Clinical Toxicology, 34(2), 169–175 (1996)

Multiple-Dose Activated Charcoal Compared to Urinary Alkalinization for the Enhancement of Phenobarbital Elimination

Maureen L. Frenia, PharmD; Jay L. Schauben, PharmD; Robert L. Wears, MD; Janet L. Karlix, PharmD; Cheryl A. Tucker, RN; Thomas A. Kunisaki, MD

University of Florida Health Science Center/Jacksonville, Jacksonville, Florida (MLF,JLS,RLW,CAT,TAK); University of Florida, College of Pharmacy, Gainesville, Florida (JLK)

ABSTRACT

Background: Urinary alkalinization and multiple-dose activated charcoal are modalities advocated for the enhancement of phenobarbital elimination in poisoned patients. However, no studies exist comparing the efficacy of these two means of elimination enhancement. We compared their effects on the pharmacokinetic disposition of intravenously administered phenobarbital. Methods: Ten healthy volunteers participated in each of three randomly ordered study phases. During each phase, 5 mg of intravenous phenobarbital per kilogram of body weight was administered. During phase I, no interventions were made in attempt to enhance phenobarbital elimination. In phase II, participants underwent 24 hours of urinary alkalinization. Throughout phase III, volunteers received six doses of activated charcoal and two doses of sorbitol over 24 hours. Results: The phenobarbital elimination half-life was 148 hours, 47 hours and 19 hours during the control, alkalinization and charcoal phases, respectively. Statistically significant differences in the elimination of phenobarbital were detected when each of the following phases were compared: I vs II, I vs III and II vs III. Conclusions: Both urinary alkalinization and multiple doses of activated charcoal are effective for the enhancement of phenobarbital elimination but multiple-dose charcoal was superior to urinary alkalinization in our study population.

Correspondence: Dr. Maureen Frenia, Boehringer Ingelheim Pharmaceuticals, Inc., P.O. Box 368, Ridgefield, CT 06877-0368. Phone: 203/798-5723, Fax: 203/791-6225.

INTRODUCTION

In recent years, the incidence of barbiturate exposures has declined, possibly due to the development and use of safer and more efficacious agents. Nevertheless, a significant number of poisonings are still being reported to poison centers annually.[1] The specific symptoms associated with phenobarbital sodium (PB) toxicity have been well described in the literature. Severe and potentially fatal cardiovascular, respiratory and central nervous system depression may develop following a significant exposure.[2-4] Even patients with a mild or moderate magnitude of poisoning may have a prolonged hospital course secondary to the long half life of PB, which ranges from 37 to 126 h.[5] In an attempt to shorten the duration of the toxic manifestations several modalities are currently advocated to enhance the elimination of PB including the administration of multiple doses of activated charcoal (MDAC) and urinary alkalinization (UA).

In the past, forced diuresis and forced alkaline diuresis were included in treatment algorithms for PB intoxication. Purportedly, the induction of enhanced diuresis decreased the time the drug was present in the renal tubule. Shortening the retention time in the renal tubule reduced the potential for the drug to diffuse back into the central circulation and subsequently increased its elimination rate. IV fluid administration geared to maintain a urine flow rate of up to 10 mL/min had been recommended.[4] Although forced diuresis did induce an increase in PB elimination, its use resulted in a variety of adverse effects from fluid overload; the most troubling of which was pulmonary edema.[3,6-11] Consequently, methods which utilize the administration of high volume loads to increase urine flow (i.e. forced diuresis and forced alkaline diuresis) are no longer recommended.

Most studies characterizing the enhancement of PB elimination have focused their evaluation on the efficacy of forced diuresis in the presence or absence of UA.[3,6,7,9-11] Large, well controlled trials involving UA without forced diuresis are nonexistent. Nevertheless, the current guidelines for the management of the PB poisoned patient advocate UA as standard therapy.

Phenobarbital, a weak acid with a pKa of 7.24, is amenable to elimination enhancement by UA due to a pH-modified increase in the ratio of ionized to nonionized drug. Since ionized molecules will not traverse biological membranes easily, this form of PB is "trapped" within the renal tubule and subsequently eliminated in greater quantities. This mechanism of elimination enhancement is most effective for those compounds possessing a small volume of distribution, which are primarily eliminated renally, and have a pKa within a narrow range amenable to the manipulation of urine pH within a physiologic range.[12,13] Theoretically then, UA without forced diuresis should enhance phenobarbital elimination. In fact, it has been postulated that UA without forced diuresis may actually be more effective than with forced diuresis, since UA is more easily accomplished without concomitant urinary dilution.[8] Other than one anecdotal report, no literature is available to support these theories.[13]

In contrast, several well designed clinical trials have described the effectiveness of administering MDAC to enhance the elimination of oral and IV administered PB.[14-20] MDAC regimens are believed to facilitate the elimination of PB by enhancing its movement down a concentration gradient from the systemic circulation into the gastrointestinal tract, whereupon it is adsorbed to charcoal and subsequently eliminated in the feces. The apparent efficacy and relative safety of MDAC regimens have forced a reevaluation of the role of UA in the management of PB toxicity.[12]

Controlled pharmacokinetic studies comparing UA to MDAC relative to the disposition of PB are currently nonexistent. Our objective, therefore, was to compare these frequently used modalities in an attempt to ascertain relative effectiveness of one method over another.

METHODS

Study Design

Twelve healthy volunteers, six males and six females, ranging in age from 24 to 40 y were enrolled. The study was approved by the Institutional Review Board and informed consent was obtained from all volunteers prior to enrollment in the study. Those potential subjects who were smokers, pregnant, on chronic medications, or those who had ingested medications or alcohol within 72 h prior to the study period were excluded.

At the beginning of each study phase, following a six hour fast, 5 mg/kg of PB was administered IV over 60 min. During the control phase (Phase I), volunteers received only IV PB with no attempt at any elimination enhancement modality. In the UA phase (Phase II), the study subjects received PB followed by the administration of a sodium bicarbonate bolus (1 mEq/kg IV) beginning 30 min after the completion of the PB infusion. Immediately following the bicarbonate bolus a maintenance infusion of 100 mEq sodium bicarbonate in 1000 mL of 5% dextrose in water was initiated at a rate of 2.5 mL/min and was thereafter titrated to maintain the pH of the subject's urine between 7.5 and 8.0. Urine pH was measured hourly. The sodium bicarbonate infusion was reduced hourly in 10 mL/h increments for a urine pH greater than 8.0 and was increased hourly in 10 mL/h increments for a urine pH less than 7.5. Twenty mmol potassium chloride were added to the initial bicarbonate infusion. Serum electrolytes and venous blood gases were evaluated every four hours throughout this 24-hour study phase. Serum pH was monitored to ensure that it remained between 7.35 and 7.55. No sodium bicarbonate titration was made based on the serum pH. During phase III, PB administration was followed 30 min later by an initial dose of 50 g activated charcoal (Paddock Laboratories, Inc.) mixed with 50 g 70% sorbitol. Subsequent activated charcoal dosing consisted of 25 g of the aqueous suspension given every four hours with 25 g of 70% sorbitol added to the charcoal slurry every 12 h. Each study phase was separated by a minimum of one week.

Assay

Five mL of blood for determination of PB serum concentration was collected via an intermittent IV catheter, prior to and 1, 2, 4, 6, 8, 10, 12, 18 and 24 h after the initiation of the PB infusion in each study phase. The serum PB concentrations were measured in duplicate using fluorescence polarization immunoassay (TDX®, Abbott Laboratories, Abbott Park, IL). Sensitivity, defined as the lowest measurable phenobarbital concentration which can be distinguished from zero with a 95% confidence interval was determined to be 1.1 μg/mL. The assay was accurate to determine phenobarbital levels to a maximum of 80.0 μg/mL. Accuracy was ensured by comparing the assay used in our study to a commercially available method and HPLC by evaluating samples from patients on phenobarbital therapy.

Pharmacokinetic Calculations

The elimination of PB is well defined by a two-compartment model. For the assessment of PB elimination parameters, we evaluated the beta-elimination phase of the individual plasma concentration vs time curves (range 2 to 24 h). The time zero and one hour serum levels were not used in the pharmacokinetic characterizations since we were not interested in the distribution of PB. The volume of distribution (V_d), elimination rate constant (K_e), elimination half-life ($t_{1/2}$), and total clearance (Cl_T) of PB were determined for each participant in each study phase. The volume of distribution was calculated using the equation dose/peak serum PB concentration (extrapolated). Half-life was calculated from the equation $0.693/K_e$ where K_e was determined from the difference in the natural logs of the PB concentration points divided by the time interval between the points. Total clearance was determined by dividing the dose by area under the curve (AUC), where AUC was calculated using the trapezoidal rule.

Statistical Analysis

The paired differences between phases I and II, II and III, and I and III were evaluated by the Wilcoxon Signed Rank Test. Differences between the phases were considered statistically significant if $p < 0.05$.

RESULTS

Ten of the 12 enrolled subjects completed all three study phases in a random order, crossover design. Two volunteers were eliminated from the study protocol due to an inability to maintain 24 h IV access in Phase II.

The mean V_d, K_e, $t_{1/2}$ and Cl_T of PB following each study phase are given in Table 1. The differences in standard error and probability values of the results are shown in Table 2. The V_d of PB was comparable in all three study phases. Contrarily, statistically significant differences in the K_e, $t_{1/2}$ and Cl_T of IV administered PB were detected

Table 1

Pharmacokinetics of Phenobarbital Following Each Study Phase (n = 10)

Phase	PB	PB + $NaHCO_3$	PB + MDAC
V_d (L/kg)*	0.55 ± 0.37	0.55 ± 0.28	0.54 ± 0.33
K_e (h^{-1})*	0.007 ± 0.019	0.016 ± 0.011	0.039 ± 0.030
$t_{1/2}$ (h)*	148.1 ± 332.1	47.24 ± 42.04	18.87 ± 14.70
Total body clearance (mL/kg/h)*	2.79 ± 9.69	8.29 ± 8.62	19.95 ± 11.55

*Mean results ± one standard deviation reported.

Table 2

Differences in Standard Error Between Study Phases (n = 10)

	I vs II	I vs III	II vs III
V_d (L/kg)*	2.891	3.081	2.071
	p = 0.834	p = 0.736	p = 0.833
K_e (h^{-1})*	0.002	0.004	0.004
	p = 0.017	p = 0.005	p = 0.005
$t_{1/2}$ (h)*	0.231	0.253	0.149
	p = 0.013	p = 0.005	p = 0.005
Total body clearance (mL/kg/h)*	0.071	0.086	0.096
	p = 0.001	p < 0.0005	p < 0.0005

*Mean results reported.

when these parameters were compared following all three study phases (i.e. I vs II, I vs III, and II vs III). The K_e for PB in phases I, II and III was 0.007 h^{-1}, 0.016 h^{-1} and 0.039 h^{-1}, respectively. Statistically significant differences in PB elimination were detected when all three study phases were compared (i.e. I vs II, II vs III and I vs III). UA and MDAC were both effective at enhancing PB elimination when compared to control. However, MDAC was significantly more effective than UA for the enhancement of PB elimination as depicted in Figures 1 and 2.

Similar trends were detected when the Cl_T and $t_{1/2}$ of PB were evaluated. The phenobarbital $t_{1/2}$ was 148 h, 47 h and 19 h in phases I, II and III, respectively. Again, UA and MDAC were both effective in the enhancement of PB elimination when compared to control, however MDAC was more effective than UA when compared to each other (ie, II vs III). The Cl_T of PB throughout the study followed the same trend as shown in Table 1.

In summary, UA and MDAC were both effective at increasing PB elimination when compared to control. However, MDAC was significantly more effective when compared to UA for the enhancement of PB elimination.

DISCUSSION

Since PB poisoning is associated with a relatively low mortality rate, it is logical to question the need for such interventions as MDAC and UA. These

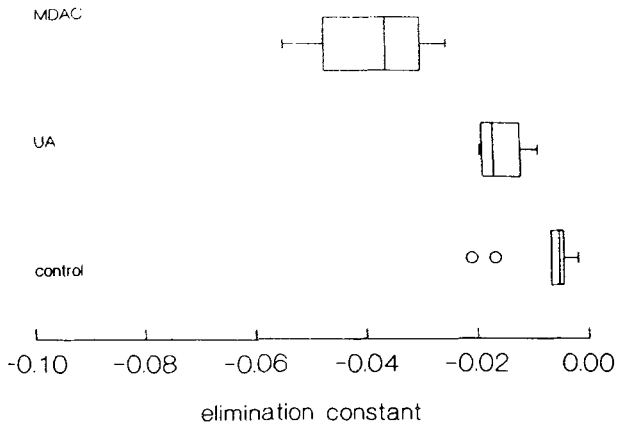

Figure 1. Phenobarbital elimination constant.

modalities have shortened the duration of symptoms by directly accelerating the declination of the serum level and theoretically should result in a shortened period of hospitalization. However, definitive improvement in mortality rates and shortened hospital stays have not been documented. Regardless, it seems rational to increase the elimination of serum PB if such a maneuver can be proven both safe and effective. It also appears unethical to allow an exceedingly high PB serum level or, for that matter, a patient with moderate to severe symptoms related to these high levels to remain untreated when effective modalities for reducing the serum concentration exist. MDAC appear to be the most effective means of accomplishing this goal.

MDAC is one of the more common modalities recommended for the management of a wide variety of poisoned patients. Our results are consistent with reports of previous efficacy studies related to the use of MDAC regimens specifically for PB intoxication. We noted a reduction in the plasma half-life from 148 h to 19 h (an 87% reduction) with the administration of MDAC. Berg *et al.*[15] evaluated the effects of MDAC in six volunteers who received IV PB. A reduction in the PB half-life from 110 h (control) to 46 h following the administration of 180 g of charcoal in divided doses was reported. Pond *et al.*[19] found a decrease in the half-life of PB from 93 h to 36 h when a single dose of charcoal was compared to the administration of multiple doses of charcoal in comatose patients. Neuvonen *et al.*[16] reported similar results when the pharmacokinetic disposition of PB with and without MDAC was evaluated. Phenobarbital half-life decreased from 110 h to 19.8 h following the administration of five doses of charcoal totaling 118 g. Additional studies and case reports have documented similar findings.[14,17,18,20]

UA has also been included in the treatment algorithms for the management of PB poisoned patients. Although many references still include this procedure as part of their treatment protocol, data supporting this recommendation are virtually non-existent. As stated previously, several case reports attempt to document the effectiveness of forced alkaline diuresis as a maneuver to enhance the elimination of PB; but no large well controlled studies are available which specifically evaluate UA without forced diuresis. Waddell[13] evaluated the effects of UA with and without the use of concomitant diuresis in two men receiving therapeutic doses of PB. In one individual, PB clearance increased from 2.5 mL/min to 7.5 mL/min concurrent with elevation in urine flow rates. It also appeared that PB clearance in one individual may have been greater (13.8 mL/min vs 3.0 mL/min) with alkaline urine (pH 8.0) than with acidic urine (pH 6.1) at somewhat comparable flow rates (2.8 mL/min vs 1.2 mL/min, respectively). However, no demonstrable conclusions can be drawn from the limited number of subjects studied in this uncontrolled setting. In the same study, UA without forced diuresis was shown to increase PB elimination by ten-fold in dogs. Myschetzky and Lasen[7] evaluated 16 patients with PB toxicity and demonstrated a reduction in the duration of coma by one-third to one-half in those patients treated concurrently with UA and diuresis. However the clinical significance of this effect with respect to the control group was not determined. Bloomer *et al.*[8] also evaluated the effects of diuresis and UA on the pharmacokinetic disposition of PB in three poisoned patients. The authors reported a doubling of the PB elimination rate when UA was coupled with diuresis. Setter and Lassen,[3,11] in separate studies, directly correlated an increase in urine flow, via the administration of fluids and diuretics, with enhancement of PB elimination in poisoned patients. More importantly, as PB elimination was increased and serum PB decreased, the duration of coma in

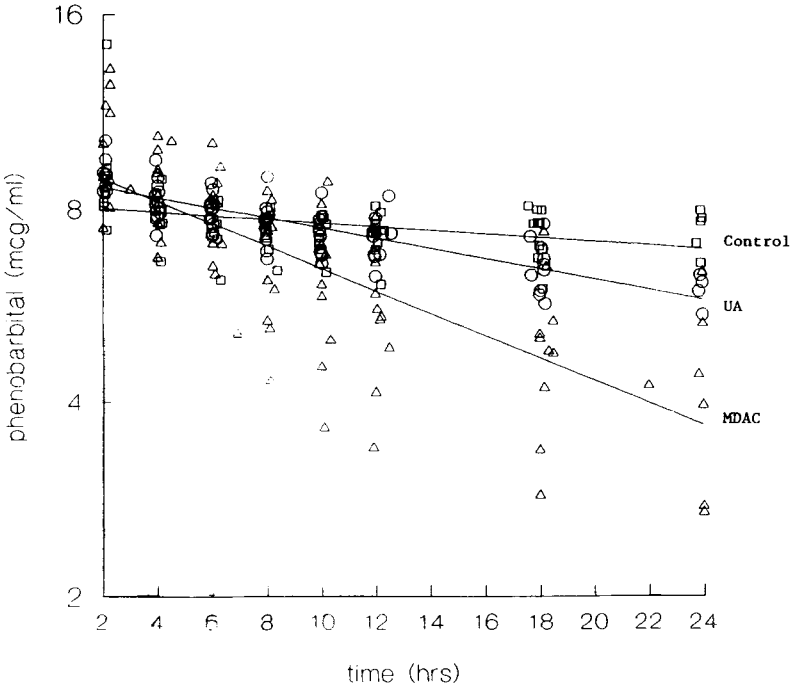

Figure 2. Average phenobarbital elimination during phases I-III.

these individuals decreased. We found a significant enhancement in PB elimination arising from the induction of UA, albeit, only about one-third as great as that found with the administration of MDAC in our study population. After assimilating data relative to the efficacy of UA, Garrettson and Geller ask: "Does ion-trapping still have a place in the physician's armoury today?"[12]

To lend additional credence to the potential replacement of UA by MDAC in the protocols used to manage PB poisoned patients, we should compare the side effect profiles of both of these interventions. We recorded minor symptoms, including vomiting or constipation, in one-half of the participants during the control and MDAC phases. These effects were self-limiting and did not require intervention. By far, the most significant symptoms noted during the study occurred in the UA phase. Concurrent with the administration of a sodium bicarbonate bolus, one participant developed bradycardia (HR 44 bpm) and mild hypotension (BP 82/50 mm Hg) which resolved within five minutes. Additionally, seven of 11 participants developed mild hypokalemia despite supplementation with oral potassium chloride throughout this phase. Serum potassium decreased on an average by 1 mmol/L, in spite of concurrent oral potassium administration. Each volunteer received, on the average, 120 mEq of oral potassium chloride in addition to the 20 mEq administered IV with the initial bicarbonate infusion. Clinicians should be aware that UA can result in significant electrolyte abnormalities necessitating the close monitoring of vital signs, fluid status, serum electrolytes, and acid base balance. Unfortunately, serum potassium was not monitored during the control and charcoal phases.

We recognize the limitations of this study. First, the study was limited to healthy volunteers who received therapeutic doses of IV PB. It is therefore difficult to apply this data directly to the poisoned patient. Second, logistical concerns prevented the conduction of additional phases to evaluate the concomitant use of MDAC and UA, or the use of a single dose of activated charcoal.

Currently, protocols for the management of moderately or severely poisoned patients include UA and MDAC for enhancement of PB elimination. Eventually, management may include the sole use of MDAC and supportive care without UA. Acceptance of this revised protocol is inevitable if, indeed, the elimination enhancement effects of these modalities are comparable in poisoned patients, regardless of the severity of PB toxicity. But perhaps the degree of a patient's PB toxicity must be considered. For example, in severely poisoned patients, UA may be used concomitantly with MDAC, hemodialysis or hemoperfusion if, at these doses, the effects of UA are eventually proven beneficial or synergistic. Contrarily, UA would be unnecessary if proven ineffective in patients with mild signs and symptoms of PB toxicity. Larger, prospective studies in poisoned patients with all levels of PB poisoning seem warranted to answer these questions.

CONCLUSION

Our results demonstrate that, in our study population, MDAC is a safer and more efficacious means of PB elimination enhancement than UA.

ACKNOWLEDGEMENTS

We are indebted to the specialists in poison information at the Florida Poison Information Center/Jacksonville and to all of our volunteers for their assistance with this project.

REFERENCES

1. Litovitz TL, Clark LR, Soloway RA. 1993 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 1994;**12**:546-584.
2. Clemmesen C, Nilsson E. Therapeutic trends in the treatment of barbiturate poisoning; the Scandinavian method. *Clin Pharmacol Ther* 1961;**2**:220-229.
3. Setter JG, Maher JF, Schreiner GE. Barbiturate intoxication. Evaluation of therapy including dialysis in a large series selectively referred because of severity. *Arch Intern Med* 1966;**117**:224-236.
4. Henderson LW, Merrill JP. Treatment of barbiturate intoxication. *Ann Intern Med* 1966;**64**:876-891.
5. Evans WE, Schentag JJ, Jusko WJ, eds. *Applied Pharmacokinetics Principles of Therapeutic Drug Monitoring*, 2nd ed. Spokane: Applied Therapeutics Inc. 1987:546-548.
6. Linton AL, Luke RG, Briggs JD. Methods of forced diuresis and its application in barbiturate poisoning. *Lancet* 1967;**2**:377-379.
7. Myschetzky A, Lassen NA. Urea-induced, osmotic diuresis and alkalinization of urine in acute barbiturate intoxication. *JAMA* 1963;**185**:936-942.
8. Bloomer HA. A critical evaluation of diuresis in the treatment of barbiturate intoxication. *J Lab Clin Med* 1966;**67**:898-905.
9. Mawer GE, Lee HA. Value of forced diuresis in acute barbiturate poisoning. *BMJ* 1968;**2**:790-793.
10. Costello JB, Poklis A. Treatment of massive phenobarbital overdose with dopamine diuresis. *Arch Intern Med* 1981;**141**:938-940.
11. Lassen NA, Copenhagen MD. Treatment of severe acute barbiturate poisoning by forced diuresis and alkalinization of the urine. *Lancet* 1960;**2**:338-342.
12. Garrettson LK, Geller RJ. Acid and alkaline diuresis. When are they of value in the treatment of poisoning? *Drug Saf* 1990;**5**:220-232.
13. Waddell WJ, Butler TC. The distribution and excretion of phenobarbital. *J Clin Invest* 1957;**36**: 1217-1226.
14. Boldy DA, Vale JA, Prescott LF. Treatment of phenobarbitone poisoning with repeated oral administration of activated charcoal. *Q J Med* 1986; **61**:997-1002.
15. Berg MJ, Berlinger WG, Goldberg MJ, Spector R, Johnson GF. Acceleration of the body clearance of phenobarbital by oral activated charcoal. *N Engl J Med* 1982;**307**:642-644.
16. Neuvonen PJ, Elonen E. Effect of activated charcoal on absorption and elimination of phenobarbitone, carbamazepine and phenylbutazone in man. *Eur J Clin Pharmacol* 1980;**17**:51-57.
17. Goldberg MJ, Berlinger WG. Treatment of phenobarbital overdose with activated charcoal. *JAMA* 1982;**247**:2400-2401.
18. Amitai Y, Degani Y. Treatment of phenobarbital poisoning with multiple dose activated charcoal in an infant. *J Emerg Med* 1990;**8**:449-450.
19. Pond SM, Olson KR, Osterloh JD, Tong TG. Randomized study of the treatment of phenobarbital overdose with repeated doses of activated charcoal. *JAMA* 1984;**251**:3104-3108.
20. Veerman M, Espejo MG, Christopher MA, Knight M. Use of activated charcoal to reduce elevated serum phenobarbital concentration in a neonate. *J Toxicol Clin Toxicol* 1991;**29**:53-58.