J. Pharm. Pharmacol. 1987, 39: 522–525
Received November 4, 1986

Studies on the mechanisms of action of activated charcoal on theophylline pharmacokinetics

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Oral administration of repeated doses of activated charcoal to volunteers and dogs significantly increased the systemic clearance of intravenously administered theophylline and decreased its elimination half-life. This effect is most likely to be due to theophylline entering the gut and being adsorbed onto the charcoal. The mechanism by which intravenously administered theophylline enters the gut has been examined. Its biliary excretion after intravenous administration to patients with T-tube biliary drainage accounted for 0·28% of the dose and a similarly small biliary excretion was found in dogs. In the latter total biliary diversion had no effect on the clearance or half-life of theophylline after intravenous administration. In two dogs the theophylline content of jejunal aspirate was comparable with that of simultaneously withdrawn venous plasma samples. These results suggest that the presence of charcoal in the gut represents a sink adsorbing theophylline entering the lumen by diffusion across the intestinal wall, and by this mechanism it increases clearance of the drug even after intravenous administration.

Orally administered activated charcoal has been used for a number of years to bind drugs in the bowel and thereby prevent absorption after an overdose. In 1980, Neuvonen & Elonen demonstrated that activated charcoal, even if administered after absorption was complete, could decrease the terminal half-life of orally administered phenobarbitone, carbamazepine and phenylbutazone. Activated charcoal thus not only inhibited absorption from the gastrointestinal tract, but also increased the clearance of drugs from the systemic circulation. The use of orally administered activated charcoal to enhance elimination (i.e. increase the clearance) of intravenously administered drugs was subsequently examined. Oral activated charcoal has been shown to increase the elimination of intravenously administered digoxin (Lalonde et al 1985), phenobarbitone (Berg et al 1982), and theophylline (Berlinger et al 1983; Brashear et al 1985; Park et al 1984). The mechanism by which orally administered non-absorbable activated charcoal could enhance the systemic clearance of drugs has not been established. Two possible explanations are (a) an interruption of an enterohepatic circulation of the drug or (b) trapping of the drug in the bowel lumen after it has diffused through the bowel wall (Levy 1982). We have examined the effect of repeated doses of oral activated charcoal on the pharmacokinetics of intravenously administered theophylline in both man and dog and the mechanism of this effect.

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METHODS

Human control and charcoal studies

The effect of oral activated charcoal on the kinetics of intravenous theophylline was studied in six healthy subjects. Theophylline kinetics were studied twice in each subject, once with the oral administration of activated charcoal and once without. The order of the procedures was randomized. Subjects were taking no medication and were non-smokers. All gave informed written consent and the study was approved by the Hospital Ethics Committee.

On the day preceding each study, subjects were asked to abstain from tea, coffee and chocolate. After an overnight fast, subjects were given a 30 min infusion of aminophylline 3 mg kg^{-1} (David Bull Laboratories) in 100 mL of normal saline; this contained 2·37 mg kg^{-1} of theophylline. An indwelling venous cannula was inserted in the opposite arm and blood samples were collected into lithium heparin tubes at 0, 0·25, 0·5, 1·0, 1·5, 2·0, 2·5, 3·0, 3·5, 4, 5, 6, 7 and 8 h. Blood samples were centrifuged and the plasma collected and stored at −20 °C for subsequent assay. Urine was collected over 8 h and similarly stored at −20 °C.

In the charcoal study the same procedure was followed except that the subjects drank 400 mL of a 10% solution of activated charcoal (Delta West, Perth WA) at 0 h and 200 mL at 2, 4 and 6 h.

Partial biliary diversion studies in humans

The possibility of biliary excretion of theophylline was investigated in three subjects with T-tube biliary drainage following a cholecystectomy and exploration of the common bile duct. Subjects were given aminophylline as for the control study (i.e. no charcoal was given). Samples were taken as previously and all bile was collected in 2 hourly fractions for the 6 h.

Dog studies

Four mongrel dogs were fitted with a Thomas fistula (Thomas 1941) giving access to the Ampulla of Vater through which the common bile duct could be cannulated as required. Three separate studies were performed in each dog as follows.

Control studies in conscious dogs. Aminophylline 10 mg kg^{-1} was given as an intravenous infusion. Samples were taken from another limb at 0, 0·1, 0·25, 0·5, 0·75, 1·0, 1·5, 2·0, 2·5, 3, 4, 5, 6, 7 and 8 h later.

Charcoal studies. The procedure was repeated as above except that charcoal was given into the duodenum via the Thomas fistula in a dose of 200 mL at 0 h and 50 mL at 2, 4 and 6 h.

Total biliary diversion. Total biliary diversion was achieved by passing, under light nitrous oxide/halothane anaesthesia, a No. 7 double lumen Swan-Ganz catheter into the common bile duct and advancing it until a reasonable bile flow was obtained. A small balloon on the end of the catheter prevented leakage, permitting complete bile collection. The dog was allowed to recover from the anaesthetic before aminophylline was administered as in previous studies. Bile was collected in hourly fractions for the 8 h duration of the experiment.

Aspiration experiments with dogs. In two of the dogs, a further study was undertaken. The concentration of theophylline in the gut content following intravenous administration was investigated by aspirating samples of succus entericus from the jejunum. Dogs were given 10 mg kg^{-1} aminophylline intravenously and blood samples were taken as previously described. A 1·2 m duodenal tube was passed anterogradely through the Thomas fistula into the jejunum. Samples of succus entericus were aspirated concurrently with blood samples.

Theophylline assay

Theophylline was assayed by HPLC as previously described (Breen et al 1982). The theophylline content of human urine and bile was determined using the same method as for plasma except that urine and bile were first filtered through a 0·22 μm millipore filter. The assay for theophylline in dog bile was complicated by an interfering peak eluting with theophylline, which could not be separated by alteration of the mobile phase. The samples were therefore purified by solvent extraction.

Plasma theophylline concentration vs time profiles were constructed for each study. Terminal elimination rate constants and half-lives were determined by least squares exponential regression. Area under plasma concentration time curve (AUC) was calculated using the trapezoidal rule with extrapolation to infinity. Clearance was calculated using the formula: CL = dose/AUC. Steady state volume of distribution (Vd) was calculated using the method of Benet & Galeazzi (1979). For all urine and bile data, the total amount of unchanged theophylline recovered in urine or bile was expressed as a percentage of the dose given. The terminal half-life and clearances were compared using either the paired, two-tailed Student's *t*-test for within group or the unpaired two-tailed *t*-test for between group comparisons.

RESULTS

Human control and charcoal studies

Mean plasma disposition curves for theophylline in the human control and charcoal studies are shown in Fig. 1. Orally administered activated charcoal

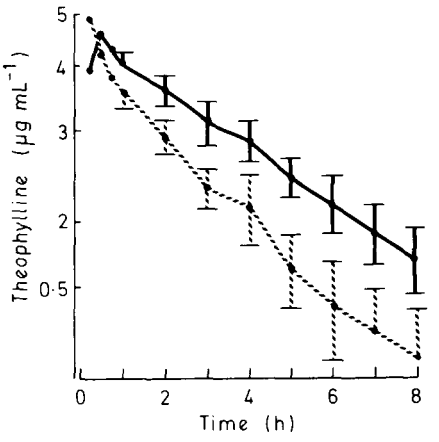

FIG. 1. The mean plasma theophylline concentration versus time curves for the human control (unbroken line) and charcoal (broken line) studies.

Table 1. Kinetic parameters of theophylline in human subjects.

Subject	Terminal half-life, h		Clearance mL min^{-1} kg^{-1}		Vol. of distribution L kg^{-1}	
	Control	Charcoal	Control	Charcoal	Control	Charcoal
I	7·22	5·50	0·88	1·44	0·70	0·80
II	1·81	1·89	2·22	4·19	0·61	0·91
III	5·50	5·02	0·87	1·06	0·52	0·63
IV	5·78	2·89	0·93	2·60	0·62	0·81
V	6·42	4·44	1·15	1·55	0·83	0·75
VI	6·42	4·12	1·15	1·55	0·76	0·69
Mean	*5·53	*4·00	†1·20	†2·07	0·67	0·77
s.e.m.	0·78	0·54	0·21	0·47	0·046	0·040

*† Statistically significant difference ($P < 0·05$, paired t-test, 5 d.f.).

increased theophylline clearance by 73% ($P < 0·05$) and reduced the elimination half-life by 28% ($P < 0·05$). There was no significant change in the volume of distribution and the urinary recovery was similar in both groups (Table 1).

Partial biliary diversion studies in man

Over the 8 h of the study, excretion in the bile was 0·28% of the dose. The clearance was lower and the terminal half-life was significantly higher in these subjects than in the control subjects (Table 2).

Table 2. Kinetic parameters from humans with T-tube biliary drainage.

Subject	Terminal half-life, h	Clearance mL min^{-1} kg^{-1}	Vol. of distribution L kg^{-1}
VII	6·80	0·86	0·63
VIII	12·84	0·45	0·60
IX	5·50	1·13	0·70
Mean	8·38	0·81	0·64
s.e.m.	2·26	0·20	0·30

Theophylline pharmacokinetics in the dog

After charcoal administration, the clearance of theophylline was increased by 31% ($P < 0·05$) and the elimination half-life was reduced by 37% ($P < 0·05$). There was no significant difference in either kinetic parameter after total biliary diversion (Table 3). A mean of 1·05% of the administered dose was recovered in the bile after total biliary diversion.

Aspiration studies. The concentration of theophylline in the gut after intravenous administration was examined in two dogs. Fig. 2 illustrates results in one of the dogs. Theophylline concentration in the jejunum was seen to follow the plasma concentration at a ratio of approximately 2:3. Smaller volumes were collected from the second dog and theophylline concentrations were slightly lower than plasma concentrations.

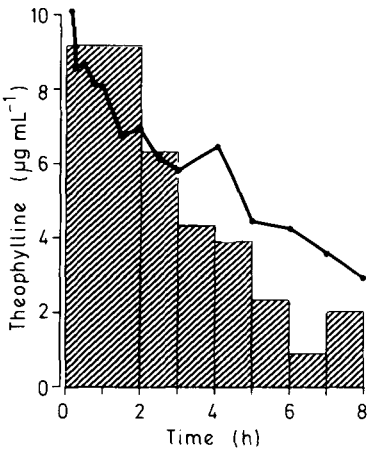

FIG. 2. The plasma theophylline concentration (solid line) versus time curve and the simultaneous jejunal theophylline concentration (hatched bars) for one dog.

DISCUSSION

Ingestion of repeated doses of activated charcoal produced a significant increase in the systemic clearance of intravenously administered theophylline in both man and dogs. The magnitude of this change is similar to that reported previously (Berlinger et al 1983; Radowski et al 1984). This effect on theophylline kinetics occurs too rapidly to be accounted for by induction of oxidative enzymes which the charcoal could conceivably cause. The increase in theophylline clearance is presumably due to the charcoal in the gut acting as a sink for the drug. The question of how theophylline reaches the lumen of the gut from the blood remains. One possibility is that this is by excretion in the bile with subsequent entero-hepatic circulation. However, very little theophylline was excreted in the bile collected from the patients with biliary diversion through a T-tube

Table 3. Kinetic parameters of theophylline in dogs.

	Terminal half-life, h			Clearance mL min^{-1} kg^{-1}			Volume of distribution L kg^{-1}		
Dog	Control	*TBD	Charcoal	Control	TBD	Charcoal	Control	TBD	Charcoal
1	4·32	2·53	3·11	39·06	64·57	51·22	0·91	1·17	0·94
2	4·24	5·19	2·35	29·85	31·84	35·59	0·68	1·06	0·57
3	5·01	8·29	3·97	28·00	15·57	32·24	1·03	0·96	0·87
4	5·92	3·74	2·92	27·32	23·91	43·60	1·17	0·68	0·94
Mean	4·87	4·94	†3·09	31·06	34·00	†40·66	0·95	0·97	0·83
s.e.m.	0·39	1·24	0·34	2·72	10·73	4·25	0·10	0·11	0·088

* TBD = total biliary diversion.
† Statistically significant difference ($P < 0·05$, paired t-test, 3 d.f.).

and the clearance of theophylline was reduced rather than enhanced in these subjects. This reduction in clearance is probably explained by these patients being older than the control subjects or perhaps by them having recently undergone major surgery. To eliminate these confounding factors, the experiments were repeated in dogs with Thomas fistulae in which the three experiments could be performed on the one animal. Again, as in man, oral charcoal significantly increased the clearance of theophylline. However there was little theophylline in the diverted bile and its exclusion from the gut produced no effect on the systemic clearance of theophylline.

The studies of the jejunal aspirate in the two dogs demonstrated that theophylline does enter the gut in a concentration approaching that in venous blood. It is therefore likely that charcoal exerts its effect on the kinetics of intravenously administered theophylline by binding theophylline which has entered the lumen by passage across the bowel wall from the mesenteric circulation.

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