THE ACTION OF SALICYLATES ON BILE FLOW IN MAN

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Following oral administration of 1.5 g of sodium salicylate or acetylsalicylate to five patients with indwelling T-tubes there was an approximately 50% increase in bile flow. The increase appeared to be in the bile-acid independent fraction of canalicular flow and was not accompanied by a change in lithogenicity. Neither agent would be of use in the medical treatment of cholesterol gallstones.

Keywords salicylates bile flow

Introduction

It has been known for over a century that sodium salicylate increases bile flow in dogs (Rutherford *et al.*, 1878), but this effect is species dependent, being absent in rabbits and guinea pigs (Pugh & Rutishauser, 1978). Our earlier studies (Cooper *et al.*, 1980) in rhesus monkeys demonstrated salicylate choleresis of a lesser magnitude than that seen in dogs (Rutherford *et al.*, 1878; Erlinger *et al.*, 1975). The action of salicylates on bile flow in normal humans is uncertain, since previous measurements have been either indirect (Rutherford *et al.*, 1878) or have involved patients with accidental biliary-cutaneous fistulas (Pfaff & Balch, 1897; Albu, 1900; Meiszner, 1926). Moreover, both an increased bile flow (Rutherford *et al.*, 1878; Pfaff & Balch, 1897; Meiszner, 1926), and a small decrease have been reported after oral ingestion of sodium salicylate (Albu, 1900). Recent work (Erlinger *et al.*, 1975) using acetylsalicylate in the dog confirmed the presence of a powerful choleresis and noted a decrease in phospholipid and cholesterol secretion. The authors suggested that salicylate 'may be of value in the treatment of cholesterol gallstones in man'. To clarify these uncertainties we studied the effect of two different salicylates on five patients with indwelling T-tubes.

Methods

Five patients with indwelling T-tubes after surgical removal of common bile duct stones were studied after giving informed consent. These studies were performed 10-12 days after operation, by which time previous studies in the rhesus monkey suggest that postoperative depression of bile flow was likely to be

relatively insignificant (Redinger *et al.*, 1971). All five patients were fully recovered from their operations with normal liver function tests and a T-tube cholangiogram demonstrating free flow into the duodenum and the absence of bile duct stones. The T-tube was clamped for 48 h prior to the investigation to restore the enterohepatic circulation and permit an accurate assessment of biliary lipid secretion. Following an overnight fast the T-tube was unclamped and bile was allowed to flow down into collecting tubes kept on ice. Bile was collected in 15 min aliquots for a 60 min baseline period and salicylate (1.8 g) was then administered orally, dissolved in 60 ml of water; the collection was continued in 15-min aliquots for a further 120 min. Two studies were performed on each patient to compare the actions of sodium salicylate and acetyl salicylate; the T-tube was clamped for 24 h between these studies. Sodium salicylate was administered first to three of the five patients.

All results were expressed per kg body weight per 24 h to facilitate comparison. The total bile acid concentration was measured by a modification of the 3-hydroxy steroid dehydrogenase method (Cooper *et al.*, 1980; Javitt & Emerman, 1968). The phospholipid content of the bile was measured by ashing (Ames & Dubin, 1960) and estimating the total inorganic phosphorus (Chen *et al.*, 1956). Cholesterol content was determined by an enzymatic technique (Roda *et al.*, 1975).

Blood was taken at 60 min after drug administration during each study for estimation of serum salicylate levels, which were determined by reaction with ferric nitrate after ethylene dichloride extraction (Trinder, 1954). Statistical analysis was performed using Student's *t*-test.

Results

Sodium salicylate rapidly increased bile flow from a baseline of $7.38 \pm 0.18 \text{ ml kg}^{-1} 24 \text{ h}^{-1}$ (mean $\pm$ s.e. mean) to $11.46 \pm 0.43 \text{ ml kg}^{-1} 24 \text{ h}^{-1}$ ($P < 0.001$), an increase of 55% (Figure 1). A similar increase (43%) in bile flow following drug ingestion was also seen with acetylsalicylate (6.76 ± 0.25 to $9.67 \pm 0.44 \text{ ml kg}^{-1} 24 \text{ h}^{-1}$; $P < 0.001$) (Figure 2).

No significant change was observed in the secretion of any of the biliary lipids following administration of either drug (Table 1). There was therefore no change in the lithogenicity of the secreted bile. Plasma salicylate levels were all within the range of 1.2–1.8 mmol l.

Discussion

Both sodium salicylate and acetylsalicylate increase bile flow in man by about 40% following oral drug administration. This response is less than the 100% choleresis seen in the rhesus monkey (Cooper *et al.*, 1980), and considerably less than the 600% increase in bile flow observed in the dog (Rutherford *et al.*, 1878; Erlinger *et al.*, 1975). No attempt was made in these studies to occlude the distal common bile duct, since it has been shown that a T-tube on dependent drainage produces complete biliary diversion (Rundle *et al.*, 1955). The exact mechanism by which bile flow is increased during the salicylate choleresis remains

Figure 1 The mean bile flow ($\text{ml kg}^{-1} 24 \text{ h}^{-1}$) in 15 min aliquots during the baseline period and following the administration of 1.8 g oral sodium salicylate.

Figure 2 The mean bile flow ($\text{ml kg}^{-1} 24 \text{ h}^{-1}$) in 15 min aliquots during the baseline period and following the administration of 1.8 oral acetylsalicylate.

Table 1 Biliary lipid secretion in $\text{mmol kg}^{-1} 24 \text{ h}^{-1}$ (means $\pm$ s.e. mean) before and after administration of sodium salicylate and acetylsalicylate

	Sodium salicylate		Acetylsalicylate	
	Baseline	With drug	Baseline	With drug
Bile acid	0.29 ± 0.04	0.39 ± 0.04	0.22 ± 0.02	0.22 ± 0.02
Phospholipid	0.08 ± 0.01	0.09 ± 0.01	0.06 ± 0.01	0.07 ± 0.01
Cholesterol	0.03 ± 0.004	0.04 ± 0.003	0.03 ± 0.003	0.03 ± 0.003

uncertain. Measurement of [^{14}C]-erythritol clearance in the dog (Erlinger *et al.*, 1975) and rhesus monkey (Cooper *et al.*, 1980) has shown that the increased bile flow is of canalicular origin.

Bile acid secretion was unaltered in man, suggesting that as in the monkey work (Cooper *et al.*, 1980), the salicylate choleresis depends on an increase in the bile-acid independent fraction of canalicular bile flow. Salicylate is mainly excreted in the urine; its biliary excretion is small and cannot play an osmotic role in generating the extra bile flow (Cooper *et al.*, 1980). In some animal systems, salicylates are known to alter membrane permeability (Wieth, 1970), but there is good evidence that this does not occur at the canalicular level and is not responsible for the choleresis seen here (Cooper *et al.*, 1980). Animal studies suggest that the choleresis is mediated by stimulation of liver cell membrane-bound Na^+ , K^+ -ATPase (Layden & Boyer, 1976) and that salicylate may be similar to phenobarbitone in this respect (Simon *et al.*, 1977).

Whilst agreeing with Erlinger *et al.* (1975) that acetylsalicylate is a choleric, these studies do not demonstrate any alteration in biliary lithogenicity.

There was in fact no difference in any respect between the two drugs and our earlier studies in the monkey (Cooper *et al.*, 1980) were also unable to show changes in biliary lipid secretion. It is of course possible that alterations in biliary lipid secretion might be a species dependent phenomenon or occur only during a more profound choleresis; Erlinger's studies having involved dogs (Erlinger *et al.*, 1975). Certainly, there is no evidence that salicylate administration could play any useful role in the treatment of cholelithiasis in man.

Oral administration of sodium salicylate to rhesus monkeys did not produce a consistent choleresis when the serum salicylate level was less than 1.0 mmol/l. Our studies in man were performed after a large loading dose, but the salicylate levels were within the therapeutic range for patients taking salicylates for rheumatoid arthritis (Seaman & Plotz, 1976).

Both sodium salicylate and acetylsalicylate increase bile flow in man by means of an increase in the bile acid-independent fraction of canalicular bile flow. Neither drug produced any alteration in biliary lipid secretion.

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