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Monitoring and Complications of Parenteral Nutrition

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ABSTRACT

A knowledge of the complications of parenteral nutrition is inherent in the design of any monitoring system. In the initial stages of therapy, the complications are usually of electrolyte imbalance. It must also be appreciated that the provision of nutrition to severely malnourished patients will expose underlying deficiencies, particularly of phosphates and trace elements. In long-term parenteral nutrition, the complications can be broadly divided into those associated with the line and metabolic complications. The line complications include: line blockage, sepsis, and pulmonary embolism. The most important metabolic complication is undoubtedly liver cholestasis, which may be associated with recurrent episodes of sepsis. Any department undertaking long-term parenteral nutrition should have an active nutrition team to avoid complications and audit outcome. *Nutrition* 1998;14:806–808. ©Elsevier Science Inc. 1998

Key words: total parenteral nutrition, cholestasis, pulmonary embolism, line sepsis

INTRODUCTION

Parenteral nutrition (PN) is an essential support for intestinal failure, providing nutrition either for an acute episode or as a long-term therapy, particularly in the management of the short-gut syndrome. PN in this type of patient is increasingly being provided at home. This form of nutrition is totally artificial and, therefore, requires close monitoring and an awareness of the possible complications that may arise. The protocols for monitoring differ according to the duration of the therapy and also to a certain extent upon the disease process itself. Any additional drug therapy may also alter the biochemistry, for example, in the case of cyclosporin where magnesium levels are usually low and need to be replaced in order to prevent toxicity, and with amphotericin, which is associated with an increased renal tubular loss of potassium. Therefore, although it is important to have protocols for the monitoring of PN, they need to be flexible enough to adapt to individual clinical needs and to be constantly reviewed in the case of long-term treatment as we become aware of new complications.

At the start of PN therapy the metabolic monitoring will depend on both the child's current nutritional status and the underlying condition. Malnutrition, particularly if this is long term, will result in depletion of the body stores of both macronutrients and micronutrients. When calories are provided the resultant release of hormones, such as insulin, may cause sudden shifts and expose underling deficiencies. This is best demonstrated in the case of potassium and phosphate. The dramatic fall in phosphate levels may result in "refeeding syndrome," which if not recognized leads to circulatory collapse and in some cases, death. These sudden changes mean that in the early stages of total parenteral nutrition (TPN) it is essential that electrolytes are measured frequently.

Surgical patients who have had a gastrointestinal resection will lose increased amounts of fluid and sodium, the degree being dependent upon the site of the resection. These must be anticipated and it is for this reason that regular weights are required in the monitoring of TPN to assess fluid balance. It is also our practice to measure urinary electrolytes, initially weekly, as this provides an early indication of sodium depletion.

Cholestatic liver disease is a particular problem of the preterm infant. This may arise early in the feeding program and, for this reason, liver function should be monitored at least twice weekly at the start of feeding. Micronutrient deficiencies, such as trace metal and vitamins, are usually a complication of long-term feeding. However, it is our practice to measure levels as a baseline, particularly in the older, malnourished child so that any deficiencies may be corrected early. Deficiencies of trace metals, particularly zinc, will result in growth failure. Although it is common practice to monitor zinc levels in plasma, it should be noted that, like many of the trace metals, plasma levels will fall in situations such as infection and surgical stress, and so may not truly reflect deficiency states.

COMPLICATIONS

Complications of PN fall into two major categories: those associated with the line and those that are associated with the

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nutrient infusions themselves. In long-term intravenous feeding it is the line complications that tend to be more frequent.

Line Complications

Line sepsis is the major complication of this type of therapy and presents acutely. In the case of gram-negative organisms, it may be life-threatening. Infection needs to be considered early, particularly in those children who are pyrexial, or who become intolerant to their dextrose infusion. The diagnosis should be confirmed by both peripheral and central line cultures. Septic events, particularly if repeated, are also associated with deterioration in liver function. The incidence of line sepsis is reduced in those patients on home therapy when compared with those in hospital; an average of 0.37 events per patient per year in one series.[1] Gram-positive organisms, such as *Staphylococcus epidermidis,* were the most common and were thought to arise from the hub of the infusion line. Gram-negative infections such as *Pseudomonas* and *Escherichia coli* may also occur, but the origin of these infections is much less clear. They are also more difficult to treat and often result in removal of a line. Some authors have suggested that these infections result from an increase in bacterial translocation from the gastrointestinal tract.[2] All infections need appropriate and aggressive antibiotic therapy for at least 10 d. Infection with *Candida*, although uncommon, needs to be considered when there is evidence of a low-grade infection, particularly when multiple courses of antibiotics have been given. This usually requires the line to be removed.

The risk of line sepsis is reduced by attention to aseptic technique. This is found to be most effective in those units that have an active nutrition team. It is also important that the line is accessed as little as possible, particularly for investigations and routine transfusions. The use of a single-lumen catheter is also advised. In long-term patients with recurrent infections the use of an antibiotic lock, in the capped-off line, may be a useful prophylactic step.[3] The latest advance is the use of antibiotic impregnated lines. There is little clinical information as yet on their use, although it is eagerly awaited.

The occlusion of centrally placed lines is a further common complication. Fibrin deposition within the lumen begins immediately after insertion. Turbulence caused by frequent blood sampling encourages clot formation that, in turn, provides a nidus for bacterial growth. The earliest sign of a problem is the failure of the line to bleed back.[4] Urokinase (5000 U in 2 mL) should be infused into the line and left in situ for 3–4 h. This must be used at the earliest sign of occlusion to have maximum benefit. Lipid and calcium deposits may also result in a blocked line. This does not respond well to the use of urokinase, but requires the use of a 70% alcohol solution left in the lumen of the catheter.[5] Lines may become occluded around the hub site; this is easily visible and may be removed by resection of the blocked portion of the line and catheter repair.

PULMONARY EMBOLISM

Pulmonary embolism has recently emerged as a significant complication of long-term PN. There had been concern for some time, but a paper from the Hospital for Sick Children, London, UK,[6] identified a major thrombus or pulmonary embolus in 12 of 32 patients on long-term therapy. Four of these patients died.[6] It is important to note that symptoms were unusual and the emboli were only reliably identified by echocardiography and ventilation perfusion scanning. An electrocardiogram may be helpful, as demonstrated by the team in Birmingham, UK, but this needs care in interpretation, particularly as ventricular predominance changes with increasing age.[7]

The etiology of these emboli is not clear at present. Hypertonic infusions may promote macrophage procoagulant activity in their own right.[8] However, recent interest has centered on the observation that some individuals have been shown to produce antiphosphatidylcholine antibodies following lipid infusions, thereby inducing an antiphospholipid syndrome. This effect is more pronounced in autoimmune states such as autoimmune enteropathy.[9]

The current position would suggest that it is essential that all children on long-term PN should be monitored by regular electrocardiogram and echocardiographic screening (six monthly in our institution). The use of routine prophylaxis with warfarin has been tried in adult patients, but more information from well-controlled trials is needed in children. Currently a multicenter survey is underway in the UK to further elucidate the extent of the problem.

METABOLIC COMPLICATIONS

Acute problems with PN are mainly associated with an imbalance of electrolytes as has already been referred to. In the early stages glucose levels need to be checked at least daily to establish that the infusion is tolerated and that there is no glycosuria, which would further complicate electrolyte balance. It is also our current practice to measure triacylglycerol concentrations during the build-up of lipid infusions to check that they are tolerated.

In the early years of this type of therapy it was not uncommon to find acidosis due to an intolerance of the amino acid solutions. Following the improvement of these solutions this is now extremely rare. We have, however, increasingly seen acidosis caused by high chloride levels. This is a result of increased volumes of sodium chloride in those patients with high ileostomies or jejunostomies requiring fluid replacement. We have, therefore, restarted measurement of pH on a weekly basis during the first weeks of infusion. In this situation the use of acetate as a buffer has been clinically effective and, indeed, has recently been described in neonates who require large volumes of sodium supplementation.[10]

CHOLESTATIC LIVER DISEASE

Cholestatic liver disease is still the most important of the metabolic complications. The etiology is not clear, but it is more common in preterm infants and those who have undergone gastrointestinal surgery. The incidence is much higher in those children who are nil by mouth and it is clear that encouraging even minimal enteral intake promotes gall bladder contraction and bile flow.[11] Mortality is significantly increased in those children who develop liver disease. One study showed as much as 31% mortality in children on PN with liver disease compared with 3% in children without hepatic involvement.[12] Repeated line infection also has a detrimental effect on liver function. This is often seen in acute sepsis with an acute rise in transaminase levels that fall again after resolution of the infection. These may become persistent. Sepsis induces the formation of proinflammatory cytokines such as interferon-γ and tumor necrosis factor from the Kupffer cells of the liver. The net effect of this is to increase hepatic fibrosis. Although PN results in a relative immunosuppression, it has recently been demonstrated that cholestasis results in an upregulation of the CD14 expression in the Kupffer cells, which may increase endotoxin binding.[13] The most likely origin for endotoxin production is bacterial translocation from the gut. The most effective method for reducing translocation is the provision of minimal enteral intake. This, coupled with the beneficial effect on bile flow of cholecystokinin release makes it essential that some feed should always be given.

Cholecystokinin has been tried as an adjunct to therapy to encourage bile flow in cholestatic disease, but it is not widely used in the UK.[14] Although animal studies were encouraging and human studies achieved some reduction in serum bilirubin levels,

results were variable and no reduction was seen in those with evidence of cirrhosis.

More recently, ursodeoxycholic acid given enterally in early liver disease seems to result in some improvement, but larger studies are required before it becomes routine.[15] It should also be noted that ursodeoxycholic acid may have a negative feedback on the production of cholecystokinin and so may lead to a reduction in intrahepatic bile flow while increasing the fluidity of bile.

The role of lipid is still unclear, but there is some basis to suggest that plant phytosterols are hepatotoxic and a reduction in lipid infusion rates will often result in an improvement in liver function. Again, larger studies are needed.

MICRONUTRIENTS

Micronutrient deficiencies are well described in long-term PN, but with the newer, commercially available trace metal solutions and with regular monitoring these are becoming less common. Particular care needs to be taken with zinc and selenium. In the case of zinc, surgical resections will result in increased losses of zinc due to failure to reabsorb endogenous secretions from the pancreas. Low-serum ferritin levels are common and there are no iron containing solutions available. Experience with these is limited and most children will need blood transfusions to replete iron stores.

In addition to micronutrient deficiency, children on PN are also at risk of micronutrient toxicity, especially where there is coexistent liver disease. There have been recent reports of manganese toxicity with deposition of manganese within the brain. This was due to the high levels of manganese in some commercial solutions. These are no longer available, but it does highlight the care that needs to be taken when using a totally artificial form of nutrition.[16]

Vitamins must be provided and their levels monitored during long-term PN. Vitamin E levels are often low and need to be maintained, particularly in view of the neuropathy of deficiency. Many commercial solutions appear to result in high vitamin A levels in association with low vitamin E, and so the extra vitamin E is commonly given enterally.

Water-soluble vitamins are essential as deficiency may develop within 2–3 wk. Particular care needs to be taken with thiamine deficiency, which may present with an acute encephalopathy. We have seen three such children present in coma due to non-compliance with vitamin supplements. All responded to an intravenous bolus of B-group vitamins.

Recently there have been reports of a reduction of glomerular filtration rate in patients. This included patients who had not received nephrotoxic antibiotics and may therefore be an effect on the PN alone. The cause and implications of these findings are as yet unknown, but we are currently measuring glomerular filtration rate on a yearly basis.[17]

CONCLUSIONS

PN is a highly complex, therapeutic intervention that needs close supervision to avoid complications. However, there seems to be very little consensus regarding the nature and frequency of monitoring protocols. A recent informal enquiry by our pharmacy department of five major UK centers showed very little agreement, particularly on long-term TPN monitoring. Long-term PN needs the experience and help of a multidisciplinary team so that complications may be anticipated early. Monitoring should be regularly checked to avoid missing emerging problems and audit carried out regularly to review both outcomes and also to enable new problems to be identified as they emerge.

REFERENCES

1. Buchman AL, Moukarzel A, Goodson B, et al. Catheter related infections associated with home parenteral infections and predictive factors of catheter removal in their treatment. JPEN 1994;18:297
2. Weber TR. Enteral feeding increase sepsis in infants with short bowel syndrome. J Pediatr Surg 1995;30:1086
3. Werlin SL, Lausten T, Jessen S, et al. Treatment of central venous catheter occlusion with ethanol and hydrochloric acid. JPEN 1995;19: 416
4. Stephens LC, Haire WD, Kotulak GD. Are clinical signs accurate indicators of the cause of central venous catheter occlusion? JPEN 1995;19:75
5. Messing B, Pietra-Cohen S, Debure A, et al. Antibiotic lock technique: a new approach to optimal therapy for catheter related sepsis in home parenteral nutrition patients. JPEN 1988;12:185
6. Dollery CM, Sullivan ID, Baurvaind O, Bull C, Milla PJ. Pulmonary embolism and long term central venous access for parenteral nutrition. Lancet 1994;344:1043
7. Pollard AJ, Sreeram N, Wright JG, et al. ECG and electrocardiographic diagnosis of pulmonary embolism associated with central venous lines. Arch Dis Child 1995;73:147
8. Wakefield A, Cohen Z, Craig M, et al. Thrombogenicity of total parenteral nutrition solutions. Gastroenterology 1989;97:1210
9. Berant M, Shah V, Ben-Barak A, et al. Thromboembolism and parenteral nutrition: the association with intravenous fat and antiphospholipid antibodies. J Pediatr Gastroenterol Nutr 1995;20:43
10. Peters O, Ryan S, Mathew L, Cheng K, Lunn J. Randomised controlled trial of acetate in preterm neonates receiving parenteral nutrition. Arch Dis Child 1997;77:f16
11. Beath S, Davies P, Papadopolou A, et al. Parenteral nutrition related cholestasis in post surgical neonates: multivariate analysis of risk factors. J Pediatr Surg 1996;31:604
12. Ginn-Pease M, Pantalos D, King D. TPN associated hyperbilirubinemia a common problem in newborn surgical patients. J Pediatr Surg 1985;20:436
13. Teitelbaum D. Parenteral nutrition-associated cholestasis. Curr Opinion Pediatr 1997;9:270
14. Curran TJ, Uzorau I, Das JB, et al. The effect of cholecystokinin-noctapeptide on the hepatobiliary dysfunction caused by total parenteral nutrition. J Pediatr Surg 1995;30:242
15. Hofmann AF. Defective biliary secretion during parenteral nutrition: probable mechanisms and possible solutions. J Pediatr Gastroenterol Nutr 1995;20:376
16. Reynolds AP, Kiely E, Meadows NJ. Manganese in long-term paediatric parenteral nutrition. Arch Dis Child 1994;71:527
17. Moukarzel A, Ament ME, Vargas J. Glomerular filtration rate of children on long term parenteral nutrition. Clin Res 1990;38:107