Failure of Desmopressin to Lower Serum Sodium or Prevent Crisis in Patients With Sickle Cell Anemia

By Samuel Charache and W. Gordon Walker

An analogue of arginine vasopressin (desmopressin, DDAVP) was evaluated for production of chronic hyponatremia and prevention of sickle cell crisis. With sodium restriction (100 meq Na+/day) and water loading (>3 liters/day), persistent hyponatremia could not be achieved, nor could crises be prevented or aborted.

In 1957, ALLISON showed that solutions of deoxynogentated hemoglobin S did not gel until their hemoglobin concentration exceeded a minimum value. In the same year, Greenberg et al. described the behavior of red cells from a patient with sickle cell trait who was severely iron deficient: these cells did not sickle under usual laboratory conditions of deoxygenation, and the authors concluded that the concentration of hemoglobin S (the mean corpuscular hemoglobin concentration, or MCHC) was too low for sickling to occur. More recent analyses have suggested that small decreases in MCHC, while not completely inhibiting sickling, might significantly ameliorate clinical course.

Knochel and Guy et al. attempted to lower MCHC by rendering plasma hypotonic, and obtained suggestive evidence of improvement in patients. The technique was never widely utilized, but recently, Rosa et al. reopened the question by reporting their experience with a synthetic vasopressin analog, desamino-D-arginine vasopressin (DDAVP, desmopressin) in patients with sickle cell anemia. By inhibiting renal water excretion, the drug caused serum sodium to fall to levels below 125 meq/liter; MCHC (and MCHSC) decreased, cells sickled less readily in vitro, and crises were reduced in number. When pain did occur, it improved rapidly after intensive therapy with the drug.

Desmopressin can be taken at home by intranasal inhalation. Its major side effect is water intoxication; patients would not comply with a regimen of lower salt and higher fluid intake. More rigorous treatment might be practical during acute sickle cell crises, and a regimen similar to that used here might be more effective in children, whose renal concentrating mechanisms are still intact.

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MATERIALS AND METHODS

A study was designed to evaluate the efficacy of administration of DDAVP for prevention of crises in outpatients with sickle cell anemia. It was recognized that rigid restriction of sodium intake and "forcing" of oral fluids might enhance effects of the drug, but long-term compliance with a strict dietary regimen seemed unlikely. The study was carried out in the Clinical Research Center, rather than the Outpatient Department, so that adherence to the dietary regimen could be monitored and drug administration assured. Patients with sickle cell anemia were asked to live in the hospital for 3 mo. Only three patients agreed to this program, and subsequent events curtailed its duration.

Narcotics were ordered by the housestaff in response to patients' complaints, without knowledge of laboratory data; the only exceptions to this rule occurred when the investigator was available to the Nursing Staff and interns were not. To prevent house officers from obtaining laboratory data from the hospital computer, patients were assigned code names ("Alpha," "Beta," and "Gamma").

Evaluation of success of the experimental regimen was based on the "Pain Index," the total daily dose of narcotic expressed in equivalents of parenteral morphine. Since placebo effects have confounded interpretation of previous studies based on relief of pain, a crossover placebo-controlled regimen was planned, but discarded later when no beneficial effects were observed during treatment with active drug. Red cell survival and blood counts were also measured.

Patients Studied

"Alpha," a 28-yr-old male practical nurse, has been transfused with nearly 180 U of blood since 1974. In addition to hemochromatosis, he has had numerous attacks of pneumonia or pulmonary infarction, meningitis, and hematuria. His last transfusion before this study was on August 12, 1980; when admitted on September 15, his blood contained 63% hemoglobin S.

"Beta," a 27-yr-old female teacher, is unable to work because of frequent crises. She has almost constant abdominal pain, for which no cause has been found.

"Gamma," the 22-yr-old brother of "Alpha," is an unemployed college dropout. He requested admission to the study after his brother agreed to participate.

Sodium and Water Intake

A diet containing 100 meq of Na+/day was ordered; urinary sodium excretion was monitored to assess compliance with the diet,
and these measurements lead to one patient ("Gamma") being confined to the nursing unit to prevent his access to saltier food.

Except for "Gamma," patients were allowed off the nursing unit for periods of less than 8 hr every other day. They were told to drink 3 liters of fluid/day, and urged to drink more; the minimum was achieved, but higher intakes were not maintained (Table I). Based on measurements of salt excretion, "Alpha" also thwarted our efforts to restrict sodium intake.

Drug Dosage

The maximum dose of DDAVP was initially planned to be that described by Rosa et al. (40 µg every 6 hr). When no beneficial results were obtained, it was increased to 200 µg/day, and eventually to 240 µg/day (see Figs. 1–3). The drug was administered by nasal inhalation, using applicators supplied by the manufacturer. No more than 0.2 ml was used per nostril; Beta complained of nasal "stuffiness" while taking the drug, but the other two patients did not.

Screening for Responsiveness to DDAVP

When it became evident that DDAVP alone could produce only minor increases in urine osmolality in the three study patients (see below), test doses of DDAVP were given to a group of outpatients with sickle cell anemia (Fig. 4). Urine osmolality was measured before and after drug administration and compared with data obtained in a small group of laboratory personnel. No attempt was made to control salt or water intake in these subjects.

RESULTS

Hyponatremia and Urine Osmolality

Significant falls in serum sodium were observed in Alpha and Beta, but the changes did not persist and were followed on several occasions by spontaneous diureses (Figs. 1–3). Even when hyponatremia was
marked, microhematocrits were never more than 2%–3% higher than those calculated by an electronic cell counter, and MCHC never fell below 32 g/dl.

Table 1 shows mean values for urine osmolality during the control period and during DDAVP administration. Only modest increases in mean osmolality were seen in the three study patients, or in the outpatients given test doses of the drug (Fig. 4).

During the last days of the study, subcutaneous desmopressin was substituted for intranasal drug, in equivalent dosage (4 μg rather than 40 μg). Neither serum sodium nor urine osmolality changed, and intranasal use of the drug was resumed.

Toxicity

The only toxicity potentially attributable to the drug was headache in Alpha and Beta at times when their Na⁺ concentration was low. Beta’s headache was accompanied by vomiting, but she did not develop papilledema or neurologic abnormalities.

Subjective Effects of Treatment

All three patients had attacks of pain while receiving desmopressin. These attacks are most clearly shown by the “Pain Index” in the figures and were often associated with changes in temperature and white blood cell count. Alpha and Beta developed crises at times (11/1/80 and 10/16/80) when serum Na⁺ was below 120 meq/liter; DDAVP administration was continued, but serum Na⁺ rose and pain persisted.

Objective Effects of Treatment

Red cell survival, measured with ⁵¹Cr (Table 2), did not change significantly during treatment, nor did reticulocyte count, hemoglobin, or serum haptoglobin concentration. In Gamma, red cell survival was somewhat longer during a period when he received no DDAVP. The percent HbA in Alpha’s blood gradually fell, but his hemoglobin concentration remained about 9.5 g/dl. Whole blood oxygen affinity did not change significantly in any patient.

Alpha was discharged when he did not return from an 8-hr leave of absence. Beta and Gamma left at the
CHANGE OF URINE OSMOLALITY IN RESPONSE TO DDAVP

Table 2. Red Cell Survival

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period</th>
<th>Treatment</th>
<th>T_{99.9}^{51}Cr-Treated Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>9/16–30</td>
<td>None</td>
<td>4 days</td>
</tr>
<tr>
<td></td>
<td>10/14–31</td>
<td>160 µg/day</td>
<td>6 days</td>
</tr>
<tr>
<td>Beta</td>
<td>9/17–30</td>
<td>None</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td>10/14–31</td>
<td>120 µg/day</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td>11/17–26</td>
<td>160 µg/day</td>
<td>8 days</td>
</tr>
<tr>
<td>Gamma</td>
<td>9/16–30</td>
<td>None</td>
<td>6.5 days</td>
</tr>
<tr>
<td></td>
<td>10/16–31</td>
<td>160 µg/day</td>
<td>6 days</td>
</tr>
<tr>
<td></td>
<td>11/11–26</td>
<td>None</td>
<td>8.5 days</td>
</tr>
</tbody>
</table>

end of the last red cell survival study. All three were offered further trials with desmopressin, and all three declined.

DISCUSSION

We were unable to maintain hyponatremia in our patients and observed no beneficial effects from the regimen used. The dose of drug used here is the same (or higher) than that used in Boston: salt intake was lower, water intake was similar, and both were more rigidly controlled since the patients described here were hospitalized.

Hypertonic urine osmolalities before drug administration, in the three study patients and in most of the outpatients, indicated that they were already under vasopressin stimulation. Only slight changes in osmolality were seen in any patient during treatment, and only slight decreases occurred in the average daily urine volume of Alpha, Beta, and Gamma. It is thus evident that the urine volume (and hence fluid intake) was determined largely by solute load and that administration of DDAVP could produce, at most, only modest additional water retention unless fluid intake was sharply increased or solute load reduced. Neither alternative was acceptable to our patients.

Lack of response to intranasal DDAVP in our patients was probably not due to impaired nasal absorption, for parenteral doses of drug had no more effect on urine osmolality than equivalent doses given intranasally. It is possible that the gradual increase in drug dosage promoted tachyphylaxis; Rosa et al. describe a similar experience, but attributed it to "dietary indiscretion or decreased fluid intake at home," and added a diuretic to their patients' regimen to compensate for it. Hydrochlorothiazide had no effect on serum Na⁺ when it was added to Beta's regimen.

Our experience with the three hospitalized patients and the larger group screened for responsiveness to DDAVP suggests that DDAVP has little to offer adult patients, at least as a preventative for painful crises, unless they are prepared to make significant changes in their salt and water intake. A more promising approach would be to administer DDAVP to patients whose renal concentrating mechanisms are still more or less intact. Young children are an obvious group to treat—for the drug might not only cause hypotension but in doing so might preserve responsiveness to DDAVP into adult life.

ACKNOWLEDGMENT

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REFERENCES

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