Parenteral Nutrition in the Very-Low-Birth-Weight Infant

J. Rigo and J. Senterre

Department of Paediatrics, State University of Liege, Bavière Hospital, B-4020 Liège, Belgium

In preterm infants an optimal nutritional supply must be provided early during the neonatal period. Indeed, undernutrition leads to growth retardation which may be hazardous for brain development (18). Growth rate is maximum during the last trimester of gestation and corresponds to about 60 cm/year (19). Therefore, contrary to young children, preterm infants after arrest of growth, whatever the cause, cannot achieve a complete return to normal growth. This fact is clearly illustrated by the follow-up of very-small-for-gestational age infants in spite of a high protein, mineral, and energy intake. Oral nutrition alone cannot maintain adequate growth in very-low-birth-weight (VLBW) infants because of their poor clinical condition and the immaturity of their gastrointestinal tract. Total or supplemental parenteral nutrition has been shown to improve the neonatal growth of VLBW infants by enhancing their caloric and nitrogen supply (4,24). In this chapter, we shall present some guidelines about nitrogen, amino acid, energy, and mineral intakes for infants on total parenteral nutrition (TPN).

NITROGEN REQUIREMENT AND AMINO ACID METABOLISM

Nitrogen requirement of VLBW infants on TPN may be estimated by nitrogen balance studies. Nitrogen retention depends upon nitrogen intake and energy available for growth (25,29). A nitrogen retention of about 300 mg/kg/day, similar to that in utero (Fig. 1), can be obtained with a supply of 450 mg nitrogen or 3.1 g amino acids/kg/day provided that the energy supply is adequate.

However, such a high intake may impose a metabolic stress because of the immaturity of several enzymatic pathways and the amino acid imbalance in the parenteral solution. In a previous study, we analyzed the factors influencing the serum amino acid concentration in 163 LBW infants fed either parenterally (N = 54) or orally with human milk or adapted formulas (N = 109). We reported that threonine metabolism is reduced in preterm infants (Fig. 2) probably because of the low activity of the serine threonine dehydratase, the principal enzyme involved in the threonine metabolism (23).
The metabolism of aromatic amino acids is also impaired in preterm infants (22). In our study, for a similar intake, serum phenylalanine concentration was higher in infants fed parenterally than in those fed orally (Fig. 3). This might be due to the bypass of the portal circulation during parenteral nutrition and possibly also to a decrease of enzymatic activities in the liver. In parenteral nutrition, tyrosine intake is very low because of its poor solubility. Neverthe-
PARENTERAL NUTRITION IN VLBW INFANTS

FIG. 3. Influence of the mode of administration on the relationship between serum phenylalanine concentration and phenylalanine intake in LBW infants fed orally (circles) or parenterally (triangles). Orally: $y = 0.0046x + 2.93$, $r = 0.31$, $p < 0.01$, $N = 109$. Parenterally: $y = 0.0056x + 6.78$, $r = 0.26$, $p = 0.07$, $N = 54$. Difference between levels: $p < 0.05$.

less, the serum levels of tyrosine are similar in preterm infants fed parenterally and in those fed orally (Fig. 4). Therefore, the phenylalanine hydroxylase activity seems to be satisfactory, and tyrosine must be considered as a semielemental rather than as an essential amino acid even in preterm infants. Similar conclusions have been drawn by others (10,16).

By contrast, Zlotkin and coworkers (27) and Anderson and coworkers (1) observed normal phenylalanine and low tyrosine serum concentrations in preterm infants with similar aromatic amino acid intakes (Table 1). The high branched-chain amino acids, in particular, the high leucine concentration in their parenteral solution, might be responsible for the low serum aromatic amino acid concentration. Indeed, experiences with parenteral nutrition in patients with hepatic failure have shown that high branched-chain amino acid intakes can decrease the serum level of aromatic amino acids (6). However, further studies are necessary to confirm this hypothesis.

In preterm infants, sulfur amino acid metabolism is impaired because of the low cystathionase and cystein sulfinic acid decarboxylase activities (9). In parenteral nutrition, cystine supply is low because of its poor solubility. In our study the increase in serum methionine concentration was less marked in parenteral than in oral nutrition (Fig. 5). Serum cystine concentration was
related to the serum methionine concentration (Fig. 6). However, at low serum methionine concentration (2 μmoles/dl), cystine level was lower in parenteral than in oral nutrition. By contrast, when serum methionine level was high (6 μmoles/dl), serum concentration of cystine was similar in both groups. In addition, serum cystine concentration also increased according to actual gestational age (Fig. 7). These observations were confirmed by recent studies of Ziotkin and collaborators (27,28). In LBW infants on TPN supplemented with cysteine, they observed an increase of the plasma cystine concentration without

![Graph showing absence of relationship between serum tyrosine concentration and tyrosine intake in LBW infants fed orally (closed circles) or parenterally (open circles).](image)

**FIG. 4.** Absence of relationship between serum tyrosine concentration and tyrosine intake in LBW infants fed orally (closed circles) or parenterally (open circles). $y = 0.0012x + 9.68$, $r = 0.09$, $p > 0.05$, $N = 163$. 

<table>
<thead>
<tr>
<th>Aromatic amino acid intake (μmoles/kg/day) and serum amino acid concentration (μmoles/kg/dl) in LBW infants on TPN</th>
<th>Ghadimi (10)</th>
<th>Ziotkin et al. (29)</th>
<th>Jones (16)</th>
<th>Anderson et al. (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylalanine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intake</td>
<td>423–910</td>
<td>500–1100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum concentration</td>
<td>8–15</td>
<td>5–7</td>
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<td>Tyrosine</td>
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<tr>
<td>Intake</td>
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<td>70–140</td>
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<tr>
<td>Serum concentration</td>
<td>7–12</td>
<td>2–4</td>
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any change in nitrogen retention or in growth. They also reported a significant activity of cystathionase in the liver, the adrenal glands, and the kidney of preterm infants. These studies and our observations suggest that the cystathionase activity is sufficient to maintain an adequate level of cystine even in the most premature infants, provided the methionine supply is sufficient.
Therefore, cystine must be considered as a semiessential amino acid rather than an essential one.

The serum branched-chain amino acid levels increased with the intake in LBW infants fed orally and parenterally. However, branched-chain amino acid metabolism was higher in preterm than in full-term infants. Indeed, as shown in Fig. 8 for valine, for a similar intake, the serum concentration was lower in the preterm than in the full-term infants.

INNOCUOUS SERUM AMINO ACID CONCENTRATION IN PRETERM INFANTS

Serum amino acid concentration in the cord blood is stable during the last trimester of gestation (12). It is not influenced by conditions of delivery (vaginal or cesarean section) (21); it is similar to the values determined by umbilical venous puncture by MacIntoch and collaborators in 10 fetuses (20) and reflects the fetal amino acid level. During gestation, serum amino acid concentration in the fetus is elevated. They provide nutrients for growth and are regulated...
The normal serum level of aromatic amino acids at birth in phenylketonuric infants of healthy mothers clearly demonstrates this fact (15).

The high serum amino acid concentrations in the fetus may be related to its high rate of growth. Indeed, in tissue culture, there is a relationship between the nitrogen uptake and the amino acid concentration in the culture medium. Consequently, it can reasonably be assumed that a blood amino acid concentration similar to that in utero is innocuous for the preterm infant and is, perhaps, a good condition to promote growth and brain development.
FIG. 8. Influence of gestational age on the relationship between serum valine concentration and intake in LBW infants fed orally (right) or parenterally (left). Orally: $z = 0.0088x$ (intake) $+ 0.43y$ (AGA) $- 8.88$, $r = 0.67$, $N = 109$, $p_x < 0.001$, $p_y < 0.01$. Parenterally: $z = 0.0098x$ (intake) $+ 0.42y$ (AGA) $- 3.93$, $r = 0.56$, $N = 54$, $p_x < 0.001$, $p_y < 0.01$. 
OPTIMAL AMINO ACID INTAKE IN PRETERM INFANTS ON PARENTERAL NUTRITION

In preterm infants, the amino acid intake must be sufficient to fulfill nitrogen requirements and to assure growth without overload in amino acids and nitrogen metabolites. By multivariate analysis of our data, we have calculated the amount of each amino acid necessary to obtain a serum concentration similar to that of the fetus in utero (Table 2). These amounts are similar in oral and in parenteral nutrition except for phenylalanine.

The total intake corresponds to 3.1 g of amino acids or 480 mg of nitrogen per kilogram body weight per day with one-half as essential amino acids. These values are in agreement with the results of nitrogen balance studies carried out in preterm infants on oral or parenteral nutrition (25,29). However, it appears that the amino acid composition of parenteral solutions is not fully adapted for preterm infants. In particular, these solutions are generally too rich in threonine and aromatic amino acids, and deficient in branched-chain amino acids, lysine, and taurine. Therefore we believe that solutions with better balanced amino acid composition must be developed to promote growth and brain development without overloading the enzymatic systems of the immature infant.

ENERGY REQUIREMENTS IN PRETERM INFANTS ON TPN

VLBW infants need a high caloric intake (13). The energy necessary for basal metabolism, thermoregulation, and muscular activity corresponds to

<table>
<thead>
<tr>
<th>Amino acids</th>
<th>μmoles/kg/day</th>
<th>mg/kg/day</th>
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<tr>
<td>Threonine</td>
<td>970</td>
<td>115</td>
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<tr>
<td>Leucine</td>
<td>2375</td>
<td>311</td>
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<td>162</td>
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<td>Valine</td>
<td>2315</td>
<td>271</td>
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<tr>
<td>Methionine</td>
<td>377</td>
<td>56</td>
</tr>
<tr>
<td>Phenylalanine orally</td>
<td>750</td>
<td>124</td>
</tr>
<tr>
<td>TPN</td>
<td>400</td>
<td>66</td>
</tr>
<tr>
<td>Lysine</td>
<td>2925</td>
<td>427</td>
</tr>
<tr>
<td>Histidine</td>
<td>750</td>
<td>116</td>
</tr>
<tr>
<td>Tryptophane</td>
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<td>50</td>
</tr>
<tr>
<td>Tyrosine orally</td>
<td>400</td>
<td>72</td>
</tr>
<tr>
<td>TPN</td>
<td>150</td>
<td>27</td>
</tr>
<tr>
<td>Cystine</td>
<td>244</td>
<td>59</td>
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<tr>
<td>Taurine</td>
<td>140</td>
<td>19</td>
</tr>
<tr>
<td>TEAA</td>
<td>11942</td>
<td>1632</td>
</tr>
<tr>
<td>TAA</td>
<td>24879</td>
<td>3100</td>
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<tr>
<td>TEAA/TAA</td>
<td>0.48</td>
<td>0.53</td>
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about 70 kcal/kilo body weight/day, whereas the total energy requirement for
growth, synthesis, and storage represents about 45 kcal/kg or 3 kcal/g of body
weight gain. In parenteral nutrition, fecal and urinary losses of energy are
generally low. Therefore, the total energy requirement can be estimated at
about 100 to 120 kcal/kg/day. This requirement can be met by fats and car-
bohydrates.

Fat solutions provide the essential fatty acids necessary for growth. Intralipid®,
the most widely used parenteral fat solution, contains 54% of linoleic
acid and it must be utilized with caution.

VLBW infants do not seem able to clear more than 2 g of lipids/kg/day.
Indeed, it has been reported that lipid serum concentration increases with the
intake and that hyperlipemia may be induced by an intake of less than 3 g/
kg/day (5).

Griffin and co-workers (11) have reported an increase in the plasma con-
centration of free cholesterol, phospholipid, and lipoprotein X during contin-
uous Intralipid® infusion. According to these authors, 50% of the increase of
plasma free cholesterol derives from endogenous sources, whereas the hyper-
phospholipemia is attributed to the lipid concentration. The exact process
responsible for the lipoprotein X formation is not clearly established. Calo-
rimetric studies (13) have shown that endogenous fat oxydation decreases with
the caloric intake. In preterm infants at 70 kcal/kg/day, endogenous fat oxy-
dation is null on parenteral nutrition with amino acids, glucose, and fat. With
a caloric intake over 80 kcal, the percentage of energy derived from fat oxy-
dation does not reach more than 30% regardless of the fat intake. It has been
calculated that preterm infants do not metabolize more than 2 to 3 g of In-
tralipid®/kg/day and that too much intake leads to tissue deposition.

Studies of body fat composition (2,8) have shown an increase in the relative
linoleate content and a decrease in the relative arachidonate content. These
modifications may lead to prostaglandin deficiency (2), to pulmonary and
reticuloendothelial dysfunctions (7), and to potential changes in myelin con-
figuration and function (3). We therefore prefer to limit the lipid intake to 2
g or 20 kcal/kg/day until additional information is available.

Most of the calories therefore must be provided by carbohydrates. However,
particularly during the first weeks of life, high glucose infusion leads to hy-
perglycemia. Fructose, which is present in some parenteral amino acid solu-
tions, may have theoretical advantages because of its rapid utilization and its
lack of dependence on insulin for its metabolism. However, acute infusion
may lead to acidosis, depletion of ATP, hyperuricemia, and hyperuricosuria.
Therefore, fructose utilization in parenteral nutrition for LBW infants is still
controversial (26).

We have analyzed the effect of carbohydrate tolerance in VLBW infants
under 1,500 g (body weight: 1,186 ± 196 g; length: 37.8 ± 2.7 cm; gestational
age: 30.2 ± 2.4 weeks). The infants parenterally received amino acids, fats,
and carbohydrates (either glucose alone, or ½ glucose and ½ fructose). In
infants fed on TPN with glucose alone, the serum glucose concentration increased with the intake (Fig. 9). However the slope of the regression line was significantly higher during the first 10 days of life than thereafter. The relationship between serum insulin concentration and serum glucose level was similar during both periods. Thus hyperglycemia during the first days of life seems to be due more to a peripheral resistance to insulin than to a relative lack of insulin secretion.

During the first 10 days of life (Fig. 10), the slope of the regression line was significantly lower in infants receiving a glucose-fructose solution than in those fed on glucose alone. Nevertheless, the relationship between serum insulin concentration and glucose level was similar in the two groups. After 10 days of life, glucose tolerance was higher and no further difference was observed between the two groups. No adverse effects such as acidosis or an increase of uric acid excretion were observed during fructose infusion. The serum fructose concentration averaged 15 mg/dl and was always below 30 mg/dl.

Therefore, during the first days of life, a supply of 25% of carbohydrate such as fructose could be used for increasing the caloric intake.

MINERAL REQUIREMENTS

Rickets has been reported in preterm infants on TPN. Adequate mineral supply is sometimes difficult to provide because of the precipitation of calcium phosphate (14,17). In our parenteral solution prepared at the pharmacy of the hospital, calcium gluconate was added to the amino acid solution. The calcium seems to be chelated to the amino acids. This solution was then diluted with glucose and electrolyte solutions. Finally, phosphorus was added as Sörensen buffer. The parenteral solution contains 33 mg of calcium, 30 mg of phosphorus, and 3.3 mg of magnesium per 100 ml. Under these conditions, a positive retention can be obtained (Table 3) and rickets may be prevented, provided vitamin D is given.

CONCLUSION

Adequate nutrition in VLBW infants is frequently difficult to achieve because of their clinical condition and the immaturity of the gastrointestinal tract. Total or supplemental parenteral nutrition is necessary to avoid undernutrition and to promote growth of VLBW infants. Satisfactory growth and nitrogen retention can be obtained on an energy intake of 100 to 120 kcal/kg body weight/day and a nitrogen intake of 400 to 450 mg or about 3 g of amino acid/kilo body weight/day. However VLBW infants are particularly vulnerable to high amino acid intakes because of the immaturity of some enzymatic pathways; new solutions with a better amino acid balance should therefore be developed. Fat intake must be limited to 2 g/kg body weight/day in order to avoid hyperlipemia and its possible toxic effects. Most of the energy intake
FIG. 9. Influence of postnatal age on the relationship between serum glucose concentration and glucose intake (left) and serum insulin concentration and serum glucose concentration (right) in VLBW infants fed parenterally (BW < 1,500 g). \( z \) (glycemia) = 0.0043x (intake) - 3.61y (postnatal age) + 97.24, \( r = 0.46, t = 2.68, N = 55, p_x < 0.01, p_y < 0.01 \). \( z \) (insulinemia) = 0.33x (glycemia) - 0.16y (postnatal age) - 5.69, \( r = 0.45, t = 2.54, N = 53, p_x < 0.01, p_y < 0.05 \).
FIG. 10. Relationship between serum glucose concentration and carbohydrate intake (left) and between serum insulin concentration and serum glucose concentration (right) in VLBW infants (BW < 1,500 g) on parenteral nutrition with glucose (circles) or glucose and fructose (triangles) during the first 10 days of life. Left: Glucose: \( y = 0.0068x + 39.16, r = 0.48, p < 0.01, N = 33 \). Glucose + fructose: \( y = 0.0031x + 63.17, r = 0.35, p < 0.05, N = 35 \). Difference of level \( p < 0.05 \). Right: Glucose: \( y = 0.22x + 5.71, r = 0.37, p < 0.05, N = 32 \). Glucose + fructose: \( y = 0.37x - 12.08, r = 0.45, p < 0.01; N = 34 \).
should be derived from carbohydrates, essentially glucose. During the first
week of life, glucose tolerance is limited and some fructose might be helpful
as a substitute. It is also necessary to provide sufficient calcium, phosphorus,
and magnesium in order to achieve a positive mineral retention.

Nevertheless, several problems remain to be resolved. Among these, we shall
mention the need to achieve an optimal intake of trace elements and vitamins
in long-term parenteral nutrition. The factors responsible for liver cholestasis
must be studied. Last but not least, follow-up studies are needed to show if
better neurological development can be achieved by improving nutrition dur-
during the neonatal period.

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and quality in low-birth-weight infants. III. Effects on sulfur amino acids in plasma and urine.


and characterization of lipoprotein X during continuous intralipid infusions in the neonate.
DISCUSSION

Dr. Perman: I am interested in your recommendation regarding the administration of fructose in total parenteral nutrition solutions in the low-birth-weight infants. As you pointed out, low-birth-weight infants are relatively fructose-intolerant, and I am curious as to whether you see in these infants a response which you might see in an infant with hereditary fructose intolerance. You mentioned that you measured the phosphorus balance, and I am wondering whether these infants had decreased phosphorus levels and perhaps increased uric acids.

Dr. Rigo: In low-birth-weight infants, kinetic studies of fructose and glucose infusions have shown that renal fructose threshold level is lower than renal glucose threshold...
level. In addition, acute fructose infusion may lead to metabolic acidosis, hypophosphatemia, and high urinary excretion of uric acid. In our study, fructose infusion corresponded to about 30% of the carbohydrate intake. Under these conditions, fructose tolerance was good: serum fructose level was below 30 mg/dl and urinary excretion of fructose represented less than 3% of the fructose intake. Serum phosphorus level and urinary excretion of uric acid were similar in the infants receiving glucose and in those infused with a mixture of glucose and fructose.

Dr. Råihä: You said that you feel that the fetal plasma amino acid level is optimal. I wonder why you come to that conclusion, because we don't use the fetal PO₂ as optimal in the newborn glucose level either. I think you can call them a reference point, but we may not want to strive at those levels.

Dr. Rigo: Regarding PO₂, I think that we can agree that oxygen consumption is not the same before and after birth. About amino acids, plasma amino acid level of the fetus in utero is high during the whole period of gestation and is similar to cord blood values. This level is probably necessary for his development and nontoxic for his brain. It is quite difficult to define an optimal reference for preterm infants. Indeed, prematurity is not a physiological status. Amino acid levels are dependent not upon only the protein intake but also upon the nitrogen retention. If we want to have a postnatal growth and a nitrogen retention similar to that existing in utero, we shall have a higher amino acid level than the one observed in term infants fed human milk. Human milk is not exactly a physiological diet for a preterm infant. So we may not consider the plasma amino acid level of low-birth-weight infants fed on human milk as a reference level. What I would conclude is that, if not a reference level, cord blood amino acid levels may be considered at least as a safe level for preterm infants.

Dr. Metcoff: Do you think that constant enteral infusion would be better than constant parenteral infusion with respect to amino acids?

Dr. Rigo: When feeding the low-birth-weight infant, we frequently carry out continuous enteral feeding or very frequent meals every 1 or 2 hrs. Except for phenylalanine, we did not observe any difference between enteral and parenteral nutrition when we consider the relationship between serum amino acids level and dietary amino acid intake.

In our unit, we tend to reduce total parenteral nutrition for very-low-birth-weight infants—we use supplemental parenteral nutrition, and the data that I gave earlier were related to the growth of infants on supplemental parenteral nutrition. However, the data presented on amino acid metabolism in preterm infants were collected in infants on total parenteral nutrition, because some years ago we used more parenteral nutrition over a longer period for infants of very low birth-weight and for those with surgical problems. I think that for the study of the metabolism of amino acids, we need to have total parenteral nutrition. Now, we have decreased the frequency of total parenteral nutrition and increased the supplemental parenteral nutrition for the low-birth-weight infant. The duration of parenteral nutrition has also decreased, and after 10 days we stop parenteral nutrition and replace it by oral nutrition. We use human milk, supplemented with protein, phosphorus, and calories, or we use a mixture of human milk and specially adapted formula for low-birth-weight infants.

Dr. Råihä: I have a question for Dr. Putet. When comparing growth in your two groups, do you think it is really an advantage for the infant to gain weight at 21.4 g instead of 15 g/kg/day? We are not so much concerned about weight gain in our infants on breast milk—they usually pick up later anyway.

Dr. Putet: I am glad that you have asked this question, because it was one of our first questions: Should we try to reach the 1U growth rate? I am not sure at all, but I believe that there is no answer at the moment. In babies gaining weight at the rate of 20 g/kg/day, we don't know what is the total body water. We need this type of information to evaluate the quality of the weight of these babies.
Dr. Metcoff: Our own data in rats as well as a myriad of other data indicate that plasma levels of amino acids correlate very poorly with levels of amino acids in almost any other tissue—muscle and liver as well. I am becoming increasingly cautious about interpreting plasma amino acid levels for any meaningful purpose.

Dr. Räihä: I think we all agree about that, but can you suggest how we could analyze amino acids from anything else? I know that Bill Hurd at Columbia has studied newborn pups on total parenteral nutrition and he has been able to show that a 10% increase or decrease in certain plasma amino acids may indicate a 100% increase in the tissue level. So I would be very worried by a change in the plasma level, because that level may indicate that the tissue level is many, many times higher or lower.

Dr. Metcoff: In response to your question, we have found a fair correlation between leucocytes and muscle. Leucocytes are fairly easy to obtain, and they can be analyzed using very small quantities of blood.

Dr. Räihä: I think that is very important and I know Bo Lindbladt in Stockholm is looking at red cell amino acids. We may have to get into that, but the reason why we are still measuring plasma amino acids is that we now have a big pool of data on plasma amino acids with various diets. If we now suddenly turn to looking at leucocyte amino acids or red cell amino acids, then we would have to do all the clinical trials and studies again, because we cannot compare the red cells to the plasma values.