HYPERNATRAEMIA AND GASTRO-ENTERITIS

Practical and Theoretical Considerations

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In 1831 the classical account by Latta concerning the effect of intravenous fluid containing sodium chloride and bicarbonate on patients with cholera appeared in the *Lancet*.²⁷ His description of the return to life of shocked, moribund and comatose patients could at that time only have been regarded as incredible. It was surprising that his therapy, based on the ingenious experiments of O'Shaughnessy²⁸ did not leave a lasting impression. It was nearly a century before such therapy was re-evaluated.

The importance of shock in diarrhoea,³⁰ the need for restoration of acid-base balance,²³ and the replacement of cell electrolyte¹⁴ have all received attention during this century. Along with knowledge concerning potassium has come the realization that renal tubular cells under the stress of disease or in the face of potassium depletion do not preserve homeostasis. The final composition of the fluid administered is important. The potassium-deficient human or animal cannot clear sodium effectively.^{4, 17, 13, 20, 37} A normal rat restricted of (but not deficient in) potassium, when given saline to drink rapidly develops sodium retention in the tissues and acute potassium loss.⁹ Without potassium restriction no changes in body composition occur. The failure to clear sodium under circumstances of potassium deficiency is related, in part, to sodium-hydrogen exchange in the renal tubule. Potassium deficiency may favour hydrogen ion secretion.³ In children with gastro-enteritis the use of loads of sodium in the region of 20 mEq/kg. during the first 24 hours of treatment prejudices the return to normal acid-base balance and favours the occurrence of oedema.⁸ Such changes occur in spite of giving 3 mEq. potassium/kg./24 hours. Smaller amounts of potassium, when combined with similar sodium loads, cause a swing from metabolic acidosis to metabolic alkalosis, and

oedema, hypokalaemia and tetany occur in 10 per cent. of patients.³⁵ That oedema can result in the human in potassium deficiency was clearly demonstrated by the work of Fourman and Hervey.²⁰

The above considerations dictate some of the rationale in our approach to the patient with gastro-enteritis. The majority of patients experience losses of electrolyte that (in terms of tonicity) exceed losses of water. The more unusual but well recognized, reverse situation where water losses exceed sodium loss also has been appreciated.^{1, 24, 36} We have come to realize more clearly in recent years the severe disturbances in body composition and vital mechanisms that accompanies hypertonic dehydration where losses of water exceed losses of sodium. The serum sodium concentration (which reflects the serum osmotic pressure) can rise to 200 mEq./l.

The clinical diagnosis of this latter condition is difficult, but failure to make it may be disastrous. Diarrhoea with hypernatraemia has a fourfold higher mortality rate than the usual hypotonic type. There is a significant weight loss which is indicative of water loss, but is not commensurate with the expected clinical picture of dehydration. If the clinical signs of sodium depletion with extracellular fluid deficit are not present (loss of skin turgor and skin elasticity), then hypertonicity should be considered. A valuable clue may be the finding of a dry mucous membrane in the mouth. Rapoport,³² who re-awakened interest in this condition, described the tissues as 'putty-like' or as resembling scleraema in severe cases. Fever may be present. Twitching, irritability or restlessness with increased or decreased deep tendon reflexes are sometimes observed in hypertonic dehydration, in contrast to the prostration of patients with hypotonic dehydration. In severe hypertonic dehydration with hypernatraemia the central nervous system is involved,¹⁷ and xanthochromia in the spinal fluid with increased protein concen-

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tration is a frequent finding. There may be a history of sodium chloride ingestion, the mother having given salt with water in good faith, but at a high concentration. This occurrence is not a consistent one, and does not account for all cases. Alternatively, and it would seem more often, the history will include a report of continued milk feeding without supplements of water.¹¹ The kidney is thereby presented with large solute or osmotic loads which, in the face of dehydration (due to stool water loss), cannot be excreted without further water subtraction.

Serum analyses reveal the usual metabolic acidosis, but also a sodium concentration from 160 to 200 mEq./l. and a chloride concentration that exceeds 120 mEq./l. Hypokalaemia may be present on admission,¹⁶ while hypocalcaemia is also frequent.³² The blood urea is sometimes high.

It is possible for this hypernatraemia and associated hyperosmolarity of the body fluids to arise during the course of diarrhoea by two distinct mechanisms:

(a) By an extra loss of water (other than via stools) resulting from a renal osmotic diuresis, due either to an extra solute load from continued milk feeding or to underlying renal insufficiency.

(b) By a failure of excretion of previous sodium loads in the presence of potassium deficiency and (possibly) coincidental adrenal stimulation.

(a) Aberrant Water Loss

Weil and Wallace,³⁸ in the course of studies on gastro-enteritis and hypernatraemia, were impressed by the finding of a low urine specific gravity in several instances. Our experience over the last year has been the same. On three occasions one has seen values as low as 1,005 with urine taken shortly after admission at a time when the serum sodium concentration was 160 to 200 mEq./l. Another patient had a urine osmolarity of only 470 mOsm./l. At the same time, a value as high as 1,200 mOsm./l. has been recorded in other patients. Colle *et al.*¹¹ presented data on urine osmolarity in seven infants with gastro-enteritis and hypernatraemia. The values were all below 700 mOsm./l. She has emphasized the superimposed water loss via renal channels and found in most instances a history of continued milk feeding in the presence of diarrhoea. Such continued milk feeding provides a load of solute which in the face of dehydration claims further amounts of water for excretion (osmotic diuresis). It must be re-emphasized that solute requiring excretion always subtracts body water—the higher the solute load the greater the volume of urine.³³ However, since some patients with hypernatraemia can concentrate their urine maximally, osmotic diuresis is not the only mechanism that

can precipitate hypernatraemia during gastro-enteritis. Sodium loading in potassium deficiency is more pertinent to this latter situation (see below). That extracellular volume is low has been indicated by the finding of up to 30 per cent. loss of volume in the chloride space in two infants with gastro-enteritis and hypernatraemia.

Following treatment, nitrogen retention appears and usually no evidence remains that underlying renal disease is present before or after the episode. During the acute phase renal function would seem to be impaired, since Weil and Wallace³⁹ demonstrated in two patients a glomerular filtration rate of 10 per cent. of normal, and it is known that water deprivation in the normal infant leads to a significant fall in glomerular filtration to failure of proper urine concentration.⁶ Argenti claims that a tubular lesion (dilatation of the cortical tubules) can be seen in the kidney in hypernatraemia, and Finberg and Harrison reported high levels for blood urea nitrogen, though this is not always present.³²

A small percentage of patients that present with gastro-enteritis, hypernatraemia and nitrogen retention have underlying renal disease. This may become apparent by the failure of the acidosis and azotaemia to disappear with treatment; or suspicion may be aroused by a failure of the child to measure up to expected growth levels. The hypernatraemia seen in this situation is related also to osmotic diuresis, since the few remaining nephrons hypertrophy and are forced to deal with the customary nitrogen and solute waste of the rest of the body. The increased amount of solute delivered to each nephron causes an extravagant expenditure of water. The more solute filtered, the more rapid the passage of fluid through the tubules and the less reabsorption of water. Recent work emphasizes that the glomerular filtration of these remaining nephrons is markedly increased and hence there is less time for the modifying effects of renal tubular function.⁵ Apparently sodium-conserving mechanisms are more effective than those related to water under these conditions.

In an attempt to reproduce experimentally hypernatraemia due to osmotic diuresis and renal insufficiency six rats (250 to 350 g.) were operated on in two stages and seven-eighths of their renal tissue removed according to the technique of Platt.²⁹ Drinking water was available. In five rats growth was interfered with, but progressed slowly over the following month. There was a 22 per cent. increase in blood urea—140 mg. to 190 mg. per cent. (24 to 32 mOsm./l.), as compared with the normal value of 30 mg. per cent. (5 mOsm./l.). The animals were sacrificed after four weeks. There was no change from normal in serum electrolyte concentrations. There was no change

TABLE 1

HYPERNATRAEMIA AND CHANGES IN BODY COMPOSITION IN A RAT SUBJECTED TO OSMOTIC DIURESIS DUE TO REMOVAL OF SEVEN-EIGHTHS OF THE RENAL TISSUE

	Serum Concentrations		(mEq./l. or Urea in milliosmols per litre)		
	Urea	Cl _s	Na _s	K _s	CO ₂ content
Observed	58.2	122	170	5.0	10.5
Expected	5.0	110	145	4.5	24.0

Total Electrolyte and Water (mEq. or ml. 100 g. of fat-free dry solid (F.F.D.S.))

	F.F.D.S.	Cl _t	Na _t	K _t	Mg _t	Ca _t	H ₂ O _t
Observed	87.3	12.42	17.3	23.5*	9.5	210.0	204*
Expected	87.3	12.47	17.6	26.4	9.4	194.0	251

Derived Data

Extracellular cation (Na) concentration in E.C.F. = 25 mEq. or mOsm./l.

Extracellular cation (K) concentration in I.C.F.:-

Assume 12.7% of chloride is outside E.C.F. as in normal rat, then E.C.F. volume = $\frac{(\text{total extracellular Cl})}{(\text{conc. Cl/l. interstitial water})} = 78 \text{ c.c.}$ (expected normal 86 c.c.) and I.C.F. volume = 126 c.c. (expected 165 c.c.), then intracellular concentration of Total K—(extracellular K)

I.C.F. volume = 183 mEq. (expected = 157, difference = 26 mEq. or mOsm./l).

* = significant reduction. Subscript t = total body electrolyte or water. E.C.F. = extracellular fluid. I.C.F. = intracellular fluid.

total body calcium, magnesium, chloride, potassium or water. Two animals lost 10 per cent. body sodium. For the most part there was no change in body composition as Platt has predicted (1952). The finding emphasizes the ability of reduced renal tissue to maintain body composition when drinking water is available. Rat 6, however, after three weeks of constant weight, suddenly lost 80 g. in six days; the animal was then sacrificed. The data obtained are particularly pertinent to the problem of hypernatraemia.

In Table 1 it can be seen that the blood urea was ten times normal and acidosis was present in hypernatraemia. There was no significant reduction of total electrolyte except for potassium. Total water, on the other hand, was 47 c.c. below expected normal (or below the water of a normal rat possessing the same fat-free dry solid). Assuming that 12.7 per cent. of chloride is non-extracellular for the rat, an amount determined by previous experiments,¹⁰ it can be seen that 10 per cent. of extracellular fluid was lost, but as much as 30 per cent. of intracellular volume. The findings emphasize the greater loss of cell water under the circumstances. While sodium concentration was 25 mEq./l. (25 mOsm.) above the expected normal, the predicted increase of intracellular potassium concentration was almost the same (26 mOsm.). A rise in extracellular osmotic pressure is offset, no doubt, by a com-

mensurate rise in intracellular osmotic pressure. These data do not predict a shift of sodium into cells to favour this osmotic adjustment.

The texture of the skin in hypernatraemia is a matter of interest and, as mentioned, this texture has been compared (in severe hypernatraemia) with that seen in scleraema. The loss of elasticity of the skin has been precisely measured in hypotonic dehydration.^{25, 26} In hypotonic dehydration the greatest volume loss is from the extracellular compartment; in hypertonic dehydration the loss is greatest from the cellular phase. That a large loss of cell water also occurs in scleraema is shown from data obtained in a three-month-old infant with pneumonia, weighing 4.75 kg., having a temperature of 105°F. and a typical scleraematous skin. Metabolic acidosis was present without hypernatraemia, but with a CO₂ content of 12.1 mEq./l., a chloride concentration of 114 mEq./l. and pH of 7.1. The total water was 46.7 per cent. of body weight—a severe reduction—while the corrected chloride space was 28.2 per cent. of body weight (a slight reduction, if any). Clearly the losses of water were greatest from the cellular phase. Weil and Wallace³⁹ found in the course of balance studies on two patients with gastro-enteritis and hypernatraemia (either during the onset or recovery) that changes in volume were related predominantly to the cellular phase. The texture of the skin must be related to this unusual distribution of water loss.

Arguments can be brought forward that superimposed water losses in this type of diarrhoea may occur via other avenues than the kidney. Stools are always hypotonic to plasma, but there is no evidence that the composition of the stools is different in hypernatraemia. Rapoport³² considered that water loss from hyperventilation might be substantial, but preliminary examination of the problem of hyperventilation by Guest *et al.*²² does not endorse this suggestion. The suggestion that fever increases insensible water loss is valid, but fever is not a consistent finding, nor does environmental heat stress represent a necessary factor.¹¹ Heat stress raises skin water losses. Pratt³¹ originally investigated the renal water requirements of the infant and recent information emphasizes a higher need than for the adult.³⁴

(b) Sodium Retention

Hypernatraemia due to excess sodium retention may be more or less frequent, depending on the amount of sodium used for treatment in various paediatric centres. Mention has already been made of the failure of adequate excretion of excessive sodium loads during circumstances of potassium deficiency, such as in gastro-enteritis. Even under normal circumstances the infant may have difficulty in excreting sodium loads.^{15, 21} Finberg¹⁹ found that hypocalcaemia occurs when sodium loading is associated with potassium deficiency. With sodium loading in gastro-enteritis cell water subtraction was demonstrated.⁸ Hypernatraemia was not found. However, Skinner and Moll³⁸ demonstrated hypernatraemia with sodium loading in gastro-enteritis. Many patients have a history of excessive intake of salt prior to admission.³⁹

The study of sodium loading in potassium-deficient rats presents some points of importance concerning the understanding of hypernatraemia and sodium retention.⁹ The replacement of drinking water by isotonic saline does not alter body composition of the normal rat over a 10-day period. An increase in body sodium content can be achieved rapidly in the above experiment if potassium intake is restricted or if potassium deficiency is first induced (by diet) over a previous 2½-week period. A 20 to 40 per cent. increase in body sodium results. This increase in amount cannot be augmented by adding sodium-retaining steroid—desoxycorticosterone acetate (DOCA)—to the experiment. There is a 20 to 30 per cent. loss of body potassium in these experiments, but no change in total magnesium or calcium.

Sodium accumulation can also be achieved rapidly by injecting sodium-retaining steroids (DOCA) into the normal rat on a normal diet, but with saline for drinking. The loss of potassium is

The Effect of Na Retaining Steroid on the Concentration and Distribution of Na in Normal and K Deficient Rats Under Conditions of Na Loading

not large in this last circumstance (9 per cent). Important points in these experiments are shown in Figs. 1 and 2. The diagrams have been constructed on the basis of a theoretical 220-g. rat. In this rat the volumes of extracellular and intracellular fluid have been carefully appraised by determining the amounts of chloride and sodium that are considered to be non-extracellular. In potassium-deficient rats that were sodium loaded there was no departure from normal in total water or in extracellular volume. It can be seen from Fig. 1 that normally 30 per cent. of body sodium in the rat is non-extracellular in bones and cells. When potassium deficiency has been induced and sodium loading is introduced the increase in body sodium is mainly outside the extracellular space. If DOCA is added to the experiment there is a transfer of excess sodium into the extracellular space and hypernatraemia develops. The second diagram of the figure represents a normal rat on a normal diet, receiving saline plus DOCA. Here we see the best example of this extracellular sodium increase. Indeed,

Theoretical Concentrations of Intra and Extra-cellular Electrolyte in Sodium Loaded, K Deficient Rats, with and without D.O.C.A.

obilization of sodium outside the extracellular space can be suspected. In this last experiment there was an increase of the extracellular volume at the expense of cell water.

In Fig. 2 the theoretical intracellular and extracellular concentrations for Na and K have been calculated in the normal and potassium-deficient

in the absence of DOCA, but in the presence of sodium loading, there is enough cellular sodium in the potassium-deficient rat to counterbalance the cell potassium loss without assuming that bone sodium (2.2 mEq.) is contributing to the cells. This is not the case when DOCA is introduced into the experiment. In an effort to explain this 'anion gap' cationic amino acids¹⁶ and hydrogen ions¹³ have been considered as playing a role in the cellular electroneutrality. One might anticipate a reorganization of cell structure when DOCA is added to the above experiment (Fig. 2) to increase osmotic pressure and to counter the extracellular hypernatraemia. *A priori* these data suggest that adrenal stimulation is particularly deleterious under circumstances of potassium deficiency and sodium loading by virtue of its ability to induce hypernatraemia.

It is probable that some children with gastro-enteritis under circumstances of sodium loading and potassium deficiency have excessive adrenal stimulation or high levels of sodium-retaining hormone, particularly as extracellular volume is reduced in gastro-enteritis. Finberg¹⁹ suggests that with sodium loading in potassium deficiency there might be an alteration in the equilibrium between bone and extracellular fluid. If sodium accumulates on the surface of the bone crystals it could play an interfering role in the maintenance of calcium homeostasis, hence the finding of hypocalcaemia.

Changes in the Central Nervous System in Hypernatraemia

Finberg, Luttrell and Redd¹⁸ have emphasized the frequency with which patients suffering from hypernatraemia and gastro-enteritis demonstrated alteration in consciousness, ataxia, spasticity, increased deep tendon reflexes or convulsions. Subarachnoid haemorrhage or subdural effusion were not unusual. Administration of hypertonic sodium solution to kittens by the intraperitoneal route produced these same central nervous system findings, while the serum sodium concentration rose to levels of 160 to 200 mEq/L.

Hyper-irritability, ataxia, tremulousness and convulsions were all recorded. Cerebrospinal fluid was tinged with blood or the fluid was xanthochromic. Subdural haemorrhage was recorded and in some instances intraventricular haemorrhage. Haemorrhage was not noticed elsewhere in the body. A chemical change was noticed in the muscle in so far as sodium was transferred to the cell and water was lost from the cell. Both of these phenomena would tend to raise the cell osmotic pressure in a compensatory manner. Brain cell sodium was not increased and these workers suggested that in brain cells a breakdown of complex ions occurred to raise osmolarity, an occurrence that would cause gross disturbance of nervous cell function.

Initial Treatment of Gastro-enteritis with Hypernatraemia

It should be noted that any sudden reduction of osmolarity of the body fluids will precipitate a convulsion¹⁷ or produce neurologic damage.¹¹ The major needs in fluid therapy would seem to be for water, glucose, potassium and calcium. Provided urine flow is satisfactory, it has been our policy to use 40 mEq./l. KCl solution in 5 per cent glucose at 8 to 10 ml./kg./hour. Under circumstances where renal function is in doubt the KCl is replaced by NaCl until urine flow is established. Calcium gluconate is incorporated in these solutions.

While sodium chloride, since the time of Latta, has been one of the most important therapeutic agents in medicine, some of the limitations of its use are now recognized.

Finally, it should be mentioned that renal dysfunction may be an important factor causing, in some instances, hypernatraemia, particularly if, for reasons as yet not defined, the anti-diuretic hormone is temporarily inactivated. Either vagal inhibition or sympathetic stimulation inhibits anti-diuretic hormone.⁷ A transient diabetes insipidus would quickly give rise to hypernatraemia under circumstances of dehydration.

Summary

Information concerning hypernatraemia during the course of gastro-enteritis has been reviewed. This situation can occur because of superimposed losses of renal water due to continued milk feeding (obligatory solute or osmotic diuresis).

Data from animal experiments are presented to show the changes in body composition, concentration and volume arising from osmotic diuresis (after removal of seven-eighths of the renal tissue). Losses of water are greatest from the cellular phase in this type of dehydration, a situation also shown to be present in a patient with 'scleraema.' The tissues in severe hypernatraemia resemble scleraema.

Hypernatraemia can also arise from sodium loading during the treatment of gastro-enteritis and in the presence of potassium deficiency. Data from rats (normal and potassium deficient) from previous experiments have been recalculated to show clearly that salt-retaining steroid (DOCA) in the face of sodium loading (saline for drinking) has a specific effect. DOCA favours the accumulation of sodium within the extracellular fluid and produces hypernatraemia. This movement of sodium may require the tissue cells to undergo reorganization of structure to meet osmotic adjustments.

Adrenal stimulation is suggested as an important factor for the development of hypernatraemia associated with sodium loading in gastro-enteritis.

It is possible that in some instances renal dys-

function and disturbance of anti-diuretic could be involved.

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