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The effect of infusion of Aminosol-glucose on the acid-base balance of low-birth-weight infants

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In seven low-birth-weight infants receiving in the early neonatal period 3.3% Aminosol-glucose solution for 16—28 hours, acid-base status and acid balance have been investigated.

1. During infusion of the nutritive mixture, metabolic acidosis developed. It was particularly pronounced in premature infants with a gestational age below 30 weeks and weighing less than 1500 g.

2. The metabolic acidosis was due to the marked positive net acid balance observed in every infant.

3. In response to Aminosol-glucose administration, a nearly three-fold rise in NH_4^+ excretion occurred during the first 4 hours of infusion, while urinary titratable acidity remained at the preinfusion level. Thereafter a further increase in NH_4^+ excretion was accompanied by a marked elevation in titratable acidity.

It is concluded that a short-term intravenous infusion of an amino acid mixture exerts adverse effects on the acid-base balance of low-birth-weight infants. Very small premature infants, in whom immaturity and perinatal complication often interfere with adaptation to extrauterine life, are particularly endangered.

Solutions of synthetic amino acid mixtures or protein hydrolysates have been used and recommended by different authors for parenteral nutrition of neonates, older infants and children suffering from conditions in which oral feeding had to be avoided for a shorter or longer period of time [6, 7, 12, 14, 15, 20]. Recently, some biochemical alterations have been reported to occur in premature infants receiving amino-acid-glucose solutions intravenously as a source of nitrogen and calories [5, 8, 10, 11, 13, 19]. It has been recognized that the infusion of such nutritive mixtures causes biochemical complications such as hyperammonaemia, hyperosmolarity, amino acid imbalance, acidosis etc., which may outweigh the beneficial effects of parenteral nutrition. Quite recently, CHAN et al. [3, 4] have offered quantitative information concerning net acid production and excretion in four 1 to 2-week-old premature infants maintained on intravenous nutrition; both casein hydrolysate and synthetic amino acid mixture were found to induce acidosis.

Perinatal acidosis is well-known as the most important biochemical disorder exerting various deleterious effects on adaptation to extrauterine life. This is particularly true for premature infants weighing less than 1500 g, in whom a moderate or severe

acidaemia resulting from different conditions (oxygen deficiency, diarrhoea, infection, immature renal function) is frequently encountered during the early and late neonatal period. It is these newborn infants who often require parenteral feeding, and in whom a load of nonvolatile acids imposed by the infusion of an amino acid mixture may cause a shift of the pH towards low values.

It was therefore thought of interest and of practical importance to examine the acidifying effect of an amino acid-monosaccharide mixture in such small premature infants requiring intravenous nutrition in the early neonatal period. The present paper reports on observations made in such infants.

Material and Methods

Seven low-birth-weight infants after unsuccessful attempts at early oral feeding have been studied. Table I summarizes their clinical data. Besides the acid-base parameters in their blood, acid input and excretion before, during and after a 16–28-hour period of 3.3% Aminosol-glucose (Vitrum, Stockholm) infusion was examined. During the 12-hour control period and after the Aminosol-glucose administration, a 10% glucose solution was infused. Two infants, who were acidotic on admission, received 2.5–4 mEq per kg of sodium bicarbonate.

Urine was fractionally collected under toluene, and the urine portions separately frozen until analyzed. Arterial blood samples were taken for determination of the acid-base status by the equilibration method of Astrup et al. [2]. Urinary titratable acid was measured by the method of Győry et al. [9], ammonium excretion by the technique of McCullough [16], and bicarbonate by determining the carbon dioxide content of the urine using a micromethod [17].

Net acid excretion was obtained from the sum of urinary titratable acid (TA) plus ammonium (NH_4^+) minus bicarbonate (HCO_3^-). Endogenous acid production was approximated at 2 mEq per kg per day, a value assumed by Albert and Winters [1]. Recent quantitative data on endogenous acid production in premature infants [3] have confirmed this theoretical value. Exogenous acid input was calculated from the volume of Aminosol-glucose infused, using the values for 14 mEq/l titratable acidity given by Wretlind [21].

Results

Outcome. Three of the seven premature infants died at the postnatal age of 72 to 86 hours. Two of them had severe apnoeic attacks before death. Intraventricular and pulmonary haemorrhage were the main pathological findings at necropsy. One infant died of sepsis; necropsy revealed haemorrhagic pneumonia and intraventricular haemorrhage. Four infants had no severe neonatal complications and survived.

Acid-base status. pH and base excess determined before and during Aminosol-glucose infusion are shown in Fig. 1. A preinfusion blood pH lower than 7.20 occurred only in two premature infants, who therefore had received glucose-bicarbonate treatment before intravenous nutrition was started. In the remainder, a normal acid-base status was observed prior to Aminosol-glucose administration.

Fig. 1 shows that during the protein hydrolysate infusion pH and base ex-

TABLE I

Clinical data of the premature infants examined

No.	History of pregnancy and delivery, Clinical diagnosis	Gestational age wks	Birth weight, g	Postnatal age at the beginning of intravenous nutrition, h	Birth weight percentile	Outcome and age at death	Findings at autopsy	Volume of Aminosol-glucose infused, ml/kg/day	Duration of infusion, hours
1	Premature rupture of membranes, Dysmaturity, Vomiting	36	1850	26	<10	Survived	—	167	28
2	Premature rupture of the membranes, Asphyxia, Aspiration syndrome, Dysmaturity	34	1880	16	<10	Survived	—	129	28
3	Threatening abortion	26	910	24	25—50	Died at an age of 82 hours	Intraventricular haemorrhage	171	28
4	Placenta praevia, Caesarian section, Asphyxia	28	1310	24	50—75	Survived	—	99	28
5	Threatening abortion, Spontaneous delivery	28	1350	20	50—75	Survived	—	127	28
6	Aspiration syndrome, Spontaneous delivery	—	1440	24	—	Died at an age of 72 hours	Intraventricular + Pulmonary haemorrhage	105	16
7	Spontaneous delivery, Asphyxia, Aspiration syndrome	34	1340	22	<10	Died at an age of 76 hours	Haemorrhagic pneumonia	109	16

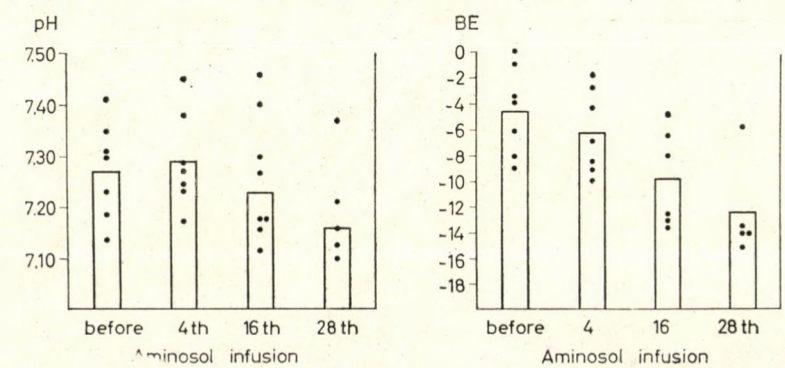

FIG. 1. Individual and mean values for pH and base excess before and during Aminosol-glucose infusion

cess gradually decreased, leading to a moderate or severe metabolic acidosis. This acidifying effect was particularly pronounced in premature infants with a gestational age below 30 weeks and weighing less than 1500 g. After four hours of infusion, only two of the seven infants showed a fall in base excess exceeding —2 mEq/l. During the further course of infusion, however, a decrease in base excess had become evident in the majority of infants. By 16 hours it dropped to a mean of —10 and by 28 hours to 14. When blood pH had decreased below 7.20, bicarbonate treatment was prescribed. In two infants who developed irregular breathing and became depressed by 16 hours of parenteral nutrition, Aminosol was discontinued and thereafter a glucose-bicarbonate mixture was infused.

Net acid balance. Using the theoretical factor of 2 mEq/kg/day for endogenous acid production, acid-balance was already found positive during the 12-hour control period with only glucose-water administration, indicative of a lack of a steady state. In one infant, urinary acid excretion was not examined prior to Aminosol-glucose infusion.

Table II presents the data for renal acid excretion, the calculated values for acid input (infused + endogenously produced acids) and the net acid balance from all infants before, during and after the Aminosol-glucose infusion. In response to the nutritive mixture, the balance was found to have increased in every infant.

In Fig. 2 it can be seen that during intravenous nutrition mean urinary total acid excretion and its two components TA and NH_4^+ increased considerably, reflecting the large amount of acids infused and produced. After the protein hydrolysate infusion, net

TABLE II

Balance data before, during

No.	Before infusion						During		
	TA μE/kg/min	NH_4^+ μE/kg/min	$\frac{NH_4 \times 100}{NAE}$	NAE μE/kg/min	NAI μE/kg/min	Balance μE/kg/min	TA μE/kg/min	NH_4^+ μE/kg/min	$\frac{NH_4 \times 100}{NAE}$
1	0.0110	0.013	83.17	0.016	1.388	1.372	0.261	0.574	71.92
2	0.0020	0.012	93.18	0.013	1.388	1.375	0.084	0.302	87.94
3	—	—	—	—	—	—	0.602	0.887	63.48
4	0.0002	0.001	106.74	0.001	1.388	1.387	0.208	0.296	65.51
5	0.0023	0.014	94.59	0.015	1.388	1.373	0.273	0.182	41.50
6	0.0009	0.014	95.77	0.014	1.388	1.373	0.212	0.075	27.83
7	0.0140	0.073	104.28	0.070	1.388	1.318	0.403	0.253	39.36
Mean	0.0050	0.021	96.28	0.021	1.388	1.366	0.292	0.367	56.79
Range	0.0002— 0.0140	0.001— 0.073	83.17— 106.74	0.001— 0.016		1.318— 1.387	0.084— 0.602	0.075— 0.887	27.83— 87.94

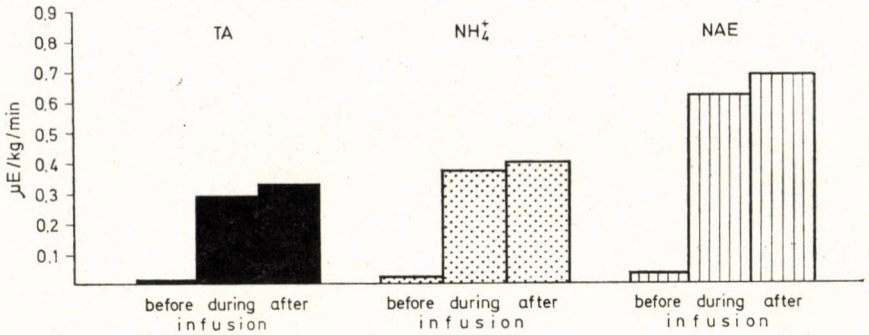

FIG. 2. Mean urinary titratable acidity. NH_4^+ and net acid excretion rate before, during and after infusion

acid excretion was still very high. In some of the infants, however, in addition to the intravenous glucose infusion, small feeds (2—5 ml cow's milk formula) in two or three-hour intervals were given during the second half of the postinfusion day. In spite of this, the high urinary net acid excretion was still largely attributable to the endogenous acids produced by the increased oxidation of amino acids retained during intravenous nutrition.

Concerning the relative contribution of urinary NH_4^+ and TA to total acid excretion (Table II), in the fasting state hydrogen ions were mostly excreted in the form of NH_4^+. During and after Aminosol-glucose infusion, great individual variations were observed in the hydrogen ion excretion

and after Aminosol infusion

infusion			After infusion					
NAE μE/kg/min	NAI μE/kg/min	Balance μE/kg/min	TA μE/kg/min	NH_4^+ μE/kg/min	$\frac{NH_4 \times 100}{NAE}$	NAE μE/kg/min	NAI μE/kg/min	Balance μE/kg/min
0.789	3.018	2.219	0.254	0.737	75.82	0.972	1.388	0.416
0.344	2.754	2.410	0.089	0.203	71.69	0.283	1.388	1.105
1.397	3.064	1.667	0.698	0.756	56.19	1.346	1.388	0.042
0.452	2.355	1.904	0.375	0.182	33.18	0.548	1.388	0.840
0.439	2.473	2.034	0.219	0.083	27.94	0.296	1.388	1.082
0.268	2.488	2.220	—	—	—	—	—	—
0.642	2.421	1.779	—	—	—	—	—	—
0.620	2.653	2.033	0.327	0.392	52.96	0.689	1.388	0.697
0.268—	2.355—	1.667—	0.089—	0.083—	27.94—	0.283—		0.042—
1.397	3.064	2.410	0.698	0.756	75.82	1.346		1.105

pattern. The proportion of NH_4^+ in the total urinary acids decreased to a variable extent in all infants; in four prematures it still exceeded 60 % of the total, in three, however, TA was found to be the largest single component. The dynamics of these responses are shown by the mean fractional TA, NH_4^+ and net acid excretion rates observed during and after the protein hydrolysate infusion (Fig. 3). During the first 4-hour-period of infusion, a nearly threefold increase occurred in the NH_4^+ excretion rate, while urinary TA remained at the preinfusion level. Thereafter, however, a further rise in NH_4^+ excretion was accompanied by a marked elevation in TA, indicating that the infants were capable of responding by both mechanisms of hydrogen ion excretion. The highest and nearly equal excretion rates of both components were achieved during the first 12-hour-collection period after Aminosol-glucose infusion.

The fractional balance values (Fig. 4) showed that the largest amount of acid was retained during the first four hours, when the response in net acid excretion was small in comparison with the later collection periods during and after Aminosol-glucose administration. Parallel to the increasing net acid excretion rate the positive balance decreased, showing an abrupt fall after intravenous nutrition had been discontinued.

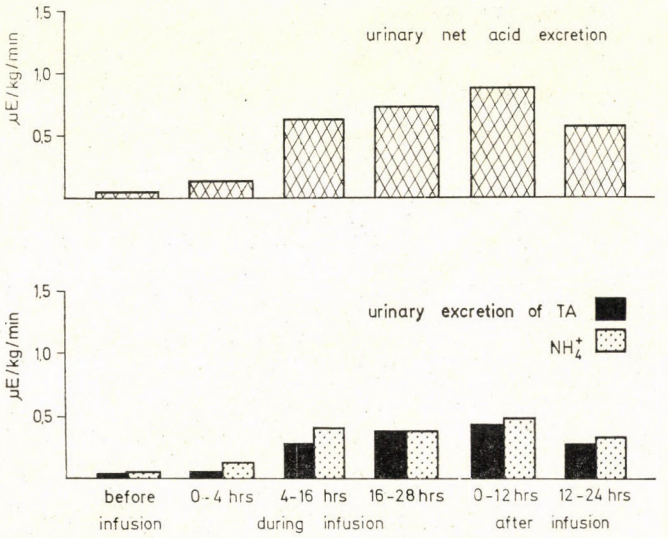

FIG. 3. Fractional urinary excretion of titratable acidity, NH_4^+ and net acid excretion before, during and after Aminosol-glucose infusion

DISCUSSION

Recent reports on the biochemical effects of parenteral nutrition clearly show that during the intravenous infusion of protein hydrolysate or of a

synthetic amino acid mixture, various metabolic complications may ensue [5, 8, 10, 11, 13, 19]. Small premature infants requiring early intravenous nutrition after birth are particularly liable to serious metabolic consequences such as hyperammonaemia, markedly increased urea-N level, hyperosmolarity, acidaemia and a highly unphysiological plasma free amino acid pattern. Therefore, when subjecting small premature infants to parenteral nutrition, it should be realized that in addition to the undesirable properties of amino acid mixtures, the biochemical and physiological immaturity of the newborn infants also contributes to the distortions in blood biochemistry. Elimination of the infused and endogenously produced metabolites by metabolic processes and through the kidney is limited, and an uncontrolled administration of amino acids may rapidly lead to dangerous and toxic levels of different plasma constituents.

Acidaemia. The mechanism of acidaemia induced by protein hydrolysates and synthetic amino acid mixtures has been studied by CHAN et al. [3, 4], and they have directed attention to the marked acidifying effect of such nutritive mixtures. These authors using the net acid balance technique provided quantitative information on endogenous acid production in 1 to 2 week-old infants maintained on parenteral nutrition for 2 to 19 days. The present observations performed on small premature infants have been aimed at providing data on the acid-base disorder caused by short-term Aminosol-glucose infusion within the first three days of extrauterine life. Besides following the parameters of the acid-base status,

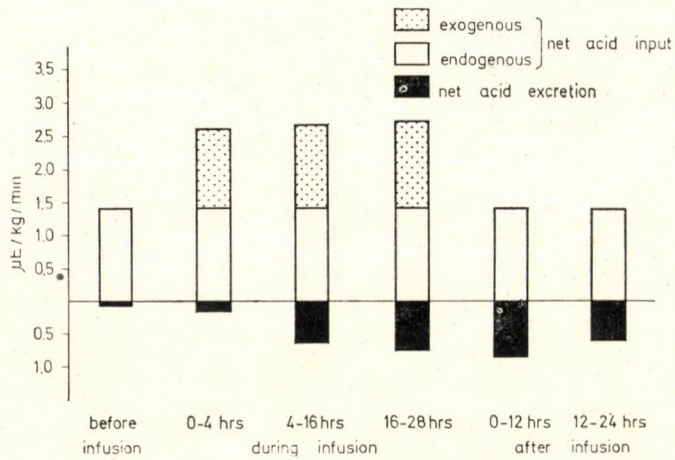

FIG. 4. Fractional acid balance values before, during and after Aminosol-glucose infusion

balance data before, during and after infusion were also obtained.

The above data show that during the first four hours of Aminosol-glucose infusion only in two infants did the fall in BE exceed 2 mEq/l. Thereafter, however, most of the infants developed a marked metabolic acidosis. It appears important that individual differences were observed in the severity and rate of development of acidaemia. They partly reflected the difference in the Aminosol-glucose infusion rate, and partly the difference in the capacity to increase the excretion rate of non-volatile and non-metabolizable acids.

Urinary H^+ excretion pattern. Concerning the components of net acid excretion, both titratable acidity and NH_4^+ excretion increased during intravenous nutrition. Thus, in the early neonatal period small premature infants were capable of responding to an amino acid load by a sizable increase in H^+ excretion. The magnitude and pattern of acid excretion, however, showed individual variations pointing to differences in the response of renal acidification. The proportion of NH_4^+ of the total net acid excretion decreased, which was particularly marked in infants weighing less than 1500 g and suffering from perinatal complications. In these cases titratable acidity constituted the major component of total urinary acids. Contrary to these findings, CHAN [3] observed a low excretion rate of titratable acidity in four 1 to 2-week old premature infants fed parenterally with amino acid mixtures, as compared with the data for a 10-year old child. In the present study, however, intravenous alimentation lasted only 28 hours, and therefore the conditions are not comparable with those applied by CHAN [3], and a prolonged administration of an amino acid mixture must lead to a different H^+ excretion pattern, than a comparatively acute amino acid load. Furthermore, postnatal age, immaturity and perinatal complications may also modify the response of renal acidifying mechanisms and lead to a different H^+ excretion pattern.

Net acid balance. The excessive acid input, and the limited renal capacity of handling this amount of non-volatile acid had increased the positive acid balance before intravenous nutrition. According to the fractional balance data, the largest amount of acid was retained during the first 4 hours of infusion which, however, was not associated with a proportionate fall in base excess, what one should expect if in the neutralization of the retained acids only extracellular buffers were involved. This discrepancy between the acid-base status of the blood, and net acid balance observed during the early period of Aminosol-glucose administration, raises the question of the possible participation of intracellular buffers in compensating an excessive gain of acids. This possibility has already been mentioned by CHAN [3] who also observed a balance exceeding the changes in base excess.

In the marked acidogenic effect, in addition to the exogenous infusion,

the endogenous production of acids must also have had a role. They have been quantitated by CHAN [3] who estimated the urinary excretion of sulphate. These investigations have shown that sulphuric acid production increased 4 to 14-fold during the infusion of synthetic amino acids or of casein hydrolysate. A considerable increment in endogenous acid production from the metabolism of amino acids has already been suggested by our study on the contribution of the three main nutrients to energy metabolism [18]; it revealed that the participation of amino acid oxidation in total heat production increases substantially in response to Aminosol-glucose.

CONCLUSIONS

The present examinations have clearly shown that even a short-term intravenous infusion of an amino acid mixture exerts unwanted effects on the acid-base balance of low-birth-weight infants. Parenteral nutrition with such mixtures appears particularly deleterious to small premature infants, in whom immaturity or perinatal complications often interfere with adaptation to extrauterine life. The present findings are not encouraging as far as early parenteral feeding with protein hydrolysate of such infants is concerned. Leaving aside the various metabolic derangements so far reported, acidosis itself should be regarded as a complication which carries serious risks and makes close monitoring necessary. The composition of the currently available solutions as well as the marked increase in amino acid oxidation associated with the administration of such mixtures are highly unphysiological, and potentially dangerous for premature infants who are incapable of rapid metabolic adjustments.

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