Nitrogen Balance in Patients Receiving Either Fat or Carbohydrate For Total Intravenous Nutrition

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Eighteen pre and/or postoperative patients underwent TIN using either fat or carbohydrate as a caloric substrate source for a similar period. Positive nitrogen balance was achieved with either solution for an equal number of days when balance studies were complete. Both groups demonstrated weight gain but it was more marked in the carbohydrate TIN group. One patient in the carbohydrate TIN group was changed to Intralipid because of a catheter related complication. This patient continued to show positive nitrogen balance while on Intralipid. There were 4 deaths in the 18 patients unrelated to TIN. It is concluded that Intralipid, when given through a peripheral vein with a nitrogen source, can produce positive nitrogen balance and is a safe and effective means for doing this.

TOTAL INTRAVENOUS NUTRITION (TIN) for critically ill patients has become accepted and has been a lifesaving treatment in many cases. We recently reported our retrospective study of patients receiving hypertonic carbohydrate as calories for TIN.[20] Because the use of hypertonic carbohydrate and central venous catheters was associated with a significant number of complications, we proposed a study in which alternate candidates for TIN were administered either intravenous fat through a peripheral vein or hypertonic carbohydrate through a central venous catheter.

Submitted for publication April 29, 1975.

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Materials and Methods

Between October 1972 and June 1973 18 (5 men, 13 women) pre and/or postoperative patients, ages 24 to 73, required management with TIN. TIN was instituted in patients with intestinal fistula, ulcerative colitis, carcinoma, pulmonary insufficiency, intestinal malabsorption, chronic intestinal obstruction, and chronic pulmonary and heart diseases who were unable to sustain adequate enteral caloric intake and had a prolonged illness which required nutritional support. Patients were alternately assigned to the fat or carbohydrate group.

The 25% carbohydrate solution used in this study contained 16.5% glucose and 8.3% fructose. This solution supplies 1,000 non-protein calories per liter, is very hypertonic, and must be administered through a central venous catheter. Silicone catheters were inserted with strict aseptic technique and were used only for TIN infusion. The entry site was cleaned daily with Betadine and covered with Betadine ointment and a sterile dressing. The entire infusion set was changed daily. Carbohydrate infusions were always given by IVAC* pump continuous infusion through a 0.22 mμ filter. Urine glucose was

*IVAC Corporation, San Diego, California measured every 6 hours, blood glucose daily, and serum electrolytes daily in patients receiving carbohydrate TIN.

The fat solution, Intralipid,* contained 10% triglyceride derived from soy bean oil with an emulsifier (1.2% egg yolk phospholipid) and 2.5% glycerol. This isotonic solution was infused simultaneously with an equal volume of 5% Dextrose, 5% protein solution (Travamin†) so the final concentration was effectively 5% triglyceride and 2.5% Dextrose which supplies 650 non-protein calories/l. The Intralipid and Travamin solutions were given with separate IVAC pumps through a common intravenous line or through separate peripheral vein sites.

The protein source for both groups was 5% casein hydrolysate, administered with a final concentration of 33.3 gm of casein hydrolysate per liter (approximately 6.85 gm nitrogen per liter). In some instances 8.5% amino acid (Freamine§) solution was substituted for the casein hydrolysate. The solutions were infused to achieve 1,000–2,000 non-protein calories/M^2/day. The Intralipid dose was never more than 4 gm/kg/24 hours.

Patients were weighed daily and 24-hour urine collected for total nitrogen which was determined by the Kjeldahl technique. Balance studies were done only during the period of intravenous nitrogen administration and discontinued when there was oral intake. Blood levels of triglyceride, electrolytes, glucose, hematocrit, prothrombin, and platelet counts were serially monitored. Fluid intake and output was measured daily.

Results

Positive nitrogen balance was achieved with both carbohydrate and fat as caloric source, open wounds and incisions healed well in both groups, and 14 patients survived.

Patients in the carbohydrate group received 1,168 calories/M^2/24 hours (average) for 15.6 (6-35) days (average). The mean body surface area was 1.70 M^2 (1.22—2.28) and the amount of nitrogen given was 5–7 gm/M^2/24 hours. The mean weight gain in this group was 3.3 kg (Fig. 1). There was a total of 115 (115/156, 73%) days of accurate and complete nitrogen balance studies and there were 94 (94/115, 82%) days of positive nitrogen balance recorded. The average total fluid intake was 2,692 cc and urine output was 1,897 cc.

Patients in the Intralipid group received 979 calories /M^2/24 hours for an average of 15.1 (4–38) days. The mean body surface area was 1.81M^2 (1.40–2.24) and the amount of nitrogen given was 5–7 gm/M^2/24 hours. The

*Intralipid, (Manufactured by Vitrum Co., Stockholm, Sweden) generously supplied by the Cutter Laboratories, Berkeley, California.

†Travenol Co., Morton Grove, Illinois

§McGaw Laboratories, Glendale, California

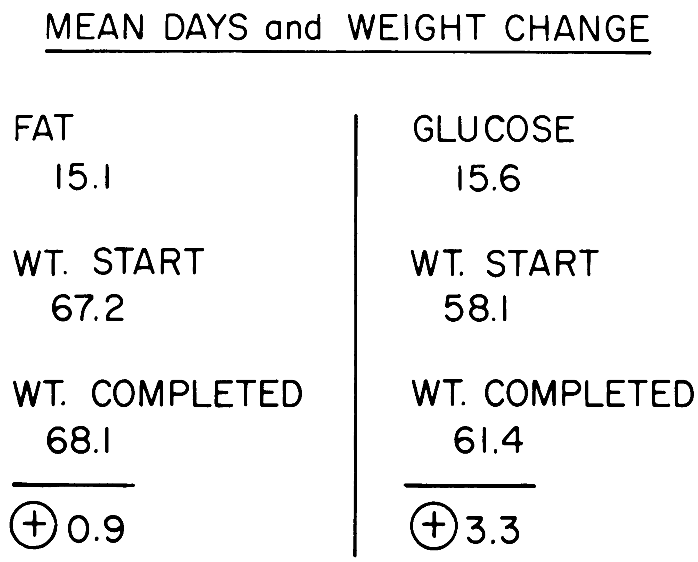

FIG. 1. Weight change in patients receiving either fat or carbohydrate total intravenous nutrition.

mean weight gain in this group was 0.9 kg (Fig. 1). There was a total of 110 (110/151, 72%) days of accurate and complete balance studies and positive nitrogen balance was recorded in 98 (98/110, 89%) days. The average total fluid intake was 3,858 cc and urine output averaged 2,634 cc.

A total of 10 patients in each group received either hypertonic carbohydrate or Intralipid. The hypertonic solution was discontinued in one patient because of a catheter related septicemia and Intralipid was given through a peripheral vein. In a second patient Intralipid was given postoperatively whereas hypertonic carbohydrate had been given preoperatively. Further use of a central venous catheter was thereby avoided since the patient had other septic complications.

Four of the 18 patients studied died from causes unrelated to TIN. No hyperosmotic coma syndromes occurred. Three patients in the carbohydrate group developed catheter-related septicemia and one of these was changed to Intralipid. Three patients in the Intralipid group developed superficial phlebitis. In one case the Travamin and Intralipid solutions were given through separate intravenous sites and phlebitis developed in the arm where Travamin was being administered. No phlebitis occurred at sites where Intralipid alone was infused. There was no catheter related septicemia in the Intralipid group, nor were there any complications with hypertriglyceridemia. Triglyceride levels in most cases ranged between 200 and 300 mg% and there was no evidence of coagulation disturbance or electrolyte imbalance. There was no unexplained anemia or fever.

Fig. 2 shows the balance study of a 51-year-old man who underwent a Bilroth I anastomosis with subsequent

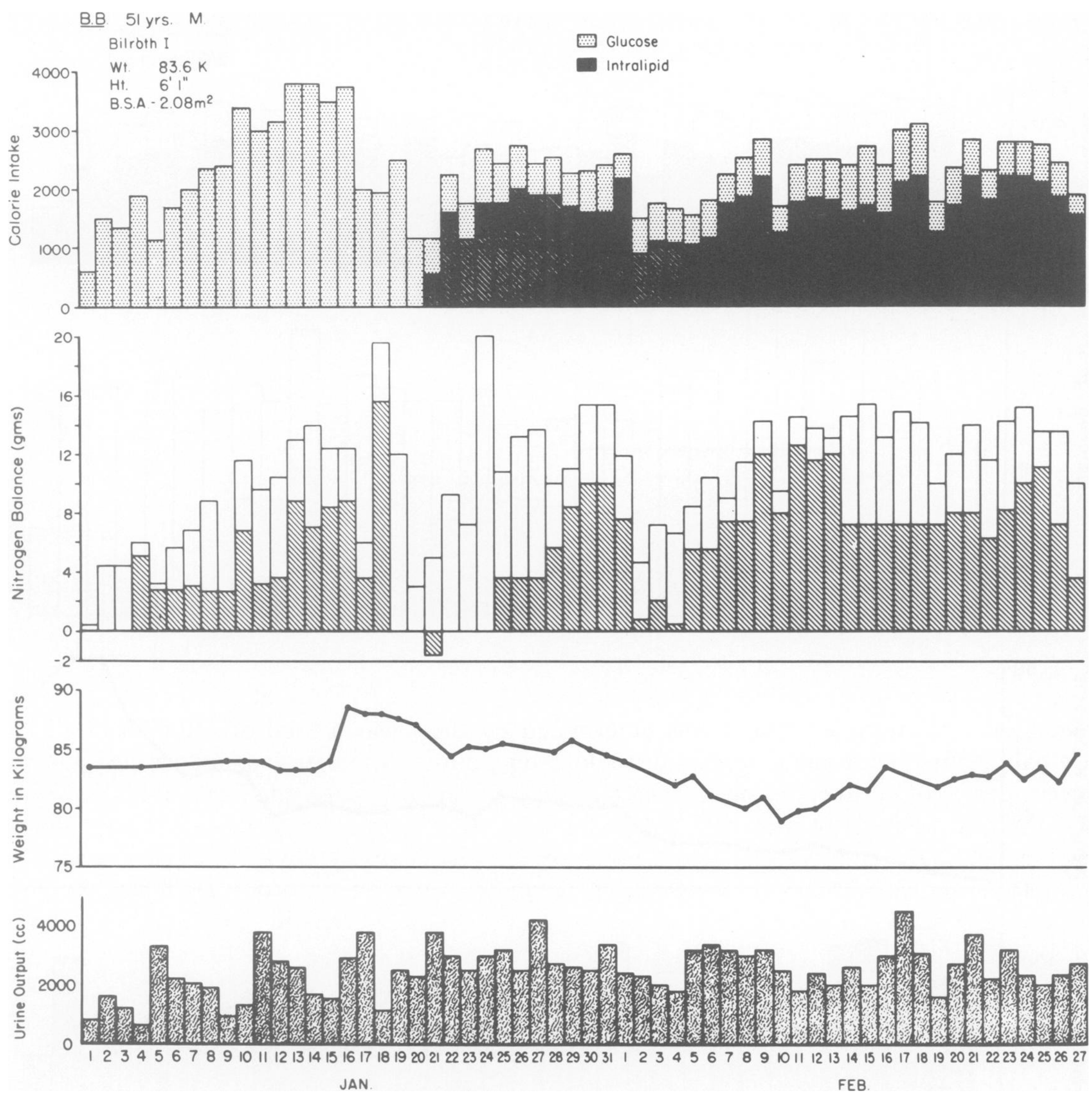

FIG. 2. Total intravenous nutrition in a patient who received carbohydrate then was changed to fat because of a septic central venous catheter.

wound dehiscence and gastroduodenal fistula. The patient initially received carbohydrate TIN for a total of 20 days when he had a catheter related septicemia. The catheter was removed and Intralipid was administered through a peripheral vein. His course following the change from carbohydrate to fat with some additional glucose resulted in positive nitrogen balance without significant weight gain, healing of his dehiscence, and near closure of his fistula. He subsequently underwent serosal patch closure of the fistula and is well.

Fig. 3 shows the course of a patient who received fat TIN for nearly 5 weeks. This patient had the Guillian-Barré syndrome as well as severe mitral stenosis which required an emergency valvuloplasty. Postoperatively, he developed pulmonary insufficiency and pneumonia which required prolonged ventilator support. He could not tolerate nutrition through a nasogastric tube because of chronic intestinal obstruction due to Crohn's disease. The patient was in positive nitrogen balance during the period of TIN and had a steady weight gain which was not associated with excessive positive fluid balance. Despite receiving TIN for 5 weeks he died from *Klebsiella* pneumonia and post-mortem examination of histologic sections of his liver, lung, and cardiac tissue revealed *Candida albicans*.

Discussion

Although hypertonic glucose solutions have been given safely to large numbers of patients in training institutions where a real effort is made to standardize administration of the solutions, these results are not always achievable in smaller hospitals without house staff and trained nursing personnel.[15,16] Hypertonic carbohydrate TIN can be life-saving which justifies the significant rate of major complications. Our initial enthusiasm for carbohydrate TIN was somewhat dampened by the numbers of compli-

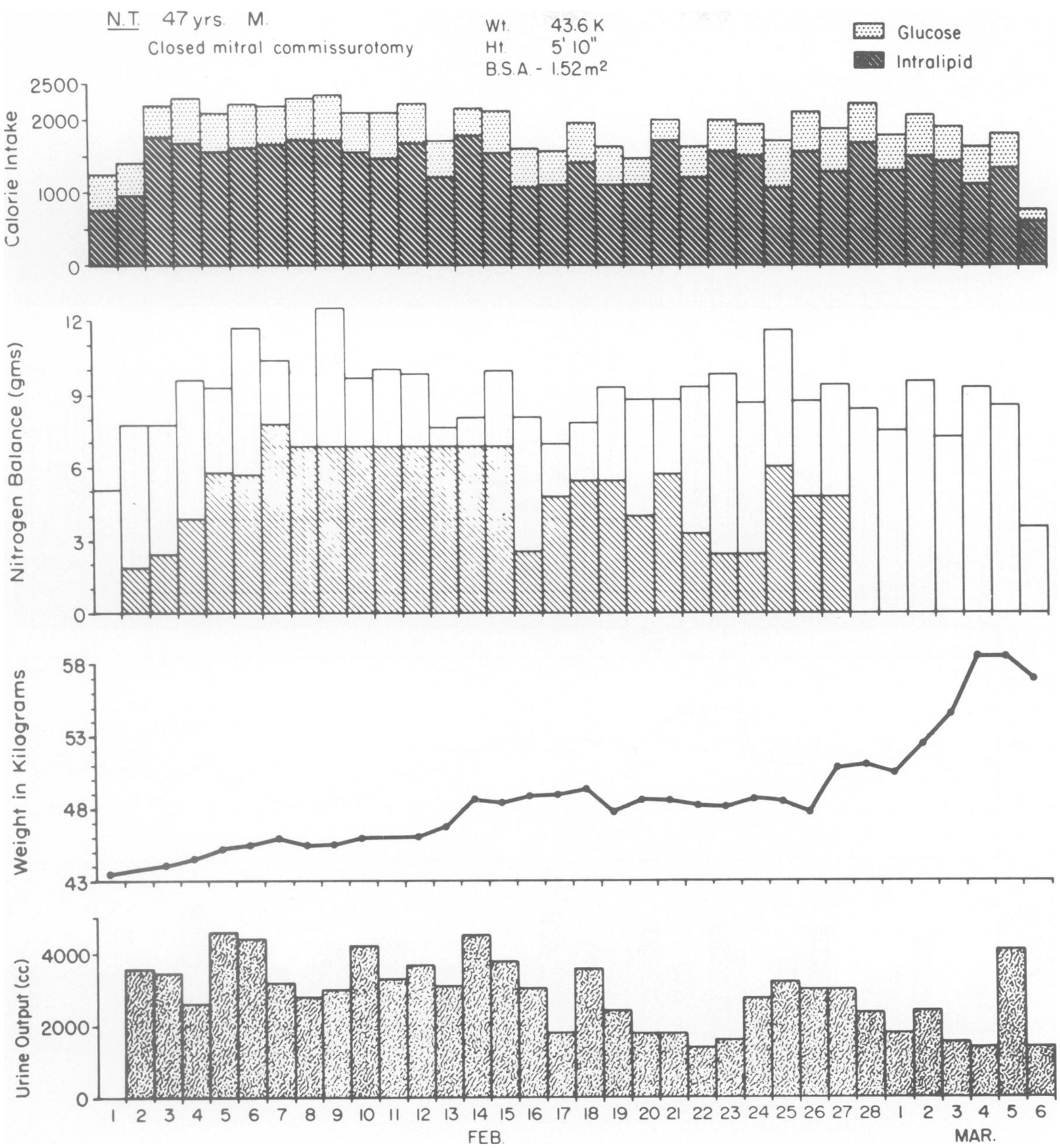

FIG. 3. Nitrogen balance in a patient receiving fat as his primary source of calories. Weight gain was gradual and positive nitrogen balance achieved.

cations related to catheters and carbohydrate metabolism,[20] and this stimulated us to look at other agents which might provide calories with fewer side effects.

Intralipid has been used for TIN in Europe and Canada for 10 or more years, and despite its administration to thousands of patients there have been few reported complications.[12] The fat overloading syndrome and febrile responses seen with other fat emulsions have not been encountered with Intralipid.[5,6,12,18] The effectiveness of TIN can be measured by survival and healing, nitrogen balance, weight gain, and calorie balance. Positive nitrogen balance with glucose TIN was sporadically achieved prior to 1968[13] but Dudrick et al.[7] proved the solutions practical and could consistently demonstrate positive nitrogen balance. Their work has been corroborated by many others.[13,19,20]

Although individual complications of carbohydrate TIN have been reported,[9,10] few authors have documented the complication rate for a consecutive series of patients. Septic complications have ranged from as low as 6% to a high of 27%.[11] These complications can be minimized by scrupulous aseptic technique in preparation of solutions and insertion and maintenance of catheters, filters, and intravenous equipment. We have found that hypertonic carbohydrate solutions must be given through silicone central venous catheters with the tip near or at the right atrial junction with the superior vena cava in order to prevent serious complications such as superior vena caval thrombosis or subclavian vein thrombosis. We have two cases of documented pulmonary emboli related to superior vena caval thrombosis in patients receiving carbohydrate TIN. We also have had a case of candida aortitis requiring aortic valve replacement in a patient who was on long-term carbohydrate TIN.[10] Beyond catheter problems is the frequent requirement for blood studies to monitor glucose as well as electrolytes. Urine samples must be tested for sugar to avoid serious glycosuria and the development of hyperosmotic coma. Patients receiving carbohydrates may require insulin because of overt or occult diabetes mellitus, insulin resistance, or the acquired diabetes mellitus seen during prolonged illness or severe trauma. None of these problems with the use of hypertonic carbohydrate in selected patients, however, outweigh the advantages.

Weight gain is another parameter for comparing caloric substrates during periods of TIN. In this study patients who received hypertonic carbohydrate had a greater weight gain than those receiving Intralipid. More calories were administered to the carbohydrate group with less fluid intake and less positive water balance. Bernard and Stahl have pointed out that weight gain may be an unreliable indicator of positive nitrogen balance and protein synthesis. Our data suggests that the greater weight gain in the carbohydrate group was due to infusion of calories in excess of actual requirement, which requires calorimetry for documentation. Caloric balance studies using indirect calorimetry are currently underway and nutritional management based on caloric consumption has proved extremely valuable in our experience.[1]

Positive nitrogen balance has been recorded in a variety of clinical conditions using intravenous fat as the primary source of calories.[2,5,6,12,14,17,18] Whether enough calories can be provided by intravenous fat as the sole source of calories in patients with large caloric demands has not been fully documented. Wilmore et al.[18] recently reported positive nitrogen balance in burn patients where 38% of the total calories were provided by Intralipid. There may be a theoretical or real limitation to the amount of fat which can be assimilated and used for calories during any given period of time.[14] In this study the limitation of 4 gm/kg/24 hours of fat was arbitrary, and perhaps more fat than this can be safely tolerated. In most cases only 1–3 gms of fat/kg/24 hours was administered but this was enough to produce positive nitrogen balance and hypertriglyceridemia was not seen.

Studies by Blackburn et al.[4] have indicated that positive nitrogen balance can occur by giving nitrogen and allowing the patient to use his own endogenous calories. In those patients who need both calories and nitrogen, however, fat appears to have many advantages over carbohydrates. We could not document any complications related to the fat solution. One patient (Case 1) who received Intralipid died and post-mortem examination showed some inclusion bodies in the Kupffer cells of the liver, not associated with abnormal liver function studies and did not contribute to his death. These inclusion bodies have been described by Hallberg[12] and their significance, if any, is not certain. Intralipid has marked advantages in ease of administration and eliminates the problem of frequent testing of urine and blood glucose. Proper positioning and adjustment of central venous catheters and extreme caution in aseptic techniques around the catheter when carbohydrate solutions are used all add up to time and effort by nurses and housestaff personnel. The difference between the solutions are shown in Table 1.

TABLE 1.

Intralipid	Carbohydrate
Advantages	*Advantages*
1. Peripheral IV (rapid infusion were tolerated)	1. 1 cal/cc
2. Isotonic	2. Readily available
3. Sterile, ready for infusion without mixing	3. Large calorie infusion
4. No metabolic complication	
Disadvantages	*Disadvantages*
1. Less than 1 cal/cc (when combined with nitrogen)	1. Hypertonic
2. Limited availability in USA	2. May require exogenous insulin
3. Limited calorie infusion	3. Central venous catheter required
	4. Frequent urine and serum monitor of glucose
	5. Mixing with nitrogen solutions prior to administration
	6. Filter and pump required (rapid infusion may be lethal)
Complications	*Complications*
1. Candida infection possible	1. Hyperosmotic acidosis and coma
2. Superficial phlebitis possible	2. Catheter related thrombosis
	3. Septicemia from contamination of fluid, tubing, or catheter

Bacteriologic studies in our laboratory have shown that Intralipid inhibits the growth of staphylococcal and gram negative organisms much the same as other intravenous solutions. However, *Candida albicans* does grow in the Intralipid solution and this may prove to be a problem if careful aseptic techniques are not used in its administration.

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