Increased Incidence of Cholestasis during Total Parenteral Nutrition in Children

—Factors Affecting Stone Formation—

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Summary: Cholelithiasis is extremely unusual in infants and children. Recently, some cases of cholelithiasis associated with total parenteral nutrition (TPN) have been reported. A group of 400 children receiving TPN were evaluated prospectively for the presence of gallstones and sludge in this report. Eight children (2%) were determined by ultrasonography to have developed cholelithiasis. All of these patients had received large amounts of amino acids (>1.8g/kg/day) and relatively low amounts of fat (<1.7g/kg/day) with a high ratio of non-protein: kcal/ml (>0.8). It was concluded that the administration of large amounts of amino acids and a high ratio of non-protein: kcal/ml enhanced the risk for formation of gallstones and sludge. Conversely, these are prevented by the administration of appropriate amounts of fat.

Key words: total parenteral nutrition — cholelithiasis — metabolic factors — ultrasonography — infants and children

Introduction

Cholelithiasis is very rare in childhood. Recently, however, there have been some reports that prolonged use of TPN predisposed patients to bile stasis and resulted in gallbladder sludge and stone formation (King et al. 1987; Matos et al. 1987; Iwafuchi, 1991; Kusafuka et al. 1991). The cholelithogenic factors in the TPN solution have not been identified. Eight patients in the present study developed sludge and stones out of 400 children who received TPN for more than 5 days. The purpose of this study was to investigate the metabolic relationship, if any, of cholestasis to TPN in children.

Materials and Methods

A total of 400 children who received TPN were studied at Kurume University Hospital from April, 1978 to March, 1991. Their ages ranged from 1 day to 21 years. The total duration of TPN varied from 5 days to 276 days. The TPN regimen consisted of an amino acid (Proteamin 12X) at 0.8-3.3 g/kg/day and fat (10% Intralipid) at 0-2.7 g/kg/day. Multivitamins, trace minerals and electrolytes were provided for all patients. These patients underwent abdominal ultrasonography between May and July, 1991, and 8 patients who developed sludge and stones were discovered.

The factors which might be involved in the formation of the gallstones were...
correlated with the development of cholelithiasis. The factors investigated were: 1) the dosage of amino acid, 2) the dosage of fat, 3) the ratio of non-protein: kcal/ml, 4) the ratio of non-protein: kcal/N, 5) the duration of TPN, and 6) any liver disorder. Comparisons between the 8 cases with cholelithiasis and the 52 cases with normal biliary tracts were made. The significance of differences between the values were determined by Mann-Whitney’s test with a probability of p<0.05 regarded as significant.

Results

Eight patients (one sludge-positive and 7 with cholelithiasis) were discovered by ultrasonography. Furosemide had been injected 10 times into one patient (case 3) and a selective vagotomy was performed in another (case 7). One patient (Case 6) had received fat-free TPN (Table 1).

The stone/sludge formation rate was 8% (1/12) in the group with TPN duration/less than 11 days, 14% (2/14) for the 11-20 days group, 9% (1/11) for the 21-30 days group and 27% (4/15) for the more than 30 days group. There were no statistical differences based on the duration of TPN. Of the cases with cholelithiasis, the shortest duration of TPN was 10 days and the patient had sludge. The effect of the dosage of amino acid was determined. The stone/sludge formation rate was 9% (1/11) in the group with less than 1.5 g/kg/day, 6% (1/18) in the group with 1.5-2.0 g/kg/day, 22% (2/9) in the group with 2.0-2.5 g/kg/day and 29% (4/14) in the group with more than 2.5 g/kg/day. No cholelithiasis occurred in the patients who received less than 1.8 g/kg/day. There was no statistically significant difference based on the dosage of amino acid.

The stone/sludge formation rate was 33% (4/12) in the group with less than 1.0 g fat/kg/day, 15% (2/13) in the group with 1.0-1.3 g/kg/day, 14% (2/14) in the group with 1.3-1.7 g/kg/day and 0% (0/13) in the group with more than 1.7 g/kg/day. There were statistically significant effects of fat (P<.05), when comparing the cholelithiasis group with the others. Furthermore, there was a definite relationship between the dosages of fat and amino acids, statistically (P<.005) (Fig. 1 and Table 2).

TABLE 1.
Clinical details of eight patients with cholelithiasis

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of TPN</th>
<th>Diagnosis</th>
<th>Diameter &amp; number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5y 1mo</td>
<td>M</td>
<td>21 days</td>
<td>Aganglionosis</td>
<td>3~5mm×5</td>
</tr>
<tr>
<td>2</td>
<td>5y10mo</td>
<td>F</td>
<td>250 days</td>
<td>Rhabdomyosarcoma</td>
<td>4mm×1</td>
</tr>
<tr>
<td>3</td>
<td>6y 7mo</td>
<td>F</td>
<td>32 days</td>
<td>Omphalocele*</td>
<td>5mm×1</td>
</tr>
<tr>
<td>4</td>
<td>10y 7mo</td>
<td>M</td>
<td>10 days</td>
<td>Intramural duodenal hematoma</td>
<td>Sludge</td>
</tr>
<tr>
<td>5</td>
<td>10y 8mo</td>
<td>M</td>
<td>63 days</td>
<td>Wilms' tumor**</td>
<td>3~4mm×9</td>
</tr>
<tr>
<td>6</td>
<td>11y</td>
<td>M</td>
<td>84 days</td>
<td>Traumatic pancreatitis</td>
<td>4~5mm×2</td>
</tr>
<tr>
<td>7</td>
<td>17y</td>
<td>M</td>
<td>16 days</td>
<td>Duodenal ulcer*</td>
<td>5mm×1</td>
</tr>
<tr>
<td>8</td>
<td>18y</td>
<td>F</td>
<td>20 days</td>
<td>Desmoid tumor</td>
<td>6~9mm×2</td>
</tr>
</tbody>
</table>

* treated 10 times with furosemide, ** fat free TPN,
A comparison of TPN factors in patients with cholelithiasis to patients with normal biliary tracts

<table>
<thead>
<tr>
<th>TPN Factors</th>
<th>Cholelithiasis group (n=8)</th>
<th>Normal group (n=52)</th>
<th>Difference**</th>
</tr>
</thead>
<tbody>
<tr>
<td>dose of Amino acid*</td>
<td>2.43± 0.67</td>
<td>2.03± 0.59</td>
<td>NS</td>
</tr>
<tr>
<td>dose of Fat*</td>
<td>0.85± 0.52</td>
<td>1.33± 0.62</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ratio of Fat/Amino acid</td>
<td>0.35± 0.17</td>
<td>0.68± 0.33</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>nonprotein Kcal/N</td>
<td>196.5 ± 31.8</td>
<td>241.2 ± 69.5</td>
<td>NS</td>
</tr>
<tr>
<td>nonprotein Kcal/ml</td>
<td>0.88± 0.09</td>
<td>0.80± 0.09</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>duration of TPN (days)</td>
<td>62±80</td>
<td>37 ±52</td>
<td>NS</td>
</tr>
</tbody>
</table>

* g/kg/day, ** Mann-Whitney’s test

Fig. 1. Relationship between cholelithiasis and the dosages of amino acids and fat.

The percentages of sludge and gallstone-positive cases were 27% (4/15) in the group with less than 200 Kcal/N of non-protein, 20% (4/20) in the group with 200–250 and 0% (0/17) in the group with more than 250. There was no statistically significant difference.

The occurrence rates were 13% (1/8) in the group with less than 0.7 Kcal/ml of non-protein, 0% (0/13) in the group with 0.7–0.8, 9% (2/22) in the group with 0.8–0.9 and 56% (5/9) in the group over 0.9. Statistically significant differences in the ratio of non-protein: Kcal/ml (P<.05) were observed, by comparing the group with cholelithiasis to the others (Table 2). Finally, liver disorders (T.B. ≥2.0, GOT, GPT ≥100) were found in 5 patients, only one of whom had a gallstone.

Discussion

The first report of gallstone formation in children maintained on TPN and furosemide was in 3 infants (Whittington and Black, 1980). Since then, Roslyn et al. (1983) have shown that prolonged TPN significantly enhanced the risk of gallstone formation already imposed by a previous ileal resection or disorder in a study group of 21 patients. This problem has also been reported in Japan (Nakamura et al. 1980; Ikebukuro et al. 1984). In addition, Suita et al. (1984) suggested that the amino acid solution itself has a direct toxic effect on the liver, and this may lead to a block of the normal bile secretion. The factors and mechanisms for the formation of gallstones induced by TPN have not been sufficiently explored.

To elucidate the factors for cholelithiasis, the following were prospectively investigated: (1) cholestegnosis, (2) infection, and (3) changes in bile constituents - such as increased absorption of bile acid from the gallbladder mucosa and increased cholesterol in the bile. Free cholesterol is totally insoluble in bile; consequently, it is incorporated into a
lecithin-bile salts micelle. However, the actual solubility of cholesterol in bile depends on the relative proportions of bile salts, lecithin, and cholesterol. The solubility also depends on the water content of the bile. Moreover, bile acid was decreased by production of cholesterol in the liver and interruption of absorption from the intestines. When cholesterol is in excess from any of these causes, cholesterol-stones are produced by precipitation of crystals in the gallbladder which are not discharged into the intestines. Also, bilirubin can be deconjugated by bacteria producing $\beta$-glucuronidase. The deconjugated bilirubin is converted into calcium crystals and produces bilirubin-stones in the gallbladder.

Allen et al. (1981) determined that the sludge caused by cholestegnosis is due to bilirubin calcium. However, no definite conclusion was reached as to whether the gallstones resulted from TPN cholesterol or bilirubin. It is also known that the synthesis of cholesterol in the liver is increased by the interruption of bile acid absorption from the ileum as a result of a resection or a disorder. The production of bile acid from cholesterol further increases the pool of bile acid. In addition, it was suspected that deconstriction of the gallbladder by fasting or vagotomy is tempered. The present results indicate that gallstone formation and the duration of TPN are not clearly related. Also the age of the patient at receiving TPN was not related.

On the other hand, Messing et al. (1983) have reported that the percentage of sludge formation during TPN increased from 5.9% during the first 3 weeks to 57.1% by the 6th week and 100% when longer than 6 weeks in 23 adult gastroenterological patients without liver disorders. It is also interesting that the sludge decreased from 88% during the first 3 weeks of oral refeeding to 0% by the end of the 4th week. However, these patients had Crohn's disease, thus TPN may not have been the only sludge formation factor.

In the present study, there was no cholelithiasis with the administration of less than 1.8 g amino acid/kg/day. This could mean that excess amino acid is an important factor in the formation of gallstones. There were a few cases with cholelithiasis involving infusion of fat emulsion, and these were generally found to have low infusions. As free cholesterol is totally insoluble in bile, the level of cholesterol in the bile may be increased with a tendency to develop gallstones during the administration of fat emulsion. Practically, Gimmon et al. (1982) reported that the serum and hepatic bile concentrations of cholesterol were increased by the addition of fat emulsion to a solution with only amino acids and glucose in rats. However, there was little cholesterol and considerable lecithin in their fat emulsion. The quantity of bile-water may have a serious influence on sludge formation in the gallbladder. Therefore, the quantity of bile-water may be closely related to the ratio of non-protein: kcal/ml of TPN. This was investigated and the results demonstrated that cholelithiasis occurred above 0.9 non-protein: kcal/ml.

Ultrasonography was very useful to study cholelithiasis during and after TPN. The proportion of diagnoses by ultrasonography has been reported to be 84-90% (Doust and Maklad, 1974; Kappelman and Sanders, 1978). A patient with sludge formation was noted who received only a short administration of TPN, therefore all patients receiving TPN should undergo ultrasonography periodically; every week during TPN, every month for the first 3 months after TPN, and then every 6 months.

In summary, these results show that the TPN factors leading to gallstone for-
mation are excess amino acids, inadequate fat and high non-protein: kcal/ml. More patients with cholelithiasis due to TPN would probably be found by careful examination.

References


