Phenobarbital Removal Characteristics of Three Brands of Activated Charcoals: A System Analysis Approach

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The *in vivo* phenobarbital removal characteristics of three brands of activated charcoal (Actidose, Charcoaid, Superchar) were studied in normal volunteers using a system analysis approach. The subjects received a 200-mg dose of oral or intravenous phenobarbital followed by a single oral dose of 30 g of one of the three charcoals in a randomized crossover design. The relative merits of the three charcoals in enhancing the removal of oral and intravenous phenobarbital were assessed using a system analysis approach. The removal clearance, time to peak (t_p), peak removal clearance (R_{max}), percentage of dose removed (PCT^{∞}), and phenobarbital removal clearance (CL_r) were calculated for the oral and intravenous treatments. Superchar had a pulse-like effect, with the shortest t_p and the largest R_{max}. Actidose and Charcoaid had similar effects, with Actidose inducing slightly greater phenobarbital removal. Superchar has the highest surface area and relative percentage of surface hydroxyl groups, whereas Actidose has the lowest surface area and relative percentage of surface hydroxyl groups of the three charcoals studied. Although correlations between the *in vitro* and the *in vivo* phenobarbital adsorption characteristics of the three charcoals may be difficult due to the presence of preservatives and palatibility enhancers in the commercial preparations, it appears that the *in vivo* effectiveness decreases as the surface area and the concentration of surface hydroxyl groups decrease. The proposed system analysis approach requires fewer assumptions than methods based on compartmental or physiologic approaches and has the advantage of describing the phenobarbital removal in a dynamic manner.

KEY WORDS: phenobarbital; overdose; detoxification; charcoal; activated.

INTRODUCTION

Due to the long elimination half-life of phenobarbital (about 110 hr), patients who take an overdose of phenobarbital may have a prolonged coma. Long-acting barbiturates account for 70% of the overdose and adverse effects to barbiturates in the United States (1). Numerous methods have been proposed for increasing the total body clearance of barbiturates from an acute overdose. These include hemodialysis (2), hemoperfusion, dopamine diuresis (3), forced alkaline diuresis (4), and orally administered adsorbants and ion-exchange resins (5–9). Orally administered activated charcoal has long been used to limit the absorption of drugs and poisons from the gastrointestinal tract and has become an important modality of decontamination (10,11). Case reports and research articles often treat activated charcoal as a generic entity, commonly failing to identify the brand of activated charcoal used. Few studies have critically evaluated the differences and comparative effectiveness of commercially available activated charcoal products for human use (8,12,13).

The application of a system analysis approach using deconvolution for evaluating the *in vivo* phenobarbital removal characteristics of multiple doses of activated charcoal has been described previously (14). The approach has also been applied successfully for evaluating the kinetics of drug removal by an extracorporeal device (15). By interpreting drug removal or elimination as a negative input of the drug, the induced drug removal processes can be characterized in a dynamic fashion. The approach is more general and requires fewer assumptions than methods that are based on specific compartmental or physiologic models or mass balance considerations (14).

EXPERIMENTAL

Healthy nonsmoking male volunteers between 20 and 40 years of age, judged to be normal on the basis of a physical exam and medical history, participated in the study following informed consent. Subjects normally experiencing more than two bowel movements per day were excluded. The study was conducted in the Clinical Research Center at the University of Iowa and was approved by the University of Iowa Institutional Review Board. Beginning 3 days prior to each treatment, the subjects were instructed to abstain from alcohol, aspirin, acetaminophen, over-the-counter medications, and marijuana. Each subject received eight treatments in a randomized crossover design. Four treatments corresponded to a 200-mg oral administration of phenobarbital and four to an intravenous phenobarbital infusion over 1 hr. The phenobarbital dose was administered after an 8-hr fast.

For the oral phenobarbital administrations, two 100-mg tablets of phenobarbital were dissolved in 150 mL of distilled water. The phenobarbital preparation was swirled for 15 min prior to administration to ensure complete dissolution of the phenobarbital. After ingestion of the phenobarbital solution, the cup was rinsed with several portions of distilled water (totaling 90 mL) and administered to the subject. For the intravenously administered phenobarbital, an equivalent of 200-mg phenobarbital free acid in the form of the sodium salt was used. The drug was placed in 100 mL of normal saline in a buretrol. The intravenous line was primed with the phenobarbital–normal saline solution. The volume of solution required to fill the intravenous line was noted, and when the volume of the phenobarbital-normal saline solution fell to 5.0 mL in the buretrol, a volume of saline equivalent to that required to fill the intravenous line was placed in the buretrol. The time for replacement was approximately 30 sec.

The following charcoal treatments were administered orally according to a randomized crossover design.

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Treatment 1: No charcoal.
Treatment 2: Charcoaid (Requa Manufacturing, Greenwich, CT 06830).
Treatment 3: Actidose (Paddock Laboratories, Inc., Minneapolis MN 55427).
Treatment 4: Superchar (Gulf Bio-Systems, Dallas, TX 75320).

The charcoal treatments were 30 g given orally immediately after the infusions or 30 min after the oral phenobarbital administration. Water (240 mL) was ingested following each charcoal dose. Venous blood samples (3 mL) were drawn at 0, 2, 4, 6, 8, 10, 12, 16, 20, 30, 40, 50, 60, 80, 100, 120, 140, 160, 180, 210, and 240 min and at 6, 8, 10, 24, 48, 96, 144, 312, and 480 hr following the oral phenobarbital dose. For the intravenous phenobarbital doses, blood samples were obtained at 0, 2, 4, 7, 10, 15, 20, 30, 40, 50, 60, 62, 64, 67, 70, 75, 80, 90, 100, 110, 120, 140, 160, 180, 200, 220, 240, and 270 min and at 6, 8, 10, 24, 48, 96, 144, 312, and 480 hr after the start of the infusion. The phenobarbital concentration in the serum was determined by a homogeneous enzyme immunoassay (EMIT, Syva, Palo Alto, CA) (16). Calibration and control samples were run with each series of unknown determinations and standard curves were prepared for a concentration range of 0–80 mg/mL. All calibrators, controls, and samples were analyzed in duplicate and were accepted if they agreed within 0.2–0.4 mg/mL.

Vital signs and mental checks were performed every 15 min for the first 2 hr, every 30 min for the next 2 hrs, every hour for the next 4 hr, and every 4 hr for the remainder of the first 24 hr. During the 24-h stay in the Clinical Research Center, each subject was placed on a low-fat diet of fruit juice (240 mL), and unbuttered toast was given 4 and 9 hr after the ingestion of oral phenobarbital or the start of the intravenous infusion. A standardized meal was given at 12 hr, with breakfast at 24 hr. Bowel movements were recorded for the first 24 hr of the study. If there were no adverse effects from the phenobarbital, the subject was discharged at 24 hr.

TOXICODYNAMIC THEORY AND ANALYSIS

A linear pharmacokinetic system is defined in the general sense as being one where the systemic drug concentration follows the superposition principle and is time invariant with respect to the systemic drug input rate. For a drug exhibiting linear, time-invariant disposition kinetics, the systemic drug concentration resulting from an input, $f(t)$, of the drug into the systemic circulation in the absence of an adsorbent is given by the following convolution relationship (17):

$$c^-(t) = c_\delta(t) * f(t) = \int_0^t c_\delta(u) f(t-u)\,du \qquad (1)$$

where $c_\delta(t)$ is the unit impulse response and the $-$ superscript denotes the absence of an adsorbent. The unit impulse response may be described by a sum of exponentials

$$c_\delta(t) = \sum_{i=1}^{n} a_i e^{-\alpha_i t} \qquad (2)$$

For a discontinuous infusion, the rate of drug input, $f(t)$, is defined as

$$f(t) \equiv \begin{cases} R & \text{for } 0 < t < T \\ 0 & \text{otherwise} \end{cases} \qquad (3)$$

where R is the rate of infusion and T is the duration of the infusion. By interpreting the drug removal process as a negative input of the drug, an expression similar to Eq. (1) can be derived for the systemic drug concentration in the presence of an adsorbent (14,15):

$$c^+(t) = c_\delta(t) * [f(t) - r(t)] = c^-(t) - c_\delta(t) * r(t) \qquad (4)$$

where the $+$ superscript denotes the presence of an adsorbent and $r(t)$ is an empirical function describing the *in vivo* drug removal process in the presence of the adsorbent. The assumptions for Eq. (1) have been summarized previously (14). It is not necessary to assume that the removal process is a linear response to the concentration or that is is continuous. It is assumed that the concentration is linearly related to the net input rate but the system need not respond linearly to the positive input in the presence of the induced removal process. The *in vivo* drug removal process may be described empirically as follows:

$$r(t) = \begin{cases} 0, & t < t_{0_{iv}} \\ \sum_{j=1}^{m} b_j e^{-\beta_j (t - t_{0_{iv}})_+}, & t \geq t_{0_{iv}} \end{cases} \qquad (5)$$

In the above expression, $t_{0_{iv}}$ is the time at which the activated charcoal begins exerting its effect. It is assumed that this is longer than the time the charcoal is administered but need not be equal to this time. Substituting for the unit impulse response and the removal function in Eq. (4) gives the concentration of phenobarbital in the presence of activated charcoal,

$$c_{iv}^+(t) = c_{iv}^- - \sum_{i=1}^{n}\sum_{j=1}^{m} \frac{a_i b_j}{\alpha_i - \beta_j} [e^{-\beta_j (t - t_{0_{iv}})_+} - e^{-\alpha_i (t - t_{0_{iv}})_+}] \qquad (6)$$

where the concentration in the absence of the charcoal, $c_{iv}^-(t)$, is given by

$$c_{iv}^-(t) = R \sum_{i=1}^{n} \frac{a_i}{\alpha_i} [e^{-\alpha_i (t-T)_+} - e^{-\alpha_i t}] \qquad (7)$$

and the $(\ )_+$ notation denotes a truncation function defined as

$$(x)_+ \equiv \begin{cases} 0 & \text{for } x \leq 0 \\ x & \text{otherwise} \end{cases} \qquad (8)$$

The oral treatments may be treated similarly by approximating the absorption profile, $f_{po}(t)$, as

$$f_{po}(t) = \sum_{k=1}^{w} g_k e^{-\gamma_k (t - t_{lag})_+} \qquad (9)$$

and the drug removal profile by

$$r(t) = \begin{cases} 0, & \text{for } x \leq t_{0_{po}} \\ \sum_{s=1}^{m} d_s e^{-\delta_s (t - t_{0_{po}})_+}, & \text{for } t \geq t_{0_{po}} \end{cases} \quad (10)$$

The drug removal profiles for the intravenous and oral phenobarbital need not be similar for obvious reasons as explained below.

The equations describing the systemic drug concentrations in the presence and absence of the activated charcoal following the oral phenobarbital treatments are, respectively,

$$c_{po}^{+}(t) = c_{po}^{-} - \sum_{i=1}^{n} \sum_{s=1}^{m} \frac{a_i d_s}{\alpha_i - \delta_s} [e^{-\delta_s (t - t_{0_{po}})_+} - e^{-\alpha_i (t - t_{0_{po}})_+}] \quad (11)$$

and

$$c_{po}^{-} = \sum_{i=1}^{n} \sum_{k=1}^{w} \frac{a_i g_k}{\alpha_i - \gamma_k} [e^{-\gamma_k (t - t_{lag})_+} - e^{-\alpha_i (t - t_{lag})_+}] \quad (12)$$

The above expressions assume that the unit impulse response is time invariant and ensure that the intrinsic phenobarbital clearance remains constant between the treatments. The phenobarbital clearance due to the included drug removal process, $CL_r(t)$, is

$$CL_r(t) = \frac{r(t)}{c(t)} \quad (13)$$

where $r(t)$ is the phenobarbital removal function [Eq. (5) or (10)] and $c(t)$ is the serum phenobarbital concentration. This approach allows the clearance to be expressed as a function of time and to be modeled continuously in a dynamic fashion rather than as a summary measure. If a summary measure of the clearance is desired, an "average" phenobarbital removal clearance, $\widehat{CL}_r$, can be determined

$$\widehat{CL}_r = \frac{\int_{t_0}^{\infty} r(u)\, du}{\int_{t_0}^{\infty} c(u)\, du} = \frac{A_{t_0}^{\infty}}{AUC_{t_0}^{\infty}} \quad (14)$$

For each subject, all possible four-treatment combinations (iv phenobarbital–no charcoal, po phenobarbital–no charcoal, iv phenobarbital + charcoal, po phenobarbital + charcoal) were used in the fitting process to determine the intrinsic phenobarbital clearance and phenobarbital removal characteristics of the charcoals. This was done by simultaneously fitting Eqs. (6), (7), (11), and (12) to the appropriate data using a general-purpose curve-fitting program (18). This approach, though computationally quite demanding, represents a compromise between simultaneously fitting all eight treatments and performing eight-parameter estimations for a particular subject.

RESULTS

Ten subjects successfully completed all eight treatments. The remaining subjects did not complete all phases of the study or incomplete data were available. For completeness, the results of all subjects that participated in the study are reported here. For all of the subjects studied, a biexponential unit impulse response sufficiently described the phenobarbital concentration–time profile following intravenous and oral phenobarbital. The phenobarbital removal was described by biexponential and triexponential expressions following intravenous and oral phenobarbital administration, respectively. In all cases the phenobarbital concentration–time data were well described in the absence and presence of charcoal and the coefficients of determination were greater than 90%. Phenobarbital concentrations were lower in the presence of than in the absence of charcoal. Figures 1 and 2 illustrate the concentration–time profiles for a representative subject (Subject 5) for the intravenous and oral phenobarbital administrations, respectively. For clarity, only the data for the first 10 and 24 hr are shown in Figs. 1 and 2, respectively.

Figures 3 and 4 illustrate the estimated removal clearance curves and cumulative percentage of dose removed for Subject 5 following oral Superchar administration after the intravenous and oral phenobarbital treatments. The solid lines in the figures represent the individual analyses of all possible four-treatment combinations and the dashed lines are the corresponding cumulative percentage of dose removed profiles. Summary measures of the effects of the various charcoals following intravenous and oral phenobarbital are illustrated graphically in Figs. 5 and 6. Figure 5 illustrates the time to peak (t_p) and maximal removal (R_{max}) values calculated for individual subjects and Fig. 6 shows the removal clearance ($\widehat{CL}_r$) and total percentage of dose removed (PCT^{∞}) values. The open symbols represent the intravenous phenobarbital treatments, and the filled symbols the oral phenobarbital treatments.

The three brands of charcoal studied differ in their peak effect, duration of action, removal clearance profile, and total percentage of dose removed. The results suggest that

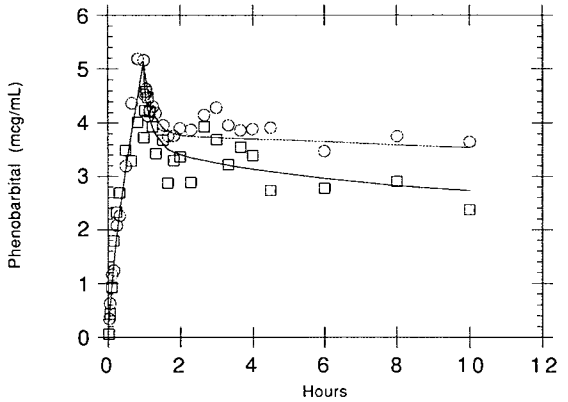

Fig. 1. Phenobarbital concentration–time profile for Subject 5 following an intravenous administration of 200 mg of phenobarbital in the absence (○) and presence (□) a 30-g oral dose of Actidose. The solid curves represent the estimated concentration using the system analysis approach.

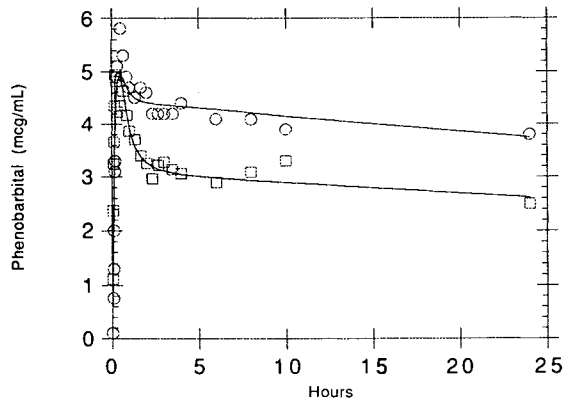

Fig. 2. Phenobarbital concentration–time profile for Subject 5 following an oral administration of 200 mg of phenobarbital in the absence (○) and presence (□) a 30-g oral dose of Actidose. The solid curves represent the estimated concentration using the system analysis approach.

Superchar induced the largest *in vivo* phenobarbital removal. This was signified by a higher PCT^{∞} and $\widehat{CL}_r$ for the intravenous and oral phenobarbital treatments for Superchar compared to Charcoaid and Actidose. Superchar had a pulse-like phenobarbital removal profile. The peak removal clearance following Superchar was reached earlier and had a higher amplitude compared to the other two charcoals. The difference between Actidose and Charcoaid was less distinct and both these charcoals induced similar phenobarbital removal. Charcoaid was slightly less effective than Actidose and had a more variable response.

DISCUSSION

The exponential functions employed were selected for their computational utility and ease of use. Although splines have also been used previously (15), splines are notorious for fitting to the error in the data and were not used in the present analysis. Since no physical significance is attached to the estimated parameters, except for their ability to describe the data, the estimated parameters are not reported. Rather, the characteristics of the three charcoals are summarized graphically in the form of statistics that represent the *in vivo* phenobarbital removal characteristics of the three brands of charcoal.

The results indicate that Superchar was the most effective in removing intravenously and orally administered phenobarbital. Activated charcoal was more effective when administered following oral ingestion of phenobarbital than after an intravenous dose. Most of the open symbols in Fig. 6, representing intravenous administration, fell in the left half of the figure, whereas the filled symbols, representing oral phenobarbital administration, fell in the right. Residual phe-

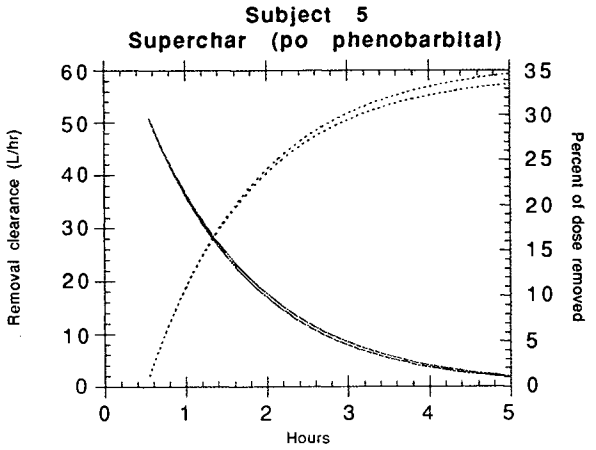

Fig. 4. Phenobarbital removal clearance profile for Subject 5 following an oral administration of 200 mg of phenobarbital in the presence of a 30-g oral dose of Superchar. The solid curves represent the estimated removal clearance profiles and the dashed curves the corresponding percent of phenobarbital removed. Each curve represents a four-treatment combination, providing graphical evidence of the amount of variability.

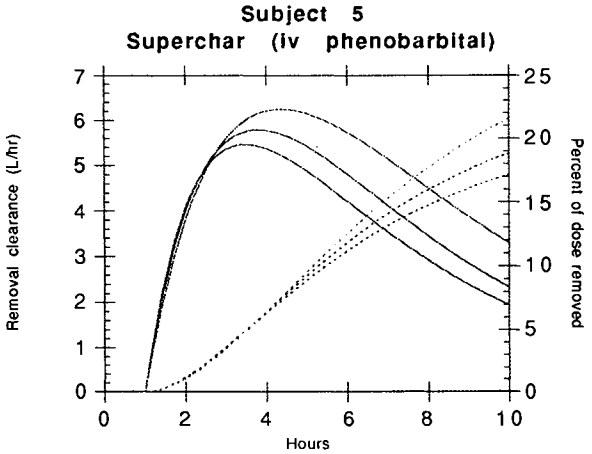

Fig. 3. Phenobarbital removal clearance profile for Subject 5 following an intravenous administration of 200 mg of phenobarbital in the presence of a 30-g oral dose of Superchar. The solid curves represent the estimated removal clearance profiles and the dashed curves the corresponding percentage of phenobarbital removed. Each curve represents a four-treatment combination, providing graphical evidence of the amount of variability.

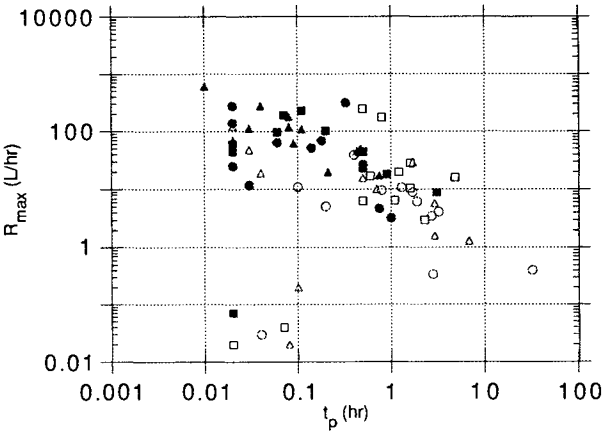

Fig. 5. Graphical illustration of t_p and R_{max} estimated to describe the *in vivo* phenobarbital removal characteristics of Charcoaid (circles), Actidose (squares), and Superchar (triangles). Each symbol represents an individual subject, with open symbols representing intravenous phenobarbital and filled symbols oral phenobarbital. For clarity, the data are shown on a logarithmic scale, with t_p values below 0.01 hr being ignored.

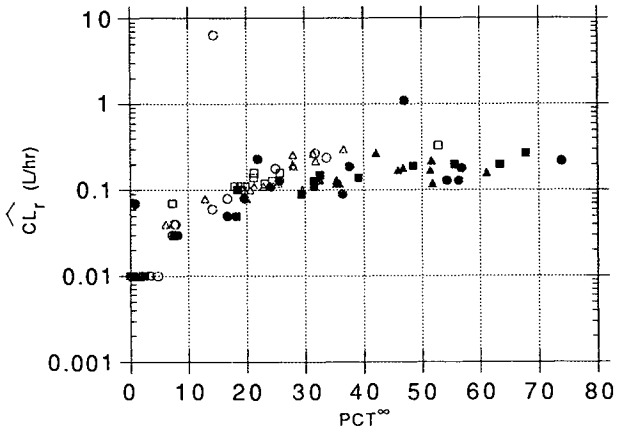

Fig. 6. Graphical illustration of PCT^{∞} and CL_r estimated to describe the *in vivo* phenobarbital removal characteristics of Charcoaid (circles), Actidose (squares), and Superchar (triangles). Each symbol represents an individual subject, with open symbols representing intravenous phenobarbital and filled symbols oral phenobarbital.

nobarbital in the gastrointestinal tract following oral phenobarbital may have been adsorbed onto the charcoal and subsequently become poorly available for absorption.

For the intravenous treatments, all the phenobarbital that is adsorbed onto the charcoal has to move from the serosal side to the mucosal side of the gastrointestinal wall before it can be adsorbed. Since there is no appreciable enterohepatic cycling of phenobarbital (19), the charcoal probably sets up a concentration gradient by adsorbing phenobarbital in the gastrointestinal fluids. Driven by this concentration gradient, phenobarbital diffuses from the blood into the gastrointestinal fluids and is subsequently adsorbed onto the charcoal (5). This phenomenon has been termed "gastrointestinal dialysis" (20), and the amount of drug extracted depends on the concentration gradient, intestinal surface area, permeability, and blood flow (7). Gastrointestinal dialysis by oral administration of activated charcoal has not been clearly established as an effective means of removing drugs which have been administered parenterally or have already been absorbed into the systemic circulation from the GI tract (21). Our results indicate that a single administration of an appropriate activated charcoal may be effective in removing intravenous phenobarbital.

Previous *in vitro* studies have shown that the degree of adsorption depends on the surface area and the specific functional groups present on the adsorbent surface (22–24). However, the results of *in vitro* work are not always readily applicable *in vivo* (12), and the amount of charcoal required to adsorb a particular amount *in vitro* may be incapable of adsorbing the same amount *in vivo* (25). Possible reasons for this include competition by gastrointestinal contents for adsorptive sites, gastrointestinal motility and secretions, and pH variations along the gastrointestinal tract, all of which can influence the adsorptive capacity of the charcoal.

Adsorption of phenobarbital by activated charcoal has been correlated with the relative percentage of hydroxyl groups on the surface (22). Superchar has the highest surface area, about 2900 m^2/g (10,23,24) and the highest relative percentage of surface hydroxyl groups (22). Charcoaid contains Norit B Supra. This activated charcoal has a surface area of 1500 m^2/g (23) and the second highest relative concentration of surface hydroxyl groups (22). Actidose contains Darco KB-B. Darco also has a surface area of approximately 1500 m^2/g (10,23,24,26) but it has the lowest relative concentration of surface hydroxyl groups (22). Although correlations between the *in vitro* and the *in vivo* phenobarbital adsorption characteristics of the three charcoals may be difficult due to the presence of preservatives and palatability enhancers in the commercial charcoals, it appears that the *in vivo* effectiveness decreases as the surface area and the concentration of surface hydroxyl groups decrease, just as observed in the *in vitro* studies.

Both Charcoaid and Actidose contain sorbitol, which has the potential for causing diarrhea and increased gastrointestinal motility (6). This may be desirable following oral ingestion of phenobarbital but would also decrease the amount of charcoal available in the gastrointestinal tract which would be undesirable following intravenous phenobarbital. Some patients may also tolerate sorbitol better than others. This may contribute to the intersubject variability in assessing the *in vivo* action of charcoal and complicates attempts aimed at seeking *in vitro* and *in vivo* correlations.

The *in vivo* results obtained in the present study may serve several clinically relevant functions. The model provides a quantitative measure of the *in vivo* activity of a single administration of charcoal. Although a single administration of charcoal is beneficial in inducing phenobarbital removal, it may be prudent to intervene more aggressively with multiple charcoal administrations or gastric lavage, particularly in cases of more serious phenobarbital intoxications. The results suggest that a 4-h dosing interval may be necessary in the case of oral phenobarbital intoxication, whereas a 6- to 8-hr schedule may make adequate use of the charcoal in cases of intravenous phenobarbital intoxication. Although oral charcoal is beneficial following intravenous phenobarbital intoxication, the relative benefit is lower than that in oral intoxications, where the charcoal also reduces further absorption.

The system analysis approach presented is more general and requires fewer assumptions than methods based on specific compartmental or physiologic models. A system analysis approach does not subscribe to a specific structural philosophy for modeling a process of interest but rather models the overall effects of the process on the observed response. The results presented assume that the phenobarbital disposition is linear and time invariant. For pharmacokinetic systems, it must be realized that no system is strictly linear. At sufficiently high doses nonlinear effects (e.g., saturable metabolism or nonlinear binding) may arise. We assume that the drug concentrations encountered in the present study do not give rise to significant nonlinear pharmacokinetic effects. The dose of phenobarbital used in the current study is similar to that used by others (14,27). It is unlikely that significant nonlinearities would be exhibited at these concentrations. Enzyme induction due to phenobarbital requires multiple drug administration. Since the present study used a randomized crossover design with a prolonged washout, it is unlikely that there would be significant enzyme induction. In cases of phenobarbital intoxications, where the dose may exceed 1 g, it is possible that the pharmacokinetics may become nonlinear and some of the assumptions necessary in

the present analysis may be invalid. In such cases, the effects of charcoal administration may be less predictable.

The linearity assumption also implies that the induced removal process does not alter the characteristic response of the system. The perturbations in the phenobarbital pharmacokinetics are due entirely to drug removal and not due to an alteration in some other disposition factors, e.g., removal of compounds that interact kinetically with the drug of interest. The linearity assumption, however, need not apply to the induced removal process for the proposed deconvolution approach. No specific structural assumptions are made about the drug adsorption or disposition processes. The method presented is more descriptive than methods based on mass balance principles and allows the phenobarbital removal to be described in a dynamic fashion rather than only in terms of discrete or summary measures.

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