Duodenal bile acids in infants with protracted diarrhoea

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SUMMARY Bile acids were estimated in the duodenum of infants with protracted diarrhoea and compared with those in a control group. Significantly lower levels of total bile acids were found in infants with protracted diarrhoea, a finding which may be due to ileal dysfunction. Low concentrations of total bile acids may contribute to the poor nutritional state of these patients by impairing the normal digestion and absorption of dietary fat and fat-soluble vitamins. The absence of deconjugated bile acids in the duodenal juice of most infants with protracted diarrhoea suggests that they do not contribute significantly to the pathophysiology of this disorder.

Protracted diarrhoea of infancy is a severe and debilitating disorder, characterised by the passage of at least 4 loose stools a day for more than 2 weeks. In some infants protracted diarrhoea is secondary to recognised gastrointestinal diseases (Larcher et al., 1977), while in others the pathogenesis remains unknown. The patients become dehydrated and malnourished due to persistent fluid loss and to difficulty in maintaining an adequate oral intake of food. Impaired digestion and absorption, resulting from a damaged small intestinal mucosa, also contribute to the poor nutritional state. As recovery of small intestinal mucosal function may be delayed by malnutrition, a vicious cycle of events occurs which perpetuates the clinical problem, and intravenous nutrition may be needed to sustain life.

Bile acid studies on infants with protracted diarrhoea have shown two principal abnormalities, either of which could contribute to the pathophysiology of this disorder. Deconjugated bile acids were detected in the duodenal juice of some infants (Gracey et al., 1969), while in experimental animals the same bile acids had cytopathic effects on the small intestinal mucosa (Dawson and Isselbacher, 1960), and inhibited the absorption of water, electrolytes, and monosaccharides from the lumen of the small intestine (Gracey et al., 1971; Harries and Sladen, 1972). Increased faecal excretion of bile acids has also been shown in infants with protracted diarrhoea (Balistreri et al., 1977). If the loss is prolonged, it may reduce the size of the bile acid pool and lower the concentration of bile acids in the small intestine. As bile acids are essential for the optimal absorption of dietary fat and fat-soluble vitamins, a fall in concentrations below the level at which micelle formation occurs in the small intestine might further compromise the poor nutritional state of the patient. Bile acids in the duodenum of a control group of infants (group A) were therefore compared with those in a group of infants with protracted diarrhoea (group B).

Materials and methods

Patients. The infants were divided into two groups (Table 1). Infants with protracted diarrhoea (group

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical details of infants studied</th>
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<tr>
<td>Cases</td>
<td>Age (weeks)</td>
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<td>Group A (controls)</td>
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<td>Group B (patients)</td>
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G. A. BROWN, research fellow
SUSAN EDKINS, senior technician
B) had been passing at least 4 loose stools daily for more than 2 weeks, without the isolation of known enteropathogenic bacteria. Stools were tested for the presence of reducing substances using Clinistest tablets (Kerry and Anderson, 1964), and significant amounts (>0.5%) were detected in 3 of them. The presence of glucose was confirmed by paper chromatography in 2 patients and lactose in one. All the infants in the control group (group A) needed tube feeding as a normal part of their medical care, and none had diarrhoea. As concentrations of duodenal bile acids have been shown to increase with age in early infancy (Challacombe et al., 1975), these infants were of approximately similar ages as those in group B.

Sampling regimen. Duodenal juice was obtained by the use of a long polyethylene feeding catheter (Argyl, 5 FG, 91 cm), weighted with a gold bead (Rhea and Kilby, 1970). The distal end of the tube was allowed to pass into the duodenum by normal peristalsis and its position in the 2nd to 4th part of the duodenum was confirmed by screening. The first sample of duodenal juice aspirated was discarded to exclude contamination by gastric juice and the 2nd sample was placed in a sterile container and stored at −20°C until analysed. Samples were taken 2 hours after a full cream cows' milk formula feed in group A and 2 hours after a 5% glucose feed in group B. The absence of significant differences in duodenal bile acid concentrations in infants 2 hours after either type of feed has been previously demonstrated (Challacombe et al., 1975).

Bile acid analysis. Bile acids were estimated using sulphuric acid fluorescence after separation by thin layer chromatography (Panvelivallala et al., 1970). Total and individual bile acids were measured in samples of duodenal bile from both groups of infants. Separate estimates of the individual taurine and glycine conjugated dihydroxy bile acids were not made because it was not possible to separate them by the chromatographic method.

Results

The results of bile acid analyses are shown in Table 2. The difference between mean values of total bile acids, taurine, and glycine conjugates, and individual bile acids in group A and group B were examined for statistical significance using Student’s t test. Differences were regarded as significant when P values were <0.05.

Concentrations of total bile acids were significantly lower in infants in group B (P<0.01). This finding was mainly due to lower mean concentrations of taurocholic (P<0.01) and glycocholic acids (P<0.05). Ratios of total glycine conjugates to total

<table>
<thead>
<tr>
<th>Cases</th>
<th>Total bile acids (mmol/l)</th>
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<tr>
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<td>Conjugates</td>
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<td>Glycine</td>
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<td>Group A (controls)</td>
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<td>4</td>
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<td>5</td>
<td>9-8</td>
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<td>Mean</td>
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<td>SD</td>
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<tr>
<td>Coefficient of variation (%)</td>
<td>25</td>
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<td>Group B patients</td>
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<td>6</td>
<td>2-1</td>
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<td>7</td>
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<tr>
<td>Mean</td>
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<td>SD</td>
<td>2-3</td>
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<td>Coefficient of variation (%)</td>
<td>74</td>
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ND = not detected.

Conversion: SI to traditional units—Taurocholic acid: 1 mmol/l = 51.5 mg/100 ml. Taurine conjugated dihydroxy bile acids: 1 mmol/l = 49.9 mg/100 ml. Taurolithocholic acid: 1 mmol/l = 43.8 mg/100 ml. Glycocholic acid: 1 mmol/l = 46.5 mg/100 ml. Glycine conjugated dihydroxy bile acids: 1 mmol/l = 44.9 mg/100 ml.
Duodenal bile acids in infants with protracted diarrhoea

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Mean

values of the glycine/taurine ratio were not

significantly raised in patients with protracted diarrhoea compared with the controls. As bile acids are mainly

conjugated with taurine in early infancy, failure to
demonstrate consistently raised glycine/taurine ratios in patients with protracted diarrhoea may be due to an

increased availability of taurine for conjugation.

Trihydroxy bile acid concentrations were significantly lower in infants in group B compared with

group A, and mean concentrations of dehydroxy bile

acids were also low, but the values did not reach

statistical significance. In adults with ileal resections the absorption of both dihydroxy and trihydroxy

bile acids has been shown to be equally impaired

(Low-Beer et al., 1974). Although ileal dysfunction

may be one explanation for the bile acid findings reported in protracted diarrhoea, further study of the

enterohepatic circulation and faecal excretion of bile

acids in this disorder will be necessary. Bacterial
growth rate in the upper small intestine (Gracey and

Stone, 1972; Challacombe et al., 1974b), a rapid

small intestinal transit time, or impaired synthesis

of bile acids by the liver due to malnutrition, could

each influence bile acid metabolism in infants with

protracted diarrhoea.

The deconjugated bile acids, deoxycholic and

chenodeoxycholic acids, have been shown to have
cytopathic and metabolic-inhibitory effects on the

small intestine of experimental animals (Dawson

and Isselbacher, 1960; Low-Beer et al., 1970; Gracey

et al., 1971; Harries and Sladen, 1972), and these bile

acids could have similar effects in patients with

protracted diarrhoea and monosaccharide mal-

absorption (Gracey et al., 1969). Cholic, chenodeoxy-

cholic, and lithocholic acids were detected in small

quantities in only one infant with protracted

diarrhoea, an infant who was also intolerant of oral

lactose. These findings suggest that deconjugated

bile acids were not important in the pathophysiology

of protracted diarrhoea in our patients, but samples

were taken from a single site only in the duodenum,

and sampling from other sites will be necessary

before the contribution of deconjugated bile acids

can be fully evaluated. Concentrations of total bile

acids in the duodenum of 4 of the 5 infants in

group B were below a level of 4 mmol/l. Badley et al.

(1969) have shown that total bile acid concentrations

in the upper small intestine should exceed this value

taurine conjugates (G/T) were not significantly different in the two groups. Mean concentrations of
taurine conjugated dihydroxy bile acids, glycine

conjugated dihydroxy bile acids, and tauroliotho-

cholic acid were also not significantly different. In

group B taurocholic acid was present in 4 out of 5,
taurolithocholic acid in 3 out of 5, and glycine

conjugated dihydroxy bile acids in 3 out of 5 infants.

In group A all bile acids were present with the

exception of tauroliothocholic acid which was not
detected in one patient. Deconjugated bile acids

were not detected in infants in group A, but cholic

acid (0.13 mmol/l; 5.3 mg/100 ml), chenodeoxy-

cholic acid (0.57 mmol/l; 22.3 mg/100 ml), and

lithocholic acid (0.25 mmol/l; 9.4 mg/100 ml) were

found in the duodenal juice of one infant in group B

who had secondary lactose intolerance. In this

infant, who has been previously reported (Challa-

combe et al., 1974a), Bacteroides sp. (obligate

anaerobes with known bile acid deconjugating

properties in vitro) were isolated from the duodenal

juice.

Discussion

Concentrations of total bile acids were significantly lower in the duodenum of infants in group B

compared with group A. Morphological and func-
tional changes in the bowel may interrupt the enter-

hepatic circulation of bile acids leading to increased

bile acid excretion in the faeces. The liver initially

compensates for the increased faecal loss by increased

synthesis, but eventually synthesis is inadequate,

leading to a depleted bile acid pool and to low levels

of bile acids in the duodenum. There is some exper-

imental evidence in favour of this proposed mech-

anism. The oral or intravenous administration of

radioactively-labelled bile acids to adults with diffuse

ileal disease leads to rapid excretion of the radio-

active label in the faeces (Meihoff and Kern, 1968).

Oral administration of C14-cholic acid to infants

with ileal resections and to infants with protracted

diarrhoea also results in increased faecal excretion of

this label (Balistreri et al., 1977). The presence of

ileal dysfunction in protracted diarrhoea is further

suggested by abnormal Schilling tests for vitamin

B12 absorption (Balistreri et al., 1977). Impaired

ileal function may be the result of associated mucosal

damage. Severe mucosal changes have been reported

in the upper small intestine (Greene et al., 1975) and

these may be sufficiently extensive to involve the

terminal ileum where most bile acid reabsorption

should occur. Ileal dysfunction may also contribute
to the protracted diarrhoea in these patients, as

excessive amounts of dihydroxy bile acids reaching

the colon have been shown to provoke excessive

water secretion by the colonic mucosa (Mekhjian

et al., 1971).

A higher ratio of glycine to taurine conjugates in
duodenal bile is usually present in adults with

terminal ileal disorders (Heaton et al., 1968), a

finding which may be due to the relative scarcity of

taurine or of its precursor cysteine, in the face of an

increased demand for bile acid conjugation. Mean

values of the glycine/taurine ratio were not

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(1969) have shown that total bile acid concentrations

in the upper small intestine should exceed this value
for optimal fat absorption to occur. The digestion and absorption of dietary fat and fat-soluble vitamins may therefore be impaired in patients with protracted diarrhoea, and absorption and nutrition may be improved by the use of medium chain triglycerides, which are well absorbed in the absence of bile acids.

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References


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