University of Lund, University Hospital, Malmö, S-205 02 Malmö, Sweden. E-mail: stefan.lethagen@medforsk.mas.lu.se

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few cases of severe fluid overload have been reported after hemostatic dosages. Uremic patients do not seem to be at risk of developing fluid overload or congestive heart failure [10]. Still, several case reports have called attention to the risk of hyponatremia and seizures after administration of desmopressin [11–21]. Most cases have occurred in children, mainly under the age of 2 years, after administration of frequent, repeated doses of desmopressin or in those receiving hypotonic intravenous fluids [16]. It is, therefore, generally recommended that desmopressin be used with caution in small children and in patients with severe congestive heart failure, and that hypotonic fluids should be used sparingly. The frequency of hyponatremia in patients receiving desmopressin is not known, as serial serum sodium levels have not been included in most reports [21]. The antidiuretic effect seems to plateau already at low dosage (2 μg parenterally or 20 μg intranasally) [1], indicating that higher dosage does not give a higher maximal antidiuretic effect. It is, however, possible that the duration of the effect is prolonged with higher dosage, which is of importance especially when repeated doses of desmopressin are given. As the duration of the antidiuretic effect of low dosage is about 12 hr [1], the kidneys may not be able to recover normal concentrating capacity if repeated closely spaced high dosages are given. The potentially most severe side effects of high-dosage desmopressin are attributable to its antidiuretic properties. It is, therefore, clinically important to evaluate them, especially considering the expected increasing home use of desmopressin nasal spray following its registration in many countries including the United States [9].

The aim of this study was to investigate the magnitude and duration of the antidiuretic effect of desmopressin in high dosage intravenously (i.v.) (0.3 μg/kg) or intranasally (i.n.) (300 μg) in healthy volunteers. Desmopressin spray was given both as single and repeated doses. The primary effect variable was the urine osmolality. Secondary effect variables were serum osmolality, serum sodium, hematocrit, and body weight.

MATERIALS AND METHODS

Study Group

Ten healthy male volunteers, 26–38 years old, with a median body weight of 76 kg (range 63–105 kg) were included. All were non-smokers. All gave their written informed consent. The study was approved by the ethics committee of the University of Lund.

Study Drug

Desmopressin spray (Octostim®, Ferring, Sweden) (1.5 mg/ml, 100 μl per actuation) was given intranasally at a dosage of 300 μg (one actuation in each nostril). Desmopressin (Octostim®) (15 μg/ml) was dissolved in saline to a total volume of 10 ml and injected i.v. during 10 min at a dosage of 0.3 μg/kg. Single doses were given of both 0.3 μg/kg i.v. and 300 μg i.n. The spray was also given as repeated doses at 12-hr intervals for 2 days, i.e., 4 doses of 300 μg, i.n. All desmopressin doses, including the spray doses, were given by the research nurse.

Study Design, Urine, and Blood Sampling

Single desmopressin doses to healthy volunteers. This was an open randomized, cross-over study. Two separate doses were given in randomized order to each volunteer, one of 0.3 μg/kg i.v. injection and one of 300 μg intranasal spray with a washout period of at least 1 week between doses. Both doses were given at 08.00 (8 A.M.). Before the first dose, urine was sampled during 24 hr at the following time intervals: between 08.00–11.00, 11.00–14.00, 14.00–18.00, 18.00–22.00, 22.00–08.00, and blood was sampled at 08.00, 11.00, 14.00, 18.00, and 08.00. After each of the two doses, urine was sampled during 48 hr at the following time intervals: day 1 between 08.00–11.00, 11.00–14.00, 14.00–18.00, 18.00–22.00, 22.00–08.00, and day 2 between 08.00–14.00, 14.00–18.00, 18.00–22.00, and 22.00–08.00. Blood samples were taken at 08.00 before each of the single desmopressin doses and thereafter at 11.00, 14.00, 18.00, 08.00, 14.00, 18.00, and 08.00.

Urine was collected in plastic containers, the volume measured, and specimens kept refrigerated for later analyses of osmolality. Venous blood was drawn into silicone-coated Vacutainer® tubes (Becton-Dickinson, San Jose, CA) with a volume of 5 ml, containing 0.5 ml EDTA, and in glass tubes with a volume of 7 ml containing no anticoagulants, for the determination of hematocrit, serum osmolality, and serum sodium.

Repeated desmopressin doses to healthy volunteers. The healthy volunteers received four doses each of 300 μg desmopressin nasal spray with 12-h intervals. Urine was sampled during 96 h at the following time intervals: between 08.00–14.00, 14.00–20.00, and 20.00–08.00. Blood samples were taken once daily at 08.00 before the morning doses of desmopressin and at 08.00, 24 h after the last spray dose.

Fluid Intake

Fluid was withheld from 22.00 (10 P.M.) the night before the test and only 150 ml of fluid was allowed in the morning. After 08.00 (8 A.M.), when desmopressin was administered and urine collection started, fluid intake was ad libitum, though not more than 2 L per 24 h. The volunteers kept records of their fluid intake.

Assessments

Osmolality in urine and serum was determined by freezing-point depression using an osmometer type Roebling 11 (Roebling Automatic, Berlin, Germany). Nor-

TABLE I. Maximal Urine Osmolality (mOsmol/kg) and Duration of the Increased Urine Osmolality in 10 Healthy Volunteers*

Dose schedule	Baseline urine osmolality (mOsmol/kg)	Maximal urine osmolality (mOsmol/kg)	Wilcoxon signed rank test for maximal urine osmolality as compared to baseline (*P* value)	Duration of urine osmolality increase (h)
0.3 μg/kg i.v. single dose		1,087 (920–1,183)	0.0051	24 (14–38)
300 μg i.n. single dose	823 (630–1,032)	1,065 (813–1,131)	0.0069	24 (10–24)
300 μg i.n. repeated doses		1,061 (881–1,203)	0.0125	48 (30–60)

*Baseline urine osmolality was defined as the morning sample at the end of the run-in period.

mal reference range for urine osmolality depends on fluid intake. Normal reference range for serum osmolality is 280–300 mOsm/kg. Hematocrit and serum sodium was assessed with standard methods. Normal reference range for hematocrit is 39–49% and for serum sodium 136–146 mmmol/l.

Baseline values were defined as follows: For urine osmolality, the value was measured over the period 22.00–08.00 during the run-in period; for body weight, the morning measurement day 1 within each treatment period directly before drug administration; for the other category analyses, the value was measured at 08.00 the first day before drug administration.

Side Effects

Side effects were actively asked for by the research nurse at specific time points and were registered. All spontaneously reported side effects were also registered.

Concomitant Medication

All medication taken by the participants was registered.

STATISTICS

Non-parametric statistics were used. Values were expressed as median and range. Differences within or between data series comprising three or more values were evaluated with Friedmann's test for two-way analysis of variance by ranks. If Friedman's test showed statistical significance, Wilcoxon rank sum test could be used to compare two values from the series.

RESULTS

All volunteers were healthy and without medication except for one who took oxymetazoline nasal spray for 2 days during the repeated dosage period because of a common cold; one who took penicillin for tonsillitis during the run-in period, paracetamol for headache during the intravenous single dose period, and doxycyklin before repeated dosage; and one who took loratadin for pollen allergy before the repeated dosage period. Two separate data analyses were made for all parameters, one including all 10 volunteers and one excluding the three volunteers who are mentioned above. As the exclusion of these three volunteers did not change the results significantly, we present only the results from the data analyses including all ten volunteers.

Fluid Intake

The study periods did not differ when it comes to fluid intake, which ranged from 1,200 to 1,800 ml per day.

Urine Osmolality

When the duration of antidiuretic effects measured in urine samples was estimated, we used the time at the end of the respective urine sampling period in the calculation. Thus, there is a risk of overestimation of the duration of the different changes.

During the run-in period, urine osmolality tended to be higher during the night with a value of 823 (630–1,032) mOsm/kg in the urine samples collected between 22.00 and 08.00, and lower during the afternoon between 14.00 and 18.00 with a value of 563 (224–963) mOsm/kg, but the differences were not statistically significant (Friedmann's test, $P = 0.1093$).

Urine osmolality changed significantly after desmopressin but there were no significant differences in maximal urine osmolality between the three dosing schedules (Table I, Figs. 1–3). When we calculated the duration of antidiuretic response, we defined the termination of the antidiuretic response as the urine osmolality value, which was followed by at least two successively decreasing values (one volunteer had to be excluded from this calculation because no such value could be identified). The duration was 24 h after both the single i.v. and the single i.n. doses, and 12 h after the last of the four repeated

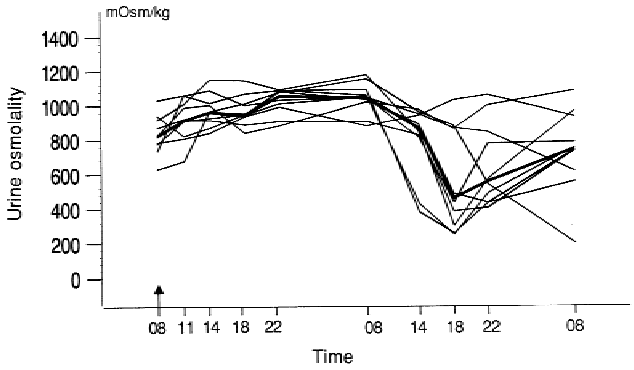

Fig. 1. Urine osmolality (mOsm/kg) in ten healthy volunteers after a single dose of desmopressin 0.3 µg/kg intravenously. Thick line represents median values.

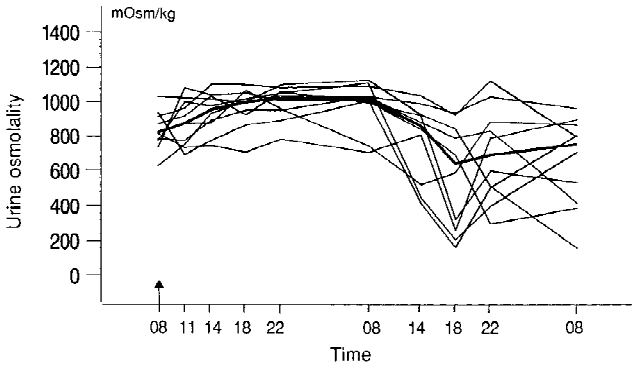

Fig. 2. Urine osmolality (mOsm/kg) in ten healthy volunteers after a single intranasal spray dose of 300 µg desmopressin. Thick line represents median values.

doses. A compensatory decrease of urine osmolality followed the initial increase. Thereafter the urine osmolality usually returned to baseline within 48 h after the single doses (Figs. 1, 2) but had not quite reached the basal levels 48 h after the last repeated dose (Fig. 3).

Serum Osmolality

Small but statistically significant changes were seen in serum osmolality both during the run-in period and after desmopressin. The serum osmolality did, however, not decrease significantly more after desmopressin than during the run-in period. During the run-in period serum osmolality decreased from 295 (291–297) mOsmol/kg in the morning to 292 (289–297) at 18.00 in the evening. We saw a decrease from 293 mOsmol/kg (288–295) to 289 mOsmol/kg (282–303) after the intravenous single dose, and from 294 mOsmol/kg (291–295) to 289 mOsmol/kg (282–292) after the intranasal single dose. After repeated intranasal doses, serum osmolality decreased from 292 mOsmol/kg (290–296) to 286 mOsmol/kg (279–290). The lowest values were seen 30 (10–34) h after single i.v., 34 (6–48) h after a single i.n. doses, and 48 (48–75) h after the first of the repeated i.n. dosages.

Serum Sodium

Serum sodium did not change significantly during the run-in period. Although the decreases after the single doses reached statistical significance, they were all within the normal reference ranges for serum sodium and did not differ statistically significantly from the run-in period (Table II). The decrease during the repeated dosage schedule differed significantly from the run-in period ($P = 0.0077$) as well as from the two single dose periods ($P = 0.0044$). Three volunteers reached serum sodium concentrations slightly below the normal range during the repeated dosage period; one volunteer had a value of 135 mmol/L after 48 h, and the two others 134 mmol/L after 72 h (Fig. 4).

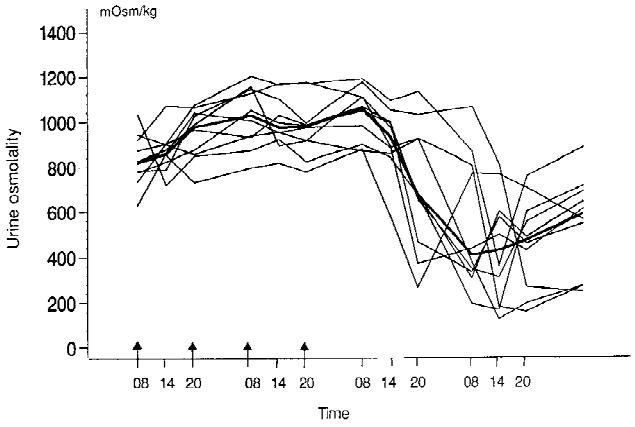

Fig. 3. Urine osmolality (mOsm/kg) in ten healthy volunteers after four intranasal spray doses of 300 µg desmopressin with 12-h-intervals. Thick line represents median values.

Hematocrit

Hematocrit did not change significantly during any of the periods studied.

Urinary Flow

Significant changes were seen in urinary flow both during the run-in period ($P = 0.0378$) as well as during the different treatment periods ($P = 0.0009$ for single i.v., $P = 0.062$ for single i.n., and $P < 0.0001$ for the repeated dosage period).

During the run-in period, the lowest urinary flow, 34 (24–64) ml/h, was seen in the night and the highest, 79 (28–228) ml/h, during the day between 14.00 and 18.00.

After the single doses of desmopressin, the urinary flow was depressed for about 24 h after which it returned to normal. In the afternoon between 14.00 and 18.00 the first day, the urinary flow was only 45 (23–91) ml/hr and 44 (23–81) ml/h after the i.v. and i.n. single doses, respectively, which is significantly lower ($P = 0.0136$) than the the flow of the corresponding time of day of the run-in period.

TABLE II. Serum Sodium Concentrations After Desmopressin

Dose schedule	Baseline (mmol/L)	Lowest concentration (mmol/L)	Wilcoxon signed rank for lowest concentration as compared to baseline (*P*)	Time to reach lowest concentration (h)
Run-in period	143 (139–145)	141 (139–144)	0.0687	3 (0–24)
0.3 μg/kg i.v. single dose	143 (141–146)	140 (139–142)	0.0051	30 (6–48)
300 μg i.n. single dose	143 (142–144)	141 (137–142)	0.0051	24 (3–34)
300 μg i.n. repeated doses	144 (141–146)	139 (134–142)	0.0051	48 (24–72)

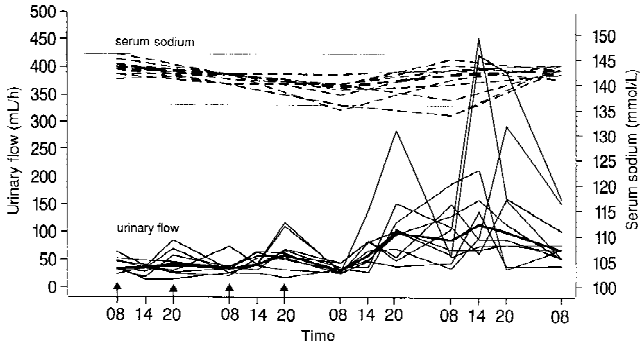

Fig. 4. Urinary flow (ml/h) and serum sodium (mmol/L) in ten healthy volunteers after four intranasal spray doses of 300 μg desmopressin with 12-h intervals. The horizontal lines indicate the upper and lower limits of the normal reference range of serum sodium.

The highest urinary flow values after the single doses were seen the second day between 14.00–18.00, 87 (42–200), and 76 (27–259) ml/h for the respective doses, which is not significantly different from the corresponding run-in period.

During the repeated doses schedule, the urinary flow was depressed as long as the desmopressin doses were repeated, after which the flow normalized. A compensatory increased flow was seen 24–42 h after the last spray dose with the highest flow values in the morning between 08.00–14.00, 113 (60–453) ml/h ($P = 0.0253$) (Fig. 4).

Body Weight

The basal body weight during run-in was 77.7 kg (64–105). The median body weight increased 0.5 kg on day two after the single spray dose ($P = 0.0069$) and decreased 0.5 kg on day two after the single intravenous dose (n.s.). During the repeated dosage period, there was an initial increase of body weight 1.3 kg above baseline on day two followed by a decrease to 1.2 kg below baseline on day five ($P < 0.0001$).

Side Effects

All volunteers were asked for side effects, but they experienced only few and mild side effects (Table III).

DISCUSSION

In this study we evaluated the antidiuretic response of desmopressin given in hemostatic dosage to healthy male volunteers. Desmopressin is a potent antidiuretic drug used for treatment of diabetes insipidus or in children with nocturnal enuresis. Being a synthetic derivative of the natural hormone vasopressin, its antidiuretic effect is more potent than vasopressin. In order to achieve hemostatic effects, 10–20 times higher dosages are used than those given for antidiuretic indications, which causes concern for the potential risk of water retention and fluid overload.

From our results we found that the urine osmolality increased to peak levels of about 1,060–1,090 mOsmol/kg, which is only slightly higher than the urine osmolality of about 950 mOsmol/kg seen after the antidiuretic dosages of 2–8 μg s.c. or 20–80 μg i.n. (1). The peak plasma concentration of desmopressin after a single dose of 0.3 μg/kg i.v. is about 1,300 pg/ml and after a single dose of 300 μg i.n. about 400 pg/ml [6]. This is in contrast to the much lower peak plasma desmopressin concentrations of about 25 pg/ml after 2 μg and 50 pg/ml after 40 μg i.n. It thus seems as if maximal amplitude of the antidiuretic effect is achieved at a relatively low plasma concentration of desmopressin and that the high concentrations obtained after hemostatic dosages do not increase the antidiuretic effect substantially. It is, therefore, not surprising that we found no difference in the magnitude of the antidiuretic response between the single doses of 0.3 μg/kg i.v. and 300 μg i.n. or the repeated spray dosage.

We found no difference in the duration of the antidiuretic effect after the single doses of 0.3 μg/kg i.v. and 300 μg i.n., whereas the duration was significantly prolonged by repeated dosages, since the antidiuretic response was sustained as long as desmopressin was reiterated. After the last spray dose, however, the urine osmolality started to decrease about 12 h after the last of the repeated spray doses as compared to 24 h after the single doses. Therefore, even if repeated doses are given, the magnitude of the antidiuretic effect is not further

TABLE III. Side Effects Within 24 H After Last Desmopressin Dose

Volunteer number	Side effect	Administration	Time of onset (h)	Duration (h)
1	Tired	i.v.	1	Until evening
	Headache	Repeated	7	8
	Serum sodium 135 (ref:136–146) mmol/L	Repeated	48	<24
2	Tired	i.v.	1	48
	Tired	i.n.	1	7
	Urthicaria	i.n.	13	Not known
	Serum sodium 134 (ref:136–146) mmol/L	Repeated	72	<12
3	Headache	i.v.	9	3
	Tired	i.n.	1	10
4	Headache	i.v.	1.30	6
5	No side effects reported			
6	Tired	i.n	6	2
	Dizzy	i.n	24	3
7	Headache	i.v.	7	3
8	Tired	i.n.	8	2
9	Serum sodium 134 (ref:136–146) mmol/L	Repeated	72	<24
10	No side effects reported			

increased as compared to a single dose, and the antidiuretic effect ceases after the last dose as fast as, or even faster than, after a single dose. The initial increase in antidiuretic response is followed by a compensatory decrease, which can be seen as a decrease in urine osmolality or an increase in urinary flow, most obvious after repeated doses.

In contrast to urine osmolality, changes in serum osmolality were small and did not differ significantly from the normal diurnal variation.

Hyponatremia is a potentially serious complication to fluid overload and may result in convulsions and coma, but is, however, rarely seen after desmopressin. There have been some case reports of hyponatremia and seizures in patients treated with desmopressin [11–21]. Proposed risk factors for hyponatremia involves pediatric use (especially <2 years of age), multiple doses of desmopressin, overhydration with hyponatremic fluids, stress, vomiting, and liver disease [16]. In this study, single desmopressin doses did not change the serum osmolality more than what is seen during normal diurnal variation, although fluid intake was allowed up to 2 liters per 24 h. We cannot rule out, however, that more liberal fluid intake could induce a more pronounced effect on serum sodium. After repeated spray dosages at 12-hr intervals for 48 hr, there was a somewhat more pronounced decrease of serum sodium, but the levels decreased below the normal range only in three individuals. Although the changes were relatively small, the decreasing slope of the serum sodium concentration curve indicates that additional doses of desmopressin may result in more marked hyponatremia. Therefore, when repeated doses are given, water intake should be restricted and the serum sodium concentration should be checked when possible. Based on our data, fluid intake should be limited to 2 L per 24 h in adults given repeated doses of desmopressin for a period of up to 48 hr. If additional doses are given, fluid intake should probably be more restricted.

The body weight was an insensitive parameter. During the repeated dosage schedule the relative increase was only 1.6% (0.8–3.8). In the two patients who reached serum sodium levels below the normal range, the body weight increased with 1.7 kg (2.2%) and 2.7 kg (3.2%), respectively. The body weight is too insensitive to be used for evaluating the antidiuretic effect. On the other hand it clearly indicates that no substantial water retention occurred.

CONCLUSION

Single i.v. dosage of 0.3 μg/kg or i.n. dosage of 300 μg by spray induces antidiuretic effects lasting about 24 h. The effect is of the same magnitude as that obtained by the much lower antidiuretic dosages. The magnitude of the antidiuretic effect measured as change in urine osmolality is not increased further if repeated i.n. spray dosages are given, but the duration is sustained as long as the administrations are repeated. The effect does not prevail longer after the last dose as compared to after a single dose. Although single desmopressin doses had no significant effect on serum sodium levels, we found a tendency towards hyponatremia when repeated doses were given. Four doses during 48 h were well tolerated, but we cannot rule out a more pronounced hyponatremia had additional doses been given.

Thus, in adults without cardiovascular disease or renal

insufficiency, single doses of desmopressin can be safely given only with a modest limitation of water intake. When repeated doses are given during 48 h, fluid intake should be limited to 2 L per day in adults, whereas it should probably be more restricted if desmopressin treatment is further prolonged. It is wise to monitor serum sodium, if treatment is prolonged over a longer period. The antidiuretic effect may be more pronounced in children. Special concern should be directed to small children given parenteral fluids in conjunction with desmopressin administration.

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REFERENCES

1. Tryding N, Sterner G, Berg B, Harris A, Lundin S: Subcutaneous and intranasal administration of 1-deamino-8-d-arginine vasopressin in the assessment of renal concentration capacity. Nephron 45:27–30, 1987.
2. Cash JD, Gader AMA, Da Costa J: The release of plasminogen activator and factor VIII by LVP, AVP, DDAVP, AT III and OT in man. Br J Haematol 27:363–364, 1974.
3. Mannucci PM, Åberg M, Nilsson IM, Robertsson B: Mechanism of plasminogen activator and factor VIII increase after vasoactive drugs. Br J Haematol 30:81–93, 1975.
4. Lethagen S, Nilsson IM: DDAVP induced enhancement of platelet retention. Its dependence on platelet-von Willebrand factor and the platelet receptor GPIIb/IIIa. Eur J Haematol 49:7–13, 1992.
5. Mannucci PM, Canciani MT, Rota L, Donovan BS: Response of factor VIII/von Willebrand factor to DDAVP in healthy subjects, and patients with haemophilia A and von Willebrand's disease. Br J Haematol 47:283–293, 1981.
6. Lethagen S, Harris AS, Sjörin E, Nilsson IM: Intranasal and intravenous administration of desmopressin: Effect on f VIII/vWF, pharmacokinetics and reproducibility. Thromb Haemost 58:1033–1036, 1987.
7. Rose EH, Aledort LM: Nasal spray desmopressin (DDAVP) for mild hemophilia A and von Willebrand disease. Ann Intern Med 114:563–568, 1989.
8. Lethagen S, Ragnarson-Tenvall G: Self-treatment with desmopressin intranasal spray in patients with bleeding disorders. Effect on bleeding symptoms and socio-economic factors. Ann Hematol 66:257–260, 1993.
9. Seremetis SV, Aledort LM: Desmopressin nasal spray for hemophilia A and type I von Willebrand disease. Ann Intern Med 126:744–745, 1997.
10. Mannucci PM: Desmopressin: A nontransfusional form of treatment for congenital and acquired bleeding disorders. Blood 72:1449–1455, 1988.
11. Lowe G, Pettigrew A, Middleton S, Forbes CD, Prentice CRM: DDAVP in haemophilia. Lancet 2:614–615, 1977.
12. Koskimies O, Pylkkänen J, Vilska J: Water intoxication in infants caused by the urine concentration test with vasopressin analogue (DDAVP). Acta Paediatr Scand 73:131–132, 1984.
13. de la Fuente B, Kasper CK, Rickles FR, Hoyer LW: Response of patients with mild and moderate hemophilia A and von Willebrand's disease to treatment with desmopressin. Ann Intern Med 103:6–14, 1985.
14. Sheperd LL, Hutchinson RJ, Worden EK, Koopman CF, Coran A: Hyponatremia and seizures after intravenous administration of desmopressin acetate for surgical hemostasis. J Pediatr 114:470–472, 1989.
15. Weinstein RE, Bona RD, Altman AJ, Quinn JJ, Weisman SJ, Bartolomeo A, Rickles FR: Severe hyponatremia after repeated intravenous administration of desmopressin. Am J Hematol 32:258–261, 1989.
16. Smith TJ, Gill JC, Ambruso DR, Hathaway WE: Hyponatremia and seizures in young children given DDAVP. Am J Hematol 31:199–202, 1989.
17. Salvatoni A, Maghnie M, Lorini R, Marni E: Hyponatremia and seizures during desmopressin acetate treatment in hypothyroidism. J Pediatr 116:835–836, 1990.
18. Binch LJC, Jacobsen MB: Hyponatremi ved behandling av von Willebrands sykdom. Tidsskr Nor Laegeforen 112:3670–3671, 1992.
19. Beach PS, Beach RE, Smith LR: Hyponatremic seizures in a child treated with desmopressin to control enuresis. A rationale approach to fluid intake. Clin Pediatr (Phila) 31:566–569, 1992.
20. Yaouyanc G, Jonville AP, Yaouyanc-Lapalle H, Barbier P, Dutertre JP, Autret E: Seizure with hyponatremia in a child prescribed desmopressin for nocturnal enuresis. J Toxicol Clin Toxicol 30:637–641, 1992.
21. Humphries KE, Siragy H: Significant hyponatremia following DDAVP administration in a healthy adult. Am J Hematol 44:12–15, 1993.