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Severe Hyponatremia After Repeated Intravenous Administration of Desmopressin

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Desmopressin (DDAVP) has recently been found to improve hemostasis in patients with congenital or acquired disorders of coagulation and to reduce operative blood loss in patients with normal hemostasis undergoing certain surgical procedures. Despite its potent antidiuretic effect, severe hyponatremia after the intravenous administration of DDAVP is felt to be rare. We report four cases of severe hyponatremia with serious clinical sequelae occurring in patients with underlying coagulopathies who were treated prophylactically with DDAVP to improve hemostasis prior to surgical procedures. Each patient received multiple (3–22) doses of DDAVP and was given intravenous hydration with hypotonic solutions before developing clinical signs and laboratory evidence of hyponatremia. We believe that the risk of significant hypoantremia after treatment with intravenous DDAVP may be higher than is generally appreciated and that patients undergoing surgical procedures, who often receive multiple doses of DDAVP and intravenous hydration, are at particular risk for this complication. Hypotonic intravenous solutions should be avoided and serum sodium levels should be monitored frequently in those patients receiving multiple doses of DDAVP.

Key words: hemophilia, von Willebrand disease, seizures

INTRODUCTION

Since the reports in the early 1970s that 1-deamino-8-D-arginine vasopressin (DDAVP, desmopressin) raises the levels of factor VIII coagulant activity (VIII:C) and von Willebrand factor (vWF:Ag) after infusion into normal volunteers [1,2], DDAVP has enjoyed widespread use for improving hemostasis in patients with bleeding disorders. Although the mechanism of action of DDAVP is not entirely clear [3], patients with mild and moderate hemophilia [4–6], von Willebrand's disease [4,7–9], and congenital or acquired platelet function defects [10–14] respond to DDAVP with improved hemostasis. In addition, DDAVP has been reported to decrease intraoperative blood loss in hemostatically normal patients undergoing spinal fusion surgery [15] or cardiac surgery [16,17].

In several large series reviewed recently [4,7] the risk of complications of DDAVP therapy has been reported to be very low. Unlike its parent compound, vasopressin, DDAVP has little effect on the V1 receptors of smooth muscle, and, hence, has little vasopressor activity [18]. It has a potent effect on the V2 receptors of the kidneys, however, and its antidiuretic effect is well known [18]. In fact, DDAVP has become the most effective agent used to treat neurogenic diabetes insipidus [18–20] and is also used to test renal concentrating ability [21,22]. Surprisingly, hyponatremia with mild clinical symptoms has been reported in only a single patient who had received five large doses (0.5 μg/kg) of DDAVP to treat a bleeding disorder [23]. We now report four cases of severe hyponatremia characterized by serious clinical man-

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ifestations in patients who had received DDAVP for treatment of a variety of bleeding disorders. Risk factors for the development of this complication of DDAVP are reviewed.

MATERIALS AND METHODS

Administration of DDAVP

DDAVP (Stimate, Armour Pharmaceutical Company, Tarrytown, NY; 0.3 μg/kg body weight in 50 cc of normal saline) was administered as a continuous intravenous infusion over 15–20 min. Blood pressure and pulse rate were measured before beginning the infusion and at 15 min intervals for 60 min thereafter.

CASES

Case 1

A 4-year-old girl with mild type IA von Willebrand's disease (vWD) was admitted to the University of Connecticut Health Center on 4/5/84 for an elective tonsillectomy and adenoidectomy. She had received previously a test infusion with DDAVP, which she tolerated well and which corrected her prolonged bleeding time. She received an initial dose of DDAVP immediately prior to surgery and an additional four doses at 8 hr intervals postoperatively. Surgical hemostasis was reported to be excellent, but she became nauseated postoperatively and was given intravenous hydration with 5% dextrose, 0.45% saline at a rate of 50 ml/hr for 40 hr to prevent dehydration. At 6:30 p.m. on 4/6/84 she suffered a tonic/clonic seizure and her serum sodium level was found to be 121 mEq/L. The most recent serum sodium level, which had been measured 5 months previously, had been 137 mEq/L. Treatment with hypertonic saline solution corrected the electrolyte abnormality and seizure activity ceased. An extensive neurological examination failed to disclose any underlying seizure disorder.

Case 2

A 28-year-old woman with a history of rheumatoid arthritis was scheduled to undergo a Caesarean section for ineffective labor on 1/17/87 and was found to be severely thrombocytopenic (platelet count less than 20,000/dl). Treatment with steroids and platelet transfusion raised the platelet count to 40,000/dl, but the bleeding time remained greater than 15 minutes. On 1/18/87 surgery was performed and she received intravenous steroids, intravenous gamma globulin, and additional platelet transfusions. Oxytocin was not given. DDAVP was administered preoperatively and an additional three doses postoperatively at 8 hr intervals. Estimated blood loss during surgery was 1,000 ml and she received 2,000 ml of 0.9% saline, 750 ml of 5% dextrose plus Ringer's lactate, and 900 ml of Ringer's lactate during surgery. Postoperatively, she received 5% dextrose plus Ringer's lactate at 125 ml/hr. Twenty-four hours after surgery she became confused and agitated and her serum sodium was found to have fallen from a preoperative level of 140 mEq/L on 1/18/88 to 118 mEq/L. Treatment with 3% saline corrected the hyponatremia and her mental status normalized.

Case 3

A 15-year-old boy with mild hemophilia A underwent transrectal drainage of a periappendiceal abscess on 10/12/87. Surgical hemostasis was assured with a pasteurized factor VIII concentrate. On 10/15/87 he was begun on DDAVP at 8 hr intervals in an attempt to decrease his factor VIII requirement. The serum sodium level prior to initiation of DDAVP was 132 mEq/L. DDAVP treatment was inadvertently continued for seven days and he received a total of 22 doses. On 10/19/88 he underwent a repeat transrectal drainage procedure with excellent hemostasis. During this period he received no intravenous hydration. However, he developed recurrent abdominal pain and fevers, and on 10/23/88 oral intake was stopped and he was given 975 ml of 5% dextrose, 0.45% saline in preparation for an exploratory laparotomy. He became obtunded and his serum sodium level was found to have fallen to 118 mEq/L. After correction of hyponatremia, he returned to his normal state of alertness.

Case 4

A 3-year-old boy with mild type Ia vWD underwent tonsillectomy and adenoidectomy on 12/17/87. His serum sodium level on the day of surgery was 138 mEq/L and he was given DDAVP before surgery and at 8 hr intervals postoperatively. Operative hemostasis was excellent. He received 400 ml of Ringer's lactate in the operating room and an additional 397 ml of 5% dextrose, 0.3% saline over the next 24 hr. At 12:30 p.m. on 12/18, after his third dose of DDAVP, he became lethargic and his serum sodium level was found to be 129 mEq/L. The intravenous solution was changed to 0.9% saline, but he suffered a tonic/clonic seizure at 4 p.m., at which time his serum sodium level was 120 mEq/L. The electrolyte imablance was corrected by the administration of 3% saline with cessation of seizure activity. He has had no recurrent seizures and no underlying seizure disorder could be found.

DISCUSSION

Despite its well-known effect on renal concentrating ability, this is the first report of severe hyponatremia

TABLE I. Clinical Summary

Case	Diagnosis	Age (yr)	DDAVP doses	Serum sodium (mEq/L)	Clinical complications
1	von Willebrand disease	4	5	121	Tonic/clonic seizure
2	Thrombocytopenia	28	4	118	Agitation, confusion
3	Mild hemophilia A	15	22	118	Obtundation
4	von Willebrand disease	3	3	120	Tonic/clonic seizure

occurring after the use of DDAVP in standard doses as a hemostatic agent. Indeed, the risk of hyponatremia due to DDAVP treatment is felt to be extremely low [3]. However, the cases reported here may represent a patient group at high risk for developing this complication-hospitalized patients who receive multiple doses of DDAVP in concert with hypotonic intravenous fluids (Table I).

When used to treat patients with mild or moderate hemophilia, von Willebrand disease, or congenital platelet defects, one or two doses of DDAVP are usually given on an outpatient basis. In our experience, this form of treatment has been safe. We have yet to observe a single instance of symptomatic hyponatremia during more than 100 administrations of single doses of DDAVP for treatment of minor bleeding episodes and to prevent bleeding during dental procedures, although we do not routinely measure serum sodium levels in these situations.

The dosage interval of 8 hr was chosen on the basis of the expected duration of response to DDAVP in hemophilia and von Willebrand's disease. The peak levels of factor VIII procoagulant activity, ristocetin co-factor activity, and shortening of the bleeding time usually occur between 30 min and 3 hr after administration of DDAVP and return to baseline within 5–8 hr [4]. Twice-daily infusions of DDAVP have also been used by other groups. It has not been determined whether the use of this schedule lowers the risk of hyponatremia or is as efficacious as the administration of three daily doses.

Other potential risk factors include postoperative stress (cases 1,2,4), nausea and vomiting (case 1), and preexisting mild hyponatremia (case 3). In this series severe hyponatremia was not limited to extremely young or old patients. Similarly, none of the patients had any history or pre-existing renal dysfunction or received other medication known to cause hyponatremia.

We have here identified a patient group in whom the risk of severe hyponatremia from the use of DDAVP may be higher than is generally appreciated and are concerned that as DDAVP is more widely used as a general hemostatic agent, more cases of severe hyponatremia will be discovered. We urge caution when using multiple doses of DDAVP, especially when patients are receiving intravenous fluid support and recommend that multiple closely spaced doses (less than eight hours) of DDAVP be avoided. If it is necessary to treat intensively with DDAVP, then patients must be watched closely and hypotonic saline solutions should probably not be used and the volume of fluid administered restricted. A prospective study of the incidence of significant hyponatremia in this setting is indicated.

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