SHORT COMMUNICATION

The effect of intrarenal infusion of bile on kidney function in the dog

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Summary

1. Obstructive jaundice sensitizes the kidney to anoxic damage. To clarify further this phenomenon the effect of unilateral infusion of bile on kidney function was studied. The contralateral intact kidney served as control.

2. Intrarenal infusion of diluted bile (1:10) resulted in an ipsilateral fourfold increase in mean rate of urinary flow \((P < 0.01)\), threefold increase in mean fractional excretion of sodium \((P < 0.05)\) and more than 50% increase in mean rates of potassium excretion \((P < 0.05)\). Urinary flow rate and electrolyte excretion returned to baseline upon cessation of bile infusion. The mean clearances of inulin and \(p\)-aminohippurate were unchanged during intrarenal bile infusion.

3. Intrarenal infusion of isotonic taurocholate solution \((20 \text{ mmol/l})\) mimicked the diuretic, natriuretic and kaliuretic effects of diluted bile, whereas intrarenal infusion of bilirubin did not cause any change in the excretion of electrolytes.

4. It is concluded that increase in circulating bile acids rather than hyperbilirubinaemia may alter kidney function during obstructive jaundice. Acute cholaemia may cause volume depletion by increasing urinary salt loss. This in turn may aggravate the direct nephrotoxicity of circulating bile compounds.

Key words: bile acids, jaundice, nephrotoxicity.

Abbreviations: \(C_{\text{inula}}\), clearance of inulin; \(C_{\text{FAH}}\), clearance of \(p\)-aminohippurate; \(\text{FE}_{\text{Na}}\), fractional excretion of sodium; GFR, glomerular filtration rate; \(U_kV\), rate of urinary excretion of potassium; \(V\), rate of urine flow.

Introduction

Patients with obstructive jaundice have an increased incidence of post-operative shock and renal failure \([1–4]\). The mechanism by which bile constituents in the circulation damage the kidney has not been clarified. Baum et al. \([5]\) implied that conjugated bilirubin sensitized the kidney to anoxic damage in the rat. In contrast, Aoyagi & Lowenstein \([6]\) suggested that it was bile salts rather than bilirubin that aggravated ischaemic damage to the rat kidney. On the background of this controversy the present investigation was undertaken to study the effect of bile constituents on kidney function. Intrarenal infusion of diluted bile or its constituents into the non-ischaemic dog kidney was utilized for this purpose.

Methods

Fourteen healthy mongrel dogs were studied under intravenous pentobarbital anaesthesia \((20–25 \text{ mg/kg body wt.})\) and mechanical ventilation. A midline laparotomy was used to obtain bile from the gall bladder and for individual cannulation of each ureter. A butterfly needle was inserted into one renal artery for infusion of various test solutions (experimental kidney) whereas the contralateral and intact kidney served as control. A sample of dog’s bile was immediately analysed for concentration of bilirubin and electrolytes. The concentration of sodium taurocholate in the bile was derived by the method of Wheeler & Ramos \([7]\).
The study was started after 1 h of equilibration, when the rate of urine flow had stabilized. Each test solution was infused into the renal artery at the rate of 1-2 ml/min for 70 min; 10 min was allowed for equilibration and thereafter urine was collected separately from each ureter in three 20 min periods. At the midpoint of each urine collection a blood sample was obtained for electrolyte and clearance studies. Central venous pressure and mean arterial pressure were monitored throughout the study. The urinary volume losses during the experiments were replaced. Glomerular filtration rate (GFR) and renal plasma flow were estimated from the clearances of inulin and p-aminohippurate respectively, by methods previously reported from this laboratory [8]. Sodium and potassium in urine and blood were determined by flame photometry and the osmolalities by cryoscopy. Urine glucose and protein content were estimated with Labstix (Ames) and bilirubin was measured by the modified van den Bergh reaction. The paired Student's t-test was used for evaluation of statistical significance.

Each dog was infused with its own diluted bile. Exogenous bilirubin (Lot no. BIC-963: stock solution of highly purified bilirubin and human albumin at a concn. of 5-5 g/dl) was obtained from Dade Diagnostics Inc. (Aguada, Puerto Rico U.S.A.), and exogenous sodium taurocholate from Sigma Chemical Co. These reagents were protected from exposure to light throughout the study.

The 14 dogs were divided into three groups according to the test solutions infused sequentially (each solution at 1-2 ml/min for 70 min): (a) Group 1 (six dogs): 0-9% NaCl; bile diluted 1:20; bile diluted 1:10; 0-9% NaCl. (b) Group 2 (five dogs): 0-9% NaCl; sodium taurocholate (10 mmol/l); sodium taurocholate (20 mmol/l); bile diluted 1:10; 0-9% NaCl. (c) Group 3 (three dogs): 0-9% NaCl; bilirubin; sodium taurocholate; bile diluted 1:20.

The concentrations of bilirubin and sodium taurocholate employed were adjusted to the values found in dog's bile diluted 1:20. It should be emphasized that all the infused solutions were isotonic.

Results

General

Mean arterial and central venous pressures remained constant throughout the study. Neither proteinuria nor glycosuria was detected after intrarenal infusion of bile. Analysis of the composition of dog's bile showed a bilirubin concentration of 180 ± 46 mg/dl (3.1 ± 0.8 mmol/l) and estimated bile salts of 203 ± 38 mequiv./l.

Effect of bile on kidney function (Fig. 1)

Infusion of diluted bile (1:10) resulted in approximately fourfold increase in the mean rate of urine flow (P < 0.01), approximately threefold increase in mean fractional excretion of sodium (FE$_{Na}$) (P < 0.01) and more than 50% increase in the rate of potassium excretion (P < 0.05).

Further dilution of the infused bile to 1:20 resulted in approximately 50% reduction in the rate of urine flow and electrolyte excretion.

The mean clearances of inulin (and of p-aminohippurate; data not presented) showed a slight but non-significant increase during intrarenal bile infusion. All the above changes returned to base line values in the post-control period (Fig. 1, column D). No changes were noted in V (the rate of urine flow), FE$_{Na}$, U$_{K}$V (the rate of urinary secretion of potassium), C$_{inulin}$ and C$_{PAH}$ in the contralateral control kidney during these experiments.

Infusion of taurocholate

Infusion into the renal artery of group 2 dogs closely mimicked the results of dilute bile infusion.

Infusion of bilirubin

Infusion into the renal artery of group 3 dogs did not change mean V, FE$_{Na}$ or U$_{K}$V.

Discussion

Our results show that intrarenal infusion of bile or sodium taurocholate has diuretic, natriuretic and kaliuretic activities. The diuretic activity is apparently dose-dependent and is terminated promptly after cessation of intrarenal infusion of the test substance. Glomerular filtration rate and renal plasma flow were not changed by intrarenal infusion of diluted bile, suggesting that when the renal circulation is intact bile does not have an acute nephrotoxic action.

Our present results with intrarenal infusion of bile in dogs are in agreement with previous similar experiments in which bile was infused into a systemic vein [9]. Our study confirms the previous findings that bile has diuretic properties, and extends that work [9] in showing (a) that it is the bile acids rather than the bilirubin in the bile
Diuretic action of bile acids

that have the natriuretic and kaliuretic properties, and (b) that this action is independent of any effect of bile on systemic haemodynamics.

Our study does not explain the mechanism of the natriuresis induced by bile salts. Bile acids interfere with intestinal fluid absorption by inhibiting Na⁺,K⁺-dependent ATPase [10]. It is possible that bile salts may also depress renal Na⁺,K⁺-ATPase activity, thus leading to natriuresis.

The present study suggests that acute cholaemia is associated with renal sodium and potassium wastage. This may aggravate volume and electrolyte depletion in patients with obstructive jaundice [2, 3] and contribute to their susceptibility to acute renal failure and shock.

References


