The syndrome of inappropriate antidiuretic hormone secretion (SIADH) was first recognized in 1957. It has been found to accompany a variety of clinical conditions which include disorders of the central nervous system, malignant tumors, acute pulmonary infections, and treatment with the vinca alkaloid, vincristine.

In two of the case reports, serum antidiuretic hormone (ADH) levels, as measured by bioassay, were markedly elevated during the period of hyponatremia. None of the reports of SIADH produced by vincristine therapy have provided information regarding its potential for recurrence, despite the fact that this agent is generally required for repeated use in patients with malignancies.

The documentation of recurrent elevations in ADH excretion in one patient, following repeated treatment with vincristine during the course of her chemotherapy for acute lymphatic leukemia, forms the basis of this report.

**MATERIALS AND METHODS**

Urinary excretion of ADH was measured by specific radioimmunoassay on 24-hr urine collections.

**CASE REPORT**

KS, a 4-yr-old white female, was hospitalized on May 29, 1973 for evaluation of pallor and easy bruising. Following appropriate hematologic investigations (including bone marrow examination), a diagnosis of acute lymphatic leukemia was made. A routine initial lumbar puncture was normal, and initial electrolytes included a sodium of 138 meq/liter, chloride of 104 meq/liter, potassium of 4.4 meq/liter, bicarbonate of 24 meq/liter, and a BUN of 19 mg/100 ml. The blood pressure was 105/75 mm Hg.
The patient was started on a chemotherapeutic regimen of oral dexamethasone, 6 mg/sq m daily, and intravenous vincristine, 2 mg/sq m weekly for three doses, the first two of which were administered on hospital days 2 and 9 (Fig. I). The early hospital course proved uneventful, but by hospital day 7, the patient had developed abdominal distention and constipation. These symptoms disappeared by day 9. On day 9, the patient experienced two episodes of generalized seizures. These were controlled with intravenous valium. Examination at this time revealed that the patient had a blood pressure of 160/90 mm Hg, and a small retinal hemorrhage inferior-medial to the disc margin. No evidence of volume depletion or overload was present, and laboratory data revealed a BUN of 5 mg/100 ml, sodium of 118 meq/liter, chloride of 84 meq/liter, potassium of 4.1 meq/liter, bicarbonate of 21 meq/liter, a serum osmolality of 243 M osmoles/liter, a urinary sodium excretion of 130 meq/liter and a urinary sodium excretion of 130 meq/liter (Fig. I). The blood sugar, serum calcium and phosphorus, urine analysis, lumbar puncture, and x-rays of the skull were all normal.

The hyponatremia was initially treated with 37 ml of 3% NaCl, followed by 160 ml of 3% NaCl over the next 4 hr. This was followed by a therapeutic trial of 5 cc ethanol. The hyponatremia, however, remained uncorrected by these therapeutic modalities. Twelve hours after the seizures,
the patient was placed on a regimen of fluid restriction at approximately 50% maintenance (Fig. 1). Complete normalization of the serum sodium level occurred following total fluid restriction by hospital day 18 (Fig. 1). On June 16, 1973, KS received her third dose of vincristine while continuing on approximately 50% maintenance fluids, and while under close surveillance for recurrent hyponatremia. The patient remained clinically asymptomatic and did not manifest a drop in her serum sodium level (Fig. 1). Fluid restriction was thereafter gradually withdrawn, and the patient discharged on hospital day 35 following a bone marrow examination that revealed her to be in remission. An EEG, brain scan, and creatinine clearance performed prior to discharge were normal, and a Risa I measurement of total blood volume revealed a value of 80.2 ml/kg (normal, 66-88 ml/kg), with a plasma volume of 52.9 ml/kg (normal, 36-49 ml/kg).

The patient was continued on maintenance chemotherapy, during the course of which she received subsequent doses of vincristine (Fig. 2). The patient was on no fluid restrictions during these subsequent dosages, and remained asymptomatic with normal serum sodiums. She received prophylactic cranial irradiation (2500 R) during the period September 12, 1973 to September 27, 1973, and at the present time continues in remission without evidence of central nervous system involvement. She manifests some signs of vincristine neurotoxicity, including decreased deep tendon reflexes, alopecia, and ptosis.

RESULTS

Urinary excretion of ADH (mU/24 hr/sq m) obtained whenever possible during the course of the patient's initial hospitalization, and thereafter following subsequent dosages of vincristine during maintenance chemotherapy, are depicted in Fig. 2.

Urinary ADH excretion at the time of the patient's initial period of symptomatic hyponatremia was markedly elevated. This rise had occurred either 8 days following the patient's initial dose of vincristine on May 30, 1973, or the day following her second dosage on June 6, 1973. Subsequent followup values revealed that the peak excretions of ADH occurred from 8 to 10 days following subsequent vincristine dosages on June 16, 1973 and August 3, 1973. Following prophylactic cranial irradiation in September 1973, urinary ADH measurements after subsequent vincristine dosages on October 2, October 30, and November 26, 1973 did not reveal evidence of increased ADH excretion (Fig. 2).
DISCUSSION

The cardinal features of SIADH include (1) hyponatremia with corresponding hypo-osmolality of the serum and extracellular fluid, (2) continued renal excretion of sodium, (3) absence of clinical evidence of volume depletion, (4) osmolality of the urine greater than that appropriate for the concomitant tonicity of the plasma, i.e., urine less than maximally dilute, (5) normal renal and adrenal function, and (6) improvement in both hyponatremia and renal loss of sodium by fluid restriction. In addition, recent studies have demonstrated that urinary excretion of ADH is increased in SIADH when ADH excretion is related to the level of plasma osmolality.

Our patient fulfills all the criteria necessary for the diagnosis of SIADH, including the documentation of high urinary ADH excretion during a period of concomitant severe hyponatremia.

In asymptomatic patients with SIADH, the accepted mode of therapy for the correction of hyponatremia has been to produce a negative water balance by severely restricting water intake. In patients with acute and symptomatic hyponatremia, therapy has included the rapid administration of a hypertonic saline solution. Unfortunately, the administration of sodium can produce further volume expansion, and most of the sodium chloride is rapidly excreted, as occurred in our patient (Fig. 1). Attempts to inhibit ADH release from the posterior pituitary by the use of alcohol proved unsuccessful in our patient. Hantman et al. have recently proposed another method for the rapid correction of the symptomatic hyponatremia of SIADH which consists of furosemide diuresis to achieve a negative water balance, accompanied by replacement of urinary electrolyte losses with a more concentrated electrolyte solution.

In the eight previous case reports of vincristine-induced SIADH, the syndrome was recognized due to the occurrence of symptomatic hyponatremia within 4–10 days of vincristine administration (Table 1). In two of these patients, serum ADH levels as measured by bioassay were markedly elevated during the period of hyponatremia. No data, however, are available in the literature on the potential for recurrence of SIADH following repeated challenge with vincristine in patients in whom this syndrome has once occurred.

This case report documents the occurrence of SIADH following administration of vincristine by the direct measurement of urinary ADH excretion. It also demonstrates the potential for recurrence of the syndrome by documenting an increase in ADH excretion, and presumably secretion, following repeated doses of vincristine.

Our findings indicate that the occurrence of repeated symptomatic hyponatremia in the face of increased ADH secretion can be prevented by rigorous fluid restriction during the time period in which the SIADH is most likely to occur. It is possible that prophylactic cranial irradiation (Fig. 2) was a factor in the subsequent inability of vincristine to provoke an increase in ADH secretion in our patient. This observation will require confirmation in other patients.

It has been suggested that the primary effect of vincristine is on the nerve cell body and that the peripheral nerve demyelination is a secondary phenomenon. In view of the fact that most patients with SIADH induced by
v vincristine have also manifested other moderately to markedly severe signs of vincristine neurotoxicity, the SIADH in these patients is possibly due to a direct neurotoxic effect of vincristine on the hypothalamus, the neurohypophyseal tract, or the posterior pituitary itself, involving sites of ADH formation and storage.

In summary, in all the reports to date in which SIADH has occurred following vincristine therapy, no patient was rechallenged with the drug because of the risk of repeated serious electrolyte disturbances. This case report documents the fact that the hyponatremia induced by vincristine is true SIADH, and that increased ADH secretion following repeated challenge with vincristine is a reproducible finding. This does not preclude the safe usage of repeated doses of vincristine in the patient with malignancy, in whom repeated doses of the drug may be deemed a therapeutic necessity.

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Syndrome of recurrent increased secretion of antidiuretic hormone following multiple doses of vincristine

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