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Pharmacokinetic Modelling of the Effect of Activated Charcoal on the Intestinal Secretion of Theophylline, using the Isolated Vascularly Perfused Rat Small Intestine

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Abstract—The effect of activated charcoal administration on the secretion of theophylline from the blood into the intestinal lumen has been examined by use of the rat isolated vascularly perfused small intestine. A closed two compartment model was used to analyse the vascular and luminal concentration-time curves obtained. An equation was derived to calculate the time-dependent intestinal clearance. From control experiments it was concluded that theophylline is secreted by a diffusional transport system through the intestinal wall. The intestinal clearance declined rapidly with time as a result of the concomitant increase in luminal theophylline concentration. After 120 min a steady state between the vascular and luminal perfusate was established. Administration of activated charcoal in the lumen had a profound effect on the kinetics of the drug. The vascular steady state concentration was depressed dramatically. The theophylline clearance remained nearly constant with time, because the blood to lumen concentration gradient was maximized. The maximal value for the intestinal theophylline clearance was estimated to be 0·88 mL min^{-1} and it equalled the value for the intestinal blood flow at the absorptive site. By use of the concept of absorptive site blood flow, the maximal effect of charcoal on systemic theophylline clearance could be adequately predicted for rats, dogs and man. Activated charcoal administration is only useful to enhance the systemic clearance of drugs or toxicants if that clearance is of the same order of magnitude as the absorptive site blood flow or lower.

Intestinal secretion may be an important route of elimination for both endogenous chemicals and xenobiotics (Lauterbach 1977; Dayton et al 1983). Secretion may occur by diffusion across the epithelial barrier and by specialized transport systems. Various methods have been described to use this excretion route as a means of detoxification (Israili & Dayton 1984). One possibility is oral dosing with activated charcoal to accelerate intestinal secretion. This concept of gastrointestinal dialysis was introduced by Levy (1982). Several studies indicate that oral administration of activated charcoal does enhance the systemic clearance of carbamazepine and phenylbutazone (Neuvonen & Elonen 1980), phenobarbitone (Berg et al 1982), digoxin (Lalonde et al 1985) and theophylline (Berlinger et al 1983; Park et al 1983; Arimori & Nakano 1985, 1986; Goldberg et al 1987; McKinnon et al 1987). Extensive adsorption of a drug on charcoal producing an increase in the blood to lumen concentration gradient for unbound drug, was proposed to be the underlying mechanism. In addition, prevention of reabsorption of the drug, secreted into the lumen via the bile, can also explain the phenomenon (Levy 1982; Pond 1986).

To seek other drugs as possible candidates for gastrointestinal dialysis a screening system is needed. In this study we demonstrate that the rat isolated vascularly perfused small intestine can be used to study the effect of activated charcoal on the intestinal secretion of theophylline. This permits us to take many samples of both vascular and luminal perfusate. Pharmacokinetic analysis of the concentration-time curves was performed to clarify the mechanism of clearance enhancement. Theophylline was chosen as a model drug because in rats a considerable amount of it is excreted in the intestinal lumen, but not in the bile (Arimori & Nakano 1985, 1988). McKinnon et al (1987) postulated that the clearance enhancement can be explained by the binding of theophylline on the charcoal after it has entered the lumen by diffusion across the intestinal wall. Moreover, in man oral dosing with charcoal resulted in a significant decrease in half-life (Berlinger et al 1983; Park et al 1983).

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Materials and Methods

Chemicals

The activated charcoal suspension was obtained from the pharmacy of the University Hospital, Utrecht (AZU) and was composed as follows: Activated charcoal (Norit A Supra R) 40 g, glycerol 85% 20 g, water (distilled) to 200 g. Perfluorotributylamine (FC43) was obtained from 3M company (Leiden, The Netherlands). All other chemicals were of the highest grade available and used as such.

Rats

Male Wistar rats (Cpb: WU, TNO, Zeist, The Netherlands, 230–260 g) which had free access to food (Muracon-1, Trouw, Nijkerk, The Netherlands) and tapwater, were used. The animals were fasted for 16–20 h before the experiment.

Perfusion set up

The entire small intestine of the rat was isolated and perfused as described elsewhere (Hartmann et al 1984). Briefly, rats

were anaesthetized by an intraperitoneal injection of pentobarbitone sodium (60 mg kg^{-1}). Sodium heparin (1000 iu) was administered by an intravenous injection into the tail vein. After cannulation of the superior mesenteric artery and the portal vein, the vascular bed was perfused. The small intestine was excised and transferred to a tissue bath. The tissue bath was placed in a perfusion chamber, kept at 37°C. Finally the lumen was cannulated and the contents were washed out with warm saline. The luminal and vascular perfusate were recirculated at a rate of 1 mL min^{-1} and 5 mL min^{-1}, respectively. The volumes of luminal and vascular perfusate were 30 mL and 100 mL, respectively (Fig. 1).

Vascular perfusion medium

The vascular perfusion medium consisted of a modified Krebs-Henseleit buffer, containing perfluorotributylamine (FC43; 20% w/v) as artificial oxygen carrier (Hartmann et al 1984). The medium was gassed with 95% O_2/5% CO_2 through a multibulb oxygenator.

Viability

The viability of the fluorocarbon-perfused preparation has been demonstrated (Hartmann et al 1984; de Vries et al 1988a). According to the criteria (rate of glucose utilization, lactate/pyruvate ratio, pH, oxygen utilization and perfusion pressure) the intestinal preparation should remain viable for at least 3 h.

Experimental design

Theophylline (2·0 mg) was administered as a bolus into the vascular perfusate and the excretion of theophylline into the luminal perfusate was measured. The luminal perfusion medium was either aqueous 0·9% NaCl (control experiments) or activated charcoal suspension (diluted at a 1:2 ratio with aqueous 0·9% NaCl) (activated charcoal experiments). Samples (0·2 mL) of vascular and luminal perfusate were taken during 180 min.

Analysis of theophylline

The concentration of theophylline in samples of vascular and luminal perfusate was determined by Fluorescence Polarization Immunoassay (TDx, Abbott). Sensitivity was 0·51 μg mL^{-1}. The coefficient of variation (between runs) was 1·65% (16 μg mL^{-1}). Samples of the luminal perfusate, containing activated charcoal, were centrifuged before analysis.

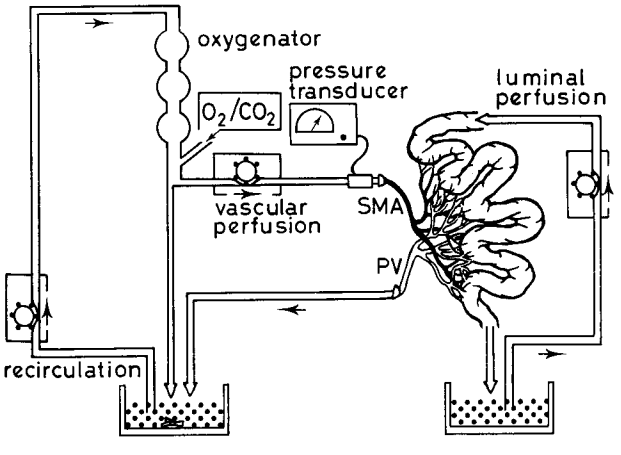

FIG. 1. Diagrammatic representation of the perfusion apparatus and circuit. SMA = superior mesenteric artery. PV = portal vein.

Pharmacokinetic analysis

The data were analysed according to a closed two compartment model. Compartment 1 represents the vascular perfusate and all readily accessible intestinal tissues. The second compartment represents the luminal perfusate.

The differential equations, describing the rate of change in the amount of drug in the compartments are:

$$\frac{dQ_1(t)}{dt} = -k_{12}Q_1(t) + k_{21}Q_2(t)$$

$$\frac{dQ_2(t)}{dt} = k_{12}Q_1(t) - k_{21}Q_2(t)$$

Solving these differential equations yields:

$$c_1(t) = \frac{D}{V_1} \times \frac{k_{12}}{k_{12}+k_{21}} \times e^{-(k_{12}+k_{21})\times t} + \frac{D}{V_1} \times \frac{k_{21}}{k_{12}+k_{21}} \quad (1)$$

$$c_2(t) = \frac{D}{V_2} \times \frac{k_{12}}{k_{12}+k_{21}} \times (1-e^{-(k_{12}+k_{21})\times t}) \quad (2)$$

Where $Q_i(t)$ = amount in compartment i at time t (μg);
$c_i(t)$ = concentration in compartment i at time t (μg mL^{-1});
k_{ij} = first order intercompartmental transfer rate constant (min^{-1});
D = doses administered in vascular perfusate (μg);
V_i = volume of distribution of compartment i (mL),

when $t -> \infty$ the term $e^{-(k_{12}+k_{21})\times t}$ will approach zero.

Equations 1 and 2 will then reduce to:

$$c_1(\infty) = \frac{D}{V_1} \times \frac{k_{21}}{k_{12}+k_{21}} \quad (3)$$

$$c_2(\infty) = \frac{D}{V_2} \times \frac{k_{12}}{k_{12}+k_{21}} \quad (4)$$

For a drug secreted into the lumen by a diffusional process:

$$c_1(\infty) = c_2(\infty) = \frac{D}{V_1} \times \frac{k_{21}}{k_{12}+k_{21}} = c_{ss} \quad (5)$$

where c_{ss} = concentration in vascular and luminal perfusate at steady state (μg mL^{-1})

Equations 1 and 2 can now be rearranged, employing the relationship $c_0 = D/V_1$ and equation 5:

$$c_1(t) = (c_0 - c_{ss}) \times e^{-\alpha\times t} + c_{ss} \quad (6)$$

$$c_2(t) = c_{ss} \times (1-e^{-\alpha\times t}) \quad (7)$$

where α = $k_{12}+k_{21}$,
c_0 = initial concentration in the vascular perfusate (μg mL^{-1})

Subtraction of equation 7 from 6 yields the relationship

between the blood to lumen concentration-gradient and time:

$$c_l(t) - c_2(t) = c_0 \times e^{-\alpha \times t}$$

or

$$\ln(c_l(t) - c_2(t)) = \ln c_0 - \alpha \times t \quad (8)$$

If secretion occurs by a diffusional process, a plot of the blood to lumen concentration-gradient versus time is monoexponential (slope $= -\alpha$).

The theophylline clearance at time t was calculated as:

$$Cl_t = -\frac{\frac{dQ_l(t)}{dt}}{c_l(t)} \quad \text{or}$$

$$Cl_t = \frac{k_{12} \times V_1 \times c_l(t) - k_{21} \times D + k_{21} \times V_1 \times c_l(t)}{c_l(t)} \quad (9)$$

The obtained vascular and luminal perfusate concentration curves were fitted separately and/or simultaneously, using a non-linear extended least squares algorithm (MK model version 1·0) (Holford 1983). This program enables simultaneous fitting of vascular and luminal concentration-time curves, yielding the best parameters to describe these independently measured profiles.

Statistical analysis

This was done using Student's *t*-test. Average values are expressed as mean ± standard deviation.

Results

Control

Fig. 2 shows concentration-time profile of theophylline in the vascular perfusate, with aqueous 0·9% NaCl as the luminal perfusion medium. After 120 min steady state concentration was reached. The curve of the time course of theophylline in the luminal perfusate is also shown. Recovery of theophylline in luminal and vascular perfusate during the 180 min was complete (97·2 ± 1·7%). Therefore, we used a closed, two compartment model in the pharmacokinetic analysis. On fitting the vascular and luminal curves separately, according to the equations 1 and 2, we found no significant difference between the steady state concentrations of theophylline in the vascular and luminal perfusate ($c_l(\infty) = 14{\cdot}1 \pm 0{\cdot}6$ and $c_2(\infty) = 13{\cdot}6 \pm 1{\cdot}7$ $\mu g\ mL^{-1}$, respectively). The difference between the concentration in the vascular and the luminal perfusate was plotted versus time on a semilogarithmic scale, according to equation 8. A correlation coefficient of at least 0·99 was obtained for the linear regression of these curves. For a representative experiment this is shown in Fig. 3. These results strongly suggest that theophylline passes from blood into the intestinal lumen by a diffusional process.

Activated charcoal

When activated charcoal was present in the luminal perfusate, equilibrium was not established within 180 min (Fig. 4). Theophylline was not detectable in the supernatant of the luminal perfusate. After 180 min, 23% of administered theophylline was found in the vascular perfusate as opposed to 70% in control experiments.

Pharmacokinetic analysis

The results of the pharmacokinetic analysis are summarized in Table 1. For the control experiments we fitted the vascular and luminal concentration-time curves simultaneously, according to equations 6 and 7. This procedure yielded the best parameters to describe the independently measured

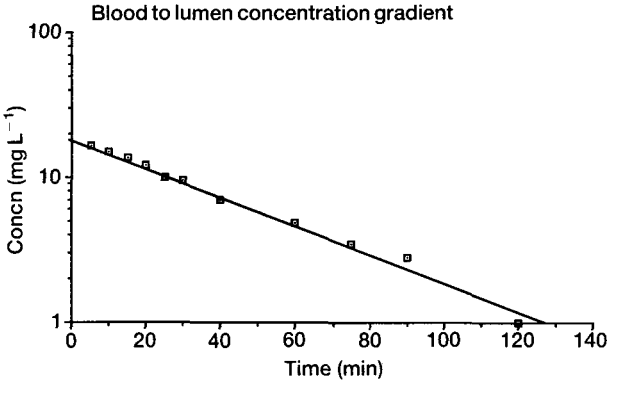

FIG. 3. Logarithmic plot of the driving force for secretion ($c_l - c_2$) versus time, according to equation 8 (representative experiment).

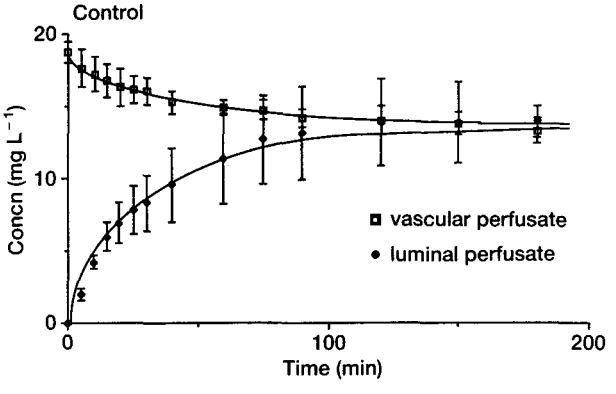

FIG. 2. Theophylline secretion in the isolated vascularly perfused intestine (control experiments ± s.d.; n = 4) □ concentration in vascular perfusion medium, ◆ concentration in luminal perfusion medium.

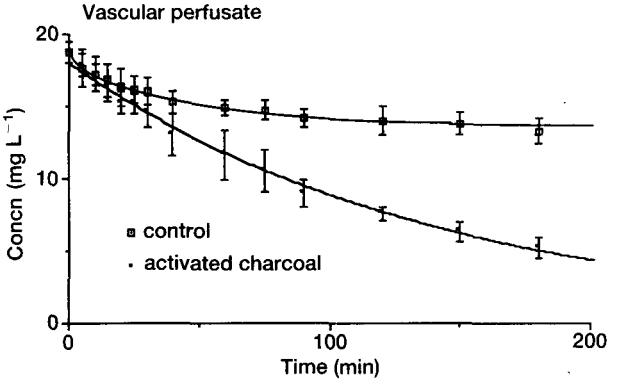

FIG. 4. Effect of activated charcoal on the theophylline secretion. □ concentration in vascular perfusate (control experiments ± s.d.; n = 4), ■ concentration in vascular perfusate (activated charcoal experiments ± s.d.; n = 4).

Table 1. Pharmacokinetic parameters for the secretion of theophylline into the lumen. (Control and activated charcoal experiments ± s.d.)

	Control	Activated charcoal
D (μg)	2000	2000
V_1 (mL)	110 ± 1	109 ± 1
α (min^{-1})	0·0250 ± 0·0010	0·0093 ± 0·0008*
c_{ss} (μg mL^{-1})	13·8 ± 0·2	2·2 ± 0·4*
k_{12} (min^{-1})	0·0060 ± 0·0012	0·0081 ± 0·0014
k_{21} (min^{-1})	0·0189 ± 0·0024	0·0012 ± 0·0004*
V_2 (mL)	35 ± 3	735 ± 103*

* Significantly different from control parameter ($P < 0·05$)

concentration-time curves. For the activated charcoal experiments we fitted the vascular concentration-time curve according to equation 3.

Activated charcoal administration into the luminal perfusate depressed the calculated steady state concentration from 13·8 (control) to 2·2 μg mL^{-1}. The value for the rate constant k_{12}, which represents the excretion into the luminal perfusate, was not significantly altered, while the value for k_{21}, which is the rate constant of resorption from the lumen, was much decreased when activated charcoal was present in the lumen. In control experiments the steady state values for the volumes of distribution of both compartment 1 (vascular perfusate) and compartment 2 (luminal perfusate) matched well with the values for their real volumes, indicating no substantial binding to intestinal tissues. However, when activated charcoal was present in the lumen, the value for the volume of distribution of compartment 2 far exceeded the value for the real volume of the luminal perfusate, as a result of adsorption of theophylline on the charcoal.

Theophylline clearance

The intestinal clearance of theophylline at different times was calculated according to equation 9 and plotted versus time in Fig. 5. In control experiments the clearance declined rapidly with time as a result of the increase in the non-bound luminal theophylline concentration. With activated charcoal in the lumen, the concentration gradient was maximized and the theophylline clearance remained nearly constant. The apparent difference between the calculated clearances at $t = 0$ in both systems is a result of the (non-significant) difference in the k_{12} values (Table 1).

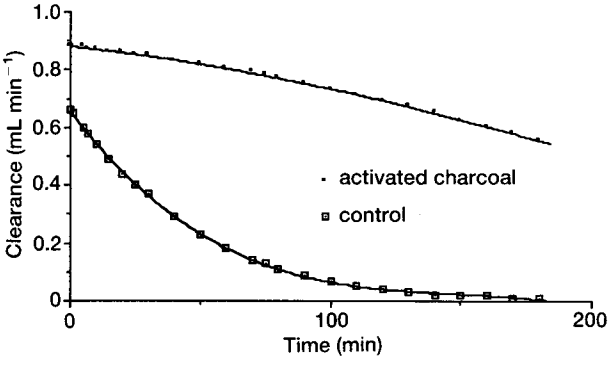

FIG. 5. Time dependency of the intestinal theophylline clearance in control (□) and activated charcoal (■) experiments.

Discussion

From the results of earlier experiments it is evident that oral administration of activated charcoal can be useful in enhancing the elimination of a drug already present in the circulation (see introduction).

In this study we have demonstrated the use of the rat isolated vascularly perfused small intestine as a screening system and have studied the clearance enhancement of theophylline by activated charcoal.

Two hypotheses on the precise mechanism of this gastrointestinal dialysis exist (Levy 1982): 1) Drugs that have diffused through the intestinal wall are adsorbed on the charcoal, thereby increasing the blood-to-lumen concentration gradient for the unbound drug. 2) Drugs that are excreted in bile can be adsorbed on the charcoal and subsequent reabsorption (enterohepatic circulation) prevented. McKinnon et al (1987) postulated that the clearance enhancement of theophylline in dogs may be explained by the first mechanism because only a small amount of drug was excreted in the bile and the concentration in the jejunal aspirate approached that in the venous blood. From the data of Arimori & Nakano (1988) it is clear that biliary secretion of theophylline in the rat is also negligible.

Our study provides supporting evidence for the hypothesis of Mckinnon. In our control experiments no difference between the vascular and luminal steady state concentrations was observed. Therefore, a diffusional transport of theophylline from blood to lumen seems to be most likely. This view was strengthened by the monoexponential decline of the blood to lumen concentration gradient time curve.

The presence of activated charcoal in the luminal perfusate had a profound effect on the kinetics of theophylline. The non-charcoal bound concentration in the luminal perfusate remained almost zero. As a result, the driving force for the secretion into the intestinal lumen, the blood-to-lumen concentration gradient, was maximized and the calculated steady state concentration in the vascular perfusate was substantially decreased.

It is often assumed that activated charcoal produces a constant intestinal drug clearance (Radomski et al 1984; Arimori & Nakano 1988). Our results demonstrate clearly that during charcoal treatment the intestinal clearance was indeed relatively constant, while in control experiments a rapid decline was observed (Fig. 5). The maximal value for the intestinal theophylline clearance in-vitro amounted to 0·88 mL min^{-1} ($Cl_{t=0}$, Fig. 5). In intact rats the total body clearance of theophylline in the absence of charcoal was estimated to be 39·9 mL h^{-1} kg^{-1} or 0·17 mL min^{-1}/250 g (Arimori & Nakano 1988), which is in the same order of magnitude. Therefore, administration of activated charcoal will enhance theophylline clearance in rat significantly. This was observed earlier by Arimori & Nakano (1988), who found that oral treatment with charcoal resulted in an increase of 88% in the total body clearance as compared with a control treatment.

It is likely that the intestinal blood flow rate is a rate limiting factor in the intestinal secretion of theophylline. This assumption is based on the following consideration. It is well known that the absorption of a highly permeable drug from the lumen is limited by the blood flow rate (Winne 1979). In

this case an equilibrium is established between the drug in the lumen and that in the blood flow at the absorption site. The absorptive site blood flow was calculated to be 15%–22% of the total blood flow (Schulz & Winne 1987; de Vries et al 1988b). In our in-vitro study the maximal intestinal theophylline clearance was estimated to be 0·88 mL min^{-1}. This implies that 18% of the total intestinal blood flow (5 mL min^{-1}) is in effective contact with the luminal contents. The value for the "exsorptive site blood flow" corresponds well with the value for the absorptive site blood flow (0·75 mL min^{-1}). Theophylline can be regarded as a high extraction drug in this exsorptive site blood flow.

Using the role of the intestinal exsorptive site blood flow it is possible to predict from our in-vitro experiments the maximal effect of activated charcoal on the kinetics of theophylline in rats and other species, including man.

In rats, Arimori & Nakano (1988) observed an increase in the theophylline clearance from 39·9 mL h^{-1} kg^{-1} to 74·9 mL h^{-1} kg^{-1}. This increase (0·14 mL min^{-1} 250 g) is smaller than predicted by our model (0·88 mL min^{-1}). It is possible that in our experiments the recirculating charcoal suspension has a maximal opportunity for theophylline binding compared with an orally administered suspension in the experiments of Arimori & Nakano.

In dogs, the control clearance of theophylline was estimated to be $31·06 \pm 2·72$ mL min^{-1} kg^{-1}. After charcoal administration the clearance was increased to $40·66 \pm 4·25$ mL min^{-1} kg^{-1} (McKinnon et al 1987). This increase could be adequately predicted with the concept of the exsorptive site blood flow (15% of the intestinal blood flow or 5 mL min^{-1} kg^{-1}; Greenway & Stark 1971).

In man the blood flow through the superior mesenteric artery was estimated to be 7 mL min^{-1} kg^{-1} (Norryd et al 1974). Assuming an exsorptive site blood flow equal to 15% of the total intestinal blood flow, the maximal value for the clearance enhancement by charcoal in man can be calculated to be 1·05 mL min^{-1} kg^{-1}. This matches well with the increase in the theophylline clearance of 0·87 mL min^{-1} kg^{-1} in man (McKinnon et al 1987). Administration of charcoal may be effective, if the systemic clearance does not exceed the exsorptive site blood flow. This is true for compounds like phenobarbitone (control clearance: 0·066 mL min^{-1} kg^{-1}; with activated charcoal: 0·33 mL min^{-1} kg^{-1}), carbamazepine (0·31 mL min^{-1} kg^{-1} and 0·57 mL min^{-1} kg^{-1}, respectively) and phenylbutazone (0·021 mL min^{-1} kg^{-1} and 0·030 mL min^{-1} kg^{-1}, respectively) (Neuvonen & Elonen 1980). The clearance enhancement of phenylbutazone by activated charcoal (0·009 mL min^{-1} kg^{-1}) is much smaller than the maximal value (1·05 mL min^{-1} kg^{-1}). This finding shows that more factors are of influence on the efficiency of charcoal, e.g. plasma protein binding, which for phenylbutazone is 98% (Martindale 1982).

From the results of our study it may be concluded that, in the rat, theophylline appears to be transported by a diffusional transport system through the intestinal wall. Administration of activated charcoal in the lumen enhances intestinal clearance by increasing the blood-to-lumen concentration gradient for the unbound drug. Using the pharmacokinetic model the maximal effect of charcoal administration on the systemic theophylline clearance in dog and man can be adequately predicted. Therefore, the rat isolated vascularly perfused intestine could be a useful tool to investigate the effect of charcoal and other adsorbents on systemic drug elimination. From our data it can also be concluded that charcoal administration after intoxication with drugs or toxicants is useful only for compounds having a systemic clearance of the order of magnitude of the intestinal absorptive blood flow, or lower.

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