

The effect of intravenous amino acids on plasma amino acid concentration during total parenteral nutrition in infants with necrotizing enterocolitis

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Summary

Plasma aminograms of infants receiving total parenteral nutrition as part of the treatment for necrotizing enterocolitis were studied. Their ages varied from 2 to 60 days and their mean birth mass was 1621 g (range 760-2550 g). The intravenous administration of amino acids produced changes in plasma amino acid levels corresponding to the concentration of individual amino acid levels in the solution employed: higher levels of amino acids in the infusate produced increased plasma levels, whereas low plasma levels were obtained for amino acids not present or present in small amounts according to the solution used. The infants did not appear to suffer in any way, but the long-term effects still have to be evaluated. Pending further knowledge in this regard it is suggested that plasma amino acid levels should be maintained as near to normal values as possible. This could probably be achieved by the use of amino acid solutions specially formulated according to the amino acid profile of breast milk or the plasma amino acid profile of normal infants.

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Neonatal necrotizing enterocolitis (NEC) carries a high mortality rate. Fatalities are usually associated with intestinal perforation and subsequent peritonitis. Oral feeds are accordingly contraindicated, and total parenteral nutrition (TPN) is an established practice.^{1,28} Amino acids are integral constituents of the mixtures administered intravenously during TPN, preferably using the laevorotator crystalline form.²⁹

Amino acid preparations which may disturb the normal plasma amino acid profile are potentially harmful to infants, since brain development may be impaired by a deficiency or an excess of plasma amino acids.^{5,14} The brain is very sensitive

during the major growth spurt, which in humans begins about the middle of gestation and ends between the second and third year of life.

Synthamin (SABAX), the crystalline amino acid solution which was commercially available to us at the time of this study for use in parenteral nutrition, is not balanced according to the needs of infants regarding its amino acid composition, and does not contain all the amino acids essential for normal growth and development (see Discussion).^{3,4} Accordingly, it was decided to study plasma amino acid levels in infants with NEC on a TPN regimen, of which Synthamin was an integral part.

Patients and methods

Plasma amino acid concentrations were measured in 64 infants receiving TPN as part of the treatment for NEC, the clinical diagnosis having been radiologically confirmed. The clinical details of these patients will be reported in a separate article.

The ages of the patients varied from 2 to 60 days, and their birth weights from 760 to 2550 g (mean 1621 g). They were treated in isolation for a minimum period of 21 days, during which time oral feeds were withheld. Synthamin, mineral salts, electrolytes, dextrose and vitamins were prepared aseptically under laminar flow and administered intravenously at a rate of 160 ml/kg/24 h. The amino acid concentration of the mixture was gradually increased to provide 2,4 g protein^{8,11} per kg body mass per day from the 4th day onwards. A fat solution (10% Intralipid) was infused daily at a rate of up to 40 ml/kg, depending on clearance from the plasma.

Tobramycin was the antibiotic used routinely, a dosage of 2,5 mg/kg/8 h being administered for 14 days. Blood or plasma, 20 ml/kg body mass, was infused weekly. Vitamins were administered as part of the treatment regimen, details of which, as well as details of clinical and biochemical observations of the patients, will be published in a separate article.

Since it was considered unwarranted and potentially harmful to draw repeated blood specimens from small, very ill infants, venous blood samples (approximately 0,5 ml) for plasma aminograms were obtained as follows: before commencing TPN (7 infants); after 4 days of TPN (8 infants); after 6-8 days of TPN (16 infants); after 14 days of TPN (9 infants); after 21 days of TPN (18 infants); and after 4 days on oral milk feeds (6 infants).

Plasma aminograms were done on the following healthy infants (controls) after having obtained informed consent from the mothers: 29 premature infants of 1 day old, with a mean birth mass of 1227 g (685-2920 g); 5 premature infants of 5-14 days old, with a mean birth mass of 1227 g (685-2920 g); and 6 full-term infants of 1-6 days old, with a mean birth mass of 2737 g (2020-3948 g).

Amino acid analysis.³¹ Blood specimens were centrifuged. Plasma was deproteinized with sulphosalicylic acid containing an internal standard, and 100 μ l of supernatant fluid was used for the measurement of amino acid concentrations. Specimens not

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analysed immediately were stored at 0°C. All measurements were performed in duplicate with a Beckman Model 119 BI amino acid analyser (Beckman Instruments Inc., Spinco Division, Palo Alto, Calif.). Chromatograms were continuously monitored and integrated on a Hewlett-Packard computer integrating system (HP 3352 B). This system employs an internal standard method and gives a recovery figure of $100 \pm 2\%$ for all amino acids.

Results

Plasma amino acid concentrations varied considerably in the individual patients, but there was remarkable similarity in the mean amino acid levels. Table I summarizes the mean plasma amino acid levels of healthy premature infants, full-term infants and NEC patients. Aminograms of NEC patients were obtained before and during treatment as well as after completion of the therapy and the commencement of milk-feeding.

The intravenous administration of amino acids produced a marked increase in the plasma levels of some of the constituent acids (Table I, Fig. 1). Plasma levels of alanine and glycine increased fourfold within days of commencing intravenous infusion. This increase was followed by a gradual decline, normal plasma concentrations being reached only on day 25, i.e. 4 days after the intravenous administration of amino acids was discontinued and oral milk feeds were started.

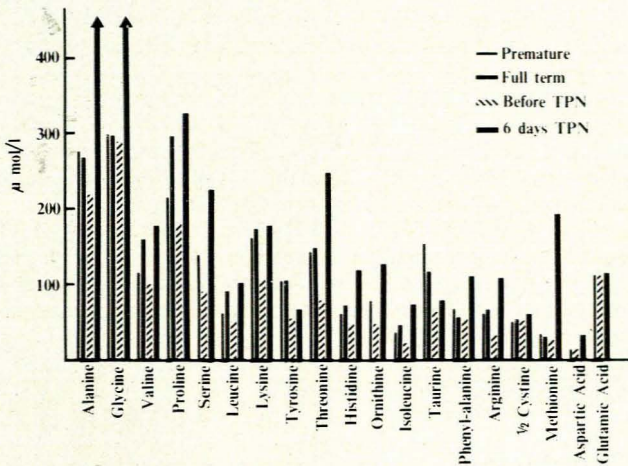


Fig. 1. Histogram of mean plasma amino acid concentrations determined in healthy premature and full-term infants compared with plasma concentrations in infants with NEC.

Plasma levels of histidine, arginine and cystine followed a similar pattern, an initial elevation and a gradual decline for arginine and histidine. The amino acid solution did not contain cystine, which may explain the low plasma levels of the latter. Plasma levels of taurine remained stable during the period of treatment, although lower than the levels for healthy infants. Taurine was not provided in the intravenous amino acid preparation administered. Methionine showed a marked increase in plasma concentration, while there was a gradual decline in tyrosine levels. Synthamin contains only a small amount of tyrosine.

A similar variation in the plasma levels of the other amino acids was observed, normal values being established only after oral feeds had been instituted. The changes in plasma amino acid levels corresponded to the concentration of individual amino acids in the solution employed. The amino acid profile of the plasma before commencement of therapy correlated well with that of breast milk. Synthamin administration produced elevated levels of those amino acids present in higher concentration in the solution (Fig. 2).

TABLE I. SUMMARY OF MEAN PLASMA AMINO ACID CONCENTRATIONS ($\mu\text{mol/l}$)

Infant	Age (d)	No. of patients	Alanine	Glycine	Valine	Proline	Leucine	Serine	Leucine	Lysine	Tyrosine	Threonine	Histidine	Ornithine	Isoleucine	Taurine	Phenylalanine	Arginine	1/2 cystine	Methionine	Aspartic acid	Glutamic acid
Full-term	1-6	6	266,8	298,2	159,5	295,7	89,7	173,7	101,8	145,5	72,5	77,3	45,3	112,5	54,2	<65,0	52,2	<28,0	12,2	112,0		
Premature	1	29	276,5	299,0	114,0	215,3	60,2	162,6	102,7	141,1	58,1	75,5	35,2	151,6	66,6	57,9	48,0	32,0	10,0	76,5		
Premature	5-14	5	335,2	185,0	186,0	238,4	116,8	131,2	193,4	189,8	83,2	46,5	60,8	18,0	79,7	60,3	40,0	27,0	12,4	111,1		
NEC before TPN		7	219,4	288,9	100,4	178,0	49,5	104,7	51,0	75,9	45,3	114,2	21,3	60,6	53,1	29,7	50,4	25,2	12,4	111,1		
NEC—TPN day 4		8	720,4	1306,8	181,3	251,3	122,3	179,6	44,8	318,3	122,3	114,2	80,9	66,8	125,8	139,3	28,1	180,6	14,8	88,6		
NEC—TPN days 6-8		16	790,7	1274,1	177,7	326,2	101,8	176,3	65,3	247,4	117,4	124,7	71,4	76,8	109,1	106,6	59,4	191,1	30,9	114,8		
NEC—TPN day 14		9	455,5	765,4	113,4	168,3	59,6	115,2	35,6	166,2	86,3	115,3	40,8	78,6	69,6	61,9	88,4	112,3	17,4	175,9		
NEC—TPN day 21		18	383,0	657,5	120,6	185,8	65,9	93,2	37,2	154,0	83,6	93,9	37,2	154,0	83,6	93,9	46,3	90,8	16,1	141,3		
NEC—on milk feeds—4		6	236,8	247,2	133,8	350,8	67,7	117,7	92,7	153,7	66,0	56,3	39,3	58,3	60,1	28,0	71,0	42,0	15,2	153,8		

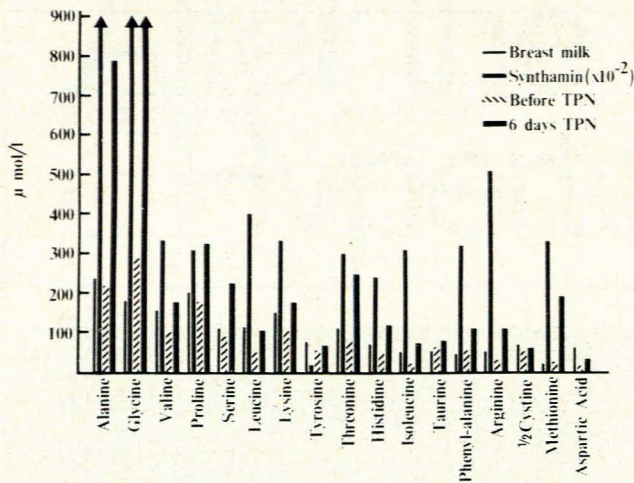


Fig. 2. Histogram of amino acid profiles of breast milk, Synthamin and plasma of infants.

It seems therefore that plasma amino acid levels in neonates are not affected by age or mass (Table I). However, the plasma levels of individual amino acids are affected by the intravenous administration of an amino acid solution, and return to normal when the amino acid infusion is discontinued and oral feeds are given. It is evident that the plasma amino acid levels during intravenous amino acid infusion vary according to the amino acid pattern of the infusate.

Discussion

Protein synthesis depends on the availability of amino acids in the plasma. The supply of protein — amino acids — to the body should be adequate to maintain a positive nitrogen balance. In the event of failure to ingest protein, it should be administered intravenously, preferably in the form of L-crystalline amino acids.²⁹

Blood, plasma and albumin are poor substitutes for an amino acid infusion, since they provide the amino acids for endogenous protein synthesis only after variable periods of time: plasma after 10 days, red blood cells after 90-120 days, and albumin only after 2-3 weeks.¹²

Amino acid preparations for intravenous infusion should contain the 20 amino acids considered necessary for the synthesis of human protein.¹⁸ The composition of the amino acid solution employed in the treatment regimen should also be adapted to the requirements of the patient according to age and specific need, e.g. 40% of an infant's protein intake should be in the form of essential amino acids. The relevant figure for adults is 19%.³¹ The FAO/WHO Expert Group on Protein Requirements^{3,4} concluded that the ideal amino acid pattern should be similar to that of human milk protein or egg protein.

At cell-level, all amino acids necessary for normal growth and development are essential. The non-essential amino acids, however, can be synthesized adequately by the body and these should be adequately provided in the infusate. Amino acid synthesis is impaired in the neonate because of the immaturity of enzyme function. Accordingly, besides the amino acids essential for adults, i.e. leucine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine, the neonate must also be provided with histidine, cystine, tyrosine, arginine, taurine, proline and alanine. The infant is incapable of synthesizing these adequately.^{6,7,10,13,17,19,20,22,24,26}

Deficiencies in any of these amino acids may affect the infant seriously, causing quantitative deficits rather than actual destruction of nerve tissue. For example, taurine is regarded as essential for the normal development of brain and retina,^{2,25,27}

and failure to provide adequate amounts of taurine in the diet or infusate may affect brain and retinal development adversely.

Preterm infants are not able to convert methionine, phenylalanine and glycine adequately to cystine, tyrosine and serine owing to poor enzyme function.^{13,15,17,23,26} Other amino acids are similarly affected. This results in inadequate availability of some amino acids and accumulation of others, which may in turn result in severe neurological damage when toxic levels are reached. Adequate amounts of amino acids should be given to infants in the proportions necessary for rapid growth, ensuring that none of these is present in excessive quantities, lest metabolic overloads occur. The amino acid may concentrate in the blood to levels as high as those observed in certain inborn errors of amino acid metabolism. There is evidence that premature infants who experience this sort of imbalance in amino acid levels may suffer intellectual or neurological impairment. In more than 50% of cases of inborn errors of metabolism, brain damage has been associated with elevated plasma amino acid levels.⁵

The administration of poorly balanced amino acid solutions will cause an overload of some metabolic pathways, with consequent elevation of plasma levels of some amino acids, while inadequate levels of essential amino acids in the solution administered will result in low plasma levels of these acids. Both situations pose a threat to the recipient infant.^{5,9,14}

The abnormal amino acid profile found in this study after intravenous infusion of the amino acid solution, Synthamin, is a matter of concern. The amino acid composition of Synthamin is not formulated according to the amino acid profile of breast milk protein, and contains large amounts of alanine, glycine, phenylalanine, methionine and arginine but is deficient in taurine, cystine, tyrosine and serine. It is known that the plasma amino acid concentrations reflect the profile of the infusate during administration.^{8,16,21} It is therefore certain that the administration of Synthamin resulted in the abnormal plasma amino acid profile found in this study (Fig. 2).

How important is this disturbed plasma amino acid profile to the well-being of the infant? Long-term effects still have to be evaluated, but infants on the treatment regimen did not appear to suffer in any way. In the light of the present knowledge of amino acid metabolism in infants, however, it seems prudent to maintain the plasma amino acid concentration of infants on TPN as near to normal values as possible.

Conclusion

This study highlights the importance of the intravenous infusion in infants of an amino acid solution which supplies adequate amounts of amino acids in proportions suitable to their special needs. It also stresses the importance of measuring amino acid levels before, during and after TPN in order to monitor the plasma concentrations.

The individual aminograms are available from: Dr J. C. Thom, Dept of Paediatrics, University of Stellenbosch, PO Box 63, Tygerberg, 7505 RSA.

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