International Journal of Pharmaceutics, 64 (1990) 109–115
Elsevier

IJP 02127

Accelerated clearance of intravenous indomethacin by oral activated charcoal in rabbits

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(Received 25 January 1990)
(Accepted 14 March 1990)

Key words: Indomethacin; Activated charcoal; Enterohepatic cycling; Accelerated elimination; Pharmacokinetic parameters

Summary

The effect of oral activated charcoal on the systemic clearance and other pharmacokinetic parameters of intravenously administered indomethacin (2 mg /kg) was studied in rabbits. Following a single oral dose of activated charcoal (10 g), a significant reduction in indomethacin serum concentrations was observed. Charcoal treatment resulted in a significant decrease in the terminal elimination half-life (1.26 ± 0.14 and 0.82 ± 0.03 h for the control and treated groups, respectively) and the mean residence time (1.29 ± 0.14 and 0.79 ± 0.03 h for the control and treated groups, respectively). Further, a 68% increase in the systemic clearance (1.92 ± 0.19 and 3.23 ± 0.15 ml/min per kg for the control and treated rabbits, respectively) and 41% decrease in the area under the serum concentration-time curve (17.56 ± 1.82 and 10.34 ± 0.48 μg h/ml in the control and treated groups, respectively) were also noted. Charcoal administration did not significantly alter the volume of distribution (V_c, V_{ss} and V_{area}). Regarding the microconstants of the two-compartment pharmacokinetic model which adequately described indomethacin kinetic in the control and treated rabbits, charcoal administration produced a significant increase in the rate of transfer of indomethacin from the tissue compartment to the central compartment (K_{21}) and out of the central compartment (K_{10}). The results indicate that administration of oral activated charcoal accelerates the systemic elimination of indomethacin. This is presumably mediated by interruption of the enterohepatic circulation of indomethacin by activated charcoal.

Introduction

Indomethacin, a non-steroidal anti-inflammatory drug, is commonly used in the treatment of rheumatoid arthritis and other inflammatory states. The drug is eliminated from the body almost entirely via hepatic metabolism (Hucker et al., 1966); it has a low plasma clearance, short plasma half-life and a low volume of distribution (Kwan et al., 1975). Indomethacin is highly protein bound (Havidberg et al., 1972), and undergoes extensive enterohepatic recycling (Duggan et al., 1975; Kwan et al., 1975).

Despite a relatively high incidence of toxicity represented primarily by gastrointestinal and CNS adverse reactions, indomethacin is a widely prescribed drug for the treatment of acute and chronic inflammatory states (Day et al., 1987). It has been reported that indomethacin is almost equally toxic to the stomach whether given parenterally or or-

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ally (Whittle, 1981; Rainsford, 1982). In addition, it is claimed that intravenous administration is associated with more severe injury in the lower intestine than in the stomach (Cioli et al., 1979; Szabo et al., 1989).

Previous studies of indomethacin metabolism and excretion have shown that indomethacin and its conjugated metabolites undergo a significant enterohepatic cycle in most animal species and in man (Duggan et al., 1975). Furthermore, it was suggested that the existence of such a cycle in man appears to be an important if not a causative factor for intestinal lesions following indomethacin administration (Duggan et al., 1975).

Activated charcoal administered orally has been shown to increase the systemic clearance of many drugs, such as aspirin (Boldy and Vale, 1986; Prescott et al., 1986), paracetamol (Galinsky and Levy, 1984), dextropropoxyphene (Karkkainen and Neuvonen, 1985), morphine (El-Sayed and Hasan, 1990), phenobarbitone (Berg et al., 1982, 1987), diazepam (Traeger and Haug, 1980), carbamazepine (Neuvonen and Elonen, 1980), dapsone (Neuvonen et al., 1983), digoxin (Boldy et al., 1985), digitoxin (Pond et al., 1981), disopyramide (Huang, 1988; Arimori et al., 1989), gentamycin (Hasan et al., 1990), quinine (Lockey and Bateman 1989), and theophylline (Berlinger et al., 1983; Arimori and Nakano, 1985). The process by which oral activated charcoal enhances the systemic elimination of drugs has been termed 'gastrointestinal dialysis'.

Although it has been shown that activated charcoal avidly adsorbs and decreases the oral absorption of indomethacin following oral administration of both (Neuvonen and Olkkola, 1984), the effect of oral activated charcoal on the systemic clearance of indomethacin has not been investigated. Indomethacin and its metabolites undergo extensive enterohepatic cycling, and this can result in a delay in drug elimination from the body. Interruption of this pathway by oral activated charcoal may hasten the systemic elimination of indomethacin and decrease the side effects of the drug.

This study demonstrates the effect of oral activated charcoal on the systemic clearance and other pharmacokinetic parameters of indomethacin following intravenous administration to rabbits. Adsorption studies in vitro were also performed.

Materials and Methods

Chemicals

Indomethacin vials (5 mg/ml) were obtained from Dumex (Copenhagen, Denmark). Activated charcoal (Darco G60, particle size mainly 50–150 μm) was obtained from Fluka (Buchs, Switzerland) and was used without pretreatment. All chemicals, reagents, and solvents used in this study were of analytical and HPLC grade.

Adsorption study

The in vitro adsorption studies was carried out at pH 7.5 (0.05 M phosphate buffer). Indomethacin solution in the same buffer was added, in separate bottles, to 100 mg of activated charcoal and the volume was adjusted to 50 ml. Indomethacin concentration ranged from 5 to 50 mg/50 ml. The bottles were shaken in a constant temperature water bath at 37 ± 0.5°C. After attaining equilibrium (1 h), aliquots were filtered (Millipore, 0.45 μm) and indomethacin was determined spectrophotometrically at 265 nm. Following adsorption from indomethacin 25 mg/50 ml solution, desorption was determined by shaking the adsorbent-adsorbate mixture with 20 ml 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 (3–5 kg) were used. The animals were fasted for 48 h before and during the experiment, and water was allowed ad libitum. Animals were immobilized in a restraining box during drug administration, and when blood samples were taken. All animals, in a random fashion, received the drug intravenously and either activated charcoal suspended in water (10 g/40 ml) for the treated group ($n = 6$), or water (40 ml) for the control group ($n = 6$) by gastric intubation. No suspending agent was employed in the preparation of charcoal and the suspension

was administered soon after shaking. The marginal vein of one ear was cannulated with a polyethylene tube (Terumo 22G) for blood sampling. 30 min after charcoal administration, indomethacin (2 mg/kg) was injected over a period of 1 min into the marginal vein of the opposite ear where the tube is introduced. Blood samples (1.5 ml each) were collected into glass tubes just prior to drug administration and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, and 6.0 h post-drug administration and allowed to clot. Serum samples were taken after centrifugation and frozen until assayed.

Analysis of indomethacin

Indomethacin serum concentrations were assayed using a specific and sensitive high-performance liquid chromatographic procedure (Al-Angary et al., 1990). This assay involves extraction of the serum samples with diethyl ether after acidification with glacial acetic acid, evaporation to dryness, followed by elution with a 4 μm C-18 reversed phase column using a mobile phase consisting of ethanol : water : glacial acetic acid (65 : 34 : 1%, v/v), at a flow rate of 1.3 ml/min, with UV detection at 254 nm. Quantitation was achieved by the measurement of the peak area ratio of indomethacin to an internal standard (itraconazole), and the absolute recoveries ranged from 94 to 97% over the concentration range 0.1–10 μg/ml. The within-day coefficient of variation (CVs) ranged between 2.7 and 5.7%, while the between-day CVs ranged between 3.6 and 6.1%.

Pharmacokinetic analysis

The data on serum indomethacin concentrations after intravenous administration were analyzed by a linear two-compartment open model with elimination from the central compartment. The concentration of indomethacin in serum (C_p) was described by the following equation:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

where A, B, α and β denote hybrid constants and t is the time. The relevant pharmacokinetic parameters such as the terminal elimination half-life ($t_{1/2}\ \beta$), the apparent volume of distribution at steady-state (V_{ss}), volume of the central compartment (V_c) the V_{area}, the area under the serum concentration-time curve (AUC), the total systemic clearance (Cl) and the mean residence time (MRT) of the drug were calculated using the following equations (Gibaldi and Perrier, 1982):

$$t_{1/2}\beta = \frac{0.693}{\beta}$$

$$\mathrm{AUC}_{0\to\infty} = \frac{A}{\alpha} + \frac{B}{\beta}$$

$$V_{ss} = \frac{\mathrm{Dose}_{\mathrm{i.v.}}\ \mathrm{AUMC}}{(\mathrm{AUC})^2}$$

$$V_{area} = \frac{\mathrm{Dose}_{\mathrm{i.v.}}}{\mathrm{AUC}\cdot\beta}$$

$$\mathrm{Cl} = \frac{\mathrm{Dose}_{\mathrm{i.v.}}}{\mathrm{AUC}}$$

$$\mathrm{MRT} = \frac{\mathrm{AUMC}}{\mathrm{AUC}}$$

where AUMC is the area under the moment curve.

Statistical analysis

The data are presented as mean $\pm$ S.D. (standard deviation). The t-test for unpaired data (two-tailed) was employed to assess the effects of charcoal treatment on the pharmacokinetic parameters. Differences between two related parameters were considered statistically significant for p values equal to or less than 0.05.

Results

The in vitro adsorption of indomethacin onto charcoal followed the Langmuir adsorption isotherm (Fig. 1). The limiting adsorptive capacity (reciprocal of slope of the isotherm) was calculated by linear regression and was found to be 280 mg/g.

The administration of indomethacin (2 mg/kg) to control and charcoal-treated rabbits produced

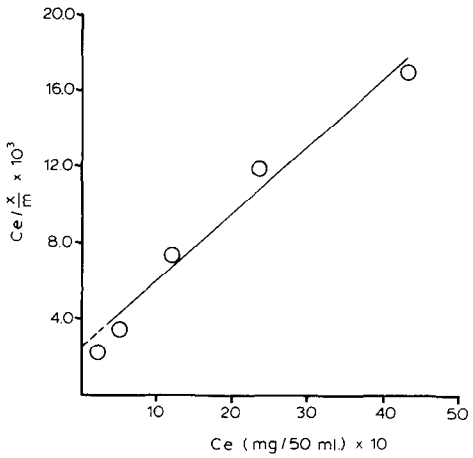


Fig. 1. Langmuir adsorption isotherms of indomethacin on charcoal.

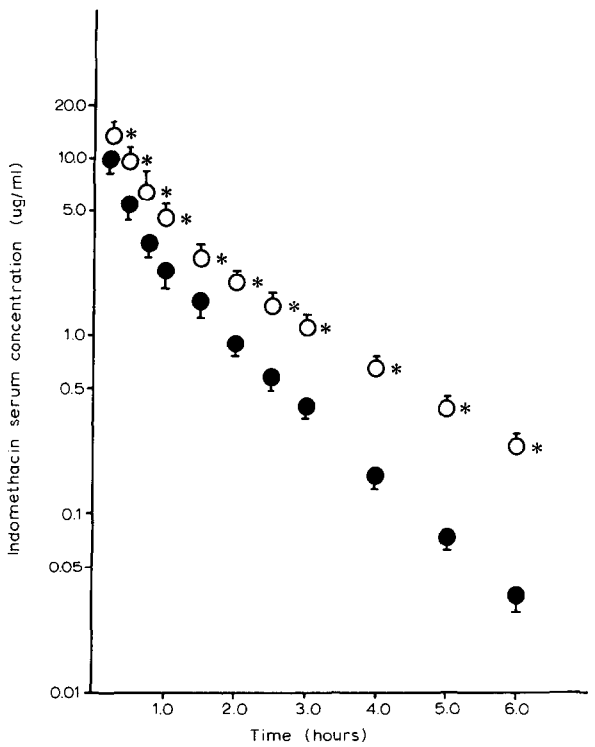


Fig. 2. Serum indomethacin concentrations after intravenous administration (2 mg/kg) to rabbits with (●) and without (○) pretreatment with activated charcoal. Each point represents the mean ± S.D. of 6 rabbits. * $p < 0.001$.

serum-concentration profiles that were adequately described by a two-compartment open model with linear pharmacokinetics. Fig. 2 shows the time course of the serum indomethacin level after intravenous administration to rabbits with or without treatment with activated charcoal. Oral administration of activated charcoal produced significant reduction in indomethacin serum concentration from 0.25 h onwards, but charcoal treatment did not affect the general shape of the serum concentration-time curve (Fig. 2).

The calculated pharmacokinetic parameters of indomethacin in the control and treated rabbits are presented in Table 1. Significant differences were noted between the control and charcoal treated rabbits in the terminal elimination half-life

TABLE 1

Pharmacokinetic parameters of indomethacin administered intravenously (2 mg/kg) to rabbits with or without treatment with activated charcoal administered orally [a]

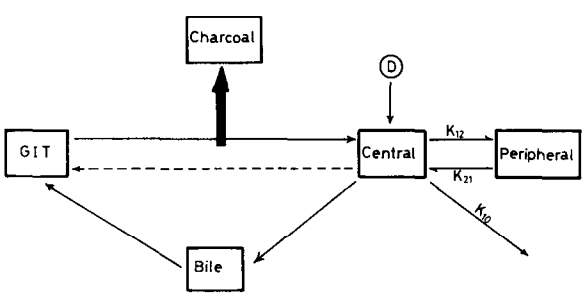
Pharmacokinetic parameter	Control	Treated	Significance *P*
AUC (μg h/ml)	17.56 ± 1.82	10.34 ± 0.48	< 0.001
Cl (ml/min per kg)	1.92 ± 0.19	3.23 ± 0.15	< 0.001
V_c (ml/kg)	84.56 ± 6.41	88.48 ± 6.17	N.S.
V_{ss} (ml/kg)	147.18 ± 19.61	152.92 ± 10.03	N.S.
V_{area} (ml/kg)	209.37 ± 37.41	229.75 ± 13.78	N.S.
MRT (h)	1.29 ± 0.14	0.79 ± 0.03	< 0.001
$t_{1/2}$ (h)	1.26 ± 0.14	0.82 ± 0.03	< 0.001
K_{12} (h^{-1})	0.82 ± 0.11	0.9 ± 0.16	N.S.
K_{21} (h^{-1})	1.14 ± 0.14	1.58 ± 0.12	< 0.001
K_{10} (h^{-1})	1.37 ± 0.15	2.21 ± 0.12	< 0.001

[a] Each value represents the mean ± S.D. of 6 rabbits.
[b] Student's *t*-test.

($t_{1/2}$ β) (1.26 ± 0.14 and 0.82 ± 0.03 h for the control and treated groups, respectively) and the mean residence time (MRT) (1.29 ± 0.14 and 0.79 ± 0.03 h for the control and treated groups, respectively). Charcoal administration showed no significant effect on either V_c, V_{ss} and V_{area} (Table 1), but the clearance was significantly increased (1.92 ± 0.19 and 3.23 ± 0.15 ml/min per kg for the control and treated rabbits, respectively) and AUC significantly decreased (17.56 ± 1.82 and 10.34 ± 0.48 μg h/ml in the control and charcoal treated rabbits, respectively). The calculated apparent gastrointestinal clearance (Cl with charcoal − Cl without charcoal) of indomethacin was found to be 1.31 ml/min per kg.

Regarding the microconstants of the two compartments (Scheme 1), no significant differences were noted in the rate of transfer of indomethacin from the central compartment to the tissue compartment (K_{12}) between the control and treated rabbits (Table 1). However, a marked increase was observed in the rate of transfer of indomethacin from the tissue compartment to the central compartment (K_{21}), and out of the central compartment (K_{10}).

The relative changes (treated/control) in the pharmacokinetic parameters of indomethacin produced by activated charcoal are illustrated in Fig. 3. These changes are compatible with a significant increase in indomethacin elimination produced by activated charcoal. Oral administration of activated charcoal induced a significant decrease in $t_{1/2}\beta$ (35.1%), MRT (38.7%), and AUC (41.1%), and a



Scheme 1. The drug (D) is administered intravenously, eliminated from the central compartment, distributed into a peripheral compartment and secreted into the bile, passed into the GIT, then reabsorbed. Broken arrow indicates drug diffusion from the central compartment into the GIT (exsorption). The thick arrow shows interruption by activated charcoal.

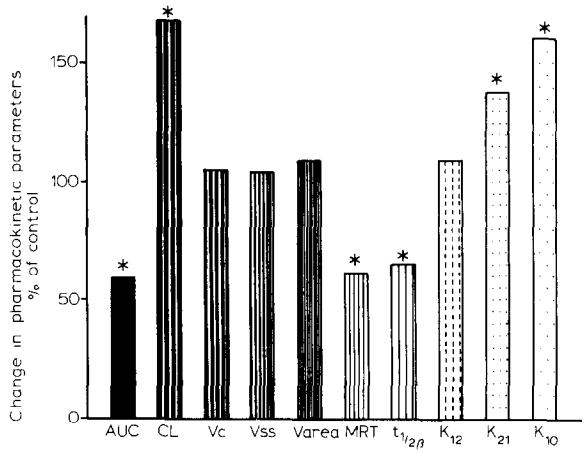


Fig. 3. Changes in the pharmacokinetic parameters of indomethacin administered intravenously (2 mg/kg) expressed as percent of control values. * $p < 0.001$.

significant increase in Cl, K_{21} and K_{10} values to 68.2, 38.6 and 61.3%, respectively. The changes in K_{12}, V_c, V_{ss} and V_{area} parameters were not statistically significant (Fig. 3).

Discussion

The results of this investigation demonstrate that orally administered activated charcoal, following intravenous administration of indomethacin, is effective in enhancing the systemic elimination of indomethacin in rabbits. Charcoal administration resulted in a significant decrease in the terminal elimination half-life and the mean residence time, and a significant increase in indomethacin clearance by 68% (Table 1 and Figs 2 and 3). Increase in elimination is further established by the significant reduction in AUC (about 41%) in the charcoal-treated rabbits (Table 1 and Fig. 3).

The lack of significant changes in the volume of distribution parameters (V_c, V_{ss} and V_{area}) shows that the adsorption of indomethacin onto activated charcoal in the gut is an irreversible process, or the desorption of the drug from charcoal is very slow in comparison to the rate of adsorption. This is in agreement with the in vitro studies which showed a high affinity of charcoal for indomethacin (280 mg/g). Only 1.2% of the drug was de-

sorbed following repetitive washings. Thus, our findings correlate with the suggestion that charcoal in the gut functions as a route of elimination rather than a distribution compartment (Huang and Tozu, 1986; El-Sayed and Hasan, 1990). The significant enhancement in the tissue compartment rate constant (K_{21}) and the rate of transfer out of the central compartment (blood) (K_{10}) show clearly that charcoal modulates not only elimination of indomethacin but also the rate of transfer from the peripheral tissue to the central compartment.

Two main mechanisms have been suggested for the enhancement of drug clearance by activated charcoal. Pond (1986) proposed that activated charcoal interrupts the enterohepatic circulation of compounds that are excreted into the bile, either unchanged or as metabolites that are converted back to the parent compound in the gastrointestinal tract. Another mechanism (Levy, 1982; Pond, 1986) postulates that activated charcoal 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 allows more drug to diffuse into the gut; this is often termed 'gastrointestinal dialysis'.

Indomethacin is highly bound to plasma proteins (> 90%) (Havidberg et al., 1972). Thus, the transported (exsorbed) amount of drug from blood to the gastrointestinal tract would be small because unbound indomethacin which can pass through the biomembrane constitutes only a small part of the total indomethacin in plasma, and this may limit the efficacy of gastrointestinal dialysis. Neverthless, this does not preclude its existence.

Indomethacin and its major conjugated metabolites were found to undergo extensive enterohepatic cycling, and between 21 and 41% of an administered dose of indomethacin is excreted in the feces due to biliary secretion (Duggan et al., 1972). Furthermore, based upon theoretical considerations, Kwan et al. (1975) estimated that between 24 and 115% of an intravenous dose undergoes biliary secretion and reabsorption. Therefore, the gastrointestinal lumen could be regarded as a main part of the extracellular space into which indomethacin is distributed. Thus, the irreversible adsorption of indomethacin, or its metabolites, that is excreted and/or exsorbed into the lumen of the gastrointestinal, onto charcoal is expected to accelerate the elimination of indomethacin due to interruption of the enterohepatic cycling (Scheme 1).

Since charcoal is not absorbed into the systemic circulation, the possibility of enhanced elimination of indomethacin as a result of enzyme induction is remote. Furthermore, the increase in clearance observed occurs too rapidly to be due to enzyme induction.

Duggan et al. (1975) developed a pharmacokinetic model, taking into account the extent and duration of enterohepatic circulation of indomethacin to predict the total exposure of the intestinal mucosa to the drug. A highly significant correlation between total biliary secretion of indomethacin and the sensitivity to intestinal lesions was achieved in rabbits and in man (Duggan et al., 1975). Furthermore, the ratio of biliary clearance to total plasma clearance of indomethacin in rabbits and in man is reported to be the same (Duggan et al., 1975). Therefore, the rabbit can be considered as a useful animal model to investigate the effect of charcoal on the gastrointestinal dialysis of indomethacin.

In conclusion, orally administered activated charcoal increases the clearance of indomethacin in rabbits. Because of reported similarities between man and rabbit in regard to the extent of biliary secretion of indomethacin, it is expected that charcoal can increase the clearance of the drug in man. Thus, charcoal treatment of acute poisoning is promising, even if a significant amount of indomethacin has been absorbed or if the drug is given by the injection route.

Acknowledgements

The authors would like to acknowledge the support of the Research Center, College of Pharmacy, King Saud University, for this research through Grant No: CPRC-39. Efficient typing by Mr K. Abbas is gratefully acknowledged.

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