THE INTESTINAL DIALYSIS OF INTRAVENOUSLY ADMINISTERED PHENYTOIN BY ORAL ACTIVATED CHARCOAL IN RATS

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The effect of oral administration of activated charcoal on total body clearance of phenytoin following intravenous administration was studied in rats. *In situ* single-pass perfusion study showed that phenytoin was exsorbed into the small intestinal lumen. The exsorption of the drug from blood into the intestinal lumen was increased in a dose-dependent manner. The exsorption rate of the drug at the dose of 10 mg/kg was 1.1% in 120 min, while that at 50 mg/kg was 2.5% in 120 min. The excretion of the conjugate of 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (*p*-HPPH) into the bile was greater than phenytoin and unconjugated *p*-HPPH and the total percentage of excretion of *p*-HPPH was significantly decreased by increasing the dose. Oral activated charcoal had little effect on the serum phenytoin levels after the 10 mg/kg dose. On the other hand, charcoal reduced the serum phenytoin levels after the 50 mg/kg dose as compared with the corresponding controls. Oral administration of activated charcoal decreased the serum half-life to 77% and the area under the serum concentration–time curve to 75% after the 50 mg/kg dose of phenytoin. The apparent volume of distribution was not significantly different between rats with activated charcoal treatment and rats without charcoal treatment. Based on these results, a mechanism of the enhanced clearance of phenytoin at a high dose (50 mg/kg) may be due to the adsorption of the drug and its metabolites transported into the gastrointestinal tract by the charcoal.

Keywords—activated charcoal; phenytoin; exsorption rate; biliary excretion; intravenous administration; serum concentration; intestinal dialysis; total body clearance; serum half-life; gastrointestinal tract

Phenytoin is one of the most frequently used antiepileptic drugs in the clinical treatment of epilepsy. However, this drug is prone to produce intoxication because of its narrow therapeutic range and saturable metabolic process.¹⁾ The symptoms of patients who have taken an overdose of phenytoin are nystagmus, ataxia, disarthria and occasionally life-threatening respiratory and circulatory depression. Therefore, phenytoin in systemic circulation in toxic concentrations has to be removed as soon as possible.

Activated charcoal has been generally recognized as an effective adsorbent of many drugs. Recently, it has been noted in studies on the transport (exsorption) of drug from blood to the gastrointestinal (g.i.) tract that the clearance of intravenously administered drugs such as phenobarbital²⁾ and theophylline^{3,4)} is accelerated by orally administered charcoal. Although there have been some reports concerning the transport of intravenously administered drugs into the intestinal lumen,^{5–11)} few have dealt with the application of intestinal dialysis in the treatment of drug poisoning. We have previous-

ly demonstrated that intravenously administered theophylline¹²⁾ and phenobarbital¹³⁾ were transported into the small intestinal lumen to a significant extent and into the bile juice to a small extent in rats and that exsorbed drugs can be removed by adsorption to orally administered activated charcoal.¹⁴⁾

It is well-known that phenytoin is highly bound to plasma protein.^{15,16)} Thus, the amounts of the drug transported from blood to the g.i. tract would be small because unbound phenytoin which can pass through the biomembrane constitutes only a small part of the total phenytoin in the plasma. Noach *et al.*¹⁷⁾ have reported that phenytoin, after i.v. administration to rats, appeared in the g.i. tract, but most of phenytoin and its metabolites were reabsorbed from the g.i. tract since only slight traces appeared in the feces.

The present study, therefore, was designed to investigate further the characteristics of exsorption and/or excretion of phenytoin into the g.i. tract and to evaluate whether the exsorbed drug can be removed by adsorption to orally adminis-

tered activated charcoal.

MATERIALS AND METHODS

Materials — Phenytoin sodium (Aleviatin[®] injection) was a product of Dainippon Pharm. Co., Osaka and 5-(*p*-hydroxyphenyl)-5-phenylhydantoin was a product of Aldrich Chem. Co., USA. Activated charcoal was a product of Inuhinode Seiyaku Co., Osaka and the particle size used in this study was less than 62 μm (250 mesh). All other chemicals used were of analytical grade.

Exsorption Study — Intestinal exsorption experiments were performed by an *in situ* single-pass perfusion technique reported previously.¹²⁾ Wistar strain male rats, weighing 290–410 g, were anesthetized by an intraperitoneal injection of ethyl carbamate (1.2 g/kg). The small intestine was exposed by a midline abdominal incision. The upper duodenum and the ileocaecal junction were cannulated with polyethylene tubing and the entire small intestine was washed with saline maintained at 37 °C. The isotonic phosphate buffer solution (0.1 M, pH 6.0) which was maintained at 37 °C was perfused at a rate of approximately 1.3 ml/min from the duodenum through the small intestine to the ileocaecal junction using a glass infusion pump (GM-24, Tokyo Rikakikai). Phenytoin sodium, 50 mg/ml, was injected over a period of about 2–5 min into the right femoral vein at doses of 10–50 mg/kg (10, 20, 30, and 50 mg phenytoin as sodium salt/kg of body weight). After injection, perfusates were collected every 15 min from the ileal outflow in a 25 ml volumetric flask and diluted with a buffer solution to 25 ml before assay. Exsorption rate was calculated as the amount exsorbed into the intestinal lumen per min. The bile was collected separately every 15 min from the cannula introduced into the common bile duct. Blood samples to determine serum drug concentrations were taken from the cannula introduced into the left femoral vein, at the midpoint of the perfusate collection time (7.5, 22.5, 37.5, 52.5, 67.5, 82.5, 97.5 and 112.5 min).

In Vivo Study — Wistar strain male rats, weighing 300–350 g, were fasted overnight with free access to water. Each experiment was carried out by a crossover design and an interval of more than two weeks was allowed prior to the next experiment. Phenytoin sodium at a dose of 10 or 50 mg/kg was administered intravenously

via the caudal vein. In the case of the treatment with activated charcoal, the activated charcoal suspended in water (150 mg/ml) was administered orally by using a catheter with an initial dose of 300 mg at time zero and additional doses of 150 mg each at 1, 2, 3, 4, and 6 h after the intravenous administration of phenytoin. No suspending agent was employed and the suspension was administered soon after shaking. In the case of the control rats, only 2 ml water at time zero was administered. Blood samples (200 μl) were collected periodically from the tail.

Protein Binding Study — The serum protein binding of phenytoin was determined by an ultrafiltration technique using Centrifree MPS-3 (Amicon Co.). Phenytoin sodium (10–50 mg/kg) was administered to rats as an intravenous bolus injection *via* the caudal vein. Blood samples were collected by heart puncture. The blood was centrifuged and the serum obtained (1 ml) was further ultrafiltrated at 1000 $\times g$ for 15 min. The filtrate was stored at –20 °C until assay.

Analytical Method — Phenytoin in the perfusate and free and conjugated 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (*p*-HPPH) in the bile juice were determined by high pressure liquid chromatography (HPLC) with phenacetin as the internal standard. A 2 ml portion of the diluted perfusate and 1 ml portion of the bile juice were extracted with 5 ml of chloroform containing the internal standard after addition of 1 ml of 1 N HCl solution. Free and conjugated *p*-HPPH in the bile juice were analyzed before and after hydrolysis. The conjugated metabolite was hydrolyzed with 6 N HCl solution prior to the extraction. Separation was performed with a LiChrosorb RP-18 column (5 μm in 4.6 i.d. $\times$ 250 mm). The mobile phase consisted of acetonitrile and water (30:70). At a flow rate of 1.0 ml/min, the effluent was monitored for absorbance at 200 nm. The concentrations of phenytoin in the serum and the bile juice were measured by a homogeneous immunoassay technique (Ames TDA, Ames Co.). This assay has a coefficient of variation of less than 3% over the range of 1–30 $\mu\text{g/ml}$. The concentrations of the drug greater than 30 $\mu\text{g/ml}$ or less than 1 $\mu\text{g/ml}$ were also assayed within the range of calibration by changing the dilution ratio with the buffer solution.

Pharmacokinetic Analysis — The disappear-

ance of phenytoin from serum followed first-order kinetics. The serum half-life ($t_{1/2}$) was determined by a least-square regression analysis of the elimination curve of serum levels. The elimination rate constant (k_{el}) was calculated from the relationship $k_{el} = 0.693/t_{1/2}$. An intercept of ordinate at time zero was used to estimate the initial serum concentration (C_0) of phenytoin. The apparent volume of distribution ($V_d = \text{dose}/C_0$), the total body clearance ($Cl_{tot} = k_{el} \cdot V_d$), and the area under the concentration-time curve (AUC) for serum extrapolated to time infinity ($AUC = C_0/k_{el}$) were also calculated. The paired t test was used to assess the effect of charcoal treatment on the pharmacokinetic parameters. The intestinal and biliary clearance values of intact phenytoin were calculated by dividing the amount of phenytoin excreted in the perfusate and in the bile juice in 2 h by AUC from 0 to 2 h, respectively.

RESULTS

Transport of Phenytoin into Intestinal Lumen

The exsorption rate of phenytoin into the perfusate across the small intestinal membrane and the concentrations of phenytoin in the bile juice and the serum were examined using the dose

range from 10 to 50 mg/kg by the *in situ* single-pass perfusion technique. Figure 1 shows the results following i.v. administration of phenytoin to rats. As shown in Fig. 1 a), phenytoin was exsorbed into the small intestinal lumen. The exsorption rate of the drug into the perfusate was increased with an increase in the serum level which was in turn increased with the increase in the dose of the drug. Accordingly, the exsorption rate of phenytoin into the perfusate reflected the serum level and was dose dependent. It was also observed that after i.v. administration of phenytoin to rats, the drug was rapidly excreted into the bile. Phenytoin levels in the bile at each dose were higher than those in the serum. Thus, it may be suggested that phenytoin is excreted into the intestinal lumen *via* the bile duct to an appreciable extent.

Dose-dependency in exsorption of phenytoin into the intestinal lumen was further examined. The relationship between the amount exsorbed in 120 min or percent of dose exsorbed in 120 min and the administered dose of phenytoin is shown in Fig. 2. When the dose of phenytoin was increased five-fold from 10 to 50 mg/kg (body weight), the amount of the drug exsorbed in 120 min was increased about eight-fold, from

FIG. 1. The Exsorption Rate of Phenytoin into the Perfusate and the Concentrations of Phenytoin in the Bile Juice and Serum after i.v. Administrations of Phenytoin (10–50 mg/kg) to Rats by the *in Situ* Single-Pass Perfusion Method

Perfusate is composed of isotonic phosphate buffer at pH 6.0. Each point represents the mean $\pm$ SEM of 3–5 rats.

Key: $\circ$ 10 mg/kg, $\triangle$ 20 mg/kg, $\square$ 30 mg/kg, $\diamond$ 50 mg/kg.

FIG. 2. Dose-Dependency in Exsorption of Phenytoin to Rat Small Intestine

Each point represents the mean $\pm$ SEM of 3–5 rats. For the experimental method, see a) in Fig. 1.

FIG. 3. Amounts of Phenytoin and *p*-HPPH Excreted into Bile Juice in 120 min

Each bar represents the mean $\pm$ SEM of 3–5 rats.

51 to 447 μg . The percentage of dose exsorbed was increased with the increase in the dose of the drug. The extent of exsorption of phenytoin at the dose of 10 mg/kg was 1.1% in 120 min, while that at 50 mg/kg was 2.5% in 120 min. On the other hand, *p*-HPPH was not detectable in the perfusate under these experimental conditions. Thus, the exsorption of phenytoin from

blood into the intestinal lumen might be increased in acute poisoning by an overdose of the drug.

The amounts of phenytoin and *p*-HPPH, its main metabolite, excreted into the bile in 120 min are shown in Fig. 3. It was observed that the excretion of the conjugate of *p*-HPPH (16.3%, 13.5%, 11.9% and 7.6% at 10, 20, 30, and

FIG. 4. Dose-Dependency in Intestinal and Biliary Clearance of Phenytoin in Rats

Each point represents the mean $\pm$ SEM of 3–5 rats.

50mg/kg dose, respectively) into the bile was larger than the excretion of the parent drug, phenytoin (0.10%, 0.15%, 0.19% and 0.21% at 10, 20, 30 and 50 mg/kg doses, respectively) and

the unconjugated hydroxylated metabolite, *p*-HPPH (0.071%, 0.060%, 0.078% and 0.041% at 10, 20, 30, and 50 mg/kg doses, respectively). Additionally, the percent excretion of the total *p*-HPPH was significantly decreased by increasing the dose. The average percentages of total *p*-HPPH which were excreted into the bile in 120 min, were about 16%, 14%, 12%, and 8% at 10, 20, 30, and 50 mg/kg doses, respectively. These results suggested that the biotransformation from phenytoin into its hydroxylated metabolite is capacity-limited. Thus, the intestinal lumen exhibits a noted exsorption/excretion function for phenytoin and its metabolites.

To express the ability of the system to excrete the drug, the concept of intestinal and biliary clearance was used. Figure 4 shows the relationship between intestinal and biliary clearance values and the dose of phenytoin administered to rats. Both clearance values are defined as volumes of serum from which the drug is removed by excretion into the intestine and bile in 1 h. It was shown that both clearance values were increased with an increase in the dose. Both clearance values at the i.v. dose of 50 mg/kg were increased about three-fold as compared with those at 10 mg/kg. These results suggested

FIG. 5. Serum Phenytoin Levels after i.v. Administration of Phenytoin Sodium (10 and 50 mg/kg) to Rats with or without Treatment with Activated Charcoal

Each point represents the mean $\pm$ SEM of 5 rats. a) $p < 0.05$.

Key: ○ no charcoal treatment, ● treatment with multiple doses of charcoal.

A) Dose, 10 mg/kg; B) Dose, 50 mg/kg.

TABLE I. *Pharmacokinetic Parameters of Phenytoin after i.v. Administration of Phenytoin Sodium (10 and 50 mg/kg) to Rats with or without Treatment with Activated Charcoal*

Pharmacokinetic parameters		10 mg/kg		50 mg/kg	
		No charcoal treatment	Treatment with multiple doses of charcoal	No charcoal treatment	Treatment with multiple doses of charcoal
$t_{1/2}$	(h)	1.27 ± 0.09	1.47 ± 0.16	6.20 ± 0.73	$4.77 \pm 0.43^a)$
V_d	(l/kg)	1.22 ± 0.18	1.41 ± 0.23	1.45 ± 0.16	1.47 ± 0.11
Cl_{tot}	(l/kg/h)	0.67 ± 0.10	0.69 ± 0.14	0.16 ± 0.01	$0.22 \pm 0.01^b)$
AUC	($\mu\text{g}\cdot\text{h}/\text{ml}$)	16.2 ± 1.95	16.7 ± 2.95	311.2 ± 19.3	$233.5 \pm 12.4^b)$

Each value represents the mean $\pm$ SEM of 5 rats. key: a) $p < 0.05$, b) $p < 0.01$.

that phenytoin permeated from blood to the intestinal lumen sufficiently to be removed at high doses of the drug.

Effect of activated charcoal on phenytoin clearance

Figure 5 shows the time course of the serum phenytoin level after intravenous administration of 10 and 50 mg/kg doses to rats with or without oral activated charcoal treatment. The serum phenytoin levels at both 10 and 50 mg/kg doses decreased in a manner obeying first-order kinetics over a period of one to 6 or 8 h after i.v. administration. The elimination rate constant of the drug from serum after the 50 mg/kg dose was smaller than that after the 10 mg/kg dose (Table I), suggesting the dose-dependence in the elimination. As shown in Fig. 5, the treatment with oral activated charcoal had little effect on the serum phenytoin levels after the 10 mg/kg dose. On the other hand, oral administration of multiple doses of activated charcoal reduced the serum phenytoin levels after the 50 mg/kg dose as compared with the corresponding controls. Its mean serum level at 8 h was significantly decreased from 13.8 to 10.4 $\mu\text{g}/\text{ml}$ by multiple doses of activated charcoal. The pharmacokinetic parameters after 10 and 50 mg/kg doses are shown in Table I. There was no significant difference after the 10 mg/kg dose in $t_{1/2}$, V_d , Cl_{tot} or AUC between control and activated charcoal treated rats at the dose of 10 mg/kg ($p > 0.05$; paired t test). On the other hand, the oral administration of activated charcoal decreased the $t_{1/2}$ and AUC after a 50 mg/kg dose to 77% and 75%, respectively. The Cl_{tot} was increased to 138% as compared with the corresponding control rats. V_d was not significantly different between the treated rats and control

rats.

DISCUSSION

A mechanism for the enhanced clearance of phenytoin at a high dose (50 mg/kg) may be adsorption of the drug and its metabolites transported into the gastrointestinal tract by the charcoal. We have previously shown that exsorption into the perfusate of theophylline¹²⁾ and phenobarbital¹³⁾ were about 12% and 6.5% of the dose in 2 h, respectively. However, the amount of phenytoin exsorbed into the perfusate was less than those of these two drugs, i.e. 1.1% and 2.5% at the low (10 mg/kg) and high (50 mg/kg) doses, respectively. The amount of phenytoin exsorbed into the gut lumen at a high dose (50 mg/kg) was approximately 2.5 fold larger than that at a low dose (10 mg/kg). It is known that the permeability of drugs through the intestinal membrane varies enormously, depending upon the nature of the drug, for example, serum protein binding, lipophilicity and molecular size of the drug. The dose-dependent change in the exsorption rate constant may be explained by the saturation of serum protein binding of the drug. It is well known that only the unbound or free drug can permeate through capillary walls to various organs.

The percentage bound of phenytoin (about 90%)^{15,16)} has been shown to be higher than those in theophylline²⁰⁾ and phenobarbital²¹⁾ (both about 60% in humans). Moreover it is also known that the free fraction of phenytoin in serum increases with increase in the total drug concentration in serum *in vitro*.^{22,23)} Thus, protein binding influences the distribution pattern of the drug in the body. On the other hand, as

FIG. 6. Free Fraction in Serum after i.v. Administration of Phenytoin to Rats ($n = 10$)

shown in Fig. 6, the free fraction of phenytoin following i.v. administration of the drug was approximately constant, about 19%, over these concentration ranges. This result suggests that the equilibrium of the free phenytoin level between blood and tissue was rapidly obtained. As a result, the increased free phenytoin in serum at a high dose tended to transport the drug from blood into the intestinal lumen.

It is well-known that phenytoin and its metabolites undergo enterohepatic recirculation.^{17,24} For example, EL-hawari and Plaa²⁴ have reported that after administration of [¹⁴C]-phenytoin (70 mg/kg, i.v.) to bile duct-cannulated rats, 69% of the label was recovered in the bile in 8 h, while only 10% was eliminated in the urine. Moreover, they showed that metabolites in the bile, mainly glucuronide conjugate of *p*-HPPH, were shown to undergo extensive enterohepatic circulation. Therefore, the g.i. lumen may serve as a major part of the extracellular space in which the drug is distributed. Thus, the elimination of phenytoin from blood may be naturally accelerated due to a greater concentration gradient between blood and the fluid in the g.i. lumen if the reabsorption of the drug and its metabolites, which have been exsorbed and/or excreted into the g.i. tract, is prevented by adsorption by activated charcoal.

As an additional effect, product inhibition may affect the elimination of phenytoin. Ashley and Levy^{25,26} have suggested that product inhibition could be involved in the dose-dependent disposition of phenytoin and have shown that the major metabolite, *p*-HPPH, inhibits further hydroxylation of phenytoin. The reabsorbed

metabolites reach both the hepatic and systemic circulation, subjecting them to conjugation and subsequent biliary excretion process until the metabolites are completely eliminated from the body by urinary or fecal excretion. In our *in situ* single-pass perfusion study, there was an apparent trend of decrease in biliary excretion rate constant of *p*-HPPH, which was considered to be inhibition of its production by saturation of metabolism in the liver, with increasing dose after i.v. administration of phenytoin. Under this condition, such as a decreased capacity for metabolism which causes accumulation of *p*-HPPH in the body, the likelihood of product inhibition may be greatest. Accordingly, a mechanism of enhanced clearance of phenytoin, which was administered intravenously at a high dose (50 mg/kg), may be not only adsorption of the drug and its metabolites to the charcoal but also prevention of product inhibition by the hydroxylated metabolite, *p*-HPPH.

The lack of effect of activated charcoal on clearance at a low dose (10 mg/kg) may be explained by the small amount of the drug excreted into the gastrointestinal tract (Fig. 2). Since phenytoin is highly bound to serum protein, there is only a small unbound fraction of the drug that is available for removal.

Pond *et al*²⁷ reported that the administration of repeated oral doses of activated charcoal had little effect on phenytoin clearance at near therapeutic levels except for one case (12–43 µg/ml). The lack of change in the plasma phenytoin level is also explained by the extensive plasma binding of the drug which makes only the small unbound phenytoin available for the diffusion into the gut lumen. Another possible reason may be the higher total body clearance of the drug (0.7 l/kg/h at 10 mg/kg dose vs. 0.16 l/kg/h at 50 mg/kg dose). Park *et al*²⁸ have reported that activated charcoal has a relatively small effect in increasing digoxin elimination in normal subjects who have short digoxin half-lives, but has a significant effect in increasing digoxin elimination in renal failure subjects. The most likely explanation for this observation is that the percent increase in digoxin clearance due to charcoal almost certainly increases as the endogenous digoxin clearance decreases. They suggested that the total clearance of a drug during treatment with activated charcoal is the sum of the normal endogenous clearance and

clearance through the g.i. tract by charcoal. In principle, if activated charcoal produces constant intestinal drug clearance, the percentage in total body drug clearance caused by the charcoal will increase as the endogenous drug clearance (by metabolism or renal elimination) decreases. Therefore, the total clearance of phenytoin with large endogenous clearance at a low dose may not be noticed.

In conclusion, oral administration of activated charcoal may enhance the clearance of the drug in acute drug poisoning with a high phenytoin level even if the drug has been parenterally administered or has been absorbed into the systemic circulation from the g.i. tract. This so-called "gastrointestinal dialysis"²⁹⁾ may play an important role for removal of toxic amounts of drugs and physiological metabolites from the blood because of the very large surface area of the gastrointestinal lumen.

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