

Total Parenteral Nutrition: The Long and The Short of It

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Introduction

Within 30 years of Harvey's discovery of the circulatory system, attempts were made to utilize intravenous routes for nutrient administration.¹ In 1656, Sir Christopher Wren infused wine into the veins of dogs via goose quills attached to a pig's bladder. Over the ensuing years, salt and sugar solutions, milk, olive oil, egg whites, and in later times, protein hydrolysates were tried with varying degrees of success. However, it was not until the 20th century that total parenteral nutrition (TPN) began to be viewed as a realistic therapeutic modality, stimulated by Wilmore and Dudrick's report of normal growth in a young infant with extensive intestinal atresia who was successfully maintained on intravenous nutrition for over 6 weeks.² Since then, there have been many advances and refinements, including the development of specialized crystalline amino acid solutions and lipid emulsions. Further investigation is currently underway to determine the effect of "medical foods", i.e., specialized nutrients targeted for specific purposes, e.g., glutamine for immunomodulation and intestinal mucosal preservation.^{3,4}

TPN is now commonly used for providing nutritional support in a variety of conditions associated with intestinal dysfunction or other causes of inability to provide adequate enteral nutrition. However, with time and experience, the initial enthusiasm for this method has been tempered by the realization that bypassing the gastrointestinal tract during delivery of nutrients is unphysiological and may have various side effects. The 2 most concerning clinical entities are TPN-associated liver dysfunction and metabolic bone disease.

Hormonal Effects

Extrauterine existence is characterized by intermittent feeding and fasting. Food intake usually occurs during wakefulness, fasting during sleep. These feed-fast and wake-sleep pattern are associated with secretory rhythms of various circulating hormones.⁵

Continuous or cycled night-time infusion of nutrients, as well as the types of nutrients infused, have been shown to cause hormonal perturbation, most notably a hyperinsulinism⁶ and suppression of growth hormone.⁷ The significance of these effects is controversial in view of the well-documented success of TPN in reversing growth failure.

Intestinal Effects

The absence of enteral feeding is associated with a number of effects upon the gastrointestinal tract.⁸ The etiology of these effects is probably multifactorial, involving lack of postprandial exposure to local mechanical stress, luminal dietary nutrients and trophic factors. Nutrients in the gut stimulate trophic pancreatic/ biliary secretions, gut hormones and neurovascular reflexes. In animals, TPN was associated with a fairly rapid onset of small intestinal hypoplasia⁹ and decreased disaccharidase activities.¹⁰ These adverse effects or secretin.¹² Colonic mucosal atrophy has also been described.⁸

In the human, perturbations due to TPN are particularly evident during early development. Plasma concentrations of various gut hormones (including gastrin, cholecystokinin, secretin, gastric inhibitory peptide, neurotensin motilin, and enteroglucagon) were decreased in preterm infants who had never received enteral feedings.^{13,14} Longitudinal manometry demonstrated that the development of mature intestinal motility patterns in the very premature infant is delayed by lack of enteral intake.¹⁵ TPN without enteral feeding results in impaired intestinal mucosal growth, as well as biochemical and functional maturation.¹⁶ These findings are reversible with even small amount of enteral feedings. In adults, intestinal hypoplasia appears to be variable, but decreased disaccharidase activity has been reported.¹⁷

Exocrine Pancreatic Effects

The exocrine pancreas is strongly stimulated by digestion products of proteins and fats. Animal studies have reported conflicting effects of intravenously administered amino acids and fatty acids upon the pancreas. However, exocrine pancreatic function in the human does not appear to be stimulated significantly by TPN,⁸ which is proven to be useful in the treatment of pancreatitis. The long term implications need to be clarified.

Hepatobiliary Effects

Biliary "sludge" and gall stones have been reported in both children¹⁸ and adults^{19,20} on TPN, suggesting bile stasis. TPN-associated cholestasis was initially observed in a preterm infant who exhibited cirrhosis, bile duct proliferation and centrilobular cholestasis at the time of death after 71 days of TPN.²¹ Since then, numerous reports have appeared describing an association between TPN and cholestatic liver disease. The incidence has varied from 7-57%.²² Although found in both children and adults, it is most commonly a disease of infants increasing in frequency with decreasing gestation age and birth weight and with increasing duration of therapy.²³ The etiology is probably multifactorial (Table 1).^{22,24}

Although none of the factors listed in Table 1 have been confirmed as causal factors, a reasonable working hypothesis might involve hepatocytes various hepatotoxic insults, e.g. poorly metabolizable amino acids, secondary bile acids, bacterial endotoxins, and slowly develop hepatic damage. The diagnosis is one of exclusion in an individual with conjugated hyperbilirubinemia who has received TPN for more than a week. Elevated total serum bile acids or cholic acid conjugates, gamma-glutamyl transpeptidase or 5'-nucleotidase have been suggested as early indicators.²⁵ Serum transaminases and alkaline phosphatase may be less valuable due to non-specificity and late occurrence. Evidence of compromised hepatic function, e.g. decreased serum albumin, prolonged prothrombin time, and also hyperammonemia are signs of impending hepatic failure.

Characteristic but no-specific histologic signs include canalicular, hepatocyte and Kupffer cell cholestasis, bile duct proliferation, periportal inflammation and/or portal fibrosis. Treatment of choice is prevention by limitation of TPN duration, aggressive institution of enteral nutrition, avoidance of hypercaloric alimentation, use of infant-adapted (taurine-supplemented) amino acid solutions. Abnormal liver function is indication for discontinuing parenteral and instituting enteral nutrition. This usually results in rapid improvement. If TPN cannot be stopped, efforts should be made to avoid hypercaloric intake, undertake TPN cycling,²⁶ and initiate low-dose enteral feedings. Treatment of bacterial overgrowth²⁷ may be helpful in infants with short gut syndrome. Supplementation of TPN to intake have been suggested. Choleric agents such as phenobarbital, ursodeoxycholic acid as well as cholecystokinin analogues have also been used.²⁸⁻³⁰ Infants with short gut syndrome have the highest risk for progression to end-stage liver disease.

Bone Effects

Metabolic bone disease is a well-recognized complication of long term (months to years) parenteral nutrition in both children and adults.³¹⁻³⁴ In children, it is often diag-

Table 1. Risk factors for the development of TPN-associated cholestatic liver disease

General risk factors	Effects
<ul style="list-style-type: none"> ▪ Prematurity ▪ lack of enteral feeding ▪ sepsis ▪ short gut ▪ lithocholic acid ▪ gut motility, 	<ul style="list-style-type: none"> hepatobiliary immaturity bile flow, gut motility bile flow bacterial overgrowth gut inflammation, surgery bacterial overgrowth
Potentially toxic factors in TPN	
<ul style="list-style-type: none"> ▪ improper dextrose load ▪ hypercaloric alimentation ▪ amino acids ▪ trace minerals (Cu,Mn,W) 	<ul style="list-style-type: none"> bile flow hepatic dysfunction bile flow, e.g. sulfur-cont,aromatic hepatotoxicity hepatotoxicity
Potential deficiencies with TPN	
<ul style="list-style-type: none"> ▪ taurine ▪ choline ▪ carnitine ▪ selenium ▪ molybdenum 	<ul style="list-style-type: none"> abnormal bile acid conjugation steatosis in rats fatty acid oxidation,detox. ofacyl groups detoxification of oxygen radicals detoxification of sulfur-containing a. acids

nosed by serial biochemical (alkaline phosphatase) or roentgenographic examination (osteopenia, rickets, fractures) as well as by clinical evidence of fractures. In adults, chief complaints include back pain, periarticular cone pain and fractures. Paradoxically, the condition is most apparent as nutritional status improves, i.e. during weight gain and "catch-up" growth. The exact frequency is unknown but the entity appears to be quite common with prolonged TPN. The etiology is unclear although a number of potential factors have been identified (Table 2). In premature infants, the major issue is clearly one of inadequate provision of calcium and phosphate. It is difficult to duplicate the efficiency of the human placenta as a delivery system. many of these infants receive chronic diuretic therapy, e.g., furosemide, that leads to Table 2. Factors implicated in metabolic bone disease^{31,33,34} increased urinary loss of calcium. In adults, there are more questions than answers due to the multiplicity of confounding factors. In particular, early problems with aluminum toxicity have muddled the picture. It is unclear whether bypassing the normal intestinal regulation of calcium/ phosphate homeostasis and providing a continuous influx of calcium and phosphate leads to metabolic bone disease.

Table 2. Factors associated with bone alterations in chronic TPN

Inadequate supply of calcium and phosphorus

- requirements of preterm infants
- limited solubility in TPN solutions
- inappropriate calcium/phosphorus ratio

Increased urinary calcium loss

- volume expansion (cyclic TPN)
- amino acid intake
- calcium intake
- inadequate phosphate intake
- aluminium toxicity
- chronic diuretic therapy (e.g. furosemide)

Increased urinary phosphate loss

- glucose intake
- phosphate intake

Effects on bone matrix formation/bone mineralization

- ammonium toxicity (contaminant of minerals, casein hydrolysate)
 - exaggerated in face of renal impairment
 - sensitivity to exogenous Vit D?
 - other factors?
 - high dose heparin
 - acetate
 - metabolic acidosis
 - unknown micronutrients?
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Renal Effects

Although short-term TPN has been shown to increase creatinine clearance,³⁵ disturbing data has recently been reported concerning impaired renal function in both children³⁶ and adults³⁷ on long-term TPN. Creatinine clearance decreased between 0.6%-15.4% in 29 out of 33 adult TPN patients on long term TPN (duration: 8.3±4.4 years; >70% of nutrition needs); Average rate of decline was 3.5% per year. The decrease of glomerular filtration rate was greater than that expected for age in patients who had received TPN >10 years. Tubular reabsorption of phosphate was impaired in 52% of subjects and correlated with glomerular filtration rate and estimated creatinine clearance. These decreases in glomerular and tubular function could not be totally ex-

plained by advancing age, nephrotoxic drug use or septic episodes and appeared to be unrelated to intravenous amino acid intake. The authors speculate that acid loading from TPN may play a role. The etiology is unclear at this time.

References

1. Rhoads JE, et al. History of intravenous nutrition. In: Rombeau JL, Caldwell MD, eds. Parenteral nutrition. Philadelphia: Saunders, 1986;1-8.
2. Wilmore DW, Dudrick SJ. Growth and development of an infant receiving all nutrients exclusively by vein. *J Am Med Assoc* 1968; 203:860.
3. Ziegler TR et al. Glutamine-enriched parenteral nutrition increases circulating lymphocytes after bone marrow transplantation. *J Parent Ent Nutr* 1994;18: 17S (Abstr).
4. van der Hulst RWJ, et al. Glutamine and the preservation of gut integrity. *Lancet* 1993; 341:1363-1365.
5. Voorhess ML. Hormone patterns and parenteral nutrition. In: Leberthal E, ed. Total parenteral nutrition: indication, utilization, complications and pathophysiological considerations. Raven Press, New York, 1986; 141-54.
6. Ricour C, et al. Hormonal adaptation in infants on total parenteral nutrition. *Acta Chir Scand Suppl* 1976;166:112-3.
7. Tulikuora I. Hormonal changes in catabolic patients during parenteral nutrition. *Scand J Clin Lab Invest* 1982;42: 19-26.
8. Rossi TM. Effects of total parenteral nutrition on the digestive organs. In: Leberthal E, ed. Total parenteral nutrition: indications, utilization, complications and pathophysiological considerations. New York: Raven Press, 1986; 173-184.
9. Heird WC, et al. Comparative effects of total parenteral nutrition, oral feeding and starvation on rat small intestine. *Pediatr Res* 1974;8:107.
10. Levine GM, et al. Role of oral intake in maintenance of gut mass and disaccharidase activity. *Gastroenterology* 1974; 67:975-82.
11. Johnson LR. et al. Action of gastrin on gastrointestinal structure and function. *Gastroenterology* 1975;68:1184-92.
12. Hughes CA, et al. Cholecystokinin and secretin prevent the intestinal mucosal hypoplasia of total parenteral nutrition in the dog. *Gastroenterology* 1978;75: 34-41.
13. Lucas A, et al. Metabolic and endocrine consequences of depriving preterm infants of enteral nutrition. *Acta Paediatr Scand* 1983;72:245-9.
14. Berseth CL. Effect of early feeding on maturation of the preterm infant's small intestine. *J Pediatr* 1992;120:947-53.
15. Berseth CL, Nordyke C. Enteral nutrients promote postnatal maturation of intestinal motor activity in preterm infants. *Am J Physiol* 1993; 264:G 1046-51.
16. Jackson WD, Grand RJ. The human intestinal response to enteral nutrients. *J Am Coll Nutr* 1991;10:500-9.
17. Guerdon C, et al. Decreased brush border hydrolase activities without gross morphological changes in human intestinal mucosa after prolonged total parenteral nutrition of adults. *Gastroenterology* 1986;90:373-8.

18. Roslyn JJ, et al. Increased risk of gall stones in children receiving total parenteral nutrition. *Pediatrics* 1983;71:784-9.
19. Messing B, et al. Does total parenteral nutrition induce gallbladder sludge formation and lithiasis? *Gastroenterology* 1983;84:1012-9.
20. Roslyn JJ, et al. Gall bladder disease in patients on long-term parenteral nutrition. *Gastroenterology* 1983; 84:148-54.
21. Peden VH, et al. Total parenteral nutrition. *J Pediatr* 1971;78:180-1.
22. Sandler RH, Kleinman RE. Cholestasis associated with parenteral nutrition. In: Walker WA, Durie PR, Hamilton JR, Walker-Smith JA, Watkins JB, eds. *Pediatric gastrointestinal disease*. BC Decker Inc., Philadelphia, 1991;1065-74.
23. Beale EF et al. Intrahepatic cholestasis associated with parenteral nutrition in premature infants. *Pediatrics* 1979;64: 342-7.
24. Balistreri WF, et al. Bile acid metabolism, total parenteral nutrition and cholestasis. In: Lebenthal E, ed. *Total parenteral nutrition: indications, utilization, complications and pathophysiological considerations*. Raven Press, New York, 1986;319-34.
25. Whittington PF. Cholestasis associated with total parenteral nutrition in infants. *Hepatology* 1985;5:693-6.
26. Collier S, et al. Use of cyclic parenteral nutrition in infants less than 6 months of age. 1994; *Nutr Clin Pract* 9: 65:8.
27. Capron JP, et al. Metronidazole in prevention of cholestasis associated with total parenteral nutrition. *Lancet* 1983;1:446-7.
28. South M, King A. Parenteral nutrition-associated cholestasis: recovery following phenobarbitone. *J Parent Ent Nutr* 1987; 11:208-9.
29. Sandler RH, et al. Use of ursodeoxycholic acid (UDCA) for children with severe liver disease from total parenteral nutrition: report of 3 cases. *Pediatr Res* 1989;25:124 (Abstr).
30. Schwartz JB, et al. Ceruletide to treat neonatal cholestasis *Lancet*. 1988;1:1219-20.
31. Klein GL, Chesney RW. Metabolic bone disease associated with total parenteral nutrition. In: Lebenthal E, ed. *Total parenteral nutrition: indications, utilization, complication and pathophysiological considerations*. Raven Press, New York, 1986; 431-3.
32. Saitta JC, et al. Metabolic bone disease in adults receiving long-term parenteral nutrition: longitudinal study with regional densitometry and bone biopsy. *J Parent Ent Nutr* 1993; 17:214-9.
33. Koo WWK. Parenteral nutrition-related bone disease. *J Parent Ent Nutr* 1992; 16:386-94.
34. Klein GL, Coburn JW. Parenteral nutrition: Effect on bone and mineral homeostasis. 1991;11:93-119.
35. Graf H. et. al. Effect of amino acid infusion on glomerular filtration rate *N Engl J Med* 1983; 308:159-60.
36. Moukarzel A, et al. New complication of long term parenteral nutrition (PN): Impairment of renal function. *Pediatr Res* 1990;27:111A.
37. Buchman AL, et al Serious renal impairment is associated with long-term parenteral nutrition. *J Parent Ent Nutr* 1993; 17:438-444.