EFFECT OF SODIUM ACETYL SALICYLATE ON CHOLESTEROL SATURATION OF FASTING GALL BLADDER BILE, WITH AND WITHOUT CHENIC ACID

R.M. KUPFER & T.C. NORTHFIELD

Norman Tanner Gastroenterology Unit, St. James' Hospital and
Department of Medicine, St. George's Hospital Medical School, London SW17

The aims of this study were (a) to determine whether sodium acetyl salicylate by itself or in combination with chenodeoxycholic (chenic) acid would decrease the cholesterol saturation index (SI) of fasting gall bladder bile in man; and (b) to confirm prospectively that 8 mg kg⁻¹ day⁻¹ chenic acid given at bedtime together with a low cholesterol diet reduces gall bladder bile SI to a level where consistent gallstone dissolution would be expected.

Seven patients were studied on each of the following regimens given in random order for 1 month each: bedtime chenic acid alone 8 mg kg⁻¹ day⁻¹; sodium acetyl salicylate alone 600 mg four times daily; bedtime chenic acid together with sodium acetyl salicylate; no treatment. Gall bladder samples were taken by nasoduodenal intubation at the end of each regimen and SI determined.

SI (mean $\pm$ s.e. mean) on low cholesterol diet with no drug treatment was 1.14 ± 0.06 . On bedtime chenic acid 8 mg kg⁻¹ day⁻¹ plus low cholesterol diet it fell to 0.83 ± 0.03 ($P < 0.05$). Sodium acetyl salicylate did not alter gall bladder bile SI. 95% confidence limits for the effect of sodium acetyl salicylate on SI were +0.03 and -0.05.

We conclude that (a) sodium acetyl salicylate does not lower SI of gall bladder bile in man; (b) an adequate fall in SI for gallstone dissolution can be achieved with a reduced dose (8 mg kg⁻¹ day⁻¹) of chenic acid given at bedtime with a low cholesterol diet.

Introduction

Chenodeoxycholic (chenic) acid makes gall bladder bile unsaturated with respect to cholesterol, and causes dissolution of cholesterol gallstones (Danzinger *et al.*, 1972; Bell *et al.*, 1972). In some patients, depending on the nature and the size of the gallstones, treatment may be lengthy and hence expensive. It is therefore important to find methods of enhancing its efficacy. We have previously demonstrated that the effect of chenic acid is enhanced by bedtime administration and by a low cholesterol diet, and a dose-response study suggested that this combined regimen would enable the minimum effective dose for gallstone dissolution to be substantially reduced from 14 to 8 mg kg⁻¹ day⁻¹ (Maudgal *et al.*, 1982), a dose as low or even lower than that recommended for ursodeoxycholic acid. In the present study we have combined this optimal regimen with sodium acetyl salicylate.

Salicylic acid derivatives are choleretic agents (Rutishauser & Stone, 1973). In addition, lysine acetyl salicylate has been shown in the dog to reduce the cholesterol saturation of hepatic bile by a reduction in both cholesterol and phospholipid secretion, the bile acid secretion rate remaining unchanged (Erlinger *et al.*, 1975).

The aims of this study were two-fold. The first aim was to determine whether sodium acetyl salicylate by itself or in combination with chenic acid decreases the cholesterol saturation index (SI) of gall bladder bile in man. The second aim was to test prospectively in a new group of patients whether the low dose of 8 mg kg⁻¹ day⁻¹ chenic acid given at bedtime together with a low cholesterol diet reduces fasting gall bladder bile SI to a mean value of 0.8, a level which is associated with consistent gallstone dissolution (Iser *et al.*, 1975).

Methods

Seven patients with radiolucent gallstones were studied. They were aged 46–71 years (mean 57 years), weight 58–92 kg (mean 70 kg). Five were male and two were female. Written informed consent was obtained from each patient and the study was approved by the local hospital ethical committee. Patients with a previous history of peptic ulcer were excluded. One month was spent on each of the following four regimens given in random order according to a Latin square design: (1) bedtime chenic acid 8

mg kg⁻¹ day⁻¹; (2) sodium acetyl salicylate 600 mg three times daily, 600 mg at bedtime; (3) bedtime chenic acid plus sodium acetyl salicylate; (4) no treatment. A low cholesterol diet (100 g cholesterol daily, Maudgal *et al.*, 1982) was taken during all four regimens. Patients were given sufficient soluble aspirin to take the full dose, but were asked to reduce the dose if side effects such as dyspepsia or tinnitus occurred.

Gall bladder bile samples were taken by nasoduodenal intubation at the end of each regimen for measurement of biliary lipid composition. Total bile acid concentration was measured by the 3 α -hydroxysteroid dehydrogenase enzyme assay as described by Talalay (1960) and modified by Admirand & Small (1968). Phospholipids were measured by the method of Bartlett (1959) and cholesterol was measured by the cholesterol oxidase method in an aliquot that was diluted at the bedside in isopropanol (1 in 10; Roda *et al.*, 1975). Saturation index (SI) was calculated using the polynomial equation developed by Thomas & Hofmann (1973), based on the limits of cholesterol solubility described by Hegardt & Dam (1971) and Holzbach *et al.* (1973). Statistical comparison of SI on the different regimens was carried out by the Wilcoxon test for paired samples.

Results

Of ten patients who started the study, three were withdrawn because of dyspepsia even at a low dose of sodium acetyl salicylate. Of the remaining seven, two patients reduced their dose of salicylate to 1.8 g daily because of dyspepsia, the remaining five patients remained on 2.4 g daily. SI of fasting gall bladder bile on a low cholesterol diet with no drug treatment was (mean $\pm$ s.e. mean) 1.14 ± 0.06 , on salicylate alone it was 1.17 ± 0.06 , on chenodeoxycholic acid it was 0.83 ± 0.03 ($P < 0.05$), and chenodeoxycholic acid plus salicylate it was 0.85 ± 0.03 (Figure 1). Ninety-five per cent confidence limits for the effect of salicylate were calculated; salicylate did not affect SI by more than +0.03 or -0.05.

Discussion

A mean cholesterol SI of 0.8 has been reported to give consistent gallstone dissolution in patients

Figure 1 Saturation indices for individual subjects on the four treatment regimens. CDCA chenodeoxycholic (chenic) acid.

treated with chenic acid, using the conventional regimen of 15 mg kg⁻¹ day⁻¹ at mealtimes on an unrestricted diet (Tser *et al.*, 1975). In the present study, however, a mean SI of 0.83 was obtained using chenic acid 8 mg kg⁻¹ day⁻¹ at bedtime with a low cholesterol diet. Only one individual bile sample remained supersaturated with cholesterol. This confirms prospectively our recent dose-response study, retrospective analysis of which suggested that the low dose of 8 mg kg⁻¹ day⁻¹ chenic acid would be sufficient to give a mean SI of 0.8 if given at bedtime together with a low cholesterol diet (Maudgal *et al.*, 1982).

We have not substantiated the hypothesis that sodium acetyl salicylate either alone or when used in combination with chenic acid lowers the SI of fasting gall bladder bile. Calculation of confidence limits demonstrates that if we had missed an effect of salicylate through a type two error, this effect would be so small that it would not be clinically important. Sodium acetyl salicylate gave rise to an unacceptable incidence of dyspeptic symptoms in the group of gallstone patients studied.

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