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Iatrogenic hyperosmolality in critically ill low-birth-weight infants

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Twenty-four desperately ill newborn infants of very low-birth-weight admitted to a referral unit were studied. Some had received sodium bicarbonate (8.4% solution) in 20% glucose as an intravenous bolus infusion before admission. After admission continuous intravenous infusion was started with 10% glucose (70—100 ml/kg/24 hr) to which 5—15 ml/kg/24 hr of 4.2% sodium bicarbonate solution was added (2.5—7.5 mEq/kg/24 hr). In a few infants at admission, and in all some time after the beginning of treatment, blood samples for determination of glucose, lactate, sodium, urea nitrogen, osmolality and acid base status were obtained. In some infants blood samples were also taken immediately before or after death.

During the course of intravenous infusion therapy, a progressive increase in mean osmolality was observed, accompanied by a rise in blood glucose, sodium and urea levels. The highest mean plasma osmolality was observed immediately before or after death. Besides continuous intravenous infusion, in several infants repeated attempts were made to correct the recurring acidosis by bolus infusion.

Hyperosmolality is a frequent consequence of vigorous infusion therapy aimed at correcting acidosis and covering fluid and caloric requirement of maintenance. A simultaneous elevation in plasma sodium and glucose is often produced on utilizing two hyperosmolar solutions (sodium bicarbonate and glucose). The progressive increase in blood urea content also contributes to hyperosmolality.

The metabolic, cellular and compartmental effects of hyperosmolality as well as the possible injury to the brain are discussed.

Hypertonic solutions (glucose, sodium bicarbonate, mannitol, mixtures of nutrients for intravenous alimentation) are often used alone or in combination in intensive care of patients suffering from acute, life threatening conditions. During the last decade it has become evident that the injudicious use of such solutions has the potential risk of hyperosmolality which may have dangerous consequences [3, 7, 14, 32]. Its deleterious effects can be particularly critical when a transient or sustained increase in osmolal concentration superimposed on various pathological alterations endangers survival by aggravating the patient's condition.

Therapy of the critically ill newborn infant utilizing hyperosmolal solutions also carries the potential hazard of marked changes in osmolal concentration of body fluids. Attention has been drawn to hyperos-

molality caused by rapid and repeated injections of hypertonic sodium bicarbonate solution for the correction of acidosis [7, 19, 24, 25], and by the sustained infusion of hypertonic mixtures of nutrients (glucose + amino acids) in parenterally fed newborn infants. Among the factors which make the seriously ill newborn infant particularly liable to marked osmolal changes are prematurity, the need for sustained infusion therapy in the early neonatal period, reduced renal functional capacity that can additionally be compromised by hypoxic damage, metabolic, circulatory and compartmental changes due to the underlying conditions. In view of the great potential risk of iatrogenic alterations in osmolality of body fluids, we thought it desirable to collect data on osmotic concentration in neonates requiring rapid correction of acidaemia and a prolonged intravenous therapy for various reasons. The aim was to establish how often and in what degree hyperosmolality occurs in response to infusion therapy in a susceptible population admitted to our newborn ward. Such a record of experience is necessary for the assessment of the iatrogenic potentiality of therapeutic procedures and techniques adopted for the treatment of critically ill newborns in a neonatal intensive care unit.

Material and Methods

The examination were performed on 24 desperately ill and mostly immature newborn infants. Mean birth weight and gestational age with ranges are shown in Table I.

Table I

Birth weight and gestational age of 24 infants studied

	Birth weight, g	Gestational age, wk
Mean	1241	30
Range	670–2940	22–44

The date of the last regular period was available only in 20 infants.

The birth weight of 9 infants ranged from 670 to 1000 g, of 5 infants from 1001–1500 g, showing that most of the infants studied were of very low birth weight. In four infants gestational age could not be determined. Immaturity, respiratory distress, severe asphyxia, proved or suspected intracranial haemorrhage were the most frequent clinical diagnoses. The extreme severity of the clinical condition of the infants was shown by the fact that all but one died within a few hours after admission. Age at admission ranged between 40 minutes and 10 hours and survival time between 12 hrs and 7 days. Subtotal atelectasis with hyaline membrane formation and intracranial haemorrhage were the predominant postmortem findings. The distribution of massive haemorrhages observed in 15 infants is shown in Table II. In 6 of these infants two or three types of haemorrhage were encountered.

Table II

Massive haemorrhage observed in 15 infants at autopsy. In 6 infants two or three types of haemorrhage were encountered

Intraventricular haemorrhage	10
Subarachnoid haemorrhage	9
Subdural or spinal epidural haemorrhage	4
Pulmonary haemorrhage	2

All infants were severely ill and acidotic. Some had received sodium bicarbonate in 20% glucose as an intravenous

bolus infusion before admission. In these instances 3—8 mEq $NaHCO_3$ (8.4% solution) were given with 20% glucose in a volume from 10 to 20 ml per infant. After admission continuous intravenous infusion was started with 10% glucose (70—100 ml/kg/24 hr) to which 5—15 ml/kg/24 hr of 4.2% sodium bicarbonate solution was added (2.5—7.5 mEq/kg/24 hr). If the pH fell again below 7.10, an additional amount of 4.2% bicarbonate solution calculated from —BE and mixed with 10% glucose solution was given as an intravenous bolus injection.

In a few infants at admission, and in every infant some time after the beginning of treatment, blood samples for determination of glucose, lactate, sodium, urea-nitrogen, osmolality and acid base status were withdrawn from a cephalic vein or from the vena cava inferior through an umbilical catheter. In a few cases blood specimens were also taken immediately before or after death either through an umbilical catheter or by heart puncture. During the course of treatment in some infants more than one blood sample (individually at different time intervals) was obtained for analysis. Except osmolality, not all the indicated blood constituents were determined in each blood sample. The number of examinations performed on different parameters are indicated in the Tables showing the results.

Blood samples were centrifuged immediately, the plasma was separated and osmolality determined by freezing point depression with Knauer's semi-micro osmometer. The majority of the values presented are averages of duplicate determinations. Using a 0.2 ml sample size the coefficient of variation for plasma osmolality was 1.5—2%. Samples showing haemolysis were not included in the study.

Sodium concentration was measured by flame photometry, blood glucose, lactate and urea nitrogen by the methods of Pryce [20], Huckabee [12] and Ceriotti [4], respectively. The acid-base parameters were determined according to Astrup.

Results

Table III and IV show the means ± SD and range of the blood and plasma parameters obtained at admission. The number of cases in which the parameters were tested is also indicated. The haemoglobin, hematocrit and acid-base values scheduled in Table III undoubtedly show that the majority of infants were anaemic and acidotic at admission. Unfortunately, osmolality, lactate, urea nitrogen and plasma sodium content were determined in a few untreated infants only, and an expected range of values was obtained (Table IV).

Table V summarizes the means ± SD and the number of infants in whom osmolality as well as blood constituents contributing to total osmotic concentrations were controlled soon after the first intravenous administration of solutions for correcting acidosis.

In Table VI the means ± SD of the pooled values obtained during the further course of intravenous fluid therapy are scheduled. In several infants repeated attempts were made to correct the acidosis by bolus infusion. It is apparent that a further increase occurred in mean osmolality as well as in blood glucose and plasma sodium during the later phase of intravenous therapy. The concentration of some solutes varied greatly and not every measurement of osmolality was accompanied by the control of solute levels contributing to osmotic concentration. Among the parameters examined only the rise in glucose and osmolality proved to be significant.

TABLE III

Haemoglobin and haematocrit values and acid-base status of the infants studied

	Hgb g per 100 ml	Htc. per cent	Acid-base status					
			pH	BB	St.bi.	BE	pCO_2	Act. bi.
Mean	15.7	48.75	7.2	38.2	17.2	9.4	51.3	18.9
Range	8.6–21.2	34–62	6.82–7.42	27–47.0	10.8–25.2	−19–+1.0	31.3–135.0	13–35.0
n	22	20	20	20	20	20	19	17

TABLE IV

Plasma osmolality and solute concentrations at admission of untreated infants

	Blood glucose mg per 100 ml	Blood lactate mg per 100 ml	Plasma sodium mEq/l	Plasma urea mg per 100 ml	Plasma osmolality mOsm/kg
Mean	52.4	36.7	144.0	17.7	290
± SD	±29.3	±18.2	± 6.9	±14.2	±8
Range	13.0–89.0	21.5–66.0	138.0–150.0	9.0–39.0	277.0–300.0
n	6	5	4	4	7

TABLE V

Plasma osmolality and solute concentrations after the first attempt at correcting acidosis and meeting fluid requirement by intravenous administration of solutions

	Blood glucose mg per 100 ml	Blood lactate mg per 100 ml	Plasma sodium mEq/l	Plasma urea mg per 100 ml	Plasma osmolality mOsm/kg
Mean	132.3	51.66	147.0	19.7	303
± SD	±78.4	±44.6	±6.4	±11.9	±21
Range	27.0–258.0	12.0–167.0	137.0–159.0	7.5–48.0	275.0–355.0
n	15	16	16	16	21

TABLE VI

Plasma osmolality and solute concentrations obtained during course of intravenous fluid therapy

	Blood glucose mg per 100 ml	Blood lactate mg per 100 ml	Plasma sodium mEq/l	Plasma urea mg per 100 ml	Plasma osmolality mOsm/kg
Mean	234.0	48.3	151.7	17.5	313
± SD	±176.9	±16.8	±7.5	±3.8	±17
Range	71.0–595.0	28.0–89.0	140.0–161.0	14.5–24.0	295.0–344.0
n	9	10	9	9	14

TABLE VII

Plasma osmolality and solute concentrations immediately before or after death

	Blood glucose mg per 100 ml	Blood lactate mg per 100 ml	Plasma sodium mEq/l	Plasma urea mg per 100 ml	Plasma osmolality mOsm/kg
Mean	153.0	82.4	151.5	28.4	344
± SD	±72.9	±81.8	±7.1	±10.1	±36
Range	72.0–286.0	14.0–225.0	142.0–159.0	14.0–44.0	301.0–410.0
n	7	8	9	9	9

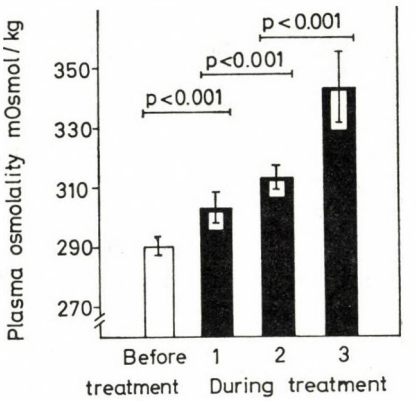

FIG. 1. Mean plasma osmolalities (±SE) before /□/ and during intravenous therapy /■/. 1 = osmolality of the first sample taken after the initial attempts to correct acidosis. 2 = osmolality during the later stages of continuous intravenous fluid therapy during which sometimes bicarbonate was given by rapid injection. 3 = osmolality in the terminal stage when in some instances vigorous attempts were made to correct the severe acidosis

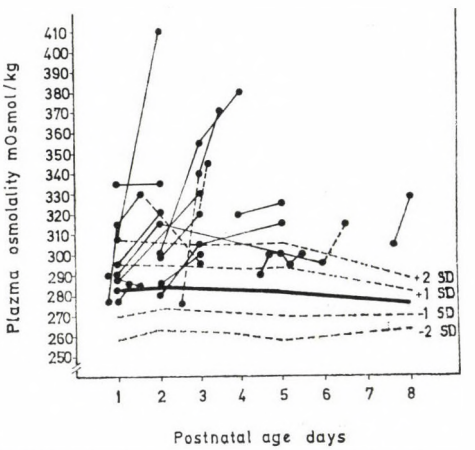

FIG. 2. Plasma osmolality in infants in whom more than one measurements were performed during intravenous fluid therapy. The changes are shown in relation to the means ±1 and 2 SD obtained in normal infants within the first eight days of life. Interrupted line represents intravenous bolus infusion and solid line continuous infusion of a fluid mixture containing sodium bicarbonate

The highest mean plasma osmolality was obtained immediately before or after death, as it is seen in Table VII.

The progressive increase in mean plasma osmolality is visualized in Fig. 1. It can be seen that the terminal status and final attempts to ameliorate acidosis were associated with a marked rise in osmolal concentration.

Fig. 2. demonstrates the individual osmolal concentrations observed during intravenous therapy in relation to the normal means ± 1 and ± 2 SD for different postnatal ages. The response to bolus and continuous

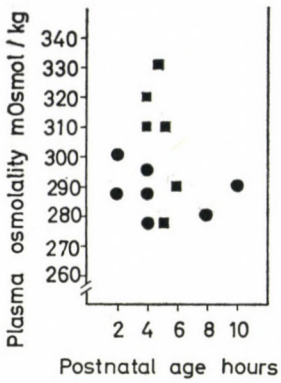

FIG. 3. Plasma osmolalities at admission of previously untreated /●/ and treated infants /■/. Treatment in the delivery room consisted of bolus infusion of a mixture of 8.4% bicarbonate and 20% glucose

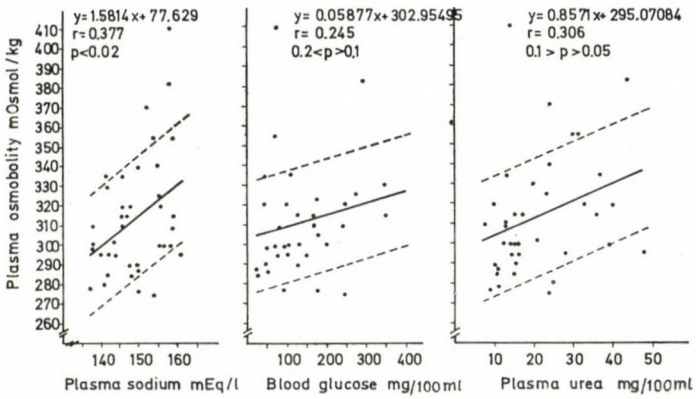

FIG. 4. Relationship between plasma sodium, urea-N, blood glucose, blood lactate and plasma osmolality in the infants studied

infusion is indicated by the interrupted and solid lines, respectively. The progressive and marked increase in osmolality associated with prolonged intravenous treatment was apparent in some of these critically ill low-birth-weight infants. Particularly high values were obtained before or immediately after death.

Fig. 3 shows the plasma osmolality of those infants who had received a bolus infusion of bicarbonate (8.4% solution) with 20% glucose before admission. /■/. For comparison, the osmolalities obtained in untreated infants immediately after admission are shown /●/.

In Fig. 4, the important plasma constituents contributing to plasma osmotic concentration, such as sodium blood glucose and urea levels are plotted against osmolality. It is seen that only plasma sodium correlated well with the osmolal changes.

Discussion

The present study performed on critically ill, and mostly very low birthweight infants showed that hyperosmolality was a frequent consequence of vigorous infusion therapy aimed at correcting acidosis and covering fluid and caloric requirement. Although the material tested consisted of extreme cases as far as maturity, severity of pathological conditions, survival chance and intensity of intravenous therapy is concerned, it shows clearly how easily hyperosmolality can be caused in a susceptible newborn population. It is this group of critically ill neonates, in whom the capacity of physiological functions involved in homeostasis are greatly reduced or impaired, and vicious circles leading to marked deviations in biochemical, physicochemical constancy may readily develop [2].

Under such conditions any attempt to correct these disturbances by rapid or prolonged infusion of hyperosmolar solutions may cause dangerous, and possibly fatal changes in osmolality of body fluids. The liability to iatrogenic disturbances, and vigorous and repeated attempts at interrupting vicious circles such as e.g. to correct acidosis, considerably limit the safety of the main goal of intensive therapy, namely to prevent death of the critically ill newborn infant.

Among the solutes whose parenteral administration carries some risk of hyperosmolality, sodium bicarbonate is the most important [7, 14, 19, 24, 25]. The hazard of transient or sustained osmolal changes induced by its use in the correction of neonatal acidosis, particularly in very sick premature infants, should be kept in mind whenever sodium bicarbonate is to be given, either as a rapid injection, or as a prolonged infusion in combination with other hypertonic solutions. The absence of efficient compensatory functions in premature infants suffering of RDS, asphyxia or other disturbances facilitate the retention of sodium, and hence the development of hypernatraemia.

Besides sodium, other substances such as glucose, urea and probably lactic acid may also be important in producing hyperosmolality. Since in severely ill infants high blood levels of these solution are frequently encountered, their combined contribution to total osmotic concentration is probably not negligible.

Hypertonic glucose solution is frequently used in low-birth-weight infants to meet the fluid and caloric need for maintenance. As a basic solution for parenteral management, it is also used in combination with sodium bicarbonate to repair acidaemia by rapid injection. In addition to the hypertonicity of the glucose solution and the technique of its infusion, a low disappearance rate of glucose from extracellular space due to the reduced peripherial glucose utilization of premature infants [26] may also contribute to the development of hyperglycaemia. In view of these circumstances it is not surprising that iatrogenic hyperglycaemia is a frequent occur-

rence during the management of critically ill low-birth-weight infants. A rise of 100 mg per 100 ml which equals a rise of 5,5 mOsm/l/ or 5.9 mOsm per kg water in osmotic concentration is, in itself, not decisive but it can be very important if osmolality has already been increased by another solute such as e.g., sodium.

A simultaneous elevation in plasma sodium and glucose is often produced by attempts at correcting acidosis and at keeping alive desperately ill newborn infants utilizing two hyperosmolal solutions (sodium bicarbonate and glucose). It is the hypertonicity resulting from the combination of hyperglycaemia and hypernatraemia [29] which can be a real hazard to such patients, if only the sodium concentration is used for approximation of the degree of increase in osmolal concentration. Therefore, in addition to sodium, monitoring of glucose is also mandatory if a more reliable quantitative assessment of hypertonicity is to be achieved.

A progressive increase in blood urea content is often seen in seriously ill premature infants. Renal damage caused by hypoxia or ischaemia may further reduce the otherwise limited renal functional capacity leading to urea retention. Increased urea production due to the catabolic state in such infants also contributes to the rise in blood urea level. Particularly high urea concentrations are produced if the infant is intravenously fed by using amino acid mixtures [5, 8, 10, 22].

Considering the osmolal equivalent of a 10 mg per 100 ml rise in urea concentration (3.6 mOsm per liter serum or 4.2 mOsm per kg water) it is obvious that under the conditions mentioned urea can significantly contribute to hyperosmolality. Although urea has a less pronounced effect upon water distribution owing to the rapid diffusion of the solute into the intracellular compartment, its contribution to osmolality should always be taken into consideration if changes in osmotic concentration are to be calculated. An increase of 20—30 mg per 100 ml in urea concentration in combination with iatrogenic hypernatraemia and hyperglycaemia, whose simultaneous occurrence was not uncommon under the conditions of the present study, could indeed be critical as far as the attainment of the limit of tolerance to hyperosmolality is concerned.

The fourth solute whose accumulation in seriously ill, hypoxic neonates can be pronounced, is lactic acid. This is partly due to the increased glycolysis associated with hypoxia and acidosis, and partly to a massive glucose load imposed by infusion of a hyperosmolal glucose solution. In an attempt to quantitate the osmotic contribution of lactic acid, REDETZKY et al. [21] concluded that every 10 mg increase in lactic acid would increase osmolality by 1.7 mOsm kg water. Although under conditions in vivo the carbonate-bicarbonate system modifies the contribution of the lactic acid concentration to the total osmolality, the marked hyperlactataemia frequently encountered in hypoxic and acidotic newborns cannot be neglected

in predicting osmolality based on chemical analysis of electrolytes and other osmotically active substances.

The metabolic, cellular and compartmental effects of hyperosmolality have been investigated in both animals [1, 6, 11, 13, 17, 28, 30, 31] and man [14, 19, 24, 32]. Acidosis induced by hypertonic solutions in animals is a well-known concequence of hyperosmolality [1, 27, 31]. It is suggested that the metabolic acidosis is mainly due to hypertonic cell injury with release of large quantities of hydrogen ion from the cells. Acidosis associated with hyperglycaemic non-ketotic coma, which in some respects can be regarded as a clinical model of the hyperosmolar syndrome, is also supposed to be the consequence of impaired cellular function and permeability caused by excessive osmotic pressure [18, 23].

Besides cellular damage and dehydration an osmotic gradient of sufficient degree can also cause formation of new osmotically active solutes (idiogenic osmols) [17, 30]. Such a change in osmotic activity, which could be due to an increase organic acid concentration or a change in intracellular binding of Na^+ and K^+, would indicate profound derangements in cellular metabolism. In view of the hyperosmolal injury of cell metabolism it is probably not irrelevant, if in a newborn infant iatrogenic hyperosmolality is superimposed on the metabolic, biochemical alterations due to the primary pathological conditions. Such additional osmolal disturbances might possibly contribute to death or permanent cellular damage.

Redistribution of water leading to cellular dehydration and expansion of intravascular volume [24] can also be deleterious in neonates suffering from potentially lethal conditions such as respiratory distress syndrome or other pathological states with a compromised circulation. Although the readjusment of body fluids is distributed over the whole body, it is mainly the hyperosmolar injury to the brain which is of great importance as for as acute or permanent clinical and pathological consequences are concerned. Experimental observations on animals [15, 16] have shown that a rapidly induced serum-cerebral osmotic gradient may lead to cerebral haemorrhage. Hypertonicity has also been suggested to be responsible for intracranial bleeding associated with hypertonic dehydration [3, 9, 7]. SIMMONS et al. [25] have compared the occurrence of hypernatraemia and intracranial haemorrhage in two different years when the amount and rate of bicarbonate infusion for correction of neonatal acidosis differed markedly. This retrospective study showed that the incidence of hypernatraemia and intracranial haemorrhage decreased significantly when more restrictive criteria for bicarbonate therapy had been adopted. The difference between the two periods suggested that hypernatraemia caused by excessive bicarbonate administration might increase the risk of intracranial haemorrhage.

In the present material, intracranial bleeding of different types, alone

or in combination, was a frequent finding at necropsy. With respect of the above observations, the question arises to what extent, if at all, is hyperosmolality responsible for the high incidence of intracranial haemorrhage? This is a question of great interest and concern to those who are dealing with seriously ill low-birth-weight infants. The present material is unsuitable for drawing valid conclusions as to the possible causal relationship between hyperosmolality and intracranial haemorrhage. The presence and interplay of many factors and circumstances (the very low birth weight, immaturity, respiratory distress, hypoxia, acidosis, hypernatraemia) on which survival and incidence of intracranial haemorrhage depend, simply preclude to assess the pathogenic importance of hyperosmolality. One thing, however, is quite clear that in several instances direct (haemorrhagic cerebrospinal fluid obtained by lumbar puncture) and indirect evidence (clinical signs and anaemia) of intracranial haemorrhage was already present at admission. In these infants factors other than hyperosmolality were responsible for the intracranial haemorrhage, and this argues against the causal and primary role of increased osmolal concentration.

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