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COMMUNICATIONS

The effect of colestipol and cholestyramine on the systemic clearance of intravenous ibuprofen in rabbits

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Abstract—The effect of oral administration of the non-absorbable anion-exchange resins cholestyramine and colestipol on the systemic clearance and other pharmacokinetic parameters of intravenously administered ibuprofen (25 mg kg^{-1}) was studied in rabbits. Single doses of colestipol hydrochloride (0·4 g kg^{-1}) or cholestyramine (0·17 g kg^{-1}) were given 30 min before ibuprofen administration. In cholestyramine-treated rabbits a significant reduction in ibuprofen plasma concentration was observed compared with both control (water only) and colestipol-treated rabbits. Cholestyramine treatment resulted in a significant decrease in the terminal elimination half-life and the mean residence time. Furthermore, a 31% increase in the systemic clearance and 23% decrease in the area under the plasma concentration-time curve were also observed in cholestyramine-treated rabbits. Colestipol treatment did not change these parameters. The volume of distribution parameters (Vd_{ss} and Vd_{area}) did not change following either treatment. The changes in the pharmacokinetic parameters are compatible with an acceleration of ibuprofen elimination induced by oral administration of cholestyramine and not by colestipol. This effect is thought to be due to augmentation of net biliary excretion through enteric binding.

Colestipol and cholestyramine are polystyrene anion exchange resins which are primarily used in the treatment of type II hyperlipoproteinaemia (Hunninghake & Probstfield 1977). These agents bind cholesterol metabolites and bile acids to form insoluble complexes in the gastrointestinal tract and, therefore, interrupt their enterohepatic circulation and increase their faecal excretion. Such binding is not limited to bile acids, so concomitant oral administration of colestipol and cholestyramine have previously been shown to alter the rate and extent of absorption of a variety of drugs (Hunninghake 1980). Of more interest, however, is the observation that for some drugs, oral administration of either colestipol or cholestyramine produced a significant increase in the rate of elimination from plasma, even when these resins are administered during the post-absorptive phase or when the drugs were administered parenterally (Meinertz et al 1977; Payne et al 1981; Guentert et al 1988; Herman et al 1989; Al-Meshal et al 1990; Herman & Chaudhary 1991). The main proposed mechanism by which colestipol or cholestyramine enhance drug elimination is by interruption of enterohepatic circulation.

Ibuprofen is a widely prescribed non-steroidal agent with anti-inflammatory, analgesic, and antipyretic properties used in the treatment of rheumatoid arthritis, osteoarthritis, and mild to moderate pain. Previous studies on ibuprofen metabolism and excretion have shown that ibuprofen and its conjugated metabolites undergo substantial enterohepatic cycling (Dietzel et al 1990; Cole et al 1992). Interruption of this pathway in the intestine may accelerate the elimination of ibuprofen and decrease the plasma concentration of this drug. A previous report demonstrated that oral administration of cholestyramine enhances the systemic elimination of intravenously administered indomethacin (Al-Meshal et al 1990), a drug that has been shown to undergo significant enterohepatic cycling (Duggan et al 1975). It has been postulated that enterohepatic recirculation of indomethacin may be interrupted and, to a lesser extent the cholestyramine in the gut could bind the drug fraction that diffuses back from the blood into the gut lumen (Al-Meshal et al 1990).

This study was carried out to evaluate the effect of oral administration of cholestyramine and colestipol on the systemic clearance and other pharmacokinetic parameters of ibuprofen following intravenous administration to rabbits. Adsorption studies in-vitro were also performed.

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Materials and methods

Chemicals. Ibuprofen was obtained from Sigma Chemical Co. (St Louis, MO, USA). Cholestyramine (Questran) was obtained from Mead Johnson Laboratories (Evansville, IN, USA). Colestipol hydrochloride (Colestid) was obtained from the Upjohn Company (Kalamazoo, MI, USA). All chemicals, reagents and solvents used in this study were of analytical and HPLC grade.

Adsorption studies. Adsorption studies were carried out as previously described (El-Sayed et al 1990). Ibuprofen solutions (5–75 mg/50 mL, buffered at pH 7·5) were added to 500 mg colestipol hydrochloride and 500 mg cholestyramine in separate bottles. The bottles were shaken at 37 ± 0·5°C in a constant temperature water bath. After attaining equilibrium (3 h), ibuprofen was determined spectrophotometrically at 222 nm. Following adsorption from ibuprofen solutions (10 mg/50 mL for colestipol and 100 mg/50 mL for cholestyramine), desorption was determined by shaking the adsorbent-adsorbate mixture with 20 mL, pH 7·4, buffer solution for 20 min at 37°C. The amount of drug desorbed after three successive washings was determined.

Animal studies. New Zealand White male rabbits, 3·1–4·3 kg, were fasted for 24 h before and during the experiment, with free access to water. All animals, in a random fashion, received the drug intravenously and either Questran (cholestyramine equivalent, 0·17 g kg^{-1}) suspended in water (1 g/10 mL) (n = 8) or Colestid (colestipol hydrochloride, 0·4 g kg^{-1}) suspended in water (1 g/10 mL) (n = 8) for the treated groups, or water for the control group (n = 8) by gastric intubation. The marginal vein of one ear was cannulated with a polyethylene tube (Terumo 22 G) for blood sampling. Thirty minutes after cholestyramine, colestipol or water administration, ibuprofen (25 mg kg^{-1}) was injected over a period of 2 min into the marginal vein of the opposite ear. The intravenous dosing solution was prepared in a 0·03 M phosphate buffer, pH 7·4. Blood samples (2 mL each) were collected into heparinized blood collection tubes just before drug administration and at 0·25, 0·5, 0·75, 1·0, 1·5, 2·0, 2·5, 3·0, 3·5, 4·0, 4·5, and 5·0 h, post-drug administration. After centrifugation, plasma samples were taken and frozen pending analysis.

Determination of ibuprofen The concentration of ibuprofen in plasma was measured by a modification of the HPLC method of Snider et al (1981). The drug and the internal standard flurbiprofen (50 ng) were extracted from 0·5 mL plasma with 5 mL hexane:ether (8:2, v/v) after addition of 150 μL 1 M H_3PO_4. The organic layer was evaporated to dryness, the

residue was reconstituted in the mobile phase (200 μL), and a portion was injected into the chromatograph and eluted with acetonitrile:water:acetic acid (59:40·5:0·5, v/v/v). The liquid chromatographic system consisted of a Model 6000A solvent delivery pump, Model U6K injector, and a Model 481 UV detector, set at 233 nm. The column was a Nova Pak C_{18} column, 4-μm particles (all from Waters Associates, Milford, MA, USA). Mean recovery for the drug was 96·4%. The practical limit of the sensitivity of the method was about 0·4 μg mL^{-1}. The coefficient of variation between runs was 6·2%.

Pharmacokinetic analysis A nonlinear regression computer program PCNONLIN (Statistical Consultants, Inc., Lexington, KY, USA), was used to fit individual plasma ibuprofen concentrations to a first-order, two-compartment open model. Initial estimates of coefficients and exponentials required by PCNONLIN were obtained from exponential curves by the use of the stripping technique (Gibaldi & Perrier 1982). Selection of the most appropriate model was based upon the application of Akaike's criterion (Akaike 1978). Once the values of the coefficients and exponential terms were determined, the relevant pharmacokinetic parameters—terminal disposition half-life ($t_{\frac{1}{2}\beta}$), the apparent volume of distribution at steady-state (Vd_{ss}), the Vd_{area}, the area under the plasma concentration-time curve (AUC), the total systemic clearance (CL), the mean residence time (MRT), and the area under the moment curve (AUMC)—of the drug were calculated using compartmental and non-compartmental equations (Gibaldi & Perrier 1982).

Statistical analysis. The data are presented as means ± s.d. The *t*-test for unpaired data was employed to assess the effect of colestipol and cholestyramine treatment on the pharmacokinetic parameters. The pharmacokinetic parameters of ibuprofen in the three treatment groups were compared using one-way analysis of variance. Any statistical differences found among parameters were further compared using Dunnett's test (Bolton 1990). Differences between two related parameters were considered statistically significant for *P* values equal to or less than 0·05.

All analysis of the data was performed with a statistical software package (Statistical Analysis System; SAS Institute, Inc., Cary, NC, USA).

Results and discussion

The in-vitro adsorption of ibuprofen onto colestipol and cholestyramine followed the Freundlich adsorption isotherm (Fig. 1). The Freundlich constant (k) for adsorption was 1·04 and 94·0 mg g^{-1} for colestipol and cholestyramine, respectively. Three successive washings of the drug-adsorbent mixture, with 20 mL buffer solution, resulted in 53·4 and 7·5% desorption for colestipol and cholestyramine, respectively.

The administration of ibuprofen intravenously (25 mg kg^{-1}) to rabbits produced concentration-time profiles characterized by a biexponential decline in all of the rabbits used during the control and treatment phases. A two-compartment model was found to be adequate for the description of the pharmacokinetic behaviour of ibuprofen in the control, colestipol- and cholestyramine-treated rabbits.

The concentration-time curves of ibuprofen in the plasma with and without oral administration of colestipol and cholestyramine are shown in Fig. 2. Treatment with cholestyramine produced a significant reduction in ibuprofen plasma from 2 h onwards, however, ibuprofen over the 5-h sampling period was not significantly altered by colestipol administration (Fig. 2).

The pharmacokinetic parameters of ibuprofen during the control and treatment phases are presented in Table 1. Significant differences were noted between the control and cholestyramine-treated rabbits in the terminal elimination half-life ($t_{\frac{1}{2}\beta}$), MRT, CL and AUC. Administration of colestipol did not produce a statistically significant effect on the mean value of any parameter (Table 1). Cholestyramine and colestipol administration showed no significant effect on either Vd_{ss} or Vd_{area}.

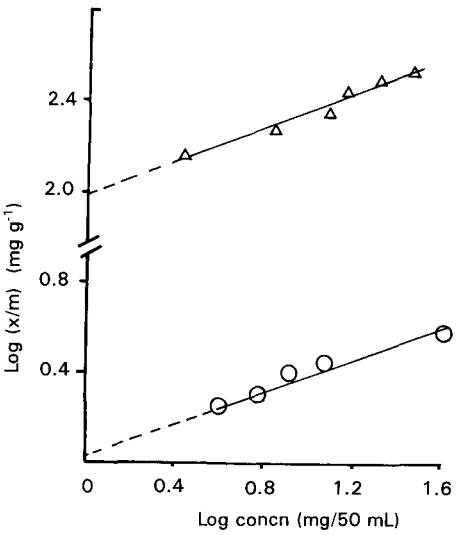

FIG. 1. Freundlich adsorption isotherms of ibuprofen on colestipol (○) and cholestyramine (△).

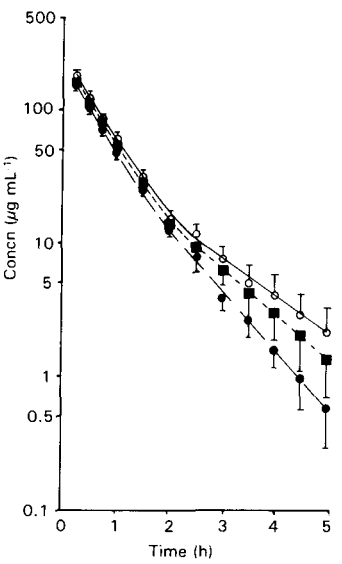

FIG. 2. Ibuprofen plasma concentrations following intravenous administration (25 mg kg^{-1}) to rabbits, after treatment with ○ water, ■ colestipol, or ● cholestyramine. Each point represents the mean ± s.d. of eight rabbits.

Oral administration of cholestyramine was effective in enhancing the systemic elimination of ibuprofen, as demonstrated by the observed increase in the systemic clearance and decrease in AUC and $t_{\frac{1}{2}\beta}$. Colestipol administration had no significant effect on the plasma half-life or systemic clearance of ibuprofen.

The proposed mechanism underlying the cholestyramine-induced enhancement of ibuprofen clearance may involve interruption of the enterohepatic circulation of ibuprofen that is excreted into the bile, either unchanged or as conjugated metabolites (which are converted back to ibuprofen in the gastrointestinal tract). Ibuprofen and its major metabolites were

Table 1. Pharmacokinetic parameters of ibuprofen administered intravenously (25 mg kg^{-1}) to rabbits with or without treatment with colestipol or cholestyramine administered orally.

Pharmacokinetic parameters	Control	Colestipol	Cholestyramine
AUC (μg h mL^{-1})	201·16 ± 13·20	189·99 ± 10·65	154·50 ± 12·01[a,b]
CL (mL h^{-1} kg^{-1})	124·82 ± 7·87	132·36 ± 7·63	162·54 ± 12·57[a,b]
Vd_{ss} (L kg^{-1})	0·12 ± 0·02	0·11 ± 0·02	0·13 ± 0·02
Vd_{area} (L kg^{-1})	0·19 ± 0·04	0·17 ± 0·03	0·16 ± 0·03
MRT (h)	1·02 ± 0·17	0·86 ± 0·11	0·75 ± 0·04[b]
$t_{\frac{1}{2}\beta}$ (h)	1·07 ± 0·21	0·89 ± 0·18	0·69 ± 0·12[b]

Each value represents the mean ± s.d. of eight rabbits. [a] $P < 0·05$ compared with colestipol. [b] $P < 0·05$ compared with control.

found to undergo substantial enterohepatic cycling; about 50% of an administered intravenous dose was excreted into the bile and most of the amount excreted in the bile was reabsorbed (Dietzel et al 1990). Therefore, the gastrointestinal lumen could be considered a major part of the extracellular space in which ibuprofen is distributed. Thus, the irreversible adsorption of ibuprofen or its metabolites onto cholestyramine is expected to accelerate the elimination of ibuprofen due to interruption of the enterohepatic cycling.

Alternatively, cholestyramine in the gut could bind ibuprofen that diffuses back from the bloodstream into the gut lumen (exsorption), termed gastrointestinal dialysis by Levy (1982). Ibuprofen is highly bound to plasma proteins (> 99%) (Lin et al 1987). Hence, the exsorbed amount of drug from blood to the gastrointestinal tract would be small, because unbound ibuprofen which can pass through the biomembrane constitutes only a small part of the total ibuprofen in plasma, and this may limit the efficacy of gastrointestinal dialysis. Nevertheless, this does not preclude its existence particularly at high plasma concentration, since the binding of ibuprofen to plasma proteins is saturable and the fraction not bound to plasma proteins increases as the dose of ibuprofen is increased (Shah & Jung 1987).

The apparent lack of effect of colestipol on the pharmacokinetic parameters of ibuprofen observed in this study, could be explained by assuming that the adsorption of ibuprofen onto colestipol in the gut is a reversible process or that the binding affinity is very low. The in-vitro adsorption studies support this explanation. Colestipol has a poor adsorption capacity for ibuprofen, and the Freundlich constant (k) for adsorption was 1·04 mg g^{-1} at equilibrium (3 h). Whereas, for cholestyramine, k was 94·0 mg g^{-1}. In addition, following repetitive washings 53·4% of the drug was desorbed in the case of colestipol and only 7·5% was desorbed in the case of cholestyramine.

In conclusion, cholestyramine enhances the systemic elimination of parenterally administered ibuprofen presumably by interrupting its enterohepatic recycling. This effect could also occur following concurrent oral administration, even when the two drugs are given at separate time intervals, and will result in lowering ibuprofen blood levels in patients who are concurrently treated with cholestyramine for hypercholesterolaemia.

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