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Effects of oral administration of colestipol and cholestyramine on the pharmacokinetics of ketoprofen administered intramuscularly in man

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Abstract

The effect of oral administration of the anion exchange resins colestipol hydrochloride (10 g) or cholestyramine (8 g) on the systemic clearance and other pharmacokinetic parameters of intramuscularly administered ketoprofen (50 mg) has been studied in six healthy male subjects. The study was performed according to a randomized three-way crossover design with a 1 week washout period between each treatment phase. After dosing, serial blood samples were collected for a period of 8 h. Plasma harvested from blood was analyzed for ketoprofen by a sensitive high-performance liquid chromatographic assay. Cholestyramine administration resulted in a significant reduction in ketoprofen plasma concentrations. No significant differences between colestipol-treated and control groups were observed in the calculated pharmacokinetic parameters (Cl, AUC, K_{el}, $t_{1/2}$ and MRT). Cholestyramine treatment resulted in a significant increase in the K_{el} (55%, $p < 0.01$), and Cl (32%, $p < 0.005$) and a significant decrease in the AUC (24%, $p < 0.001$), $t_{1/2}$ (33%, $p < 0.01$) and MRT (30%, $p < 0.001$). These results indicate an enhancement of ketoprofen elimination following cholestyramine administration and a lack of interaction between colestipol and ketoprofen.

Key words: Ketoprofen; Cholestyramine; Colestipol; Pharmacokinetic parameters

1. Introduction

Ketoprofen, a phenylpropionic acid derivative, is a non-steroidal anti-inflammatory drug widely used in the treatment of rheumatoid arthritis, degenerative joint disease and mild-to-moderate pain of various etiologies (Williams and Upton, 1988). The drug is rapidly and completely (100%) absorbed following oral, rectal and intramuscular administration (Ischizaki et al., 1980; Williams and Upton, 1988), has a low plasma clearance, short elimination half-life, and a low volume of distribution (Upton et al., 1981; Debruyne et al., 1987). The drug is eliminated from the body almost entirely via hepatic metabolism (Delbarre

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et al., 1976; Upton et al., 1980) and between 18 and 40% of an administered dose undergoes enterohepatic recirculation (Foster et al., 1988; Product Information Orudis®, 1992).

Colestipol and cholestyramine are polystyrene anion exchange resins which are primarily used in the treatment of type II hyperlipoproteinemia (Hunninghake and 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, therefore the concomitant oral administration of colestipol and cholestyramine has 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 were administered during the post-absorptive phase or when the drugs were administered parenterally (Meinertz et al., 1977; Payne et al., 1977; Guentert et al., 1988; Herman et al., 1989; Al-Meshal et al., 1990; Herman and Chaudhary, 1991; El-Sayed et al., 1994). The main proposed mechanism by which colestipol or cholestyramine enhance drug elimination following parenteral administration is by an interruption of enterohepatic circulation and/or binding of the drug that diffuses back from the blood stream into the gut lumen (Al-Meshal et al., 1990; El-Sayed et al., 1994).

This study demonstrates the effect of oral administration of cholestyramine and colestipol on the systemic clearance and other pharmacokinetic parameters of ketoprofen following intramuscular administration to healthy male volunteers. Adsorption studies in vitro were also performed.

2. Materials and methods

2.1. Adsorption study

The in vitro adsorption study was carried out at pH 7.4 (0.01 M phosphate buffer). Ketoprofen solutions (6.25–400 mg/100 ml) in the same buffer were added to glass vials containing 50 mg of either colestipol or cholestyramine resin. The vials were agitated at 37 ± 0.5°C in a constant temperature water bath. After attaining equilibrium (2 h), ketoprofen was determined spectrophotometrically at 258 nm. Following adsorption from ketoprofen solutions (25 mg/100 ml for colestipol and 200 mg/100 ml for cholestyramine), desorption was determined by shaking the adsorbent-adsorbate mixture with 10 ml of pH 7.4 buffer solution for 20 min at 37°C. The amount of drug desorbed after three successive washings was determined.

2.2. Subjects

Six healthy male adult volunteers participated in the study. Their age (mean ± SD) was 36.8 ± 2.9 years (range 32–40 years), body weight 73.2 ± 9.7 kg (range 60–83 kg) and height 171.3 ± 6.6 cm (range 163–178 cm). On the basis of medical history, physical examination and laboratory screening (hematology, blood biochemistry and urine analysis), no subject had a history or evidence of cardiac, renal, hepatic or gastrointenstinal disease or drug allergy. The volunteers were asked to abstain from taking any drug for at least 2 weeks prior to and during the study. Informed consent was obtained from the subjects after explaining the nature and purpose of the study. The study protocol was approved by the College of Medicine Research Center (CMRC), King Saud University, Riyadh.

2.3. Study design and plasma samples

The volunteers were studied on three different occasions in a randomized three-way crossover design with a 1 week washout period between each phase. Every subject received on the three occasions a single intramuscular injection of 50 mg ketoprofen (Profenid, 100 mg/5 ml, lot no. 23362, Specia, Rhone-Poulenc, France). 30 min prior to ketoprofen administration subjects received, in the fasting state (at least 10 h), either 10 g colestipol hydrochloride (suspended in 200 ml water) (Colestid®, Upjohn Co., Kalamazoo,

MI, U.S.A.) or 8 g cholestyramine (suspended in 200 ml water) (Questran®, Mead Johnson, Evansville, IN, U.S.A.). During the control phase the subjects took 200 ml of water only. Subjects were allowed to eat a standard breakfast at 3 h and a standard lunch at 7 h after drug administration. Beverages and food containing caffeine were not permitted over the entire course of the study. For a period of 8 h following drug administration, the volunteers were under direct medical supervision in an outpatient clinic.

Multiple blood samples (7 ml) were collected in evacuated glass tubes (heparinized vacutainers, Becton & Dickinson, CA, U.S.A.) through an indwelling cannula placed in the forearm veins before and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h after dosing. To avoid deconjugation of ketoprofen metabolites (Upton et al., 1980) each set of blood collection samples were immediately centrifuged, the plasma separated and stored frozen at −70°C pending analysis.

2.4. Analysis of plasma samples

Plasma concentrations of ketoprofen were quantitated by high-performance liquid chromatography (HPLC) according to a slightly modified method of Verbeeck et al. (1988). The drug was extracted with diethyl ether (6 ml) in 0.1 M phosphoric acid (300 μl) from a 1 ml plasma sample enriched with phenylbutazone as internal standard. After mixing, centrifugation and evaporation of the organic layer, the residue was dissolved in 200 μl of the mobile phase and ultracentrifuged before injection. The chromatographic conditions were as follows: column, μ Bondapak C_{18}; mobile phase, methanol/5 m M phosphate buffer adjusted to pH 6.8 (45:55%, v/v); flow rate, 1.2 ml/min; detection wavelength, 254 nm. The minimum detectable concentration in plasma is 50 ng/ml. The test samples from the dosed volunteers were always analyzed along with standard and quality control samples. Standard curves for the analyte in plasma were generated daily and were linear ($r > 0.999$) within the range of 0.1–10 μg/ml over the entire period of the study. The coefficient of variation for the slopes was 1.83%, which is indicative of high stability and precision for the assay.

2.5. Pharmacokinetic analysis

Pharmacokinetic parameters for ketoprofen were determined from the plasma concentration-time data. Non-compartmental analysis based on statistical moments was used to investigate the influence of colestipol and cholestyramine on ketoprofen kinetics (Yamaoka et al., 1978). The area under the plasma concentration-time curve up to the last time (t_{last}) showing a measurable concentration (C_{last}) of the analyte (AUC_t) was determined by using the linear trapezoidal rule. The apparent elimination rate constant (K_{el}) was calculated by the technique of least-squares regression from the data for the last five points of each plasma concentration-time curve. The AUC_∞ values were determined by adding the quotient of C_{last} and the appropriate K_{el} to the corresponding AUC_t. The sampling period covered, on average, 94% of the total AUC. The area under the first moment curve ($AUMC_t$) was estimated according to the linear trapezoidal rule and extrapolated to infinity using the following equation:

$$AUMC_\infty = AUMC_t + t_{last} \cdot C_{last}/K_{el} + C_{last}/K_{el}^2$$

The mean residence time (MRT) was calculated from the area under the moment curve divided by the area under the curve. The total body clearance (Cl/F) and the apparent volume of distribution at steady state (Vd_{ss}/F) (Benet and Galeazzi, 1979) were calculated using the following equations:

$$Cl/F = dose/AUC_\infty$$

$$Vd_{ss}/F = dose \cdot AUMC_\infty/(AUC_\infty)^2$$

2.6. Statistical analysis

The influence of colestipol and cholestyramine on the pharmacokinetic parameters of ketoprofen were evaluated statistically using one-way analysis of variance for repeated measurements. Student-Newman-Keul's test (SNK) and the least significant difference (LSD) method were applied to

find the source of possible differences between various treatment phases of the study. Plasma concentrations at each sampling time were also statistically analyzed by the above tests. Further, the contrast 'carry over' test for linear trend for residual effect of the phases was performed (Bolton, 1990). Differences between two related parameters were considered statistically significant for p values equal to or less than 0.05. All analyses of the data were performed with a statistical software package (Statistical Analysis System; SAS Institute, Inc., Cary, NC, U.S.A.).

3. Results

The data for in vitro adsorption of ketoprofen onto cholestyramine and colestipol were best fitted to the Freundlich isotherm. Ketoprofen was strongly adsorbed on cholestyramine (Freundlich K constant, 209.0 mg/g). Colestipol was found to be less efficient as an adsorbent with a K value of 14.8 mg/g. The strong adsorption of ketoprofen on cholestyramine was also reflected in the total amount desorbed after three successive washings, which was 2.4%. The amount desorbed from colestipol, on the other hand, was 9.3% indicating a relatively weaker affinity for ketoprofen.

The administration of ketoprofen intramuscularly produced concentration-time profiles characterized by a bioexponential decline in all of the subjects during the control and treatment phases. Fig. 1 depicts the mean plasma concentration-time curves for the six subjects after the three administration modes. Treatment with cholestyramine produced a significant reduction in ketoprofen plasma concentrations 1.5 h onwards ($p < 0.01$). However, ketoprofen concentrations over the 8 h sampling period were not significantly altered by colestipol administration.

The pharmacokinetic parameters of ketoprofen during the control and treatment phases are presented in Table 1. A significant decrease was observed between control and cholestyramine-treated subjects in both the terminal elimination half-life ($t_{1/2}$) (2.47 ± 0.38 and 1.64 ± 0.39 h for the control and cholestyramine-treated groups,

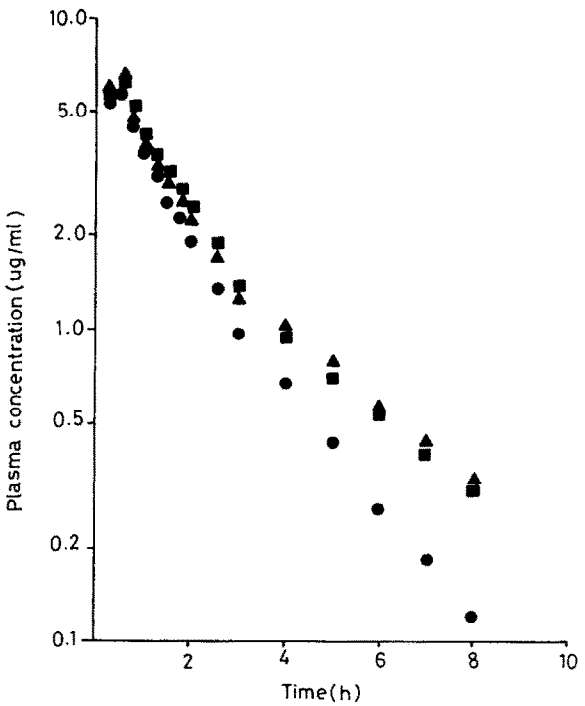

Fig. 1. Mean plasma concentrations of ketoprofen following intramuscular administration (50 mg) to six healthy male subjects, after treatment with (■) water, (▲) colestipol, or (●) colestyramine.

respectively) and the mean residence time (MRT) (2.95 ± 0.27 and 2.07 ± 0.23 h for the control and treated groups, respectively). Treatment with cholestyramine significantly increased the total systemic clearance (Cl/F) (3.53 ± 0.2 and 4.66 ±

Table 1
Pharmacokinetic parameters of keotoprofen administered intramuscularly (50 mg) to healthy subjects with or without treatment with colestipol and cholestyramine administered orally

Pharmacokinetic parameters	Control	Colestipol	Cholestyramine
AUC_∞ (μg h ml^{-1})	14.23 ± 0.86	14.38 ± 0.85	10.82 ± 1.07 [a]
Cl/F (l/h)	3.53 ± 0.21	3.49 ± 0.20	4.66 ± 0.46 [a]
Vd_{ss}/F (l)	10.38 ± 1.1	10.45 ± 0.76	9.61 ± 0.93
MRT (h)	2.95 ± 0.27	3.00 ± 0.25	2.07 ± 0.23 [a]
K_{el} (h^{-1})	0.29 ± 0.05	0.28 ± 0.03	0.44 ± 0.09 [a]
$t_{1/2}$ (h)	2.47 ± 0.38	2.52 ± 0.34	1.64 ± 0.39 [a]

Each value represents the mean ± S.D. of six subjects.
[a] $p < 0.05$ compared with control and colestipol.

0.46 l/h for the control and cholestyramine treatments, respectively) and resulted in a significant reduction in the area under the plasma concentration-time curve (AUC_∞) (14.23 ± 0.86 and 10.82 ± 1.07 μg h ml^{-1} for the control and cholestyramine treatments, respectively). The elimination rate constant (K_{el}) was also significantly increased following cholestyramine treatment (Table 1). The calculated apparent gastrointestinal clearance (clearance with cholestyramine minus clearance without cholestyramine) of ketoprofen was found to be 1.14 ± 0.29 l/h. There was no significant difference in the apparent volume of distribution at steady state (Vdss/F) between the control and cholestyramine-treated subjects (Table 1).

Colestipol administration, on the other hand, did not produce a statistically significant effect on the mean value of any pharmacokinetic parameters (Table 1).

The relative changes (treated/control) in the pharmacokinetic parameters of ketoprofen produced by cholestyramine administration are illustrated in Fig. 2. These changes are compatible with an acceleration of ketoprofen elimination induced by oral administration of cholestyramine.

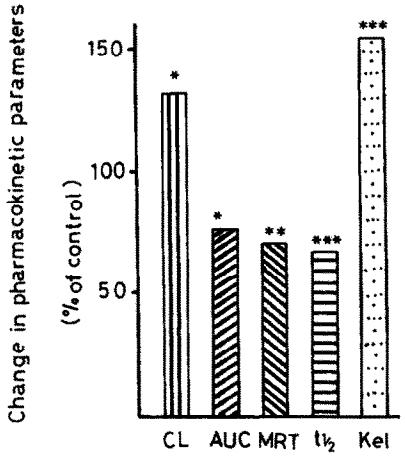

Fig. 2. Changes in pharmacokinetic parameters of ketoprofen administered intramuscularly (50 mg) following cholestyramine ingestion expressed as percent of control values. * $p < 0.005$, ** $p < 0.001$, *** $p < 0.01$.

No subject had any adverse effects associated with the administration of ketoprofen, cholestyramine or colestipol.

4. Discussion

The absorption of ketoprofen, following intramuscular administration, is rapid reaching a peak plasma concentration in about 25 min (range 15–30 min) of dosing in the control and treated subjects. No statistical difference was found between the three treatment groups in either the time or the magnitude of the peak generated (SNK and LSD). The disposition of ketoprofen in all subjects is characterized by a rapid initial distribution phase followed by a slower terminal elimination phase (Fig. 1).

The rate of ketoprofen elimination depended on resin administration. When cholestyramine was given the elimination rate constant increased (55%), and the elimination half-life was reduced (33%) compared to the control and colestipol treatments (Table 1 and Fig. 2). The difference reached statistical significance in both parameters ($p < 0.01$), and was caused by an increase in apparent systemic clearance (Cl/F) after cholestyramine treatment (32%, $p < 0.005$). As a consequence of the increased clearance in the presence of cholestyramine, the mean residence time of the drug in the body (MRT) and the area under the plasma concentration-time curve (AUC_∞) were decreased (30 and 24%, $p < 0.001$, respectively). However, the distribution of the drug was unaffected by cholestyramine; the apparent volume of distribution at steady state (Vd_{ss}/F) remained unchanged (Table 1). The change in pharmacokinetic parameters was independent of the treatment sequence (ANOVA), and is compatible with an acceleration of ketoprofen elimination induced by oral administration of cholestyramine. The calculated apparent gastrointestinal clearance (Cl with cholestyramine minus clearance without cholestyramine) of ketoprofen was found to be 1.14 ± 0.29 l/h. The values obtained for the Cl/F and Vd_{ss}/F in the control subjects are similar to those reported previously following oral and intravenous admin-

istration of ketoprofen to humans (Upton et al., 1981; Debruyne et al., 1987).

Colestipol administration, on the other hand, did not produce a statistically significant effect on the mean value of any pharmacokinetic parameters (Table 1).

The results of the one-way analysis of variance of the pharmacokinetic parameters, AUC_{∞}, Cl/F, MRT, Vd_{ss}/F, K_{el} and $t_{1/2}$ indicated that none of these variables showed any significant difference with regard to subject and period effects between the three treatments.

Cholestyramine is not absorbed after its oral administration and exerts its effect by sequestering the drug in the gut. The most plausible explanation for the enhanced elimination of ketoprofen following cholestyramine administration is by interruption of the enterohepatic circulation of ketoprofen that is excreted in the bile, either unchanged or as metabolites which are converted back to ketoprofen in the gastrointestinal tract, eventually causing their excretion in the faeces. Another alternative explanation is that cholestyramine enhances the rate of drug diffusion from the body into the gastrointestinal tract by efficiently adsorbing the drug from the gastrointestinal fluids, thus decreasing the amount of diffusable drug from these fluids and simultaneously increasing the concentration gradient which allow more drug to diffuse into the gut; this is often termed 'gastrointestinal dialysis' (Levy, 1982). Ketoprofen is highly bound to plasma proteins (> 90%) (Williams and Upton, 1988). Thus, the transported (exsorbed) amount of drug from blood to the gastrointestinal tract would be small because unbound ketoprofen which can pass through the biomembrane constitutes only a small part of the total ketoprofen in plasma, and this may limit the efficacy of gastrointestinal dialysis. Nevertheless, this does not preclude its existence.

Since cholestyramine is not absorbed into the systemic circulation, the possibility of enhanced elimination of ketoprofen as a result of enzyme induction or altered plasma protein binding of ketoprofen is remote. Furthermore, the increase in clearance observed occurs too rapidly to be due to enzyme induction.

The apparent lack of effect of cholestyramine on the volume of distribution (Vd_{ss}/F) could, at least in part, be explained by assuming that the adsorption of ketoprofen onto cholestyramine in the gut is practically an irreversible process or that the desorption of the drug from cholestyramine is very slow in comparison to the rate of adsorption. The in vitro adsorption and desorption studies support this explanation. Cholestyramine has a high adsorptive capacity for ketoprofen (209 mg/g), and a small amount (2.4%) of the drug is desorbed following repetitive washings. The unaltered volume of distribution observed in vivo is consistent with the nearly irreversible adsorption observed in vitro. The ketoprofen adsorbed onto cholestyramine in the gastrointestinal lumen is distant from the central pool of the drug in the body, therefore, the gastrointestinal tract in the presence of cholestyramine could represent an elimination compartment (Fig. 3).

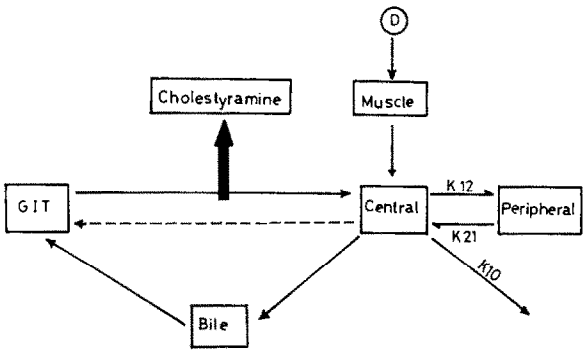

Fig. 3. The drug (D) is administered intramuscularly, absorbed to and eliminated from the central compartment, distributed into a peripheral compartment and secreted into the bile, passed into the gastrointestinal tract (GIT), then reabsorbed. The broken arrow indicates drug diffusion from the central compartment into the GIT (exsorption). The thick arrow shows interruption by cholestyramine.

The lack of effect of colestipol on the pharmacokinetic parameters of ketoprofen observed in this study could be explained by assuming that the adsorption of ketoprofen onto colestipol in the gut is a reversible process and/or that the binding affinity is very low. Colestipol has a poor adsorption capacity for ketoprofen in vitro with a maximum binding capacity of 14.8 mg/g, and a relatively larger amount (9.3%) of the drug is desorbed following repetitive washings. Similarly,

colestipol was found to have lower sorption capacity for bile acids compared to cholestyramine (Zhu et al., 1992).

In conclusion, significant interaction can occur between cholestyramine and ketoprofen in patients under concurrent therapy even if the latter is administered intramuscularly or the former is administered during the postabsorptive phase.

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