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Enhancement of Morphine Clearance Following Intravenous Administration by Oral Activated Charcoal in Rabbits

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Abstract—A single dose of activated charcoal (10 g) significantly reduced the half-life of elimination (1·02 ± 0·10 and 0·70 ± 0·04 h for the control and treated groups, respectively) and mean residence time (1·01 ± 0·12 and 0·76 ± 0·05 h for the control and treated groups, respectively) of morphine in rabbits. A 40% increase in the systemic clearance (85·73 ± 7·72 and 122·64 ± 16·32 mL min^{-1} kg^{-1} for the control and treated groups, respectively) and a 30% decrease in AUC (204·38 ± 22·20 and 140·03 ± 19·32 μg h L^{-1} in the control and treated groups, respectively) were also noted. Charcoal administration did not significantly alter the volume of distribution (V_{area} and V_{SS}) or the apparent distribution half-life. A two-compartment model adequately described morphine kinetics in control and treated rabbits; charcoal administration produced a significant increase in the tissue compartment rate constant (K_{21}). This finding indicates that activated charcoal not only enhances the systemic elimination of morphine, but also accelerates the rate of transfer of morphine from the tissue compartment to the central compartment.

Activated charcoal administered orally has been shown to enhance the systemic clearance of carbamazepine (Neuvonen & Elonen 1980), dapsone (Neuvonen et al 1983), diazepam (Traeger & Haug 1986), digitoxin (Pond et al 1981), digoxin (Boldy et al 1985), disopyramide (Huang 1988; Arimori et al 1989), gentamicin (Hasan et al 1990), phenobarbitone (Berg et al 1982), quinine (Lockey & Bateman 1989), salicylate (Hillman & Prescott 1985) and theophylline (Berlinger et al 1983). The process by which oral charcoal enhances the systemic elimination of drugs has been termed "gastrointestinal dialysis" (Levy 1982).

Morphine and its major metabolite, morphine-glucuronide, are subjected to extensive enterohepatic cycling in man (Jaffe & Martin 1985) and animals (March & Elliot 1964; Spector 1971; Walsh & Levin 1975; Iwamoto & Klaassen 1977), and the drug circulates in the plasma largely unbound (Olsen 1975). Therefore it is likely that oral charcoal would be effective in enhancing the systemic elimination of morphine. However, Huang (1988) has postulated that drugs with a higher hepatic extraction ratio such as morphine (Iwamoto & Klaassen 1977; Stanski et al 1978; Sawe et al 1981) are unlikely to be subjected to a significant enhancement of systemic elimination by activated charcoal.

This paper reports the effect of oral activated charcoal on the systemic clearance and other pharmacokinetic parameters of morphine following intravenous administration to rabbits.

Materials and Methods

Chemicals

Morphine sulphate ampoules (10 mg mL^{-1}) were purchased from Elkins-Sinn, Inc., Cherry Hill, NJ. Activated charcoal, AX-21, was obtained from Anderson Development Co., Adrian, MI and was used as supplied. All chemicals and solvents used in this study were of analytical grade.

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Animal studies

New Zealand adult male rabbits, 2·5–4·0 kg, were fasted for 12 h before and during the experiment, with free access to water. Animals were immobilized in a restraining box during drug administration and when blood samples were taken. At all other times animals were kept in standard rabbit cages. The marginal vein of one ear was cannulated with polyethylene tubing (Fr. no. 2) for blood sampling and morphine (1 mg kg^{-1}) was injected over 30 s into the marginal vein of the opposite ear. Activated charcoal in water (10 g in 50 mL, n = 6), or water (50 mL, n = 6), was administered orally immediately following drug administration. Blood samples (1 mL) were collected into glass tubes just before drug administration and at 0·25, 0·50, 0·75, 1·0, 1·5, 2·0, 2·5, 3·0, 4·0, 5·0 and 6·0 h following drug adminstration. Serum was prepared and stored at −20 °C pending assay.

Determination of morphine concentrations

Morphine serum concentrations were quantitated by a solid-phase ^{125}I radioimmunoassay (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, CA, USA) using a Beckmann 5500 Gamma Counter with a DP 5500 microprocesser for data reduction (Beckman Instruments, Inc., Irvine, CA, USA). Intra-assay and inter-assay precision were obtained by analysing control samples of normal rabbit serum to which had been added known amounts of morphine (5·0, 50·0 and 100·0 ng mL^{-1}). The coefficient of variation was 4·9–8·2% and the detection limit was approximately 0·3 ng mL^{-1}. All analyses were performed in duplicate.

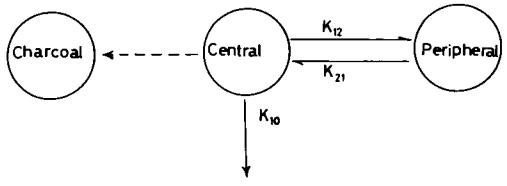
Pharmacokinetic analysis

The data on serum morphine concentrations after intravenous administration were fitted to a two-compartment open model. The concentration of morphine in serum (Cp) was described by the following equation:

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

where A, B, α and β are hybrid constants and t is the time. The distribution half-life ($t_{\frac{1}{2}}\alpha$), the terminal disposition half-

life ($t_{\frac{1}{2}}\beta$), the apparent volume of distribution at steady-state (V_{SS}), the V_{area}, the area under the serum concentration-time curve (AUC), the total systemic clearance (CL), the mean residence time (MRT), the area under the moment curve (AUMC), and the microconstants (K_{21}, K_{12} and K_{10}, Scheme 1) of the drug were calculated using the following equations (Gibaldi & Perrier 1982):



Scheme 1. Two compartment linear pharmacokinetic model with elimination from the central compartment.

$$t_{\frac{1}{2}}\alpha = \frac{0{\cdot}693}{\alpha} \qquad t_{\frac{1}{2}}\beta = \frac{0{\cdot}693}{\beta}$$

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta} \qquad V_{SS} = \frac{Dose_{i.v.}AUMC}{(AUC)^2}$$

$$V_{area} = \frac{Dose_{i.v.}}{AUC.\beta} \qquad CL = \frac{Dose_{i.v.}}{AUC}$$

$$MRT = \frac{AUMC}{AUC} \qquad K_{21} = \frac{A\beta + B\alpha}{A+B}$$

$$AUMC = \frac{A}{\alpha^2} + \frac{B}{\beta^2} \qquad K_{12} = \alpha + \beta - K_{21} - K_{10}$$

$$K_{10} = \frac{\alpha\beta}{K_{21}}$$

Statistical analysis

The data are presented as mean ± s.d. The *t*-test for unpaired data was employed to assess the effects of charcoal treatment on the pharmacokinetic parameters. Differences were considered statistically significant for $P < 0{\cdot}05$.

Results

The administration of morphine intravenously (1 mg kg^{-1}) to control and charcoal-treated rabbits produced serum-concentration profiles that were adequately described by an open two-compartment kinetic model with a rapid initial distribution (Fig. 1). Activated charcoal produced significant reduction in morphine serum concentrations from 0·5 h onwards, but charcoal treatment did not affect the general shape of the serum-concentration curve (Fig. 1).

The derived pharmacokinetic parameters of morphine in the control and treated rabbits are presented in Table 1. No significant difference was observed in the apparent distribution half-life ($t_{\frac{1}{2}}\alpha$) between the control and charcoal-treated rabbits (0·17 ± 0·02 and 0·15 ± 0·03 h for the control and treated groups, respectively). On the other hand, marked and significant differences were noted in $t_{\frac{1}{2}}\beta$ (1·02 ± 0·1 and 0·70 ± 0·04 h for the control and treated groups, respectively) and MRT (1·01 ± 0·12 and 0·76 ± 0·05 h for the control and treated groups, respectively). Charcoal administration had no significant effect on either V_{area} or V_{SS} (Table 1), but the clearance was significantly enhanced (85·73 ± 7·72 and 122·64 ± 16·32 mL min^{-1} kg^{-1} for the control and treated groups, respectively) and AUC significantly decreased (204·38 ± 22·20 and 140·03 ± 19·32 μg h L^{-1} in the control and treated groups, respectively). The apparent gastrointestinal clearance (CL with charcoal − CL without charcoal) of morphine was calculated and found to be 36·91 mL min^{-1} kg^{-1}.

No significant differences were found in the rate of transfer of morphine from the central compartment to the tissue compartment (K_{12}) between the control and treated rabbits (Table 1). However, a significant increase was observed in the rate of transfer of morphine from the tissue compartment to the central compartment (K_{21}).

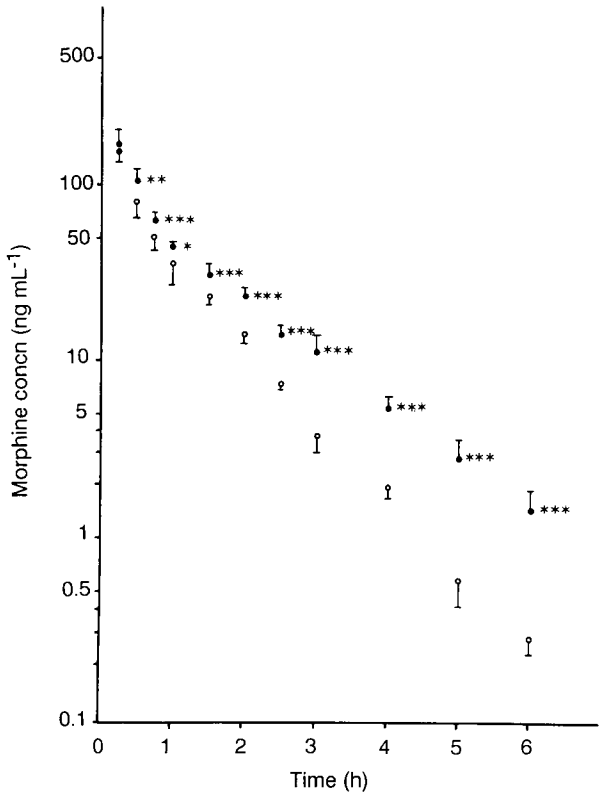


FIG. 1. Serum morphine levels after intravenous administration (1 mg kg^{-1}) to rabbits with (○) and without (●) pretreatment with activated charcoal. Each point represents the mean ± s.d. of 6 rabbits. * $P < 0{\cdot}05$; ** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$.

Table 1. Pharmacokinetic parameters of morphine administered intravenously (1 mg kg^{-1}) to rabbits with or without treatment with activated charcoal[a] administered orally.

Pharmacokinetic parameter	Control	Treated
AUC (μg h L^{-1})	204·38 ± 22·20	140·03 ± 9·32**
CL (mL min^{-1} kg^{-1})	85·73 ± 7·72	122·64 ± 16·32**
V_{SS} (L kg^{-1})	5·26 ± 1·09	5·60 ± 1·02
V_{area} (L kg^{-1})	7·64 ± 0·98	7·46 ± 1·26
MRT (h)	1·01 ± 0·12	0·76 ± 0·05*
$t_{\frac{1}{2}}\alpha$ (h)	0·17 ± 0·02	0·15 ± 0·03
$t_{\frac{1}{2}}\beta$ (h)	1·02 ± 0·10	0·70 ± 0·04**
K_{12} (h^{-1})	1·40 ± 0·24	1·43 ± 0·44
K_{21} (h^{-1})	1·42 ± 0·16	2·09 ± 0·15**
K_{10} (h^{-1})	2·02 ± 0·37	2·30 ± 0·43

[a] Each value represents the mean ± s.d. of 6 rabbits.
* $P < 0{\cdot}01$, ** $P < 0{\cdot}001$ by Student's *t*-test.

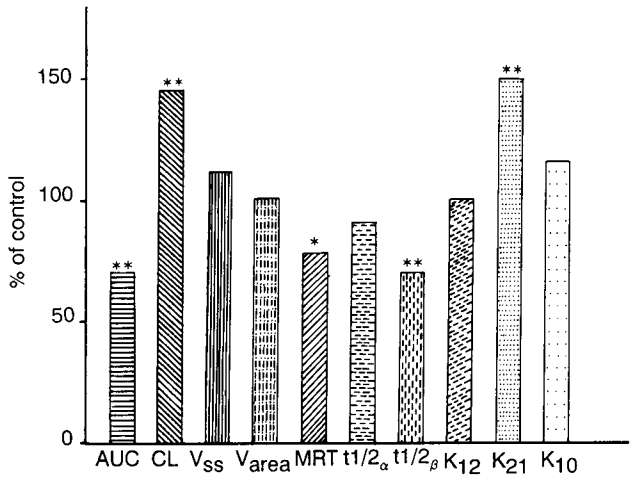


FIG. 2. Changes in the pharmacokinetic parameters of morpine administered intravenously (1 mg kg^{-1}) expressed as percent of control values. * $P < 0.05$; ** $P < 0.001$.

The relative changes (treated/control) in the pharmacokinetic parameters of morphine produced by activated charcoal are depicted in Fig. 2. These changes are consistent with an acceleration of morphine elimination induced by charcoal administered orally. Activated charcoal produced a significant decrease in $t_{\frac{1}{2}}\beta$, MRT and AUC to 69·6%, 78·3% and 70·1%, respectively, and a significant increase in K_{21} and CL values to 149·0% and 145·0%, respectively. The changes in $t_{\frac{1}{2}}\alpha$, K_{12}, K_{10}, V_{area} and V_{SS} parameters were not statistically significant (Fig. 2).

Discussion

The results obtained from this investigation demonstrate the efficacy of oral activated charcoal in enhancing the elimination of intravenously adminstered morphine to rabbits.

The lack of significant changes in the volume of distribution parameters (V_{area} and V_{SS}) indicates that adsorption of morphine onto activated charcoal in the gut is an irreversible process, or the desorption of the drug from charcoal is very slow in comparison with the rate of drug elimination. Thus, our findings are consistent with the suggestion that charcoal in the gut serves as a route of elimination rather than a distribution compartment (Huang & Tzou 1986). The significant increase in the tissue compartment constant (K_{21}) indicates an increase in the rate of drug transfer from the peripheral tissue to the central compartment upon treatment with activated charcoal (Scheme 1). Therefore the gut may be considered as part of the overall peripheral compartment into which the drug is distributed.

There are two main proposed mechanisms by which activated charcoal increases the clearance of drugs from the body. The first mechanism is that activated charcoal interrupts the enterohepatic circulation of compounds (Pond 1986). The second mechanism, often termed "gastrointestinal dialysis", is that activated charcoal establishes a concentration gradient between the blood and the gastrointestinal fluids (Levy 1982; Pond 1986); activated charcoal adsorbs the toxin from the gastrointestinal fluids thus decreasing the amount of diffusable drug from these fluids and at the same time optimizing the concentration gradient which allows more drug to diffuse into the gut (Levy 1982).

Morphine and its major metabolite, morphine-glucuronide, undergo enterohepatic recirculation; about 10% of administered morphine appears in the faeces from biliary secretion (Jaffe & Martin 1985), and on the same basis in an in-vitro experiment on the caecum of the rat, it has been suggested that conjugated morphine is readily hydrolyzed and then reabsorbed (Walsh & Levine 1975). Therefore, the gastrointestinal lumen could be considered a major part of the extracellular space in which morphine is distributed. Thus, the systemic clearance of morphine would be affected by the concentration gradient between blood and the fluid in the gut lumen.

On the basis of theoretical considerations and experimental evidence, Huang (1988) postulated that drugs of high hepatic extraction ratio would not be prone to appreciable enhancement of systemic elimination by activated charcoal administered orally. Furthermore, it has been suggested that the charcoal effect in enhancing drug clearance would be more pronounced for drugs characterized by low systemic clearance (Adler et al 1986). Morphine is characterized by both a high hepatic extraction ratio and high clearance (Iwamoto & Klaassen 1977; Stanski et al 1978; Sawe et al 1981), and therefore activated charcoal should be unlikely to enhance drug clearance. Contrary to this prediction, activated charcoal produced significant enhancement of morphine clearance (Table 1, Fig. 2). Although the increase in clearance (about 40%) is not dramatic when compared with the results reported on drugs characterized by low hepatic extraction ratio and low clearance, such as theophylline (Huang 1987), the observed increase in morphine clearance found by us may suggest a role for oral activated charcoal in increasing morphine clearance in patients with renal impairment.

For example, it has been found that in the presence of induced renal failure in rabbits, activated charcoal produced marked apparent enhancement of gentamicin clearance compared with the effect observed in normal rabbits receiving similar treatment (Hasan et al 1990). It has also been reported that charcoal was more effective in enhancing digoxin clearance in patients with renal failure compared with the effect seen in normal subjects (Park et al 1985). Further studies are needed to quantitate the role of hepatic extraction ratio and endogenous clearance on the absolute and relative values of charcoal-induced clearance (apparent gastrointestinal clearance) of morphine by induction of liver failure and bypassing the liver by portocaval shunting.

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