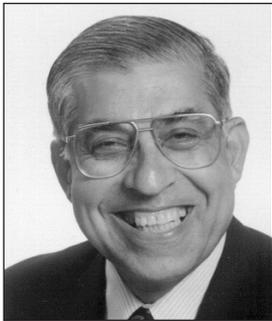


Management of PN-induced Cholestasis



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Parenteral nutrition (PN) can result in a spectrum of conditions related to liver dysfunction. In many patients there is less than a 2-fold elevation above normal of aspartate and alanine transaminase as well as alkaline phosphatase. These abnormalities, if stable, are of little clinical consequence. If progressive, and in particular if the bilirubin level rises, there is need to exclude the standard causes of such abnormalities including drug toxicity, biliary disease and viral hepatitis. If investigations show no other cause than PN, it is necessary to review the nutrient intake and mix so as to avoid the excessive infusion of fat and carbohydrate as well as total calories. In addition, a search should be undertaken for systemic sepsis and bacterial overgrowth in the intestine. Reduction of calories and treatment of sepsis and/or bacterial overgrowth often solves the problem. In long standing refractory cases where there is progressive liver fibrosis, transplantation may have to be considered. An algorithm is provided to address these issues.

INTRODUCTION

Parenteral Nutrition (PN) allows the introduction of nutrients and associated additives directly into the blood stream. This process results in three different problems related to the fact that the protective effect of the gut is breached. These are first the almost unlimited ability to infuse nutrients such as glucose and lipid, second to infuse additives such as preservatives and additives and finally introduce bac-

teria. The liver, as the target organ of these aspects of parenteral nutrition (PN), can be seriously damaged causing fibrosis and hepatic failure. This paper will provide the reader with ways in which these problems can be prevented and treated. As in all aspects of disease, prevention is better than cure.

PN-INDUCED CHOLESTASIS DEFINED

Cholestasis is a condition of impaired canalicular secretion of bile or frank biliary obstruction. It presents as a rise in the levels of alkaline phosphatase and/or conju-

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gated bilirubin with a variable change in transaminases and gamma glutamyl transpeptidase. PN-induced cholestasis is a progressive rise in alkaline phosphatase and/or conjugated bilirubin and is diagnosed in patients receiving PN who develop cholestasis not due to other liver diseases or biliary obstruction. It implies the development of cholestasis and absence of other causes.

PATHOPHYSIOLOGY OF LIVER DISEASE IN TPN

Role of Nutrients

Glucose

When PN became a popular form of nutritional support, the rubric was to infuse as many calories as possible in the mistaken belief that all patients were markedly hypermetabolic and required thousands of calories. Excessive rates of glucose infusion result in a marked stimulation of insulin release. In addition, patients given PN are often traumatized and septic making them insulin resistant. In turn, insulin resistance increases the need for insulin. Insulin in the portal circulation stimulates acetyl coenzyme A carboxylase and fatty acid synthase, thereby increasing fatty acid synthesis from the infused glucose. Furthermore, high insulin levels inhibit fatty acid oxidation. Fatty acids in hepatocytes are stored as triglycerides, which are then excreted as lipoproteins. When the ability to secrete lipoproteins exceeds the synthesis of fatty acids, triglycerides accumulate in the liver, cause an inflammatory reaction and can progress to fibrosis and cirrhosis.

A similar process occurs in patients with Type II diabetes who develop a fatty liver and inflammatory process called Non-Alcoholic Fatty Liver Disease (NAFLD).

An analysis of patients on home PN receiving only 0.45 kcal/kg lipid, showed that alkaline phosphatases were positively correlated with erythrocyte sedimentation rate, tumor necrosis factor-alpha levels, and IL-6; γ -Glutamyltranspeptidase (GGT) was correlated with tumor necrosis factor-alpha and soluble IL-2 receptors. These abnormalities were linked to the infusion of glucose but not fat calories (1).

Lipids

Recently, using regression analysis, Cavicchi, et al (2) showed that patients on long-term PN who received

intravenous lipid infusions exceeding 1.0 g/kg/d had an increased incidence of liver disease. As in the case of glucose, liver injury is related to over feeding rather than the nutrient itself. The probable mechanism of liver injury with intravenous lipids is that when the liver receives lipid at a rate, which exceeds its ability to clear the phospholipids and fatty acids from the lipid particle, they then accumulate in Kupffer cells and hepatocytes respectively. In contrast, Reimund, et al found that it was glucose calories and not fat which was correlated with cholestasis (1). In a controlled trial of short term PN, a balanced energy intake resulted in a lower bilirubin level, but in this study patients were not cholestatic (3).

Amino Acids

It has been suggested that excess glycine in amino acid mixtures used in PN, as well as a deficiency of sulfur containing amino acids, contributed to an excess of relatively insoluble bile salts in bile. The lack of sulfur containing amino acids in PN reduces the availability of taurine, which is produced by the metabolism of methionine in the PN solution. Taurine is conjugated with bile acids to produce a soluble bile salt called taurocholate. In contrast, when glycine is present in excess, the bile acids are conjugated to produce glycocholate, which is relatively insoluble and may promote cholestasis. Unfortunately, the infusion of tauroursodeoxycholic acid did not influence cholestasis in children (4).

Trace Elements

PN solutions contain copper and manganese. Both of these metals can be hepatotoxic but the amounts in PN are well below toxic levels. However, they are excreted by the liver and any cholestasis reduces the excretion of these elements and increases retention. While retention for a short period has not produced clinical effects, long-term manganese retention is concentrated in the basal ganglia and potentially can induce parkinsonian syndromes.

Role of Sepsis and Endotoxemia

It has been known for years that infections, especially with gram-negative organisms, can result in jaundice. The mechanism is that endotoxins in these bacteria activate a variety of proinflammatory cytokines, which then alter the

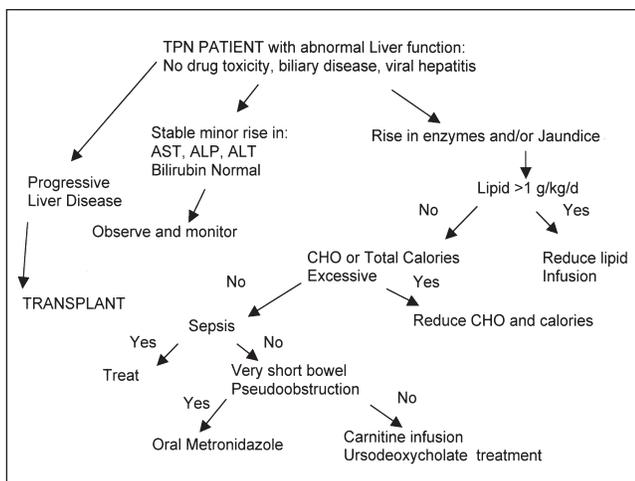


Figure 1.

membrane function of the bile canaliculi and reduce bile flow. In addition, even without sepsis, the absorption of endotoxin from the bowel can cause jaundice.

Intestinal Failure and Liver Disease

The incidence of cholestasis rises with increasing loss of bowel and is more likely to occur in patients with an end-jejunosomy or duodenostomy (5,6). It is not due to nutritional deficit (6) but to bacterial overgrowth in the remnant loop. Cholestasis also occurs in patients with pseudoobstruction who have stasis in dilated bowel loops with bacterial overgrowth (7). Endotoxins absorbed from the lumen of the bowel results in reduced bile salt-dependent and -independent bile flow causing cholestasis (8)

Sepsis and Endotoxemia

Sepsis is often associated with a rise in circulating bilirubin (9) and aminotransferases. Often the rise in bilirubin is early and disproportionate to the rise in alkaline phosphatase (10). Patients on PN who have recurrent catheter sepsis or intraabdominal sepsis or inflammation, will develop biochemical signs of cholestasis. In particular, those with inflammatory phlegmons associated with Crohn’s disease may develop cholestasis.

In addition to overt sepsis, animal studies have shown that following intestinal resection, bacterial endotoxins and peptidoglycans will be transported by

the portal circulation to the liver (11) where they act on the biliary canalicular membranes to reduce bile flow. As well they activate macrophages to produce Tumor Necrosis Factor (TNF) and thus induce inflammation, hepatocyte injury and fibrosis. We have demonstrated that endotoxemia contributed to cholestasis in a patient on home PN with a very short bowel, showing that the above mechanism operates in humans (12). Interaction of both glucose and fat calories with endotoxemia seem to intensify liver injury (1,2). The role of the activation of TNF as a cause of cholestasis is supported by the observation that the infusion of anti-TNF antibodies markedly reduced cholestasis.

Cyclical Parenteral Nutrition

Continuous PN maintains a high insulin level and promotes a fatty liver. Cyclical PN by alternating periods of fasting and feeding reduces this problem and allows mobilization of fat during periods of fasting (13). Some practitioners cycle the TPN down daily by 2–3 hours to reach a target of 12 to 14 hours, while others convert the patient directly to a 12–14 hour infusion, depending on the tolerance of the patient to the rapid infusion and the volume to be infused.

Enteral Feeding

In infants, the inability to feed enterally is associated with early cholestasis. In adults, resumption of oral nutrition usually reduces or eliminates cholestasis. However, it is quite unclear whether it is enteral feeding that prevents cholestasis or, conversely, that a very short bowel both prevents enteral feeding, and promotes cholestasis. On the other hand, lack of enteral nutrition causes gallbladder stasis and the development of complications such as gallbladder sludge and stones, which can promote cholestasis.

THERAPEUTIC APPROACHES

Minor increases in aminotransferases occur frequently in patients on PN. It should be recognized that PN is usually given to patients with serious illness and sepsis, which can increase bilirubin, aminotransferase, GGT

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and alkaline phosphatase levels irrespective of the administration of PN. Minor elevations of aminotransferases (less than twice the upper limit of the reference range for normals) without an elevation of bilirubin are extremely common in PN patients and usually fall within a few weeks. Such elevations require only follow-up and an evaluation of calorie intake to reaffirm that the patient is not being infused with excessive calories. No specific treatment is necessary unless there is a progressive increase in bilirubin levels.

Exclude Other Causes of Cholestasis

If there is a rise in bilirubin, or progressive rise in aminotransferases, alkaline phosphatase or GGT, then the patient should be evaluated in the same way as any other patient who has similar findings to exclude:

1. Biliary obstruction
2. Viral hepatitis
3. Drug toxicity
4. Use of herbal supplements (such as valerian, comfrey, Chinese herbs which include Ma-Huang and Lycopodium under the name Jin bu Huan). It is important to be aware that many herbs can cause hepatotoxicity.

It will be necessary to start with a history and physical examination to evaluate the patient for these problems. In particular, a history of risk factors for viral hepatitis and a drug history should be obtained. The use of herbal preparations can be a hidden source of hepatotoxins. Is the liver enlarged and tender?

Obtain an ultrasound of the liver and biliary system to evaluate size, texture and signs of biliary obstruction. If the findings on ultrasound examination are equivocal for biliary obstruction or pancreatic disease, a magnetic resonance cholangiopancreatogram (MRCP) should be ordered.

Viral serology, especially for hepatitis C and EB virus should be ordered. The diagnosis of PN cholestasis should be made after a global evaluation of the clinical condition and results of the investigations. In particular, it is necessary to exclude or identify that other causes are not responsible or have a minor role in the cholestatic picture of the patient. In some cases where the diagnosis is not clear, a liver biopsy may need to be

done. The findings are usually those of a bland cholestasis and macrovesicular fatty change.

Adjust PN Calories and Regimen

The next step is to examine total calorie intake and lipid infusion. How much does the person absorb of an oral intake. Reduce lipid infusion to no greater than 0.5 g/kg/d and then adjust carbohydrate intake to 15 kcal/kg/d and initiate cyclical PN. At the same time, maximize oral calorie intake to such that hyperphagia results, or more total intake for gut stimulation.

Usually short bowel patients absorb about 50% of intake and those with a colon in continuity can absorb complex carbohydrates by fermenting them to short-chain fatty acids. Total (PN+Oral) calorie needs approximates about 30 kcals/kg/d depending on the patient.

Since PN will provide about 20 kcals/kg/d, the patient will need to eat approximately 20 kcals/kg/d, assuming 50% absorption. This approach will provide enteral feeding and reduce PN calories. If the cholestasis resolves then adjust total calories to maintain body weight or to achieve nutritional goals.

Trace Elements

While the patient is cholestatic, do not give copper and manganese in PN. It is best to give zinc, selenium and chromium while treating this problem. The amount of zinc will depend upon the presence of gastrointestinal losses as suggested by Wolman (14). Recheck copper in 2–3 months to ensure a deficiency does not develop.

Sepsis and Endotoxemia

1. Check catheter exit site for sepsis.
2. Draw blood cultures while PN is running.
3. Examine clinically for any source of infection.
4. CT scan of the abdomen in patients with abdominal surgery, trauma and inflammatory bowel disease.
5. Barium studies of the small bowel to determine whether there are dilated loops of bowel and an area of bowel obstruction. In addition, these studies will assess the length of the remaining small intestine.

- In patients with the small bowel ending in a stoma, determine if there is excluded colon, which can be usefully joined back to the small bowel.

Having made these observations, treat any sepsis with antibiotics, or if necessary, surgically drain or remove septic foci. Where cholestasis persists and there is available colon, consider joining it back. Colon in continuity reduces the need for PN and increases calories absorbed from complex carbohydrates.

Bacterial Overgrowth

If there are obstructed loops of bowel, or small bowel dilatation, then a course of Metronidazole 250 mg tid may be beneficial. Even if there are no dilated loops, Metronidazole has been shown to prevent cholestasis (15,16).

Other Therapeutic Approaches

Carnitine deficiency has been shown to be associated with cholestasis. In refractory cases, carnitine levels should be measured, and if low, then carnitine should be infused intravenously as Carnitor® 50 mg/kg per day repeated for three days (17).

Ursodeoxycholate has been used to successfully treat chronic PN cholestasis in patients with a colonic at a dose of 600 mg/d in adults (18) and at a dose of 15–30 mg/kg/d in infants (19). These high doses are recommended, as the remaining small bowel absorption is likely to be limited. However, there is no data showing a dose-response in short bowel patients.

Transplantation

Long-standing cholestasis, particularly in children on PN, results in liver fibrosis and cirrhosis (20). PN-induced cholestasis has a high mortality in children. When the measures suggested above fail to improve cholestasis, then the patient should be assessed for small bowel or combined small bowel-liver transplant. Since there is a long wait for donors, it is better to consider patients for transplant early and later take them off the list if they improve, than to wait until liver failure sets in and it is not possible to transplant. ■

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