Renal Effects of Anesthesia and Operation Mediated by Endocrines

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Neuroendocrine responses to trauma modify the minima and maxima of various renal functions to a degree that demands clinical recognition, understanding and application. Therapy by the parenteral route of water and electrolytes during and after an operative trauma must be determined by a knowledge of the alterations which occur in order to provide these essential elements with the greatest possible accuracy in amounts and in timing of administration.

Volume and tonicity of the body fluids are considered to be two of the most closely guarded constituents of physiological functions in the normal individual. Alterations in volume or tonicity, or both, of body fluids profoundly affect renal function either primarily or through secondary effects.

Tonicity Homeostasis

Water is essential for maintenance of normal physiology. It must be present in proper volume, distribution, and concentration. There is much evidence available for a profound disturbance in primary water metabolism after trauma and operation which is best explained by fundamental alterations in the normal homeostatic mechanisms mediated through the thirst—hypothalamic—neurohypophyseal—renal system.

Normal activity in the homeostatic system is rather well known. Continuous obligatory losses of water promoting a rise of only 1 or 2 per cent in the effective total solute concentration of the serum is sufficient to stimulate maximal release of antidiuretic hormone (ADH) from the neurohypophysis. The ADH then acts upon the renal tubules to promote increased reabsorption of water. A small volume of concentrated urine results, and water is maximally conserved. When water is ingested (or parenterally injected) the resulting dilution of the body fluids inhibits secretion of antidiuretic hormone, tubular reabsorption of water is reduced and a diuresis of dilute urine rids the body of excess water. Physiologic limits of tolerance for water in normal individuals are determined, in addition, by the availability of solute for excretion (fig. 1).

The ability to excrete a water load after operation or trauma is severely restricted. Figure 2 illustrates the degree of impairment. Before operation normal subjects are able to excrete about 80 per cent of an intravenously administered water load of 200 ml. per square meter per hour for eight hours during the course of the infusion; on the day of operation the same subjects are able to excrete less than 20 per cent in the same time period. The intolerance for a water load is present to a significant degree for about two to three days postoperatively.

To evaluate the nature of the intolerance for an administered water load, a comparison is made between operation and the administration of ADH (vasopressin). Figure 3 illustrates the anticipated changes in serum and urine osmolality, urine flow, free water clearance* and osmolar clearance* when ADH is added to the infusion of a subject undergoing

* Osmolar clearance was calculated as $U_{\text{osm}}/S_{\text{osm}} \times V$; $V$ = the rate of urine flow (ml. per min.) and $C_{\text{osm}} = V - C_{\text{osm}}$. Osmolar clearance is considered to be the amount of solute excreted expressed in terms of the volume of iso-osmotic fluid it represents. The volume of urine excreted represents this iso-osmotic fluid volume after either dilution or concentration has been effected, depending at least in part on the presence of ADH.

"Free" water clearance, the difference between the two, is negative when water is being conserved at the expense of solute.
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Fig. 1. Range of water tolerances. The large dotted triangular area of tolerance is dependent on an intact thirst—neurohypophysal—renal mechanism. The vertical limits of tolerance are determined by urine solute excretion plotted along the abscissa. The small cross-hatched areas indicate the limits of tolerance for a patient subjected to an operation. (Reprinted with permission from Hayes, M. A., Williamson, R. J., and Heidenreich, W. F.: Surgery 41: 353, 1957.)

Fig. 2. The ability to excrete a water load during the time of the infusion. On the operative day and the first few days postoperatively there is a marked interference with the renal excretion of water. (Reprinted with permission from Hayes, M. A., Williamson, R. J., and Heidenreich, W. F.: Surgery 41: 353, 1957.)

a water diuresis. The changes that occur when a water load containing ADH is given to a dehydrated patient are indistinguishable, by these measurements, from those observed in a patient undergoing a cholecystectomy (fig. 4). The low urine osmolality rises to high levels, the serum osmolality falls, urine flow decreases, and the positive clearance of "free" water promptly becomes negative. These findings persist several hours after the infusion has been stopped and the operation has been terminated.

A lesser degree of operative trauma is associated with a lesser interference with normal homeostasis. An uncomplicated herniorrhaphy shows a transient effect similar to the other patients, but the abnormality in water metabolism is not detectable six hours after the operation and before the infusion had been completed. An even more transient response (fig. 5) is seen in a patient with the same medications and anesthetic management but
Fig. 3. Control study with ADH. The effect of ADH administered during an established water load and the subsequent diuresis. I.V. = start of infusion; E.I.V. = end of infusion. (Reprinted with permission from Hayes, M. A., Williamson, R. J., and Heidenreich, W. F.: Surgery 41: 353, 1957.)

Fig. 4. The effect of a moderate degree of operative trauma (cholecystectomy) on renal excretion of water in a hydrated patient. Note the similarity in response to ADH control in figure 3. I.V. = start of infusion; P.M. = premedication; A = start of anesthesia; O.P. = start of operation; E.O.P. = end of operation; E.I.V. = end of infusion. (Reprinted with permission from Hayes, M. A., Williamson, R. J., and Heidenreich, W. F.: Surgery 41: 353, 1957.)
with the negligible trauma of radon seed implantation into a mouth lesion. The preanesthetic medications and anesthetics used for the patients observed in these studies varied from patient to patient. Usually atropine was given, followed by various agents such as nitrous oxide, cyclopropane and ether.

It is apparent that, while anesthesia may initiate a disturbance in water excretion, operative trauma is necessary to perpetuate it. There is, furthermore, a distinct correlation between the magnitude of the operative trauma and the duration of the altered ability to excrete a water load. Serial studies performed daily on patients undergoing operations of average magnitude indicate that water intolerance is barely evident on the third postoperative day and absent by the fifth.

Though biologic identification of ADH is lacking in studies reported, the experimental results make it mandatory to accept some antidiuretic mechanisms operative in the post-traumatic period indistinguishable from the action of ADH. Since the water retention occurs in the presence of progressive and often alarming, decrease in serum osmolality (a mechanism normally inhibiting ADH release), it could be assumed to be "centrally driven." Further evidence for the forcible release of ADH is the failure of alcohol to inhibit its release during operation.

If patients' renal water requirements are to be met with accuracy, it is essential to quantify the limits of water tolerance which this postoperative antidiuretic mechanism has defined. When the ADH mechanism is not disturbed, the limits of tolerance with normal renal function are determined to a large degree by the availability of solute material to be excreted (fig. 1); this is equally true during operation and the few subsequent days (fig. 6—controls). In figure 6, despite the fact that the control patients receive much more water than they are able to excrete, the
osmolal excretion (mosmols per square meter per 24 hours) on the operative day is 205 ± 60 mosmols, on the first postoperative day 250 ± 45 mosmols, and on the second postoperative day 302 ± 37 mosmols.

It is known that the normal limits of water concentration in the urine are 0.7 ml. per mosmol as a minimum and 10.0 ml. per mosmol as a maximum. Coincident with trauma (fig. 7), antidiuresis reduces urine water concentration almost to the minimum. Prior to operation urinary water concentration varies from 2 to 4 ml. per mosmol. On the day of operation (fig. 7—control patients) urinary water concentration decreases to 1.2 ± 0.5 ml. per mosmol; on the first postoperative day, 1.8 ± 0.3 ml. per mosmol; on the second postoperative day, 1.6 ± 0.5 per mosmol.

Knowing the total osmolal excretion and the urinary water concentration, accurate water requirements for renal function (milliliters per square meter per 24 hours) are: day of operation, 250 ml.; first postoperative day, 450 ml.; for the second postoperative day, 480 ml.

Graphically, the limits of tolerance for water in the immediate postoperative period are severely restricted (fig. 1).

Though insensible losses are not specifically under hormonal influences, they do represent obligatory losses and may secondarily influence hormonal, renal, and metabolic responses to volume deficits if not replaced accurately.

Studies have shown that normal and postoperative individuals moderately covered display a relatively constant rate of insensible weight loss over customary ranges of environmental temperature and humidity. The rate of insensible loss in afebrile individuals is 40.9 ± 5.1 g. per square meter per hour over the ranges of environmental temperature from 20°C to 25°C. and relative humidity of 20 per cent to 60 per cent if lightly covered. This amounts to 984 ml. per square meter per 24 hours insensible water loss. Since 197 ml. of water per square meter per 24 hours are

Fig. 6. Solute excretion expressed as mosmols per square meter per 24 hours. Control patients received fluids only as 5 per cent dextrose in water. Experimental patients received fluids only as lactate-Ringer's solution. (Reprinted with permission from Hayes, M. A., Williamson, R. J., and Heidenreich, W. F.: Surgery 41: 353, 1957.)

Fig. 7. Urine water concentrations. Control patients received fluids as 5 per cent dextrose in water. Experimental patients received fluids as lactate-Ringer's solution. The urine water concentration after trauma is the same in both groups: (cf. figure 6) the urine flow would be greater in the group given solute. (Reprinted with permission from Hayes, M. A., Williamson, R. J., and Heidenreich, W. F.: Surgery 41: 353, 1957.)
available from endogenous metabolism, the actual amount to be supplied is 787 ml. per square meter per 24 hours, a figure in very close agreement with those obtained from recalculated metabolic data. These data apply only to normothermic (afebrile) individuals.

A temperature correction for insensible water loss only of 7 per cent for each degree Fahrenheit that the rectal temperature is above 99.6° F. must be made. The volume of 787 ml. is rounded off for convenience to 750 ml. per square meter per 24 hours. If this amount is added to the amounts recommended for renal function, total requirements, excluding abnormal losses, total 1,000 ml. per square meter per 24 hours for the operative day, adding 250 ml. per square meter for each of the two successive days.

The calculated amount theoretically should be administered over the entire 24 hours period, thus supplying the water as it is metabolized (42 ml. per square meter per hour). If the properly calculated required volume is given more rapidly, temporary serum dilution occurs with temporary falls in serum sodium and serum osmolality (fig. 8).

It appears to be the effective total solute concentration that is regulated through the thirst—neurohypophyseal—renal mechanism. Practically this means regulation of the serum sodium concentration. An increase in serum tonicity produced by the infusion of urea is less effective in stimulating antidiuresis than an
infusion of isosmolar solution. It is probable that the neurohypophyseal osmoreceptors are sensitive to shrinkage or swelling induced by osmotic gradients across their cell membranes. There are exceptions, however, as in the hyperglycemia of uncontrolled diabetes mellitus, hyperlipemic states, and uremia.

Volume Homeostasis

Sodium occupies a central position in the regulation of body fluid volume. Since the concentration of sodium in the extracellular fluid is regulated by the above described provisions for diuresis-antidiuresis, normally the volume of extracellular fluid is determined by the quantity of sodium it contains. For this reason, the clinical state of hydration, largely determined by extra-cellular fluid volume, is a direct function of the extra-cellular content of sodium.

Cytologic studies in the experimental animal and physiologic studies in animal and man have indicated that a portion of the adrenal cortex, primarily concerned with electrolyte metabolism and located in the zona glomerulosa, is independent of pituitary control. It appears that facultative retention or excretion of sodium by the kidney is a function of some volume receptor mechanism in the body. The release of aldosterone from the adrenal cortex

Fig. 10. Total study on patient receiving all fluids as lactate-Ringer’s solution (cf. figure 9). Note the increase in percentage of glomerular filtered sodium appearing in the urine on the operative day and postoperatively. (Reprinted with permission from Hayes, M. A., and others: Surgery 46: 123, 1959.)
is the end effect of stimulation of the postulated volume receptor mechanism mediated, at least in part, by the angiotensin system.

The mechanism controlling the release of aldosterone from the adrenal cortex is to be compared with the mechanism for the pituitary control of hydrocortisone release from the adrenal cortex. It appears that, operating at the plasma level usually found after trauma, hydrocortisone has little effect on the renal handling of sodium. If any action is present, it appears to be one of promoting natruresis, sodium loss.

Balance studies in which postoperative patients are given sodium show a significant retention of sodium in the immediate postoperative period, such as in figure 9. Since this sodium retention appeared simultaneously with increased pituitary-adrenocortical activity, it was erroneously assumed that the increased pituitary-adrenocortical activity caused the sodium retention. This requires careful examination.

In order to provide adequate fluid as a balanced salt solution, it must be remembered that lactate-Ringer’s solution has an osmolar concentration of 263 mosmols per liter or 3.8 ml. of water per milliosmol. From this it is easy to determine water requirements when they are supplied as lactate-Ringer’s solution only. Since it is known that the urinary water concentration in the immediate postoperative period averages 1 ml. per milliosmol, then, of 3.8 ml. of lactate-Ringer’s solution supplied, 2.8 ml. represents unobligated water which is available for metabolism. It is possible, therefore, to supply free water as lactate-Ringer’s solution by giving 1.4 times (3.8/2.8) the

Fig. 11. Total study on patient receiving all fluids as 5 per cent dextrose in water. Note the presence of, but decrease in, the percentage of glomerular filtered sodium appearing in the urine. This is to be correlated with the high K/Na ratio. (Reprinted with permission from Hayes, M. A., and others, Surgery 46: 123, 1959.)
Fig. 13. Correlation of body weight changes in the patient from figure 11. (cf. figure 12.)
(Reprinted with permission from Hayes, M. A., and others, Surgery 46: 123, 1959.)

amount calculated as 5 per cent glucose in distilled water.

Figure 10 represents the data obtained from requirements during and three days after operation were met by the administration of exactly the study of a patient whose entire water re-calculated volumes of lactate-Ringer's solution. During the postoperative period, the serum osmolality decreased only slightly and the urine osmolality increased, violating the homeostatic control of ADH release. Glomerular filtration rate (GFR) returned to control levels immediately after completion of the operation, suggesting that renal blood flow (RBF) also returned to normal. During the operative procedure the amount of glomerular filtered sodium appearing in the urine was very high and, in general, remained above control levels for the three postoperative days. It must be emphasized that this increased amount of glomerular filtered sodium appearing in the urine, was measured in the presence of increased plasma levels of hydrocortisone. It was also present in the face of a balance study disclosure of a very positive sodium balance (fig. 9). There was, then, sodium retention but it was not due to hydroxycorticosteroid induced renal tubular reabsorption or the presence of aldosterone (low K/Na ratio). The only explanation was the sequestration of extracellular fluid in the area of tissue trauma comparable to a burn. This is suggestively supported by the data in figure 12, which compares actual body weight changes with calculated weight changes in which 142 milliequivalents of sodium represents 1,000 g. of extracellular fluid.

By contrast, a similar study conducted with fluid requirements met by 5 per cent dextrose in water only is illustrated in figures 11 and 13. The balance data illustrate that when fluid requirements are met by an electrolyte free solution, there is a loss of body sodium, which must mean a constriction of the extracellular space, if hyponatremia does not develop (fig. 13). Figure 11 shows that GFR (and RBF) do not return to preoperative levels, presumably due to reduced extracellular...
fluid volume. Maximal tubular reabsorption of sodium is occurring and aldosterone excretion is high (K/Na ratio).

Figure 14 shows the results of actual assays for aldosterone in the urine of patients contrasted with the urinary excretion of 17-hydroxycorticosteroids. The control patients received electrolyte free fluids and demonstrated a parallel increase in hydroxycorticosteroid and aldosterone excretion rates. The experimental patients received all fluids calculated as lactate-Ringer's solution. The increase in 17-hydroxycorticosteroid excretion shows a pituitary-adrenal cortical response to trauma comparable to that of the control group. In contrast, however, there was no significant increase in urinary excretion of aldosterone.

The temporary depressions in GFR during the operative procedure are probably due to increase in circulating pressor amines (fig. 15) since GFR is maintained during operative procedures conducted under high spinal sympathetic denervation.

**Summary**

During operation and in the immediate postoperative period, as in other major disturbances of normal physiology, *tonicity* and *volume* of the extracellular fluid must be maintained as near normal as possible. After operation, the normal limits of tolerance for water and electrolyte administration are distorted. Water requirements must be calculated as related to metabolic requirements and must be met exactly. A greater volume or more rapid administration leads to retention and serum dilution; too little leads to pre-renal azotemia.

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**Fig. 14.** Urine hydrocortisone and aldosterone excretion in two groups of patients. The control group received fluids as given routinely on the wards of the hospital. The experimental group received exactly calculated volumes of lactate-Ringer's solution. (Reprinted with permission from Hayes, M. A., Williamson, R. J., and Heidenreich, W. F.: Surgery 41: 353, 1957.)
Fig. 15. Values for epinephrine and norepinephrine in peripheral venous blood in eight patients. PPM = prior to premedication; Pre-A = prior to anesthesia; Pre-op = prior to operation.

Fig. 16. Percentage change in glomerular filtration rate from preoperative mean values for two groups of patients. The open symbols represent values for patients who received all fluids exactly calculated for 5 per cent dextrose in water; the closed symbols represent values for patients who received all fluids exactly calculated for lactate-Ringer’s solution. (Reprinted with permission from Hayes, M. A., and others: Surgery 46: 123, 1959.)
These requirements have been quantitated and can be administered in this fashion.

There are evidences that water requirements can be met with a balanced salt solution with better maintained renal function, as shown by the glomerular filtration rate (fig. 16) and the ability to combat metabolic and respiratory acidosis. If effective extracellular fluid volume is maintained by such a solution, there will be no increase in aldosterone excretion and the kidney will excrete the sodium administered which is in excess over that required "to fill" the sequestered "third space" of trauma, which cannot be measured otherwise.

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Bibliography

LIVER DISEASE In right heart failure and hepatitis, prothrombin and coagulation factors VII, IX and X are reduced. Factor V remains normal. In cirrhosis these values remain normal for unknown reasons. In liver congestion, if serum bilirubin is elevated SGOT, SGPT and LDH are also raised. (Wenger, R.: Influence of Cardiac Congestion on Intra-abdominal Organs, Deutsch. Med. Wschr. 1: 25 (Jan.) 1963.)