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ANTIDIURETIC EFFECT OF PERRECTALLY ADMINISTERED DDAVP IN CENTRAL DIABETES INSIPIDUS

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Summary

At present, the intranasal administration of DDAVP (1-deamino-8-D-arginine vasopressin) is widely applied in the treatment of central diabetes insipidus, achieving excellent results. However, when the nasal mucous membrane is inflamed, such as immediately after transsphenoidal operation of pituitary tumor or in case of rhinitis, pernasal administration of DDAVP does not exert a sufficient antidiuretic effect because of poor absorption through the nasal mucous membrane. For these reason, to search another route of DDAVP administration, an attempt was made to administrate DDAVP perrectally, sublingually or pernasally to patients with central diabetes insipidus. The favorable antidiuretic effect was obtained in the cases of perrectally administration of DDAVP. In conclusion, although the pernasla administration of DDAVP is the routine method, we think that it should be substituted by perrectal administration if pernasal administration is impossible.

Introduction

At present, the intranasal administration of DDAVP (1-deamino-8-D-arginine vasopressin) (Zaoral and Šorm 1986)[1] is widely applied in the treatment of central diabetes insipidus, achieving excellent results[2)3)4]. However, when the nasal mucous membrane is inflamed, such as immediately after transsphenoidal operation of pituitary tumor, or in cases of rhinitis, pernasal DDAVP does not exert a sufficient antidiuretic effect because of poor absorption through the nasal mucous membrane[4)5]. In these cases, intravenous drip or intramuscular injection of water-soluble Pitressin is used instead, although this agent produces pain or adverse effects such as gastrointestinal symptoms, often causing difficulty in treating diabetes insipidus. In addition, it is known that the blood concentration of DDAVP shows variations closer to physiological variations in endogenous AVP (arginine vasopressin) than does water-soluble Pitressin[6]. Thus, the usef of DDAVP is desirable if possible.

For these reasons, another route of DDAVP administration would be desirable. In this regard, however, only a few reports on sublingual or oral administration have been published to date[5)7]. In the present study, we administered DDAVP perrectally to patients with central diabetes insipidus. The favorable results thus obtained are reported together with the findings after pernasal and sublingual administration.

Key Words: DDAVP, Central diabetes insipidus, Perrectally administration of DDAVP

Subjects and Methods

The subjects were three patients, a 49-year-old man with a pituitary tumor (case 1), an eight-year-old girl with craniopharyngioma (case 2), and a 23-year-old woman with pinealoma (case 3). Case 1 and 2 developed postoperative diabetes insipidus, and case 3 had inreuersible diabetes insipidus, which had been treated for six years with DDAVP

(10 μg × 2/day).

In each patient, a ureteral catheter was placed to determine the urine volume, the urinary osmotic pressure and the specific gravity of urine every 30 minutes. DDAVP was given if the combined volume of two successive urine samples exceeded 4 ml/kg• weight/h with a specific gravity of less than 1.010. During the DDAVP treatment, fluid replacement in terms of the volume of the excreted urine was undertaken in cases 1 and 2, whereas no fuid therapy, but water, was given ad. libitum in case 3.

Three routes of administration, i.e., pernasal, sublingual and perrectal, were examined. A calibrated plastic tube was used for pernasal administration. For sublingual administration, DDAVP was mixed with 10 g of thick malt syrup just before use. In cases of perrectal administration, DDAVP diluted with 0.5 ml of 5% glucose solution was infused into the rectum with an injector using an 18G Elaster cannula.

The DDAVP test was performed in cases 2 and 3, and the doses of DDAVP that showed a level of −1 to −1.5 ml/min for free water clearance were used for treatment[8]. Consequently, both the pernasal and perrectal doses were 5 μg in case 2 and 10 μg in case 3. In case 1, the intranasal tampon was removed two weeks after transsphenoidal operation of pituitary tumor. However, because the patient did not respond to the DDAVP test, the upper limit of a single dose for adults, 20 μg, was used for pernasal and perrectal administration. The sublingual dose was twice as much as the pernasal and perrectal dose, being 40, 10 and 20 μg in cases 1, 2 and 3, respectively.

Results

With regard to pernasal administration, cases 2 and 3 responded a decrease in the urine volume and increases in the urinary osmotic pressure and specific gravity 30—60 minutes after admiistration, showing an antidiuretic effect of DDAVP. In contrast, case 1 showed no changes in the urine volume, urinary osmotic pressure or urinary specific gravity, demonstrating no antidiuretic effect (Fig. 1).

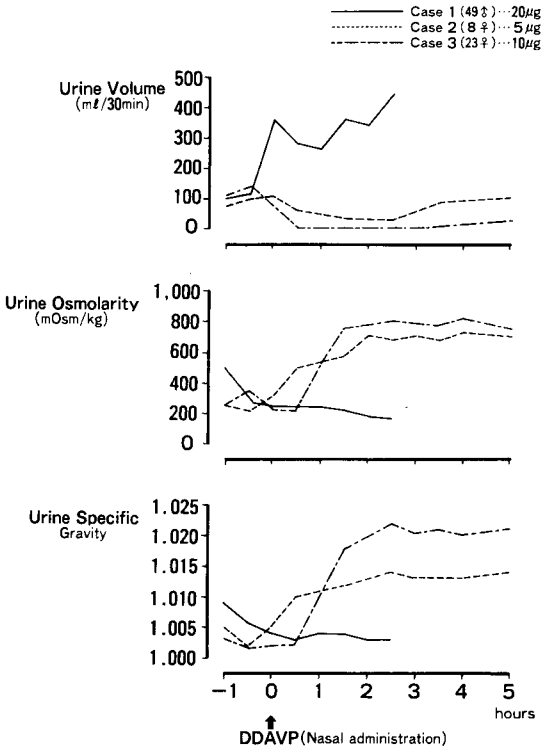

Fig. 1 Nasal administration of DDAVP.

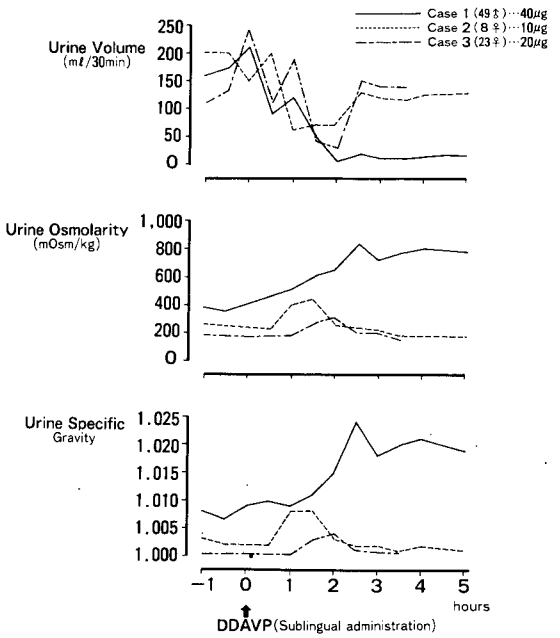

Fig. 2 Sublingual administration of DDAVP.

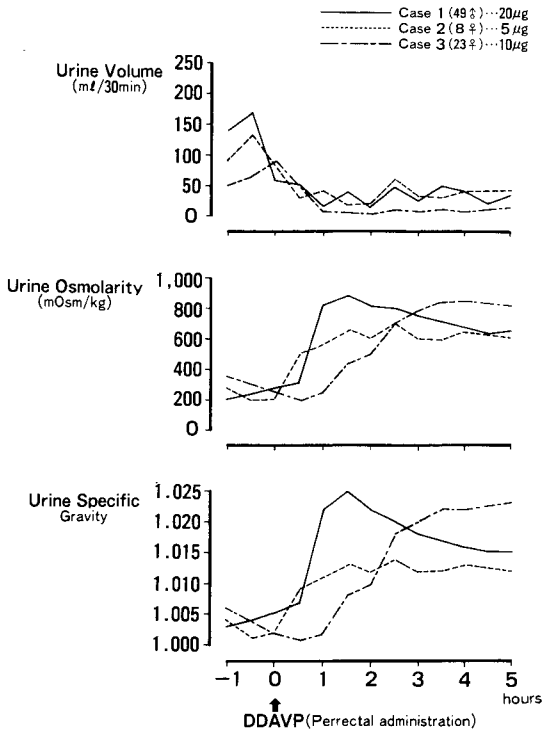

Fig. 3 Perrectal administration of DDAVP.

Sublingual administration was associated with a decrease in the urine volume and increases in the urinary osmotic pressure and specific gravity in case 1, 60—90 minutes after administration, these trends continuing up to about eight hours after administration. In cases 2 and 3, a decrease in the urine volume, a slight increase in the urinary osmotic pressure and an increases in the urinary specific gravity occurred 60—90 minutes after administration, but these values returned to those before administration two hours later (Fig. 2).

By perrectal administration of DDAVP, a marked decrease in the urine volume and increases in the urinary osmotic pressure and specific gravity occurred in cases 1, 2 and 3, 30-90 minutes after administration (Fig. 3), and the antidiuretic effect was found to continue for 8—12 hours.

Discussion

The usefulness of DDAVP, a vasopressin analogue first synthesized by Zaoral et al.[1] in 1966, has already been reported in many papers[2)3)4)]. In Japan, this agent is now clinically used only as a collunarium. Although subcutaneous, intramuscular and intravenous routes were also discussed at the time this agent was developed[1)2)9)] it seems that pernasal administration has come to the fore because of its simplicity. In recent years, Lanci et al.[5)] reported on the sublingual administration of DDAVP in clinical cases, and Vilhardt et al.[7)] indicated the usefulness of DDAVP solution in clinical oral administration. However, there were no reports of the intrarectal administration of this agent in clinical cases within the scope of our search in the literature.

In many cases who received transsphenoidal operation of pituitary tumor, the intranasal administration of DDAVP does not exert a sufficient antidiuretic effect within 1—2 weeks after the operation. this is probably because inflammation of the nasal mucous membrane impedes the absorption of DDAVP. Judging from the results of the present study, the sublingual administration of DDAVP is not necessarily reliable in its effectiveness.

This problem is complicated by the factors such as the dose of DDAVP and the quality of solvent for the agent, requiring further study. In contrast, the perrectal administration of DDAVP showed a consistent antidiuretic effect at the same dose at that for pernasal administration in all the three patients including one (case 1) who did not respond to pernasal DDAVP. In conclusion, although the pernasal administration of DDAVP is the simplest method, we think that it should be substituted by perrectal administration if pernasal administration is impossible.

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中枢性尿崩症に対するDDAVP（1-deamino-8-D-arginine vasopressin）の経直腸投与の有用性

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現在，中枢性尿崩症の治療にはDDAVPの鼻腔内投与が広く行なわれている．しかし，鼻炎患者や経鼻的下垂体手術の術直後などでは，鼻粘膜からの吸収が悪く充分な抗利尿効果が得られない．そこで，3例の中枢性尿崩症患者にDDAVPの経直腸投与を試みたところ，良好な結果が得られたので，鼻腔内投与および舌下投与の結果と対比し報告する．

経直腸投与では，3例とも投与後30～90分で尿量の著明な減少が認められ，投与前の1/3以下の尿量となった．また，尿比重は1.010以上に，尿浸透圧は投与前値の2倍となった．さらに抗利尿効果は投与後8時間以上持続した．これに対し，通常の経鼻投与では，経鼻的下垂体手術後の1例に全く無効であり，また，舌下投与では1例で著明な尿量の減少をみたが，他の2例ではわずかな減少に過ぎず，かつ効果の持続時間は3時間程度であった．

これらの結果からDDAVPの経直腸投与は，経舌下投与より効果は確実であり，通常の鼻腔内投与が不可能な場合には，充分代わり得る有用な方法と考えられた．