

Prophylactic Efficacy of Desmopressin Acetate for Diabetes Insipidus after Hypophysectomy in the Dog

Yasushi HARA¹, Hiroyuki MASUDA¹, Takahiro TAODA¹, Daisuke HASEGAWA², Yukihiro FUJITA¹, Yoshinori NEZU¹ and Masahiro TAGAWA¹

¹Divisions of Veterinary Surgery and ²Veterinary Radiology, School of Veterinary Medicine, Nippon Veterinary and Animal Science University, 1-7-1 Kyonan-cho, Musashino-shi, Tokyo 180-8602, Japan

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ABSTRACT. The prophylactic efficacy of desmopressin acetate (DDAVP) on diabetes insipidus (DI) after hypophysectomy was investigated in the dog. In the control group, hypernatremia with a plasma level of 155 mEq/l or higher persisted for 12 hr from the 4th to the 16th hour after hypophysectomy, and symptoms of DI developed within five days after surgery. In the DDAVP treatment group, these changes were not observed, showing that administration of DDAVP (4 µg, instillation, twice daily) effectively prevented hypernatremia that develops immediately after surgery and DI-like symptoms that persists for about one week after surgery.

KEY WORDS: canine, desmopressin acetate, hypophysectomy.

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As modern imaging procedures such as magnetic resonance imaging and computed tomography have become widely used in the field of veterinary medicine, the precision of antemortem diagnosis of pituitary tumor has increased in recent years [3, 7]. In veterinary neurosurgery, transsphenoidal hypophysectomy is recognized as useful for pituitary adenoma of the anterior and intermediate lobes accompanied by Cushing's syndrome in dogs and cats, and these surgical procedures and results of such surgery in clinical cases have been reported [6, 7, 9, 12]. However, total resection of pituitary tissue, which plays a central role in endocrine function, induces endocrinological abnormalities after surgery such as diabetes insipidus (DI), hypoadrenocorticism, and hypothyroidism, requiring careful postoperative management mainly by hormone supplementation therapy. Among these pituitary hormone deficiencies, DI due to antidiuretic hormone (ADH) deficiency is an important clinical problem encountered soon after surgery because it causes the loss of a large volume of hypotonic fluid into urine, hypernatremia, and an acute decrease in the circulating blood volume, which may induce hypovolemic shock [18]. In the field of veterinary medicine, a V2-receptor selective agonist, desmopressin acetate (generic name: 1-deamino-8-D-arginine-vasopressin acetate trihydrate, DDAVP), is used to treat spontaneous central DI [1, 21]. The use of DDAVP for management of postoperative DI after hypophysectomy in the dog with pituitary tumor was reported [7]. In that report, however, the dogs had endocrinological abnormalities before surgery caused by pituitary tumor, and surgery was followed by hormone supplement therapy using glucocorticoids, mineralcorticoids, and thyroid hormones. Therefore, it was difficult to evaluate the efficacy of DDAVP alone for postoperative DI after hypophysectomy. In this study, we evaluated fluid and electrolyte abnormalities due to antidiuretic hormone deficiency after surgery and investigated the prophylactic efficacy of DDAVP on DI in the dog after

hypophysectomy.

MATERIALS AND METHODS

Experimental animals: Clinically healthy beagles, seven males and three females (mean age 3.6 years, mean body weight 12.5 kg), were used. No abnormality was observed in physical examination, complete blood count, biochemistry, and urinary analyses before the experiment in any animal.

Transsphenoidal hypophysectomy: All animals underwent transsphenoidal hypophysectomy under general anesthesia using isoflurane [9, 12]. Lactated Ringer solution was continuously infused at a rate of 10 ml/kg/hr from immediately after induction of anesthesia till awakening. Dogs were placed in sternal recumbency with an elevated head and maximally opened mouth. The oral mucosa and tongue were disinfected with 10% povidone iodine-physiological saline. After incision of the soft palate and the mucoperiosteum, the ventral surface of the sphenoid was exposed. The median region of the sphenoid was burred using an air drill to approach the ventral side of the pituitary fossa. After cruciate incision of the dura mater, the pituitary was exposed. Then, the pituitary was completely resected from the hypophyseal stalk using forceps. Hypophysectomy was completed by grossly confirming the outflow of cerebrospinal fluid from the opening of the third ventricle (median eminence). After the pituitary was excised, the mucoperiosteum and then the soft palate was sutured, and the surgery was completed.

Postoperative management: Perioperative analgesic management was achieved by the pre- and post-operative administration of butorphanol (0.2 mg/kg, iv). Butorphanol was administered twice a day for 3 days after surgery at the same dosage. Two antibiotics (chloramphenicol, 30 mg/kg, bid for seven days; enrofloxacin, 5 mg/kg, sid for 14 days)

were also administered after surgery. No transfusion was given after surgery. Animals were given drinking water *ad libitum* after awaking from anesthesia.

The handling of experimental animals, such as during the experimental surgery and postoperative period, was performed according to the guidelines for handling experimental animals prepared by the Laboratory Animal Committee of Nippon Veterinary and Animal Science University.

Establishment of experimental groups: Two groups were established at random. One group (n=6) received DDAVP (DDAVP treatment group) for 14 days after surgery and the control group (n=4) did not receive such treatment but were observed over a period of 30 days. In the DDAVP treatment group, 4 $\mu\text{g}/\text{head}$ of DDAVP nasal drops (Desmopressin intranasal Kyowa; Kyowa Hakko Co., Japan), was dripped into the conjunctival sac immediately after surgery and twice daily at 9:00–10:00 and 21:00–22:00 the day after surgery and thereafter [1].

Measurement of the physiological parameters: All animals were maintained in simple metabolic cages and daily water consumption (DWC), daily urine volume (DUV), and urine specific gravity (USG) were measured for 30 days after surgery. The DWC and DUV were measured twice daily at 9:00 and 21:00. For measurement of the USG, a fresh urine sample was collected using a catheter or by manual compression of the urinary bladder by hand. Plasma sodium concentration was measured every two hours for 24 hr after surgery and daily for 30 days. Plasma arginine vasopressin (AVP) concentration was measured by radioimmunoassay before surgery and on days 1, 15, and 30 after surgery. Beginning the second day after surgery, blood sampling time was fixed at 9:00.

Statistical analysis: The plasma electrolyte concentration 24 hr after hypophysectomy was compared between the control and DDAVP treatment groups. The DWC, DUV, USG, plasma electrolyte concentration, and plasma AVP concentration during the 30-day period after hypophysectomy were compared between the control and DDAVP treatment groups by one-way analysis of variance. Fisher's PLSD comparison procedure was used to test for significant differences between groups at error rate of $p < 0.05$.

RESULTS

Experimental surgery: Experimental surgery was conducted by surgeons fully trained to perform this procedure, and the condition was stable throughout the surgery in all dogs. No complications occurred during or after surgery in any animal. The resected tissue was confirmed by microscopy to be normal pituitary tissue.

Physiological parameters: Changes in DWC and DUV in the control and DDAVP treatment groups are shown in Figs. 1 and 2, respectively. In the control group, values for DWC and DUV on day 1 after surgery were 337.6 ml/kg/day and 258.5 ml/kg/day, respectively, and recovered to preoperative levels about five days after surgery. In the DDAVP treatment group, DWC and DUV changed within the normal

ranges for 14 days after surgery. However, after completion of DDAVP administration, DWC and DUV increased on days 18–21 after surgery. Peak values of DWC and DUV

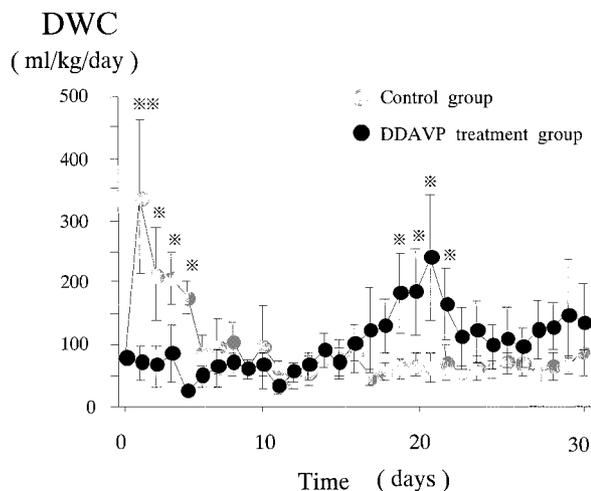


Fig. 1. Sequential change of daily water consumption (DWC) after hypophysectomy in the dog. In the control group, DWC on the 1st day after surgery increased to 337.6 ml/kg/day, and recovered to the preoperative levels about five days after surgery. On the contrary, DWC changed within the normal ranges for 14 days after surgery in the DDAVP treatment group. However, after the completion of DDAVP administration, DWC increased transiently to 238.7 ml/kg/day. *** : $p < 0.01$ * : $p < 0.05$.

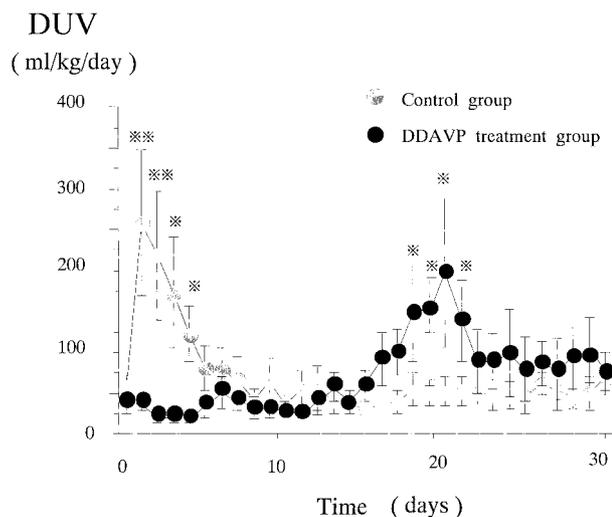


Fig. 2. Sequential change of daily urine volume (DUV) after hypophysectomy in the dog. DUV of the control group increased to 258.5 ml/kg/day on the 1st day after surgery, and recovered to the preoperative levels about five days after surgery. In the DDAVP treatment group, DUV changed within the normal ranges for 14 days after surgery. However, after the completion of DDAVP administration, DUV increased transiently to 196.8 ml/kg/day on the 20th day after surgery. *** : $p < 0.01$ * : $p < 0.05$.

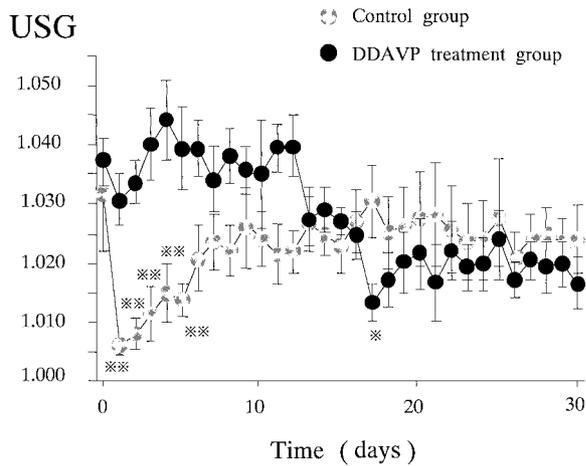


Fig. 3. Sequential change of urine specific gravity (USG) after hypophysectomy in the dog. In the control group, USG ranged from 1.006 to 1.015 for 5 days after surgery and recovered to the preoperative level with time. On the contrary, USG changed within the normal range for 16 days after surgery in the DDAVP treatment group. However, it decreased transiently to 1.013 on the 17th day after surgery. ※※: $p < 0.01$.

were 238.7 ml/kg/day and 196.8 ml/kg/day, respectively, on day 20 after surgery. On days 1–4 after surgery, DWC was significantly higher in the control group than in the DDAVP treatment group ($p < 0.01$ – 0.05), but on days 18–21 after surgery, DWC was significantly higher in the DDAVP treatment group than in the control group ($p < 0.05$). The pattern of changes in DUV was similar to that of DWC.

Figure 3 shows changes in USG in the control and DDAVP treatment groups. In the control group, USG ranged from 1.006 to 1.015 on days 1–5 after surgery and was significantly lower than in the DDAVP treatment group ($p < 0.01$). In the control group, this value recovered to the preoperative level over time. In the DDAVP treatment group, USG became within the normal range for 16 days after surgery, but decreased to 1.013 on day 17 after surgery, showing a transient decrease ($p < 0.05$ vs control group).

Plasma sodium concentration: In the control group, the mean plasma sodium concentration ranged from 156.3 to 167.4 mEq/l 4–16 hr after surgery, indicating hypernatremia (Fig. 4) and reached the maximal level 10 hr after surgery (mean: 167.4 mEq/l). The highest plasma sodium concentration during this observation period was 213.7 mEq/l. In the DDAVP treatment group, the plasma sodium concentration during the 24-hr period after surgery was 143.0–145.8 mEq/l, which is a normal value. The plasma sodium concentration was significantly higher in the control group than in the DDAVP treatment group 4–12 hr after surgery ($p < 0.05$).

During the one-month period after surgery, the plasma sodium concentration reached the maximal level on day 1, then decreased slightly until day 30 after surgery in the control group (Fig. 5). On the other hand, the level tended to

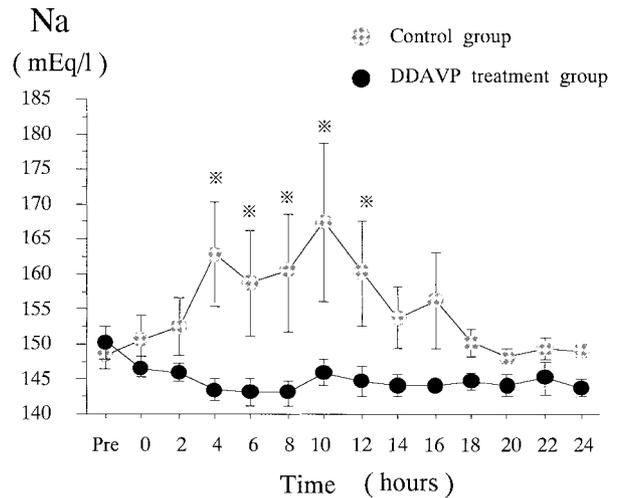


Fig. 4. Sequential change of plasma sodium concentration during 24 hr after hypophysectomy. Hypernatremia was confirmed to develop at 4–16 hr after surgery with the plasma sodium concentration in 156.3–167.4 mEq/l in the control group. In the DDAVP treatment group, on the contrary, the plasma sodium concentration during the 24-hr period after surgery ranged from 143.0–145.8 mEq/l, showing normal level. ※: $p < 0.05$.

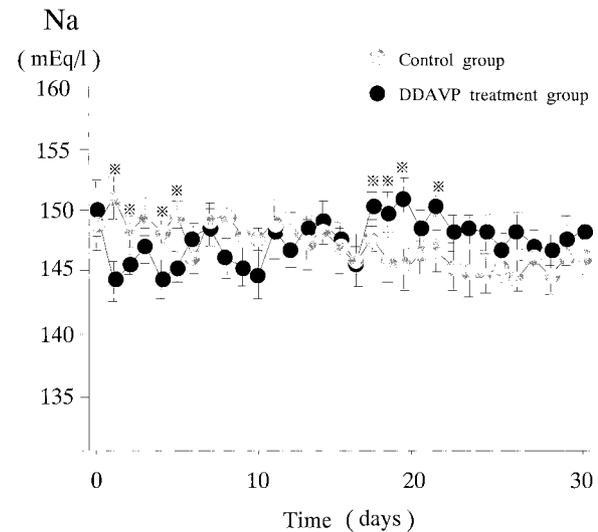


Fig. 5. Sequential change of plasma sodium concentration during 30 days after hypophysectomy. In the control group, the plasma sodium concentration reached the maximal level on the next day after surgery, then slightly decreased with time until the 30th day. On the contrary, in the DDAVP treatment group, the level was maintained during about 2 weeks. However, transient increase of plasma sodium concentration was recognized on days 17, 18, 19, and 21 after surgery. ※: $p < 0.05$.

increase transiently after day 17 in the DDAVP treatment group. The plasma sodium concentration was significantly higher in the control group than in the DDAVP treatment group on days 1, 2, 4, and 5 after surgery ($p < 0.05$). How-

ever this value was significantly increased in the DDAVP treatment group on days 17, 18, 19, and 21 after surgery and after completion of drug administration ($p < 0.05$).

Changes of other electrolytes were as follows. Changes in plasma chloride concentration almost paralleled that of sodium concentration in the control group, with the mean chloride concentration reaching a maximal level 10 hr after surgery (mean: 132.8 mEq/l). During the one-month period after surgery, the plasma chloride concentration ranged from 113.0–119.0 mEq/l. On the other hand, in the DDAVP treatment group, mean chloride concentration during postoperative at 24 hr and 30 days were 113–117 mEq/l and 112–120 mEq/l, respectively.

With regard to changes of plasma potassium concentration, transient hypokalemia, decreasing to 2.6 mEq/l, was confirmed after surgery in the control group, but recovered to a normal range soon after surgery. The plasma potassium concentration ranged from 3.5–4.7 mEq/l during the postoperative 30 days. In the DDAVP treatment group, potassium values during the postoperative 24 hr and 30 days were 3.4–4.2 mEq/l and 3.8–4.6 mEq/l, respectively.

Plasma AVP level: The plasma AVP level was lower than the preoperative level (mean: 2.7 pg/ml) on days 1, 15, and 30 after surgery in the control and DDAVP treatment groups (Fig. 6). Significant differences could not be detected between the two groups at any point.

DISCUSSION

For DI after hypophysectomy, prevention or improvement of hypertonic dehydration accompanied by hypernatremia is important, and supplementation therapy using AVP or its derivative drug is required [1, 16]. There are two types of receptors for arginine vasopressin (AVP) physiologically secreted from the posterior pituitary: V1-receptors, which are distributed in vascular smooth muscle throughout the body and are related to the pressor effect, and V2-receptors, which are located in renal tubules, mainly in the collecting tubules, and are related to the antidiuretic effect [4, 14]. DDAVP used in this study exhibits an antidiuretic effect for eight hours, which is relatively long, and its effect on V2-receptors is strong, about three-fold higher than that of AVP. Because of this selective agonistic character of DDAVP for V2-receptors, DDAVP is used for the treatment of central DI [1, 21]. Meijer *et al.* treated postoperative DI by administering one drop of 0.01% desmopressin into the conjunctiva every eight hours for two weeks [7]. However, the dogs used had accompanying with endocrinological abnormalities caused by functional pituitary tumor preoperatively, and were simultaneously treated with other hormones including glucocorticoids and thyroid hormones. On the contrary, we used clinically normal dogs in the present study. Therefore, we can not compare postoperative findings in the present study with those in the previous report [7]. For the present study, we selected the dosage of DDAVP based on the clinical dose for the spontaneous central DI, and the administration period was decided base on

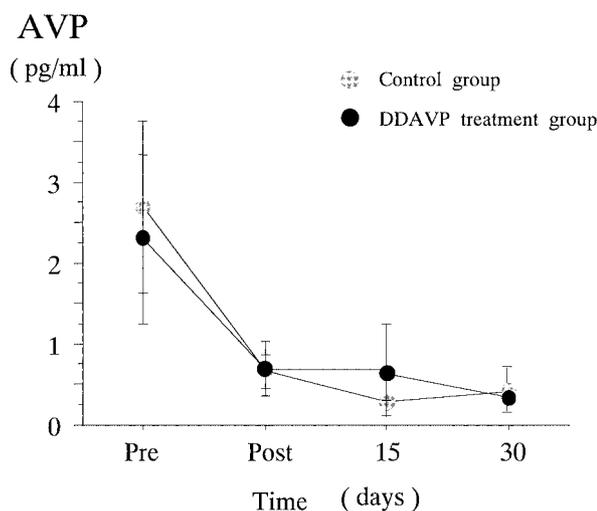


Fig. 6. Changes of plasma arginine vasopressin (AVP) concentration after hypophysectomy in the dog. The plasma AVP level was lower than the preoperative level on days 1, 15, and 30 after surgery in both the control and DDAVP treatment groups. Significant difference could not be detected between the both groups at any point.

the report by Meijer *et al.* [1, 7, 16].

In this study, hypernatremia with a plasma sodium concentration of 155 mEq/l or higher persisted for 12 hr, from the 4th to 16th hr, after hypophysectomy in the control group. The maximal level (mean: 167.4 mEq/l) was reached 10 hr after surgery, with a 18.9 mEq/l increment from the preoperative level (mean: 148.5 mEq/l). This rapid increase in the plasma sodium concentration during a short period induces osmotic injury in vascular endothelial cells and is considered to be the major cause of central pontine myelinolysis [13]. It was demonstrated in rats that a rapid increase in the plasma sodium concentration (39 mEq/l or more in 6–12 hr) induces demyelinating encephalomyelitis in the thalamus, brain stem, tegmentum, and hippocampus [20]. Histological evaluation of the brain stem was not performed in this study. However, no clinical neurological abnormality related to hypernatremia was observed. In the DDAVP treatment group, the mean plasma sodium concentration ranged from 143.0 to 146.7 mEq/l and other electrolyte concentrations also changed within the normal ranges. Furthermore, no clinical features suggesting water intoxication, such as subcutaneous edema, were observed during the period of DDAVP administration. Therefore, it was clarified that administration of DDAVP (4 μ g, instillation, twice daily) can effectively prevent the hypernatremia that develops within 24 hr after surgery and DI-like symptoms that develop within approximately a week after surgery.

Changes in DWC, DUV, and plasma sodium concentration during the 30-day period after surgery were also evaluated in this study. DI-like symptoms, including increases in DWC and DUV and a decrease in USG, persisted for seven days after surgery in the control group, and these were con-

sistent with those reported by Niebauer *et al.* [11]. In contrast, in the DDAVP treatment group, DWC, DUV, and USG remained within normal range during the 14-day DDAVP administration period, but DWC and DUV increased and USG decreased transiently after completion of DDAVP administration, reaching peaks on day 20 after surgery. This might represent a rebound phenomenon. Based on physiological findings in the present study, it was considered that the period of DDAVP treatment was suitable for one week after hypophysectomy. Moreover, tapering of the dosage before the completion of DDAVP therapy may be needed.

Several causes were considered for the rebound phenomenon. One is the possible lack of endogenous stimulation related to AVP production or secretion in the hypothalamus due to maintenance of relatively normal plasma osmotic pressure during the DDAVP administration, which may have resulted in the absence of an up-regulation of V2-receptors in the collecting tubular cells in the kidney. In patients with central diabetes insipidus, persistent AVP deficiency for a prolonged period maximally promotes the expression of V2-receptors and a response to even a low concentration of AVP, i.e., upregulation of V2-receptors, is observed [14]. This phenomenon may have been involved in both the control and DDAVP treatment groups in this study. Specifically, although the plasma AVP concentration was maintained at a lower level than the preoperative level in both groups, clinically, DWC and DUV recovered to normal ranges after day 7 in the control group and after day 20 in the DDAVP treatment group. These findings were consistent with the results reported by Meij *et al.* [8], when they performed hypophysectomy in dogs and evaluated the posterior pituitary function over time. DI-like symptoms remitted 10 weeks after hypophysectomy but response to the hypertonic saline loading test was not recovered. In hypophysectomy in actual practice, the location of the surgical resection of the pituitary is important. With regard to the function of the hypothalamus-posterior pituitary system after resection of the hypophyseal stalk, sequential triphasic changes as reported by Fisher *et al.* are generally noted as follows [2]. Surgical invasion caused functional paralysis of ADH-secreting cells after resection of the hypophyseal stalk and induced acute DI [2]. During the normal intermediate period, ADH stored in the posterior pituitary was involuntarily released into the circulation and symptoms of DI subsided. After release of ADH from the posterior pituitary was completed, ADH was depleted and the condition progressed to chronic DI. When the hypophyseal stalk was resected near the diaphragm of sellae, which is relatively lower than the hypophyseal stalk, neurons regenerated and neurosecretory substances were retained in the stump of the resected hypophyseal stalk, forming a pseudoposterior lobe [5]. DI clinically remitted with the formation of a pseudoposterior lobe. When the hypophyseal stalk was resected near the hypothalamus, no pseudoposterior lobe was formed and permanent diabetes insipidus was observed clinically [5]. Since the hypophyseal stalk connecting to the

third ventricle was completely resected in the experimental surgery in the present study and the plasma AVP concentration was continuously lower than the preoperative level for 30 days after surgery, it is less likely that the former triphasic changes or compensatory responses such as the latter pseudoposterior lobe formation were involved in our findings.

It has been known that DI occurs accompanied by intracranial disorders or hypophyseal surgery in the field of human neurosurgery [10, 15, 17]. This postoperative hyponatremia with a Na concentration lower than 135 mEq/l was observed in 21–35% of patients who underwent transsphenoidal surgery and the frequency was particularly high (61%) in patients with Cushing's syndrome. With regard to the mechanism, organic disorder of the hypothalamus-posterior pituitary system and a relative deficiency of AVP secreted from the posterior pituitary into the circulation are considered to be the major causes [19]. Hyponatremia after transsphenoidal hypophysectomy in veterinary neurosurgery contradicts hyponatremia after transsphenoidal surgery in human neurosurgery. This may be due to differences in the surgical technique in the two fields. In human neurosurgery, generally, the pituitary is not completely resected and only adenoma tissue is excised selectively, preserving the posterior pituitary. However, in small animal neurosurgery, partial resection of only adenoma tissue is difficult in many cases and all pituitary tissue is resected.

In this study, hypernatremia with the highest mean plasma sodium concentration of 167.4 mEq/l persisted for 12 hr from 4th to 16th hr after hypophysectomy in dogs, and administration of DDAVP (4 μ g/head, instillation, twice daily) effectively prevented the development of postoperative DI about a week after surgery. However, a transient rebound was observed after completion of DDAVP administration. It was considered that a period of DDAVP treatment lasting for a week after hypophysectomy would be suitable. Moreover, tapering may be necessary at the completion of DDAVP therapy.

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