Postoperative Hyponatremia with the Inappropriate Release of Antidiuretic Hormone

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A detailed description of 11 elderly patients who developed symptomatic dilutional hyponatremia in the postoperative period is presented. Sustained and inappropriate secretion of antidiuretic hormone (ADH) together with the administration of fluid is postulated to be the cause of the changes in levels of consciousness observed. Factors related to anesthesia, operation, and the postoperative period which may contribute to the stimulation and maintenance of ADH liberation are described. Anesthesiologists should be aware of this syndrome, the diagnosis and treatment of which is so simple.

AN ABNORMALLY low serum sodium concentration is a frequent finding in the postoperative period. Often, the hyponatremia can be attributed to excessive loss of fluid and electrolytes from the gastrointestinal tract. However, it has become apparent that hyponatremia due to over-hydration and dilution may be a more common finding than hyponatremia associated with sodium depletion. LeQuesne [1] emphasized the importance of postoperative dilutional hyponatremia in a group of patients who developed severe water intoxication the result of failure to excrete large excesses of parenterally administered water. Zimmerman and Wangensteen,[2] Hayes and Goldenberg [3] and Moore [4] have reviewed some of the metabolic responses to operation which result in impaired water excretion.

In normal individuals postoperative antidiuresis is a transitory phenomenon, most patients recovering within five to seven days after operation.[3] However, we have observed a group of patients in whom the postoperative antidiuresis was more severe and prolonged. All of these were "elderly" patients who, except for one, had undergone major operation. Following operation, they developed a variety of diffuse neurological abnormalities ranging from marked restlessness and disorientation to profound stupor. These patients had moderate to marked hyponatremia and other features resembling the syndrome of inappropriate secretion of antidiuretic hormone (ADH).[5] This syndrome had previously been observed in patients with bronchogenic carcinoma and a variety of metabolic and cerebral diseases. The salient clinical features may be summarized as follows:

(1) Hyponatremia and low serum osmolality.*

(2) Persistent excretion of a hypertonic urine, which under conditions of high fluid intake may contain large quantities of sodium despite hyponatremia.

(3) Absence of azotemia.

(4) Normal adrenal function.

(5) Absence of signs of extracellular fluid volume contraction such as dehydration and hypotension that would foster antidiuresis.

(6) Absence of edema.

(7) Improvement in hyponatremia and decrease in renal sodium excretion following fluid restriction.

Sustained secretion of antidiuretic hormone has been postulated as the cause of the antidiuresis because of the presence of an inappropriately elevated urine osmolality in the presence of a normal glomerular filtration rate, and the fact that these patients resemble normal subjects given vasopressin and water for several days.[6] The term *inappropriate* is used because hypotonicity of body fluids normally inhibits ADH secretion.

It is the purpose of this paper to review our experience with the hyponatremic syn-

* Osmolality is a term expressing the total solute concentration (tonicity) of a solution irrespective of the specific solutes expressed as milliosmols per kilogram of solvent (water). The normal range of serum osmolality is 275 to 290 mosm./kg.

TABLE 1. General Description of Patients with Postoperative Hyponatremia

Name, Age, Race, Sex	Diagnosis	Operation	Anesthesia	Postoperative Narcotics Sedatives	Symptoms	Day of Onset	Duration of Symptoms	Therapy
H. H. 63 W, F	Ovarian cancer; right flank abcess	I & D of abcess	Thiopenta N_2O-O_2	None	Lethargic to semicomatose	7	14	Fluid restriction to 1,500 ml./day
J. P. 63 W, M	Gastric ulcer	Gastrectomy	Thiopental N_2O-O_2 Fentanyl Prinadol‡	Morphine, 10 mg. Librium,* 25 mg.	Confused Hallucinations	4	9	No fluid restriction; 600 ml, 2% NaCl
M. K. 66 W, M	Hydronephrosis	Nephrostomy	Spinal; Thiopental	Meperidine, 50 mg.	Confused	1	9	Fluid restriction; 300 ml, 2% NaCl
R. N. 70 W, M	Femoral artery embolism	(1) Femoral artery exploration (2) Leg amputation	(1) C_3H_6-N_2O-O_2 (2) C_3H_6-O_2	Codeine, 60 mg.	Disoriented	5	10	Fluid restriction
R. C. 73 W, F	Cholecystitis	Cholecystectomy; C.D.E.	Thiopental, C_3H_6-O_2	Meperidine, 50 mg. Codeine, 30 mg.	Somnolent Disoriented	3	8	No fluid restriction and oral salt
J. W. 75 W, M	Inguinal hernia	Inguinal herniorrhaphy	Thiopental, N_2O-O_2 DTC	Fentanyl, 0.05 mg. Paraldehyde†	Restlessness Somnolent Disoriented	1	2	Fluid restriction; 1,000 ml, P.S.S., I.V.
N. M. 75 W, F	Cancer of colon	Colostomy	General		Restlessness		60	Fluid restriction to less than 1,000 ml./day
M. W. 83 W, F	Ovarian cyst	Ovarian cystectomy	Thiopental C_2H_6-O_2 DTC, Fentanyl	Fentanyl, 0.1 mg. Thorazine†	Restlessness Lethargic Stuporous	2	5	Fluid restriction to 500 ml., P.S.S.
E. B. 85 W, M	Cancer of colon	Right colectomy	Thiopental N_2O-O_2 DTC	Fentanyl Morphine, 8 mg. Paraldehyde†	Confused Disoriented	1	4	No fluid restriction
F. R. 86 W, F	Fracture of hip	Hip pinning	Spinal; N_2O-O_2 Prinadol‡	Morphine, 5 mg.	Lethargy Disoriented	1	5	Fluid restriction to less than 1,000 ml, p.o. per day
A. M. 86 W, M	Cancer of colon	Anterior resection	Spinal; Thiopental N_2O-O_2	Prinadol,‡ 0.5 mg. Meperidine, 25 mg.	Restlessness Disoriented	4	7	Fluid restriction to less than 1,000 ml./day

* Librium (Chloridazepoxide)—for disorientation.
† Paraldehyde, Thorazine (Chlorpromazine)—for restlessness.
‡ Prinadol (Phenazocine).

TABLE 2. Laboratory Analyses During Hyponatremia

Name	Intake in Previous 24 Hours		Serum		BUN (mg.%)	Urine	
	Total Fluid (ml.)	Sodium (mEq.)	Sodium Conc. (mEq./l.)	Osmolality (mosm./kg.)		Osmolality (mosm./kg.)	Sodium Excretion (mEq./24 hr.)
H. H.	3,000	150	127	270	9	420	48
J. P.	5,000	300	122	244*	11	1.013†	312
M. K.	4,500	0	118	266	18	852	302
R. N.	2,000	0	114	251	8	640	
R. C.	2,500	0	128	249	8	423	95
J. W.	2,500	75	122	250	8	550	
N. M.	?	?	124	244	8	640	79
M. W.	2,000	0	119	228	16	325	
E. B.	2,800	150	118	236*	15	1.020†	
F. R.	2,000	0	131	262*	5	1.012†	
A. M.	2,400	150	114	239	8	325	

* Estimated 2X sodium conc. mEq./l.[22]
† Specific gravity of urine.

drome in the postoperative period and to present some of the intra-operative and postoperative factors contributing to this disturbance.

Method of Study and Results

There were 11 postoperative patients with hyponatremia whom members of the Chemical Section of the Department of Medicine had been asked to see in consultation from 1959 to 1965. Hospital records and laboratory analyses were reviewed. A summary of the records is presented in tables 1 and 2. An illustrative case history is presented in detail.

CASE HISTORY

R. C., 73 year old, white woman, weighing 90 pounds, was admitted for cholecystectomy with a diagnosis of chronic cholecystitis and cholodo-colithiasis. Two months prior to admission a cholecystostomy had been performed for acute cholecystitis. Common duct stone was revealed by postoperative cholangiogram. On admission she was described as an alert, thin, elderly lady with evidence of recent weight loss. Blood pressure was 120/80, pulse 84, respiration 15. Physical examination was within normal limits. Hemoglobin was 11.7 g./100 ml. No preoperative serum electrolyte values were determined.

Cholecystectomy and choledochostomy were carried out on the day following admission. Premedication was meperidine, 50 mg., and scopolamine, 0.4 mg. Anesthesia was induced with thiopental, 75 mg. and maintained with cyclopropane and oxygen. Succinylcholine, 40 mg., was administered

prior to tracheal intubation. Decamethonium, 3 mg., was used for muscle relaxation. Vital signs were stable throughout and in the recovery room. Awakening was prolonged (four hours). She was given nikethamide 0.5 ml., intravenously on one occasion with little effect. On discharge from the recovery room she was alert. Meperidine, 50 mg., was given one time on the day of operation for pain. She received 2,500 ml. of 5 per cent dextrose and water, and excreted 650 ml. of urine on the day of operation. One hundred milliliters of T-tube drainage was also measured.

On the first postoperative day she was alert and received codeine, 30 mg., on one occasion for pain. Two and one-half liters of 5 per cent dextrose and water were administered intravenously. Urine output was not measured. T-tube drainage was 225 ml. She was alert on the second and third postoperative days. Serum sodium on the second postoperative day was 125 mEq./liter Normal saline 1.0 liter and 0.5 liter were given intravenously on the second and third postoperative day along with one liter of 5 per cent dextrose and water. The patient also drank about 1 liter of clear fluids on both days. Urine output was 1.0 and 1.3 liter on these days, and T-tube drainage was 300 ml. per day. On the fourth postoperative day she became somnolent and on the fifth day she was quite disoriented. Serum sodium concentration was 122 mEq./liter at this time. A diagnosis of a midbrain central nervous system lesion was considered. Oral fluids and salt tablets were given. After consultation with the Chemical Section serum and urine osmolatities were determined. Serum osmolality was 249

mosm./kg. with a serum sodium concentration of 128 mEq./liter. Urine osmolality was 423 mosm./kg. distinctly higher than the serum osmolality. A spot urine sodium was 90 mEq./liter. Over the next three days on small quantities of oral fluid and salt tablets she became mentally clear. Serum sodium concentration was 134 mEq./liter at that time. Vital signs and body temperature were normal at all times during the postoperative period.

This patient illustrates the development of symptomatic hyponatremia with fluid retention in the postoperative period. She was thought to have organic central nervous system disease. However, the absence of focal neurological signs and the improvement when the hyponatremia was corrected strongly suggests that water intoxication was the correct diagnosis. Clearly urine osmolality was greater than serum in the face of low serum sodium concentration. Urine sodium excretion was also greater than would be expected in view of the hyponatremia. With time, the antidiuresis abated and she no longer retained fluid.

Description of the Patients. The mean age of the group was 75 years with a range from 63 to 86 years. There were six males and five females. Ten of the eleven had major operative procedures. These patients did not have excessive loss of gastrointestinal fluid by vomiting, diarrhea, or nasogastric suction. Arterial pressures during the periods prior to and during symptoms were within normal limits for all patients except one, J. W. M. had one episode of hypotension in the recovery room which responded to administration of blood. Body temperature ranged from 98° to 101° F. prior to and during the period of hyponatremia. At no time was there evidence of peripheral edema in any patient.

Premedication. Premedication varied from atropine alone in 5 patients to narcotics and atropine, or secobarbital and atropine. One subject received amitriptyline (Elavil) 20 mg. and atropine 0.4 mg.

Anesthesia. Eight of the 11 patients received general anesthesia with a variety of agents. The remaining three had spinal anesthesia supplemented with thiopental-nitrous oxide and oxygen or a narcotic alone.

Postoperative Narcotics. All except one patient received narcotics in the postperative period either in the recovery room or on the ward. Nine of the 11 who developed symptoms received narcotics on the day prior to or on the day that symptoms were first noted. Generally, the quantity administered was small, probably because of the advanced age of the patients.

Time of Onset and Duration of Symptoms. Symptoms began in all but one patient within the first five postoperative days. The other patient developed symptoms on the seventh postoperative day. Duration of symptoms varied widely from two days to two months. Most patients remained symptomatic for two to ten days.

Symptoms. There were moderate to marked changes in level of consciousness from extreme restlessness and confusion to semicoma. Four were given sedation. Two received paralydehyde, one received chlorpromazine and pentobarbital and one received chlordiazepoxide (Librium). Medical and neurological consultations on 2 patients resulted in diagnoses of midbrain or brain stem vascular insufficiency. Upon correction of hyponatremia all became alert and returned to their normal levels of consciousness.

Blood Chemistry Values. Serum sodium concentration during the syndrome ranged from 118 to 131 mEq./liter with a mean of 122. Eight determinations of serum osmolality ranged from 228 mosm./kg. to 270 with a mean of 239, clearly subnormal. Mean serum sodium following the return to normal levels of consciousness was 133 mEq./liter with a range from 125 to 140. Blood urea nitrogen in all patients was within normal limits before and during the symptomatic period. Creatinine clearance when measured in 3 patients was within normal limits.

Urine Volume and Osmolality and Sodium. Urine volume prior to the appearance of symptoms ranged from 0.3 to 3 liters/24 hours. Mean urine osmolality in the 8 patients was 522 mosm./kg. with a range from 325 to 852. In each instance when measured urine osmolality was greater than serum osmolality. Urine sodium when determined was greater than the expected low excretion in the face of hyponatremia, if the latter were due to sodium depletion. Twenty-four hour urinary 17 hydroxycorticoids were measured in one subject (R. N.) and were within normal limits on two occasions.

Fluid Administration Prior to the Development of Symptoms. All patients received two or more liters of water per day prior to the development of symptoms. About half of them became symptomatic on oral fluid intake. When first discovered hyponatremia was frequently treated by the inclusion of a liter of physiological saline in the daily fluid order.

Therapy. Fluid restriction of 0.5 to 1.5 liters of physiological saline per twenty-four hours was instituted in 7 of the 11 subjects. Two patients were given 300 and 600 ml. of 2 per cent saline. Four had no fluid restriction. With more knowledge and recognition of water retention, fluid restriction has become the therapy of choice for this problem.

Discussion

A brief review of the factors concerned in the regulation of the extracellular sodium concentration and the effects of prolonged administration of ADH in man may clarify the behavior of these patients postoperatively.

Regulation of Extracellular Sodium Concentration. Serum sodium concentration ranges normally between 135 and 145 mEq./liter despite large variations in the intake of salt and water. While plasma proteins play a role in the distribution of fluid between the intravascular and interstitial spaces, salts of sodium are the major osmotically active solutes in the extracellular fluid. Maintenance of total solute concentration of serum between 275 and 290 milliosmols per kilogram of water is the result of the factors which regulate water balance. These are the physiological systems responsible for the regulation of water intake (thirst), and water excretion (ADH secretion by the neurohypophysis and renal tubular reabsorption of free water).

Withdrawal of fluid from a normal individual results in little change in serum osmolality. A small rise in total solute concentration in the serum stimulates osmoreceptors presumably within the hypothalamus that results in release of ADH from the posterior lobe of the pituitary gland.[7, 8] ADH then stimulates water reabsorption from the renal tubules and serum solute concentration returns towards normal. Excessive water ingestion, on the other hand, lowers serum osmolality and inhibits ADH secretion, resulting in urinary dilution and free water excretion by the kidney.

In addition to osmotic stimuli, a variety of other factors have been presumed to evoke ADH release. There is evidence that pain, fear,[8] and a variety of drugs including nicotine, histamine, narcotics,[9] barbiturates and general anesthetics[10] may be potent stimulators of ADH secretion. Hemorrhage,[11] continuous positive pressure breathing,[12] and trapping of blood in the extremities by means of tourniquet[13] are known to evoke the release of ADH presumably by the stimulation of volume receptors within the thorax.

The Effects of Prolonged ADH Administration in Man. Leaf and his co-workers[6] observed that administration of long acting vasopressin preparations to normal subjects on a constant high intake of water and salt resulted initially in an abrupt rise in urinary concentration and a fall in urine volume. Water retention by the kidney resulted in a reduction in serum sodium concentration and a gain in body weight. On the third day of vasopressin administration, however, an intense salt diuresis was observed in association with an increase in glomerular filtration rate. Bartter and his co-workers,[14] utilizing a similar protocol, observed that the "expansion" natriuresis was associated with a fall in urinary aldosterone excretion.

Symptoms produced by the simultaneous administration of vasopressin and water are those of water intoxication. There is difficulty in concentrating, restlessness, anorexia, headache, apathy, nausea and vomiting. If allowed to continue without treatment there is progression to stupor, coma, and generalized convulsions. The central nervous system symptoms are the response of the brain cells to dilution of the extracellular fluid. These cells imbibe water, swell and intracranial pressure increases because of the nonexpansible bony compartment of the skull.

Marked restriction of water during vasopressin administration results in a reduction in sodium excretion and restoration of serum sodium concentration to normal.

Antidiuresis During Anesthesia and Operation. The association of a antidiuresis with anesthesia and operation has been recognized since the observations of Pringle and co-workers,[15] that urine volume was markedly reduced during and after diethyl ether anesthesia. Several factors associated with an-

esthesia, operation, and the postoperative period may contribute to the production of antidiuresis. Among them are:

Dehydration. Fluid restriction for eight to twelve hours in the preoperative period is not an uncommon event. In addition, fluid is frequently lost via nasogastric suction. Certainly this may affect the volume and concentration of urine excreted. Dehydration is a physiological stimulus that can be inhibited by hydration.

Premedication. Narcotic and barbiturate preanesthetic medication have been observed to produce a reduction in urine volume in subjects undergoing a water diuresis. Papper and co-workers [16, 17] found no increase in urine osmolality with reduction in urine volume and concluded that the reduced glomerular filtration rate produced by these drugs was responsible for the antidiuresis observed. However, some studies have revealed increased ADH levels in animals following the administration of narcotics.[9] Narcotic analgesics are frequently administered in the postoperative period and may be a factor in sustaining the antidiuresis observed during operation.

Pain and Emotional Stimuli. It is generally agreed that these stimuli result in the liberation of ADH.[8] Certainly they are present in both the pre- and postoperative period in many patients.

Stimuli Associated with Operation. Moran and Zimmerman,[18] utilizing a bio-assay technique, observed large increases in blood ADH levels associated with incision, and stimulation of the pleura and peritoneum during general and regional anesthesia. Major surgical procedures resulted in the highest blood levels and most prolonged liberation of ADH.

Hemorrhage. Reduction in circulatory blood volume by hemorrhage or redistribution as in stasis within the extremities produced by tourniquets is known to result in an acute antidiuresis secondary to both ADH liberation, and changes in renal hemodynamics. The ADH liberated by application of tourniquets can be blocked by the prior administration of ethyl alcohol, a known inhibitor of ADH secretion.[13]

Positive Pressure to the Airway. Continuous positive pressure breathing results in an antidiuresis which can be blocked by the prior administration of ethyl alcohol.[12] This is probably not a frequent occurrence during and after surgery.

General Anesthesia. All general anesthetics have been found to produce a marked reduction in urine volume.[19] In a recent study [20] of renal function before and during halothane anesthesia in 14 well-hydrated subjects who received no preanesthetic medication and who were not undergoing an operation the following were observed:

With induction of anesthesia urine volume was reduced from 12 to 0.83 ml. per minute per 1.73 m.^{2} body surface area, and urine osmolality rose from 84 to 609 milliosmols per kilogram of water. In 7 of 11 subjects both of these alterations were reversed by the intravenous administration of 5 per cent ethyl alcohol. This suggests that ADH is released following the induction of general anesthesia with halothane and is one of the factors responsible for the antidiuresis.

General anesthesia is also associated with marked changes in renal hemodynamics which may effect water and electrolyte excretion during anesthesia and operation.[11, 20] Reductions in glomerular filtration rate and effective renal plasma flow have been reported with all the anesthetics commonly employed clinically. An acute fall in glomerular filtration rate may in itself, cause decrease in urine flow, a rise in urine osmolality, and a reduction in sodium excretion.[20]

In each patient described in this report serveral of the factors mentioned could have been responsible for the production and maintenance of the postoperative antidiuresis. Certainly the nonosmotic stimuli of ADH (pain, anesthesia and narcotics) could have played a role.

There was no evidence that a reduction in glomerular filtration rate in the postoperative period played a role in the production of the antidiuresis.[21] Creatinine clearance was measured in 3 patients and found normal. Natriuresis rather than reduced sodium excretion was observed. Increased sodium excretion is not observed with acute reductions in glomerular filtration rate. No evidence for congestive heart failure or adrenal insufficiency was present to explain the hyponatremia. No evidence for true sodium depletion on the basis of excess loss from the gastrointestinal tract was present. True sodium depletion unlike dilu-

tional hyponatremia is characterized by a lowered arterial pressure, loss of skin elasticity and elevated hematocrit. Large quantities of sodium are not excreted by the kidneys in true sodium depletion. Sodium replacement is the treatment for this form of hyponatremia.

Conclusions

It is apparent from this analysis that hyponatremia secondary to fluid retention in the postoperative period may be related to a persistent and inappropriate secretion of ADH. One must not assume that changes in level of consciousness in this period are the result of organic central nervous system disease. It would appear that the elderly are more prone to development of a sustained antidiuresis, and therefore fluid replacement in this age group must be carefully planned. In the absence of fever and excessive losses of gastrointestinal fluid and electrolytes 1.4 to 1.7 liters of fluid are generally required in the elderly to replace urine volume and insensible water loss. Excessively large volumes of dextrose and water and prolonged administration of narcotics should be avoided. Serum electrolytes should be measured in the postoperative period, especially with changes in levels of consciousness. If the diagnosis of dilutional hyponatremia is made and is the result of over-hydration in the face of persistent antidiuresis, fluid restriction must be enforced.

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