Total intravenous alimentation in low-birth-weight infants: A preliminary report

Nine infants with birth weights less than 1,200 Gm. received total intravenous alimentation for 5 to 24 days. In six infants, alimentation was started within 48 hours of birth; in three others, the procedure was started at 12 to 14 days of age. When a caloric intake of more than 100 Cal. per kilogram per day was achieved, weight gain averaged 15.3 Gm. per day and nitrogen balance averaged 0.23 Gm. per day. No significant deviations were observed of plasma sodium, potassium, calcium, phosphorus, and acid-base values. The time required to regain the initial body weight after institution of intravenous nutrition was significantly improved over that expected in conventionally managed infants of similar weights. The results demonstrate that the technique, when properly used, warrants further controlled investigation in premature infants.

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Table I. Summary of clinical data

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Birth weight (Gm.)</th>
<th>Estimated gestational age (wk.)</th>
<th>Weight classification</th>
<th>Clinical problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>850</td>
<td>28</td>
<td>AGA</td>
<td>Pulmonary insufficiency*</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>1,150</td>
<td>30</td>
<td>AGA</td>
<td>Pulmonary insufficiency; respirator 9 to 19 days</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>930</td>
<td>28</td>
<td>AGA</td>
<td>Recurrent apnea; patent ductus arteriosus; died age 21 days of respiratory failure</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>720</td>
<td>26</td>
<td>AGA</td>
<td>Recurrent apnea; pulmonary insufficiency; died age 20 days of respiratory failure</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>720</td>
<td>26</td>
<td>AGA</td>
<td>Recurrent apnea; died at 5 days of Candida sepsis</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>1,020</td>
<td>28</td>
<td>AGA</td>
<td>Prematurity</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>1,070</td>
<td>30</td>
<td>AGA</td>
<td>Recurrent apnea</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>870</td>
<td>28</td>
<td>AGA</td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>760</td>
<td>28</td>
<td>SGA</td>
<td>Pulmonary insufficiency; recurrent apnea; died age 51 days of aspiration pneumonia</td>
</tr>
</tbody>
</table>

AGA = appropriate for gestational age, SGA = small for gestational age.

*Pulmonary insufficiency of premature as described by Burnard and associates.15

Total intravenous alimentation* has been effectively and safely used for protracted periods of time in newborn infants (usually full-term infants) with surgically reparable gastrointestinal anomalies6-9 and in older infants with chronic malabsorptive disorders.10-11 Thus far, there are no systematic studies of the response of very small premature infants to total intravenous alimentation. Because of the possibility of a favorable short-term effect upon somatic growth, as well as a positive long-term effect upon the developing nervous system, we have undertaken a preliminary study of this technique in a group of low-birth-weight infants.

CLINICAL MATERIAL AND METHODS

Patients. Nine infants with birth weights less than 1,200 Gm. were studied during periods of intravenous alimentation. Table I summarizes the clinical data of these infants.

*The term, total intravenous alimentation, as used in this paper is defined as provision of all nutrients by vein with nothing being given by mouth. This term should be differentiated from complete intravenous alimentation which implies that all necessary nutrients are provided in adequate quantities by vein. Clearly the latter is impossible due to lack of an accurate definition of both "all requirements" and "all nutrients." The term, hyperalimentation, is avoided entirely since it implies overfeeding.

An infant was accepted for intravenous alimentation if clinical evaluations at 12 hours of age revealed no clinical radiologic evidence of respiratory distress syndrome and if the values for blood pH were greater than 7.20 and for plasma Pco2 were less than 50 mm. Hg. Six infants satisfied these criteria. In these infants, an umbilical artery catheter was passed so as to lie 1 cm. above the level of the diaphragm and the intravenous nutrients were infused by this route. After 48 hours the condition of the infant was re-evaluated; if he still showed no evidence of idiopathic respiratory distress syndrome and if oral feeding could not be tolerated, a catheter was passed into the superior vena cava (see below) and intravenous alimentation was continued by this route.

Three patients in whom intravenous alimentation was started later in life, after unsuccessful attempts at oral feedings, had central venous catheters placed at that time.

Placement of catheter. A silicone catheter (inside diameter, 0.020 inch, outside diameter, 0.037 inch) was inserted into the internal jugular vein and threaded into the superior vena cava proximal to the right atrium. The catheter was secured within the vein with a fine silk ligature, with the distal segment being tunneled subcutaneously to
exit through the parietal scalp behind the ear where it was fixed in place with a nylon suture. Betadine ointment was applied to neck and scalp wounds after which they were covered by occlusal dressings. The position of the catheter in the superior vena cava was immediately verified by x-ray after the instillation of 2 c.c. of sterile contrast material.

In order to reduce the risk of infection, the scalp dressing, infusion line, and Millipore filter were changed every other day under strict aseptic conditions. The central venous catheter was used only for infusion of the alimentation fluid; it was never employed for the procurement of blood samples or for the administration of medications or transfusions.

**Infusate.** During the first 24 hours, the infusate generally contained 10 Gm. per kilogram of glucose and 2.5 Gm. per kilogram of a beef fibrin hydrolysate (Aminosol). The first three patients received 4.0 Gm. per kilogram of protein equivalent, but an adjustment in the protein concentration was made after observation of elevated levels of urea nitrogen in these patients. Electrolytes, calcium, inorganic phosphate, magnesium, and vitamins were added to each daily infusate as shown in Table II. The solution was initially infused at a rate of 100 ml. per kilogram per day and was progressively increased to 120 to 130 ml. per kilogram per day over the first 96 hours. The glucose content was gradually increased to 25 to 27.5 Gm. per kilogram per day in accordance with the patient's tolerance for glucose based upon serial urine and blood sugar determinations. The infusate was prepared daily in a laminar flow hood by a registered pharmacist under the direction of one of the investigators who carefully assessed the infant's clinical status and laboratory data before specifying the amount and the content of the next day's infusate. All fluids were administered at a constant rate which was maintained by a constant infusion pump. A 022½ Millipore filter was placed in the infusion line as a final filter for removal of debris or microorganisms.

**Monitoring.** Inexperience with the technique and lack of information regarding the metabolic responses of the premature infant necessitated frequent chemical monitoring; this was carried out using microchemical methods described previously. All urine and stool passed were saved and the nitrogen content determined by the micro-Kjeldahl method.

After the first two or three weeks of total intravenous alimentation, the clinical status of each infant was assessed with respect to feasibility and safety of oral feedings. When oral feedings were initiated, the intravenous alimentation solution was proportionately decreased and finally discontinued when adequate fluid and calories could be provided by the enteral feedings alone.

**RESULTS**

**Weight gain.** Table III shows the average daily weight gains over the entire course of total intravenous alimentation. With one exception, all patients gained weight ranging from 1.1 to 14.7 Gm. per day. The pattern of weight change was similar to that expected in conventionally managed infants with an initial weight loss followed thereafter by a persistent weight gain. But, as shown in Table III, the time required to regain initial body weight after institution of intravenous nutrition varied from four to eighteen days representing a significant improvement over that expected in conventionally managed infants of similar weights (Fig. 1). A significant fraction of this period (two to seven
Fig. 1. Weight curves of eight of nine infants (see Table I) who received intravenous alimentation compared to those of conventionally managed infants. (Case 5 is not shown since she died after only 5 days of alimentation.) The smooth, dashed lines represent predicted weight curves of Dancis and associates in groups of premature infants managed conventionally. The irregular, solid lines represent periods of intravenous alimentation. The interruptions in the solid curves represent periods of oral feeding.

Table III. Changes in body weight during total intravenous alimentation

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at onset (days)</th>
<th>Initial* weight (Gm.)</th>
<th>Time to regain initial weight (days)</th>
<th>Time to achieve &gt;100 Cal./Kg./day (days)</th>
<th>Duration of intravenous nutrition† (days)</th>
<th>Final body weight (Gm.)</th>
<th>Average changes in body weight (Gm./day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>850</td>
<td>5</td>
<td>2</td>
<td>16</td>
<td>1,020</td>
<td>10.6</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1,150</td>
<td>6</td>
<td>6</td>
<td>24</td>
<td>1,400</td>
<td>10.4</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>850</td>
<td>9</td>
<td>5</td>
<td>24</td>
<td>1,140</td>
<td>12.1</td>
</tr>
<tr>
<td>4‡</td>
<td>0</td>
<td>720</td>
<td>15</td>
<td>(20)</td>
<td>19</td>
<td>740</td>
<td>1.1</td>
</tr>
<tr>
<td>5§</td>
<td>2</td>
<td>660</td>
<td>—</td>
<td>—</td>
<td>5</td>
<td>580</td>
<td>-16.0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1,010</td>
<td>18</td>
<td>5</td>
<td>23</td>
<td>1,080</td>
<td>3.0</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>940</td>
<td>4</td>
<td>2</td>
<td>17</td>
<td>1,140</td>
<td>11.8</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>890</td>
<td>4</td>
<td>3</td>
<td>17</td>
<td>1,140</td>
<td>14.7</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>810</td>
<td>10</td>
<td>7</td>
<td>21</td>
<td>1,040</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*Weight at beginning of intravenous alimentation.
†Interval of total intravenous alimentation without supplemental oral feedings.
‡Patient died at 20 days and never achieved a caloric intake > 100 Cal. per kilogram per day but did achieve intakes of 80 to 90 Cal. per kilogram per day from Day 11 to Day 20.
§Patient died at 5 days and never achieved a caloric intake of > 100 Cal. per kilogram per day.

Gain in body weight averaging 15.5 Gm. per day (range of 11.0 to 19.3 Gm. per day), and all showed positive nitrogen balances averaging 0.23 Gm. per day (range of 0.20 to 0.28 Gm. per day).

Blood acid-base status. Nearly all infants developed a chronic respiratory acidosis, with plasma Pco₂ values above the upper limit of normal (taken as 42 mm. Hg). None of these acid-base changes was believed to be related to the infusate, but rather they were attributed to the pulmonary insufficiency which is commonly seen in such low-birth-weight infants.
Table IV. Body weight and nitrogen balance in five infants receiving total intravenous alimentation (> 100 Cal. per kilogram per day)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Weight* (Gm.)</th>
<th>Final weight (Gm.)</th>
<th>Duration† (days)</th>
<th>Average gain in body weight (Gm./day)</th>
<th>Average nitrogen balance (Gm./day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>800</td>
<td>1,020</td>
<td>14</td>
<td>15.7</td>
<td>+ 0.24</td>
</tr>
<tr>
<td>2</td>
<td>1,180</td>
<td>1,400</td>
<td>20</td>
<td>11.0</td>
<td>+ 0.28</td>
</tr>
<tr>
<td>3</td>
<td>780</td>
<td>1,140</td>
<td>19</td>
<td>18.9</td>
<td>+ 0.20</td>
</tr>
<tr>
<td>4</td>
<td>840</td>
<td>1,080</td>
<td>19</td>
<td>12.6</td>
<td>+ 0.22</td>
</tr>
<tr>
<td>5</td>
<td>850</td>
<td>1,140</td>
<td>15</td>
<td>19.3</td>
<td>+ 0.22</td>
</tr>
<tr>
<td>Averages</td>
<td>890</td>
<td>1,156</td>
<td>17.4</td>
<td>15.3</td>
<td>+ 0.23</td>
</tr>
</tbody>
</table>

*Weight at which caloric intake of > 100 Cal. per kilogram was established.
†Duration of intravenous alimentation after caloric intake > 100 Cal. per kilogram was established.

Infants. Because of rising plasma Pco₂, blood pH tended to fall initially with a subsequent rise to or toward normal. This secondary rise was reflected by a rising blood base excess resulting from renal compensation, since exogenous base therapy was not administered to any of these infants.

Plasma electrolytes. With few exceptions, the plasma sodium and potassium concentrations showed little variation from the expected values. In the few instances in which abnormal values were observed, appropriate readjustment of the electrolyte composition of the subsequent infusate was associated with prompt return to normal values.

As would be expected, a fall in the plasma chloride concentration was noted secondary to a rise in plasma bicarbonate concentration incident to renal compensation for the respiratory acidosis.

Blood glucose and urea nitrogen. Blood glucose and blood urea nitrogen values are plotted in Fig. 2. Five of the nine patients had hyperglycemic episodes on more than one occasion. These episodes were accompanied by glucosuria and, in two infants by an osmotic diuresis. Most such episodes occurred in the first ten days of total intravenous alimentation and were attributed to failure of the infants to adapt to the higher glucose concentrations. Two episodes occurred late in the course of total intravenous alimentation; these were related to unintentional increases in the infusion rates. Small doses of regular insulin (0.5 to 0.75 units) were given to three hyperglycemic patients with return of blood glucose values to normal within eight to twelve hours.

Blood urea nitrogen concentrations exceeding 20 mg. per 100 ml. occurred largely in the first week of intravenous alimentation and most often in infants receiving a protein concentration of 4.0 Gm. per kilogram per day. No value exceeding 50 mg. per 100 ml. was noted. In all instances, decreasing the protein content of the infusate was accompanied by a fall in blood urea nitrogen concentration.

Plasma total calcium and inorganic phosphorus concentration. Values for plasma total calcium and inorganic phosphorus are shown in Fig. 3. Infants who received both calcium and inorganic phosphate in the infusate (see Table II) maintained normal plasma values; however, two infants who inadvertently received no inorganic phosphate in their infusate developed hypercalcemia and hypophosphatemia. Deletion of calcium from the infusate did not alter these abnormalities, but addition of inorganic phosphate (2 mM. per kilogram per day) promptly corrected both abnormalities.

Complications. One infant died of Candida sepsis on the fifth day of infusion. The diagnosis was not suspected clinically; no evidence of oral moniliasis or monilial diaper dermatitis was noted ante mortem. This complication was the only one related to the presence of the indwelling catheter.

Metabolic complications were more frequent. Episodes of hyperglycemia occurring early in the course were more frequent during our earlier experience with these patients. Later, when more careful attention was paid to serial blood and urine glucose levels and when smaller incremental changes in car-
bohydrate concentration of the infusate were made, hyperglycemia occurred less frequently. Prevention of hyperglycemia obviously avoids the associated problems of osmotic diuresis and dehydration.

In three infants, histologic examination of the liver post mortem revealed evidence of cholestasis, extramedullary hematopoiesis, and steatosis. In one of these infants, hepatocellular degeneration and disruption of the architecture were observed. These pathologic changes have been previously described. Despite these findings, serial transaminase studies were normal in all these infants and there was no clinical evidence of jaundice or hepatomegaly. The precise relationship between these findings and the infusate are conjectural at the present time.

Two infants (Cases 2 and 9) had radiographic evidence of skeletal demineralization which was noted during the course of total intravenous nutrition. Neither infant had abnormal plasma concentrations of calcium or inorganic phosphorus. In both cases, earlier unsuccessful attempts at oral feeding without added vitamins had been tried. With vitamin D in the infusate at a level of 100 I.U. per day, these x-ray changes had reverted to normal by the termination of total intravenous alimentation.

**DISCUSSION**

Since recent evidence seems to indicate that there is a critical period of brain growth which is dependent upon optimal nutrition, the search for better means of guaranteeing early optimal nutrition of the low-birthweight infant is justified. Our results show that infants in whom total intravenous alimentation is started within the first 48 hours after birth can regain birth weight faster than expected. Furthermore, their subsequent growth, as measured by gain in body weight, is equivalent to, or in excess of, that observed...
in conventionally managed infants. Such preliminary results are encouraging, particularly if it can be shown that maturation of the brain of these infants proceeds optimally. Clearly long-term studies of neurologic, behavioral, and mental development are indicated. Such studies are in progress.

The probable quality of the weight gain observed in these infants can be inferred from the nitrogen balance data obtained in five infants. Since the deposition of 1 Gm. of nitrogen accounts for about 30 Gm. of lean body mass, the average nitrogen balance of 0.23 Gm. per day is equivalent to 6.9 Gm. of lean body tissue. The average weight gain of these infants was 15.2 Gm. per day; thus the remaining 8.3 Gm. must be explained. It is unlikely that all of this unexplained weight gain represents additional water; cumulatively, it would amount to about 150 Gm. of water (or about 15 per cent of body weight) over the entire period of intravenous alimentation and would have produced massive edema. Minimal, if any, edema was detected in this group. We conclude, therefore, that the weight gain not attributed to a change in lean body mass was due largely, if not entirely, to fat. This conclusion necessitates an average daily gain in fat of about 8.3 Gm., a figure which is relatively comparable to the estimated daily gain of fat cited by Fomon for his male reference infant.

It is generally believed that hypercapnia and/or acidemia exert a catabolic effect on nitrogen metabolism. To test this point, we compared the daily nitrogen balances of five patients with the daily values observed for blood pH and plasma Pco₂. Figs. 4 and 5 show that there was no clear relationship between the degree of either hypercapnia or acidemia and the degree of positive nitrogen balance achieved. Indeed, positive nitrogen balances were achieved despite Pco₂ values as high as 85 mm. Hg and blood pH values as low as 7.15.

The case of fatal Candida sepsis highlights the risk of infection with the technique of intravenous alimentation. It also points out that even with meticulous care of the catheter site and strict adherence to aseptic technique during preparation of the infusates, infection is an ever-present hazard. The over-all incidence of infection in this series (11 per cent) is considerably less than the 44 per cent which has been observed in the over-all published pediatric experience with intravenous alimentation. Such a high over-all average, however, should not lead to a premature abandoning of this promising new technique. In our total experience with 30 infants, the incidence of sepsis has been 6 per cent, and comparable records have been achieved by others who have assembled an extensively trained team highly committed to implementing this technique.
The number of metabolic complications was relatively high, but in no case were they serious. We attributed this result to the fact that our patients were closely monitored chemically and that rapid adjustments in the composition of the infusate could be made in accordance with feedback information obtained from such monitoring. However, it is reasonably certain that if monitoring were less frequent or if a “standard” mixture had been used for all patients, serious (perhaps even fatal) metabolic complications could have ensued.

Asymptomatic as well as symptomatic hyperammonemia has been reported in low-birth-weight infants receiving either protein hydrolysates or synthetic L-amino acid preparations. Possible mechanisms are discussed in more detail in the reports of Johnson and associates and Heird and associates. Blood ammonia levels were not measured in this study, but in the future they should be carefully monitored when either hydrolysates or synthetic amino acid preparations are used.

The findings of this study, although highly preliminary, are encouraging. In contrast to the opinion of others, this study shows that the intrinsic hazards of the technique can be reduced to a level whereby further controlled clinical investigation can be justified. The results further show that the low-birth-weight infant can readily metabolize the infusate without serious variations in plasma electrolyte concentration, blood acid-base status, plasma calcium and inorganic phosphorus concentrations, or blood glucose and urea nitrogen levels. Clearly, however, many other questions must be answered before the technique of intravenous alimentation can be recommended unconditionally for routine use in the care of low-birth-weight infants.

REFERENCES


