Management of diabetes insipidus in neurosurgical patients

WILLIAM A. SHUCART, M.D., AND IVOR JACKSON, M.D.

Departments of Neurosurgery and Endocrinology, Tufts-New England Medical Center Hospital, Boston, Massachusetts

The authors present a brief review of the problem of diabetes insipidus in neurosurgical patients, with particular emphasis on the differential diagnosis of postoperative and posttraumatic polyuria and the management of diabetes insipidus in these periods. A listing of drugs currently used in its treatment is given.

KEY WORDS: diabetes insipidus · polyuria · drug therapy

A BRIEF REVIEW of the current concepts that concern the pathophysiology and treatment of diabetes insipidus is presented with special emphasis on the problems as they may present to the neurosurgeon. Mention is also made of other aspects of this condition of which the neurosurgeon should be aware.

Physiology of Diabetes Insipidus

Vasopressin, the antidiuretic hormone (ADH), is an octapeptide synthesized in the supra-optic nucleus of the anterior hypothalamus. It is transported along the neurohypophysial pathway attached to a large carrier protein (neurophysin) to be stored in the posterior lobe of the pituitary. It is released in response to many stimuli, the most important being increased plasma osmolality as in dehydration and hypovolemia as occurs with hemorrhage. Pain, stress and various drugs, such as morphine and barbiturates, may also act by means of neural pathways to stimulate ADH release. All such factors can assume considerable importance following trauma, including surgery, and result in oliguria which may last for some time. It should be noted, however, that following head trauma either excess ADH output or ADH deficiency (diabetes insipidus) can occur. The latter may on occasion be further complicated by damage to the thirst center in the hypothalamus. Inability to secrete vasopressin results in the excretion of a dilute urine. Failure to counter this fluid loss results in dehydration, hemoconcentration and hypovolemia. Destruction of the hypothalamic centers or division of the supraoptic tract above the median eminence causes permanent diabetes insipidus. Transection below the median eminence, even removal of the posterior pituitary lobe, causes only a transient polyuria. It appears that sufficient ADH can be released from fibers ending in the median eminence.

Antidiuretic hormone is transported in the blood to the distal renal tubule where, after binding to the cell membrane, it activates adenyl cyclase. As for many other peptide hormones that act at other sites, 3'5' cyclic
adenosine monophosphate (3'5' cyclic AMP) is generated and operates as an intracellular (second) messenger. The net effect of this hormonal activity is that the cells of the distal renal tubules and collecting ducts are rendered more permeable to water which is reabsorbed from the nephron back into the circulation.4,23

Classification of Diabetes Insipidus

Vasopressin Deficiency. Vasopressin deficiency can cause 1) Primary diabetes insipidus, which may occur as an idiopathic condition or rarely be familial;15 or 2) Secondary diabetes insipidus, which may result from head trauma, neurosurgery, and neoplastic or granulomatous deposits in the hypothalamus.24

Nephrogenic Diabetes Insipidus (Idiopathic). This is a sex-linked inherited condition in which the renal tubules are unresponsive to ADH.

Nephrogenic Diabetes Insipidus (Acquired). The presence of hypercalcemia or hypokalemia may make the renal tubular cells unresponsive to ADH. Correction of the electrolyte disturbance restores normal responsiveness to ADH.9

Diagnosis of Diabetes Insipidus

Signs and Symptoms

The diagnosis of chronic diabetes insipidus has been discussed in detail elsewhere.15,18,20,27 The major differential diagnosis of the office patient presenting with a complaint of polyuria usually involves differentiation from diabetes mellitus, psychogenic polydipsia, chronic renal failure, and the various forms of nephrogenic diabetes insipidus mentioned earlier. This differential diagnosis is usually in the province of the internist. The most commonly used diagnostic test at present is restriction of fluid intake (without allowing loss of more than 5% of the body weight) with measurement of urine volume and concentration. A normal subject can reduce urine flow to less than 0.5 ml/min and increase urine osmolality to greater than 800 mOsm/kg. If this does not occur, responsiveness of the renal tubule should be demonstrated by vasopressin administration; aqueous vasopressin by slow intravenous drip (5 μg/min) or by intramuscular injection of 5 units of pitressin.

The diagnosis of diabetes insipidus of acute onset following surgery or trauma may be more difficult, for polyuria can occur in this period secondary to a variety of causes.12,20,25,30 No arbitrary level of urinary output will satisfy all clinicians as to what constitutes polyuria. As a rule of thumb whenever the urine output exceeds the fluid intake an abnormal cause of polyuria should be suspected; the absolute urine volume is usually in excess of 2 to 3 liters per day.

When polyuria begins in the immediate postoperative period it is necessary to establish whether it is secondary to water or solute excretion.20 A solute diuresis may be a result of hyperglycemia,20 inability to retain sodium secondary to corticosteroid deficiency,5 high urea levels, or the residual effect of the osmotic diuretics so commonly used in neurosurgical procedures.12 When the diuresis is secondary to solute excretion the urinary specific gravity is usually between 1.009 and 1.035; the urine osmolality is usually 250 to 320 mOsm/kg; the serum sodium is normal or slightly decreased and thirst is not usually a complaint. When the diuresis is secondary to water excretion the urinary specific gravity is usually between 1.001 and 1.005; the urine osmolality is between 50 and 150 mOsm/kg; the serum sodium is usually normal or increased; and thirst is usually a prominent feature. The latter picture is, of course, what is seen in diabetes insipidus.

Differential Diagnosis

When it is determined that the diuresis is secondary to the excretion of a water load, the differential diagnosis includes:

1. Diabetes insipidus. This is secondary to the causes listed previously
2. Chronic renal insufficiency. Renal function tests will be abnormal and the patient is usually azotemic
3. Multiple myeloma, amyloidosis, sickle cell disease, and a peculiar phenomenon sometimes seen after relief of obstructive uropathy are rarer causes of an inability to concentrate urine. These problems usually cause little difficulty in the differential diagnosis6
4. Recovery phase of acute tubular necrosis. The clinical sequence of events in this problem usually makes the diagnosis clear
5. Fluid overload. Careful attention must
Diabetes insipidus in neurosurgical patients

be paid to fluid administration during the intraoperative and immediate postoperative periods when the patient may receive excessive amounts of parenteral fluids. Particularly if these fluids are electrolyte-free and do not cause a solute diuresis, the patient may retain excessive quantities of water. As the patient excretes this excessive water load he may have an output which exceeds his intake.\(^{31}\)

Postoperative Phases of Diabetes Insipidus

Diabetes insipidus following head injury or surgery in the hypothalamic-pituitary area can follow a variety of patterns in its development and may be transient. Early prognostication as regards permanence of the diabetes insipidus should not be made because of marked variation in the eventual outcome.\(^ {29,30}\)

After any brain trauma, cerebral edema generally appears within 12 to 24 hours and is most marked at 48 to 72 hours. This edema may functionally impair cells which are structurally intact. A temporary diabetes insipidus can develop and subsequently resolve as the edema clears. There are varying degrees of chronic ADH deficiency with the urinary output being related to the number of viable cells.\(^ {18}\) Long-term treatment is dependent on the degree of polyuria.

The clinical picture presented in postoperative diabetes insipidus comprises four distinct syndromes:

1. The most common situation seen in the postoperative period is transient polyuria that begins 1 to 3 days after surgery and lasts from 1 to 7 days. It may follow traction on the pituitary stalk and its appearance is not dependent on an intact posterior lobe of the pituitary gland. It seems to be primarily hypothalamic rather than pituitary dysfunction. The time course is compatible with the onset and dissolution of local edema.\(^ {29,30}\)

2. A triphasic pattern has been described both in humans and experimental animals. Polyuria beginning 1 to 2 days after surgery and lasting 1 to 7 days is followed by a period of normal urinary output. After 24 hours to several days this is followed by a resumption of abnormally large urinary output which persists. This triphasic response is classically produced in experimental animals by transection of the pituitary stalk and destruction of the hypothalamic median eminence if the posterior lobe of the pituitary is left in place. If the posterior lobe of the pituitary is removed there is an immediate and permanent polyuria. The interphase is probably secondary to the release of previously stored ADH in the posterior pituitary. When this ADH has been completely utilized permanent diabetes insipidus ensues.

3. Polyuria may begin within the first 2 to 3 days postoperatively followed by a small decrease in the total urinary volume over the next several days. These patients probably have a partial ADH deficiency which is magnified in the initial stages because of superimposed local edema.

4. Permanent polyuria can develop within the first 2 to 3 days postoperatively and continue thereafter with no interphase and no significant change in urinary output volumes. These patients probably have immediate extensive damage to the hypothalamus and, after the previously formed ADH is used up, there are no borderline viable cells capable of producing or storing enough ADH to allow some modification in the postoperative course.\(^ {10,13,15,25,32,33}\)

Treatment of Acute Diabetes Insipidus

Once the postoperative diagnosis of diabetes insipidus secondary to ADH insufficiency is made, the patient's management should be planned with the above-mentioned patterns of response in mind. A program that uses long-acting medications and long-range plans is obviously not feasible when the degree and duration of the disease process are uncertain.

Those patients with diabetes insipidus preoperatively seldom have any improvement after surgery. It is reasonable in these particular patients to return to the preoperative medical treatment as soon as is practical.

Those patients who are likely to develop diabetes insipidus after surgery, that is, operations for lesions in and around the hypothalamic-pituitary area, are treated in an
expectant manner until polyuria becomes apparent. In the postoperative pre-polyuria phase the average adult is treated with standard parenteral fluid replacement. Urinary output is closely monitored with volume and specific gravity readings every 1 to 2 hours if the patient has an indwelling bladder catheter, otherwise as it is obtained. Body weight is recorded prior to surgery and at least once a day in the postoperative period. During this pre-polyuria phase the serum electrolytes, blood urea nitrogen (BUN), and hematocrit are measured every other day. When the patient is able to take fluids by mouth he is allowed to drink as he wishes, but careful charting of intake and output continues. It is essential that the patient report all fluid intake to the nursing staff.

If polyuria appears there are general guidelines to follow. The method of treatment is mainly determined by the patient's clinical status. If the patient is alert and taking his diet by mouth, he will usually regulate his fluid intake satisfactorily as dictated by the thirst mechanism. The fluid balance must, however, be carefully monitored. There is no need for electrolyte supplementation. Body weight and serum electrolytes are measured daily. If urinary output exceeds 250 ml/hr for 2 consecutive hours or 6 to 7 l/day, or the patient is unable to maintain adequate intake, aqueous pitressin is administered. When a stable level of diabetes insipidus has been reached, pitressin tannate-in-oil or one of the preparations discussed below is used.

The patient unable to take adequate oral fluids, particularly if he is lethargic or obtunded, poses the greatest problem in management. Since he cannot inform the staff of his thirst a good clinical parameter is lost. Meticulous fluid intake-output records and twice-daily weights provide a valuable guide to the state of hydration. If fluid intake and output are approximately equal, the patient may maintain his weight, will probably lose a small amount of weight, but should never gain weight. If urinary output is very large or there is concern about the patient's status, the serum electrolytes, BUN, and hematocrit are measured twice a day; with lower levels of urinary output, once a day is adequate. The serum osmolality can be measured directly or estimated if the serum electrolytes and blood sugar are known. The serum osmolality (within 5%) equals 2 × Na + K (mEq/l) + \( \frac{\text{blood glucose}(mg\%)}{18} \).

With normal blood sugar a fairly reliable rough estimation is 2 × the serum sodium (mEq/l) + 10. Fluid intake and output are kept equal over a 24-hour period. These are balanced at intervals from 1 hour to 1 day depending on the degree of polyuria. If the patient has a large urinary output (400 to 500 ml/hr) it is best to maintain balance on an hourly basis. If the urinary output is under 200 ml/hr it is adequate to maintain fluid balance on a 4 to 6 hour basis.

Urine volume and insensible loss are usually the only significant factors in calculating the patient's 24-hour fluid output. Insensible water loss, primarily water vapor, in the afibrile patient averages 1000 ml in men and slightly less in women. The urine in the polyuric phase of diabetes insipidus contains a small amount of electrolytes per liter of urine. The primary body loss in diabetes insipidus is water; therefore, the primary replacement indicated is water.

Fluid intake should be almost solely dextrose-in-water solutions if given intravenously or tap water if given by mouth. The only electrolyte replacement given in this period is that of a normal postoperative patient which is administered as one liter of balanced electrolyte solution, and should not be distributed through several infusions. Saline solutions deliver a continuing solute load to the kidneys which aggravates the renal loss of water since solute concentration cannot be increased in the absence of ADH. 3,6,24,33 The administration of saline solutions as replacement for the urinary loss in diabetes insipidus is probably the commonest error in the management of this problem. Metabolic water, from the oxidation of fat and protein to provide daily caloric requirements, provides about 200 ml of endogenous water per day, but may increase greatly in the presence of fever or extensive trauma. This fluid is free of sodium but rich in potassium.

It is possible to replace very large urinary outputs, but, particularly in the very young or older patients with other problems such as cardiac disease, it is preferable to keep fluid intake at lower levels. Pitressin can be used at any time in the postoperative period if there is careful monitoring of the fluid balance. Water intoxication, manifest by lethargy, confusion,
Diabetes insipidus in neurosurgical patients

seizures, and coma, can occur if excess pitressin is administered. This symptomatology is due to hyponatremia and cerebral edema. The volume expansion created causes sodium excretion and peripheral edema rarely occurs. What actually occurs is an "iatrogenic inappropriate ADH syndrome." This complication can and should be avoided with careful management.1,11,20,35

Aqueous pitressin is preferable treatment in the early stages of diabetes insipidus for two reasons. First the duration of action is only 4 to 6 hours, so errors in fluid balance can be quickly corrected. Secondly changes in the degree of diabetes insipidus are quickly appreciated. In many cases the problem lasts only 2 to 3 days and there is no need for further treatment. Initial treatment with aqueous pitressin is in the range of 5 to 10 IU per dose. This is usually given intra-muscularly. Intravenous doses, if used, must be carefully monitored to guard against an undue pressor response. If polyuria persists a stable level is usually not reached for 10 to 14 days after surgery. Until that time long-term regimens are not practical.

The two most important things to remember in the management of acute diabetes insipidus are that the primary loss in this disease is water and the process is not static but dynamic.

Treatment of Chronic Diabetes Insipidus

Posterior Pituitary Hormone Preparations

Aqueous Vasopressin. Aqueous vasopressin is a partially purified vasopressin obtained from animal pituitaries available in 0.5 and 1 ml ampoules of 20 IU/ml. The short duration of action (4 to 6 hours) makes this preparation unsuitable for prolonged use. In the acute stage a slow continuous infusion of not more than 3 IU/hr or intermittent intramuscular injections of 0.1 to 1.0 ml are usually effective.

Pitressin Tannate-in-Oil. Pitressin tannate-in-oil is also obtained from animal sources, and supplied in 1 ml ampoules with a strength of 5 IU/ml. It is given intramuscularly and is effective in doses of 0.25 to 1 ml. This agent has a variable but long duration of action (24 to 72 hours) and is therefore suitable for chronic severe cases. If the vial is not warmed and shaken thoroughly prior to administration the active moiety may precipitate out.

Lysine Vasopressin Nasal Spray. Lysine vasopressin nasal spray is a synthetic preparation and therefore is much less likely than the above agents to cause allergic reactions. It is supplied in a plastic bottle (5 ml) containing 50 IU/ml. Administration of one or two sprays up each nostril three to four times/day may produce good control of the diabetes. Each spray delivers approximately 2 IU. This agent is most effective in mild cases.

Desamino-8-Arginine Vasopressin (DDAVP). This vasopressin analogue is a synthetic preparation which is administered intranasally twice per day in a dose of 10 to 20 µg. Its altered chemical structure, relative to vasopressin, apparently retards its degradation. It is not yet available for routine clinical use in this country, but Edwards, et al., enthusiastically hail this agent as the drug of choice for vasopressin-sensitive diabetes insipidus.

We do not use intra-nasal preparations for 3 months after transsphenoidal hypophysectomy since they may cause local vaso-constriction of the nasal mucosa.

Non-Pituitary Preparations

In recent years it has been appreciated that a number of drugs may be effective in reducing urine volumes when given orally.16,19,22 Among these are:

Chlorpropamide. This oral hypoglycemic agent may effectively reduce the polyuria in hypothalamic but not nephrogenic diabetes insipidus. The drug appears to act by potentiating the antidiuretic effect of low levels of endogenous ADH. It is most effective in mild cases where the usual dosage is 50 to 250 mg/day. "Antabuse"-like symptoms with this drug occasionally cause problems as a side effect.21,24

Thiazide Diuretics. Paradoxically, thiazide diuretics are the only effective drugs for nephrogenic diabetes insipidus. The presence of vasopressin is not required for action and the mechanism is probably contraction of the extracellular fluid volume secondary to loss of sodium. Hydrochlorothiazide should be used in doses of 50 to 100 mg/day. Potassium supplements may be required.7 The use of chlorpropamide and hydrochlorothiazide together, often in only small doses, may be effective due to a synergistic effect. Further, the thiazide diuretic helps to counteract the hypoglycemia which may be a problem in
patients with growth hormone or ACTH deficiency.

Other Agents. Carbamazepine (Tegretol) used as an anticonvulsant and in the treatment of tic douloureux, the antineoplastic agents vincristine and cyclophosphamide, the hypolipidemic agent clofibrate and the analgesic acetaminophen may all be effective in mild diabetes insipidus by effecting the release of vasopressin from the neurohypophysis. Carbamazepine, in particular, may potentiate the action of chlorpropamide.

References
29. Schwartz WB, Bennett W, Curelop S, et al: A syndrome of renal sodium loss and hyponatremia probably resulting from inap-
Diabetes insipidus in neurosurgical patients

propriate secretion of antidiuretic hormone. 
30. Sharkey PC, Perry JH, Ehni G: Diabetes insipidus following section of hypophyseal stock. 
*J Neurosurg* 18:445–460, 1961
31. Smith HW: Salt and water volume receptors. 
34. Wales JK, Fraser TR: The clinical use of chlorpropamide in diabetes insipidus. 
35. Zak GA, Brun C, Smith HW: The mechanism of formation of osmotically concentrated urine during the antidiuretic state. 

This work was supported in part by National Institutes of Health grant AM 16684.

Address reprint requests to: William A. Shucart, M.D., Department of Neurosurgery, Tufts-New England Medical Center Hospital, 171 Harrison Avenue, Boston, Massachusetts 02111.