Chronic demeclocycline therapy in the syndrome of inappropriate ADH secretion due to brain tumor

Case report

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The treatment of the syndrome of chronic inappropriate antidiuretic hormone (ADH) secretion by fluid restriction is often attended by poor patient compliance. The following case report illustrates successful management of this condition by oral demeclocycline therapy in a patient who had hyponatremia in association with angioblastic meningioma of the sphenoid ridge.

KEY WORDS: hyponatremia • demeclocycline • vasopressin • ADH • meningioma • antidiuretic hormone • inappropriate ADH secretion

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can occur with a variety of central nervous system disorders, including meningitis, brain abscess, head trauma, and brain tumor. Neurological dysfunction resulting from the accompanying hypomolarity may confuse the clinical picture and complicate patient management. The syndrome is usually self-limited, resolving with treatment of the underlying disorder, but in those instances where it is persistent, the strict fluid restriction required to maintain a normal serum osmolality is often too exacting a regimen for the patient to adhere to. A few reports have recently described a favorable response of patients with SIADH to lithium and demeclocycline, drugs that block the effect of ADH on the kidney tubule, that is, create a nephrogenic diabetes insipidus. Lithium therapy has the disadvantage of a narrow margin of safety with potential cardiac, neurological, and hematological toxicity; it requires frequent determination of serum levels, and has numerous side effects even when levels are in the therapeutic range. In addition, at least one investigator has noted a failure of response in chronic lithium treatment of a patient with SIADH. For these reasons, we chose to use demeclocycline, an agent relatively devoid of toxic effects, in treating a patient with SIADH in association with angioblastic meningioma of the sphenoid wing.

Case Report
This 51-year-old woman was hospitalized because of a seizure characterized by transient loss of consciousness following an
episode of lip smacking and repetitive conjugate lateral eye deviation. Three years earlier, she had had a "nervous breakdown" and had been treated with Stelazine (trifluoperazine) 5 mg four times daily since then. She had gained 30 lbs during this interval, but had had no somnolence, memory loss, further personality change, headache, or visual loss. Menses were regular until menopause, 8 years before admission, and she denied decreased libido, galactorrhea, cold intolerance, and weakness. No oliguria or polyuria had been noted.

Examination. She was an alert, cooperative woman with optic atrophy in the right eye, and lower nasal and temporal visual field cuts. She had a right Marcus-Gunn pupil, and visual acuity was 20/100 on the right and 20/20 on the left. Neurological examination was otherwise normal. No galactorrhea was elicited, and there were no signs of hypopituitarism.

Admission laboratory studies revealed a marked hyponatremia and hypoosmolality with a concentrated urine, and normal renal, hepatic, adrenal, thyroid, and anterior pituitary function. Laboratory values were as follows: hemoglobin, 12.9 gm/dl; hematocrit, 35.6%; white blood cell count, 8100/cu mm; blood urea nitrogen (BUN), 12 mg/dl; creatinine, 0.7 mg/dl; sodium, 111 mEq/l; potassium, 4.8 mEq/l; chloride, 76 mEq/l; CO₂, 24 mEq/l; calcium, 8.7 mg/dl; albumin, 4.5 mg/dl; phosphorus, 3.0 mg/dl; cortisol, AM, 26 μg/dl; PM, 25 μg/dl; T4, 14 μg/dl; T3, 135 ng/dl; prolactin, 28 ng/ml; follicle stimulating hormone, 25 mlU/ml; luteinizing hormone, 48 mIU/ml; and osmolality, serum, 233 mOsm/kg, urine, 756 mOsm/kg.

Skull series showed enlargement of the sella turcica, erosion of the sella floor with elevation of the anterior clinoid process, and a soft tissue density projecting into the sphenoid sinus. A large parasellar stain was seen at angiography, extending inferiorly into the right sphenoid sinus region, laterally into the middle fossa, and posteriorly into the posterior fossa along the clivus. The right internal carotid artery was narrowed, suggesting tumor encasement. In addition to the above, computerized tomography scan showed invasion of the sphenoid sinus. All studies were consistent with a large medially sphenoid ridge meningioma.

Hospital Course. Stelazine was discontinued. The patient was treated with a fluid restriction of 250 to 500 cc/day and attained a serum sodium of 134 mEq/l after 1 week. She underwent craniotomy which revealed a large mass arising from the right sphenoid ridge and filling the temporal fossa, densely adherent to the right optic nerve, internal carotid artery, and walls of the cavernous sinus. The mass was highly vascular and filled the sinus, and excision in the sella region was limited because of bleeding. Pathological diagnosis was angioblastic meningioma with small admixture of meningothelial elements.

The patient sustained transient right III, IV, and VI cranial nerve pareses and loss of the right corneal reflex postoperatively. When she was allowed ad libitum fluid intake, hyponatremia with inappropriate urinary hyperosmolality again became manifest. Five days of fluid restriction to 250 cc/day resulted in a rise of serum sodium from 118 mEq/l to only 125 mEq/l. Demeclocycline was then begun at a maximum dosage of 300 mg four times daily. Serum sodium gradually normalized despite a fluid intake of approximately 1000 cc/day. The postoperative course was complicated by wound infection, and hypernatremia developed while the patient was febrile. Over the course of the next few weeks, adjustments in demeclocycline dosage and fluid intake were made to determine the minimum effective dosage of demeclocycline. Figure 1 details changes in serum sodium with the patient on different amounts of water intake and various dosages of demeclocycline while in the hospital and for 6 months thereafter when she was followed as an out-patient. Optimum water balance was achieved with a dose of demeclocycline of 300 mg three times daily and 1500 cc/day fluid restriction, an amount quite comfortable for the patient. At the 8-month follow-up examination, a marked improvement in cranial nerve function was found, with only minimal limitation of abduction and adduction of the right eye. Radiotherapy was begun because of the angioblastic nature of the meningioma. The most recent serum sodium was 137 mEq/dl.

Discussion

Several authors have reported induction of reversible dose-dependent urinary concentrating defects in otherwise healthy in-
Inappropriate ADH secretion treated with demeclocycline

![Graph showing serum Na levels over time with demeclocycline treatment](image)

**Fig. 1.** Course of patient treated with demeclocycline for SIADH due to brain tumor. Note the continued climb of sodium serum (Na) for 72 hours at the time of wound infection, despite reduction of the dosage of demeclocycline.

Individuals treated with demeclocycline for acne and other minor infections. In those tested with exogenous vasopressin, a blunted response was observed. Their observations were extended to the treatment of patients with SIADH by De Troyer and Demanet and Cherrill, _et al._, who each described a single case of SIADH due to oat-cell carcinoma of the lung. In both patients hyponatremia was reversed by oral administration of demeclocycline (600 to 1200/day) despite _ad libitum_ water intake. The latter authors also documented failure to concentrate urine during a 12-hour dehydration test in their SIADH patient during demeclocycline therapy, as had been observed in the group of acne patients. Our patient similarly illustrates this abrogation of normal physiological control of water balance due to demeclocycline, in that she failed to conserve water even when she was markedly hypernatremic while on 900 mg/day.

As for the character of drug action, we can confirm the impression that there is a threshold-type of response to demeclocycline, since doses of 300 and 600 mg/day were without effect in inducing water diuresis. The changing fluid restriction at the time of institution of demeclocycline therapy obfuscates effects due solely to the drug; however there appeared to be a 24- to 48-hour delay in the onset and termination of action of the drug. The prolonged action is illustrated in our patient by the continued climb of serum sodium to markedly high levels after reduction of demeclocycline dosage (see Fig. 1). Despite these fluctuations in serum sodium, the patient continued to do well, and a maintenance dosage of 900 mg of demeclocycline therapy per day for the most part stabilized her serum electrolytes.

The exact mechanism of demeclocycline blockade of ADH action is not fully understood, but _in vitro_ studies have shown modes of action both dependent on and independent of cyclic adenosine monophosphate (AMP). The delay in onset and termination of drug action suggests that conversion to an active metabolite is required for action and that tissue binding and saturation kinetics may be important. Whatever the underlying biochemical events, we have shown that demeclocycline can be a well tolerated and remarkably effective way of treating patients

J. Neurosurg. / Volume 47 / December, 1977 935
with SIADH over prolonged periods of time without tachyphylaxis, when the underlying condition is not amenable to direct therapy. Recently, however, there have been two reports of progressive renal insufficiency associated with the use of demeclocycline administration to patients with hyponatremia secondary to hepatic cirrhosis. 

Because of the reports it is important to make sure that patients who might be selected for demeclocycline therapy and have SIADH, do not have concomitant cirrhosis.

References


This work was supported in part by USPHS Training Grant AM07039-02 to Dr. Graze.

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