Therapeutic Drug Monitoring
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Pharmacokinetics of Phenobarbital During Certain Enhanced Elimination Modalities to Evaluate Their Clinical Efficacy in Management of Drug Overdose

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Summary: This work was performed to study the pharmacokinetics of phenobarbital during renal clearance enhancement, intestinal clearance enhancement, and a combination of both to determine which method is clinically more effective in the management of drug poisoning. Thirty young patients with phenobarbital overdose were enrolled in the study. They were classified according to the method of treatment to enhance the elimination of phenobarbital into three equal groups: those treated with multiple-dose activated charcoal (MDAC) alone; those treated with urinary alkalinization alone; and those treated with a combination of the two methods. All patients received the required supportive care at the same time as the elimination procedures. Plasma phenobarbital levels were determined on admission and at 6, 12, 18, 24, 30, 36, 42, and 48 hours after admission by the enzyme multiplied immunoassay technique. The results showed that the decrease in plasma phenobarbital levels with MDAC was significantly greater than with either urinary alkalinization or the combined use of both. The results also revealed statistically significant greater total body clearance for phenobarbital and consequently a shorter half-life with MDAC treatment versus either urinary alkalinization alone or the combined use of both. Thus, the authors conclude that the management of drug overdose in the case of weak acidic drugs that have small volumes of distribution should include the sole use of MDAC and supportive care, without urinary alkalinization. **Key Words:** Drug overdose—Enhanced elimination modalities—Pharmacokinetics—Phenobarbital.

Management of a drug overdose usually depends on enhancing the elimination of the drug from the body (1). Many clinical procedures have been used in attempts to shorten the duration of the drug's toxic manifestations (2). The most important modalities are the enhancement of urinary excretion by changing the pH of the urine and gastrointestinal dialysis by using multiple-dose activated charcoal (MDAC) (3). Enhancement of drug renal clearance is usually accomplished by altering the tubular passive reabsorption by altering the pH of urine. For example, renal excretion of acidic drugs such as phenobarbital and salicylates can be enhanced by alkalinizing the urine; for basic drugs such as amphetamine, the goal is to acidify the urine. Urinary excretion of an acidic compound is particularly sensitive to changes in urinary pH if its pKa is within the range of 3.0 to 7.5. For basic compounds, the corresponding range is 7.5 to 10.5 (4). For the drug to respond to pH manipulation of urine, it must not be predominantly eliminated by hepatic or tissue metabolism, it must be a weak electrolyte with pKa in the appropriate acidic or basic pKa range, and it must have a small volume of distribution and minimal plasma protein binding (<70–80%) (4,5).

In the case of secretion of the drug into the gastrointestinal tract, reabsorption of the drug can occur by the usual mechanisms, which led to its absorption in the first place. Therefore, if activated charcoal can somehow be

Received August 21, 2000; accepted February 2, 2001.

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introduced into the small intestine after the initial absorption of the drug, the net result of transfer of the drug across the walls of the gastrointestinal tract to the gut lumen can be enhanced, and the drug that passes through the walls can be trapped by adsorption to the charcoal. Such a process can be called gastrointestinal dialysis because the membrane of the gastrointestinal tract, with blood vessels on one side and charcoal on the other side, can act in much the same manner as the membrane in conventional hemodialysis (6). Drugs that have a small volume of distribution (<1 L/kg), such as theophylline, phenobarbital, and digitoxin, are expected to be well removed by gastrointestinal dialysis (7). Drugs that have a large volume of distribution, and hence a low concentration in the blood, are secreted into the gastrointestinal tract in small amounts. Thus, charcoal has a small effect on elimination (e.g., imipramine) (8). With the exception of phenytoin, all of the drugs reportedly eliminated by gastrointestinal dialysis have a small volume of distribution (<1 L/kg) and low protein binding (<70–80%). These characteristics are thought to be prerequisites for MDAC to act by gastrointestinal dialysis (9).

Phenobarbital has a pKa of 7.24 (1), a volume of distribution of 0.54 to 0.7 L/kg (10–12), and plasma protein binding of 50% (10,12), and it is excreted unchanged (20–40%) in the urine (12). In the current work, we have selected phenobarbital as an example to study its pharmacokinetics during renal clearance enhancement, intestinal clearance enhancement, and the combined use of both to determine which method is clinically more effective in the management of drug poisoning.

PATIENTS AND METHODS

Patients

Thirty young men with phenobarbital overdose were selected from the inpatient toxicology center of El Demerdash University Hospital, Cairo, Egypt, to be enrolled in this study (which was approved by the Hospital Committee). Patients were selected after examination, full investigations, resuscitation measures, and toxicologic screening were performed. Coma scores on admission, according to Pulm and Posner (13), ranged from 12 to 30. The lowest score a patient could obtain was 10 (completely unresponsive); the highest was 39 (alert, conscious). This assessment of neurologic status involved verbal responses, eye opening, pupillary reaction, spontaneous eye movements, oculocephalic responses, corneal reflexes, respiratory pattern, motor responses, deep tendon reflexes, and skeletal muscle tone (13). The study design excluded patients with organ dysfunction and patients with positive toxicologic screening for any drug except phenobarbital. Patients whose toxicologic screening showing plasma phenobarbital levels of 80 to 120 μg/mL were candidates for the study. Patients were selected to have nonsignificant variations in terms of demographics and pretreatment clinical presentation.

Methods

Patient Grouping

Patients were stabilized using intensive and supportive measures including fluids, pressor agents, and antibiotics (when necessary). Mechanical ventilation was added when the vital signs were unstable. These measures were continued during the enhanced elimination procedures. Patients then were classified into three groups according to the method of treatment to enhance the elimination of phenobarbital. Group 1 (MDAC group) comprised 10 patients with a mean age of 27.6 ± 6.5 years and weight of 71.4 ± 11.5 kg. They were treated with MADC (Nasr Pharmaceutical Chemical; Cairo, Egypt) at an initial dose of 75 g followed by four successive doses of 50 g each, every 4 hours (14). Each dose was administered in slurry with water through a nasogastric tube while the trachea was intubated. The initial dose of charcoal was mixed with 10 g sorbitol (Memphis; Cairo, Egypt, under license from Laboratories Delalande; Marseille, France) (15). Group 2 (urinary alkalinization group) comprised 10 patients with a mean age of 28.1 ± 7.4 years and weight of 74.7 ± 12.9 kg. They were treated with intravenous infusion of $NaHCO_3$ (Abbott Laboratories; Chicago, IL) at a dose of 2 mg/kg mixed in 0.5 N saline as 15 mL/kg at an infusion rate of 5 mL/minute. Urine was checked every hour to maintain the pH at 7.5 to 8.0 (by using reagent strips from Chungdo Pharm. Co., Ltd., Seoul, Korea) and the volume at a minimum of 3 to 6 mL/kg per hour (3). Group 3 (combined group) comprised 10 patients with a mean age of 30.2 ± 7.4 years and weight of 70.0 ± 10.2kg. They were treated with a combination of MDAC and $NaHCO_3$ using the same doses and administration procedures described previously.

Sampling and Plasma Analysis

A venous blood sample of 3 mL was withdrawn into a heparinized syringe from each patient on admission (zero time or baseline time) and at 6, 12, 18, 24, 30, 36, 42, and 48 hours after admission. The samples were centrifuged immediately after collection to separate the plasma fractions, which were kept frozen until analysis for phenobarbital concentrations. Phenobarbital levels in each

plasma sample were determined by the enzyme multiplied immunoassay technique (Emit, Palo Alto, CA, USA) using Syva Instruments (Syva; Palo Alto, CA) and the reagents of the Emit phenobarbital assay. All samples were analyzed for phenobarbital concentrations in one setting after calibration of the apparatus by duplicate determinations of the assay calibrators and construction of a standard curve that was validated and recalibrated by the control results. The calibrators ranged from 0 to 5 and contained phenobarbital concentrations of 0, 5, 10, 20, 40, and 80 μg/mL, respectively. The assay control contained a phenobarbital concentration of 30 μg/mL. In addition, duplicate determinations of the same sample, calibrator, and control were carried out so as not to differ by more than 6ΔA units, and the result of any duplicate determinations were averaged. Patient samples containing more than 80 μg/mL phenobarbital (baseline samples and those expected to be >80 μg/mL) were diluted with one part of calibrator 0 that contained a concentration of 0, and the results were then multiplied by the dilution factor (16).

Pharmacokinetics and Data Analysis

Plasma phenobarbital concentrations were plotted in a normal coordinate and a semilog manner as a function of time for each patient for a rough estimation of drug pharmacokinetics. The pharmacokinetic parameters of phenobarbital in each patient were determined by using a commercially available, nonlinear regression software program (PCNONLIN; SCI Software, Lexington, KY, USA). The elimination rate constant (K_e) was calculated as the slope of the terminal phase of the log-linear plasma concentration-time curve, and the apparent elimination half-life ($t_{1/2}$) was determined as $0.693/K_e = t_{1/2}$. Considering the volume of distribution (V_d) of phenobarbital equals 0.6 L/kg (12), total body clearance (CL) was calculated based on $CL = K_eV_d$. The pharmacokinetic parameters were then expressed as mean ± standard deviation for each group of patients to be compared and analyzed using one-way analysis of variance.

Plasma phenobarbital levels at each time interval for each treatment group were expressed as mean ± standard deviation to be plotted as a function of time. The decrease in plasma phenobarbital level from baseline at each time interval was calculated for each patient. The decreased values at each time interval for each treatment group were expressed as mean ± standard deviation for comparison among the groups using one-way analysis of variance. Comparison among groups for the parametric variables of the pretreatment clinical presentation and patient outcome data were carried out by analysis of variance; nonparametric data were compared using the chi-square test.

RESULTS

Demographic data and the pretreatment clinical presentation of patients (baseline clinical presentation) are presented in Table 1. The selected patients were classified into the three groups in such a way that there were no significant differences in terms of demographic data or baseline clinical presentation. This was done so that the only variations among the groups would be those resulting from the type of treatment used to enhance phenobarbital elimination, which was the aim of the study.

Patient outcome is presented in Table 2. Mechanical ventilation was required in 15 patients (5 per group). Patients treated with MDAC alone required mechanical ventilation for a shorter time than patients treated with urinary alkalinization alone (significant effect, by comparing the least significant difference and the difference between the corresponding two means) or patients treated with the combination of MDAC and urinary alkalinization (nonsignificant effect). The time to mental alertness and orientation and the time for extubation were reduced significantly when MDAC was used alone compared with either the use of urinary alkalinization alone or the combined modalities. Time of mechanical ventilation, time to mental alertness and orientation, and time for extubation were significantly reduced by the combined use of MDAC and urinary alkalinization versus urinary alkalinization alone.

The mean value of plasma levels of phenobarbital at admission for the 30 patients was 101.6 ± 12.5 μg/mL, with a coefficient of variation of 12.3%. Patients were selected to have plasma phenobarbital levels of 80 to 120 μg/mL to reject possible variations in plasma levels among patients at baseline; therefore, subsequent differences in plasma levels could easily be explained on the basis of differences in the elimination procedures. The baseline plasma levels were not significantly different among groups ($P > 0.05$), as presented in Table 1.

The effect of MDAC, urinary alkalization, and the combination of both on plasma phenobarbital levels is shown in Figure 1. The decrease in plasma levels of phenobarbital from baseline as a result of the three elimination procedures is shown in Table 3. The decrease from baseline was significantly greater with MDAC alone versus either urinary alkalinization alone or the combined modalities. This significant effect of MDAC started early, just from the first time interval after baseline (6 hours after admission), and the effect remained

TABLE 1. *Pretreatment data and clinical presentation of patients enrolled in the study**

Studied variable	Group 1†	Group 2‡	Group 3§	Statistical test method
No. patients	10	10	10	
Sex	10 males	10 males	10 males	—
Age (y)	27.6 ± 6.5	28.1 ± 7.4	30.2 ± 7.4	
Weight (kg)	71.4 ± 11.4	74.7 ± 12.9	70.0 ± 10.2	
Coma score	20.6 ± 5.3	19.8 ± 4.7	20.7 ± 6.3	
Rectal temperature (°C)	36.6 ± 0.9	36.7 ± 1.1	36.9 ± 1.0	
Plasma phenobarbital concentration	103.2 ± 12.2	100.6 ± 12.6	100.8 ± 12.6	
SBP (mm Hg)	107.4 ± 17.3	111.7 ± 18.2	113.4 ± 18.5	
DBP (mm Hg)	67.3 ± 11.6	68.1 ± 10.8	70.2 ± 10.9	
HR (beat/min)	96.6 ± 9.8	95.2 ± 8.8	93.7 ± 8.5	
Serum sodium (mmol/L)	139.8 ± 1.7	140.1 ± 1.5	139.6 ± 1.4	
Serum potassium (mmol/L)	3.9 ± 0.4	3.9 ± 0.3	3.90 ± 0.4	
Serum creatinine (mg %)	1.01 ± 0.10	1.00 ± 0.11	0.09 ± 0.11	
Arterial blood gases				
pH	7.4 ± 0.1	7.40 ± 0.1	7.4 ± 0.1	
Po_2 (mm Hg)	90.2 ± 37.4	93.3 ± 40.3	92.5 ± 41.5	
Pco_2 (mm Hg)	47.2 ± 6.5	45.9 ± 8.9	46.3 ± 8.9	
HCO_3 (mEq/L)	24.8 ± 3.9	23.5 ± 3.6	24.3 ± 4.1	
Time between drug ingestion and admission				
Unknown	6 patients	5 patients	6 patients	
<1 h	1 patient	—	1 patient	
<6 h, >4 h	—	1 patient	1 patient	
<8 h, >6 h	1 patient	1 patient	—	
<10 h, >8 h	1 patient	1 patient	—	
<15 h, >10 h	1 patient	1 patient	1 patient	
Between 15 and 20 hours	—	1 patient	1 patient	
Ingested dose				
Unknown	5 patients	6 patients	6 patients	
<2 g	—	1 patient	1 patient	
<4 g, >2 g	2 patients	1 patient	1 patient	
<6 g, >4 g	3 patients	2 patients	2 patients	
Type of drug				
Unknown	4 patients	5 patients	5 patients	
Sominal tablets‖	6 patients	5 patients	5 patients	
Patients required mechanical ventilation	5 patients	5 patients	5 patients	
Patients required fluids and pressor drugs (IV infusion of normal saline and dopamine hydrochloride)	2 patients	2 patients	2 patients	
Patients required antibiotic therapy (crystalline penicillin)	1 patient	1 patient	—	

ANOVA one way statistical analysis

χ^2-statistical analysis

SBP, systolic blood pressure; DBP, diastolic blood pressure.

* There were nonsignificant differences among the three groups ($P > 0.05$ by the statistical test method specified for each variable).

Parametric variables were expressed as mean ± standard deviation.

† Group 1: patients who were treated with multiple-dose activated charcoal (MDAC).

‡ Group 2: patients who were treated with urinary alkalinization.

§ Group 3: patients who were treated with both MDAC and urinary alkalinization.

‖ Each tablet contains 60 mg sodium phenobarbitol (Alexandria Pharmaceutical; Alexandria, Egypt).

significant to the end of the study. This is clear by comparing the least significant difference and the difference between the corresponding two means at each time interval. In the same manner, there was a significantly greater decrease in the plasma phenobarbital level from baseline as a result of the combined use of MDAC and urinary alkalinization versus urinary alkalinization alone.

The influence of the three modalities on the pharmacokinetic parameters of phenobarbital in the selected patients is shown in Table 4 and Figures 2 and 3. There was a significantly greater clearance and shorter half-life for phenobarbital in patients treated with MDAC alone versus either urinary alkalinization alone or the combined modalities. The plasma half-life and total body clearance of phenobarbital were 38.6 ± 6.6 hours and 10.8 ± 1.8 mL/kg per hour, respectively for patients treated with MDAC alone, 81.1 ± 14.6 hours and 5.1 ± 0.9 mL/kg per hour for patients treated with urinary alkalinization alone, and 51.4 ± 9.8 hours and 8.1 ± 1.5 mL/kg per hour for patients treated with the combined modalities.

DISCUSSION

Clinically, the use of barbiturate therapy is decreasing with the development of nonbarbiturate sedatives such as

TABLE 2. *Patient outcome*

Studied variable	Group 1†	Group 2‡	Group 3§	Statistical analysis F	Statistical analysis LSD
Time of mechanical ventilation (for patients who needed it)*	40.2 ± 12.5	79.4 ± 20.9	51.7 ± 17.3	13.7 (calculated F at P 0.05 = 3.89)	16.20
Time to mental alertness and orientation	24.4 ± 9.6	50.6 ± 12.5	37.2 ± 11.4	13.6 (calculated F at P 0.05 = 3.35)	10.05
Time for extubation	29.7 ± 10.3	54.2 ± 12.8	43.2 ± 11.6	11.2 (calculated F at P 0.05 = 3.35)	10.90

F, variance ratio calculated by ANOVA one-way statistical analysis; LSD, least significant difference calculated by ANOVA one-way statistical analysis;.

* Time expressed in hours as mean ± standard deviation.

† Group 1 patients were treated with multiple-dose activated charcoal (MDAC).

‡ Group 2 patients were treated with urinary alkalinization.

§ Group 3 patients were treated with both MDAC and urinary alkalinization.

benzodiazepines and the clinical success of the new antiepileptic drugs such as felbamate, gabapentin, lamotrigine, and tiagabine (17,18). However, phenobarbital still has a role as a sedative or a hypnotic and is still the drug of choice in certain epileptic conditions (19–21). Barbiturate poisoning can occur as a result of drug abuse because barbiturates have a high abuse potential, and it may be suicidal or accidental poisoning in children (1,17). Patients with phenobarbital overdose would remain several days without actual improvement if they received only supportive care without any other measures to enhance phenobarbital elimination. This is due to the drug's long half-life. This study was performed to evaluate and compare the efficacy of MDAC, urinary alkalinization, and the combination of both in enhancing drug elimination in patients with drug overdoses. Phenobarbital was chosen as an example for drugs whose elimination is significantly affected by MDAC and urinary alkalinization (1).

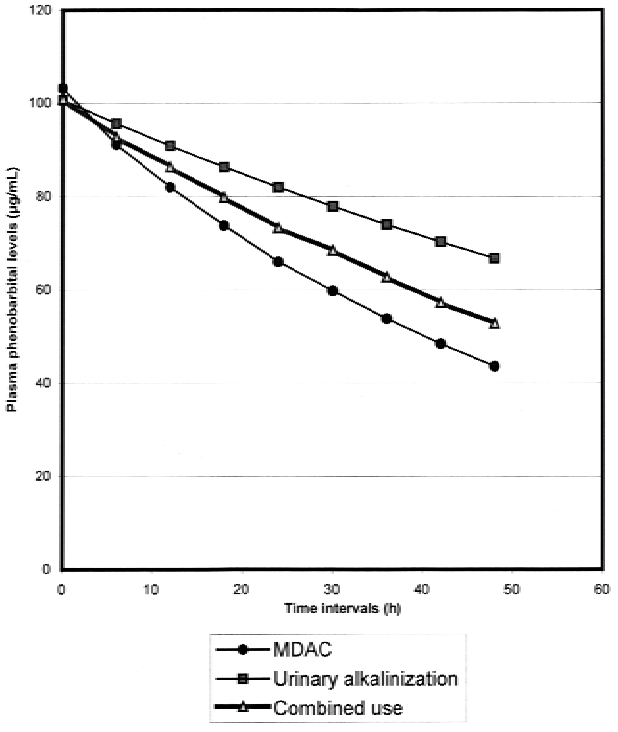

FIG. 1. Effect of MDAC (Group I), urinary alkalinization (Group II) and combination of both (Group III) on plasma phenobarbital levels in patients with phenobarbital overdose.

The reported elimination half-life and clearance of phenobarbital are approximately 5 days and 4 mL/kg per hour, respectively (22). Many authors have reported that MDAC could reduce the half-life and increase the clearance of phenobarbital, but most of the previous studies have been carried out using healthy volunteers. In the current study, MDAC alone decreased the elimination half-life to 38.6 ± 6.6 hours and increased clearance to 10.8 ± 1.8 mL/kg per hour. These results are nearly in agreement with the previous data available in the literature concerning the effect of MDAC on the pharmacokinetic parameters of phenobarbital. Neuvonen and Elonen (23) found that MDAC alone reduced the elimination

TABLE 3. *Evaluation of the decrease in plasma levels of phenobarbital from baseline as a result of three modalities*

Time intervals (h)	Group 1* mean ± SD	Group 2† mean ± SD	Group 3§ mean ± SD	Statistical analysis F	Statistical analysis LSD
6	11.1 ± 1.4	5.0 ± 0.6	8.1 ± 1.1	77.6	1.0
12	21.2 ± 2.8	9.8 ± 1.3	14.5 ± 2.0	75	2.0
18	29.4 ± 4.0	14.4 ± 1.9	21.0 ± 2.8	62.2	2.8
24	37.2 ± 5.2	18.7 ± 2.6	27.6 ± 3.9	53.0	3.8
30	43.5 ± 5.9	22.8 ± 3.2	32.4 ± 4.5	49.4	4.4
36	49.4 ± 6.9	26.8 ± 3.5	38.1 ± 5.2	44.5	5.0
42	54.8 ± 7.7	30.4 ± 4.3	43.6 ± 6.3	38.5	5.9
48	59.7 ± 8.4	33.9 ± 4.8	48.1 ± 6.7	36.4	6.4

F, variance ratio calculated by ANOVA one-way statistical analysis (calculated F at P 0.05 = 3.35); LSD, least significant difference calculated by ANOVA one-way statistical analysis; MDAC, multiple-dose activated charcoal; SD, standard deviation.

* MDAC.

† Urinary alkalinization.

‡ MDAC and urinary alkalinization.

TABLE 4. *Pharmacokinetic parameters of phenobarbital in patients with phenobarbital overdose*

Time intervals (h)	Group 1* mean ± SD	Group 2† mean ± SD	Group 3‡ mean ± SD	Statistical analysis F	Statistical analysis LSD
$t_{1/2}$ (h)	38.6 ± 6.6	81.1 ± 14.6	51.4 ± 9.8	10.2	7.2
CL (mL/kg per hour)	10.8 ± 1.8	5.1 ± 0.9	8.1 ± 1.5	36.7	1.4

CL, total body clearance; F, variance ratio calculated by ANOVA one-way statistical analysis (calculated F at P 0.05 = 3.35); LSD, least significant difference calculated by ANOVA one-way statistical analysis; MDAC, multiple-dose activated charcoal; SD, standard deviation; $t_{1/2}$, elimination half-life.

* MDAC.

† Urinary alkalinization.

‡ MDAC and urinary alkalinization.

half-life of phenobarbital from a mean value of 110 to 19.8 hours in healthy volunteers who received therapeutic doses of phenobarbital. Also, Berg et al. (24) reported that the half-life of phenobarbital in healthy volunteers who received an intravenous therapeutic dose was reduced by MDAC alone from a mean value of 110 to 46 hours; clearance was increased from a mean value of 4.4 to 12 mL/kg per hour. In patients with phenobarbital overdose, Goldberg and Berling (25) found that the elimination half-life of phenobarbital in two patients was less than 24 hours after treatment with MDAC. Pond et al. (26) reported that the half-life of phenobarbital was reduced in their randomized study from a mean value of 93 hours (patients treated with a single dose of activated charcoal) to 36 hours (patients treated with MDAC). Boldy et al. (27) also reported similar results. No reports are available in the literature regarding the comparison

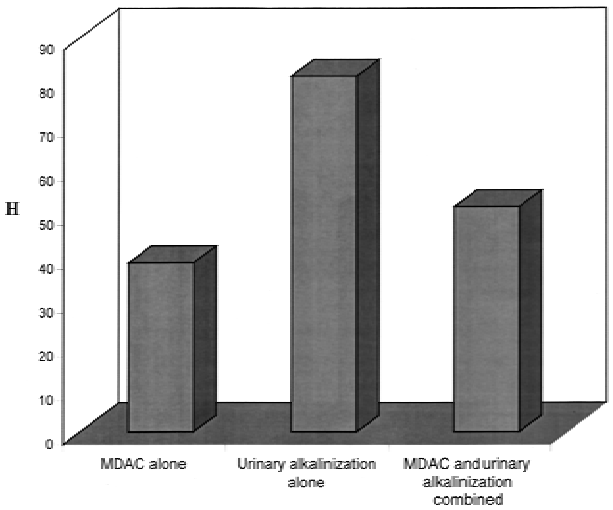

FIG. 2. The effect of MDAC alone, urinary alkalinization alone, and combination of both on the elimination half-life of phenobarbital.

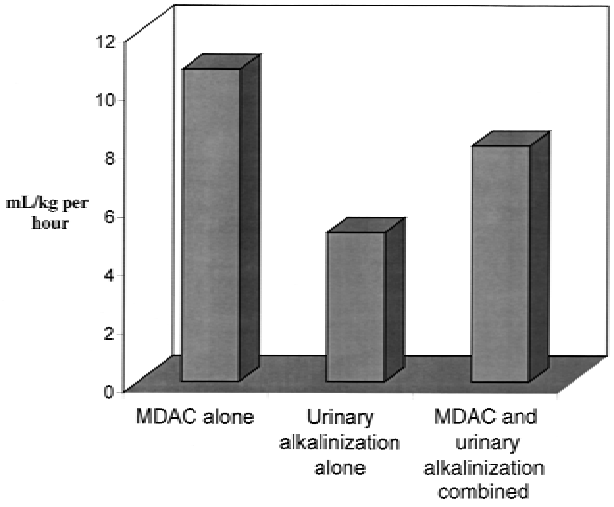

FIG. 3. The effect of MDAC alone, urinary alkalinization alone, and combination of both on the total body clearance of phenobarbital

between the effect of MDAC versus urinary alkalinization or the combination of both in the treatment of drug overdose. In the current study, MDAC produced a significantly shorter elimination half-life and greater clearance for phenobarbital and consequently improved patient outcome compared with urinary alkalinization or the combined modalities.

Data concerning the effect of urinary alkalinization on the pharmacokinetics of phenobarbital are virtually nonexistent, although many textbooks include this procedure as a main part of the treatment protocol in phenobarbital overdose (1–4). In the current study, urinary alkalinization alone for patients with phenobarbital overdose caused a significantly longer elimination half-life and smaller clearance values for phenobarbital (81.1 ± 14.6 hours and 5.1 ± 0.9 mL/kg per hour, respectively) compared with either MDAC alone or the combined use of both. It was reported that the duration of coma in 16 patients with phenobarbital overdose was reduced by one third as a result of treatment with urinary alkalinization (28). However, another report mentioned that urinary alkalinization had little effect on phenobarbital elimination in patients with phenobarbital overdose (29). Frenia et al. (2) reported that urinary alkalinization or MDAC alone was effective in enhancing phenobarbital elimination in healthy volunteers, but MDAC was significantly superior. They reported that the values of elimination half-life and clearance for phenobarbital in those volunteers were 148 hours and 3.0 mL/kg per hour, respectively, for control, 47 hours and 8.3 mL/kg per hour for urinary alkalinization, and 19 hours and 19.95 mL/kg per hour for MDAC. Many investigators have reported that urinary alkalinization has the disadvantage of causing

significant electrolyte abnormalities that necessitate the close monitoring of vital signs, fluid status, serum electrolytes, especially potassium, and acid–base balance (5,14).

The pharmacokinetic parameters of phenobarbital (elimination half-life and clearance) in the selected patients who were treated with the combined use of MDAC and urinary alkalinization in the current study were 51.4 ± 9.8 hours and 8.1 ± 1.5 mL/kg per hour, respectively. Unfortunately, few studies have evaluated the concurrent use of MDAC with urinary alkalinization. Mofenson et al. (30) studied the effect of that combination in five adolescent patients with phenobarbital overdose; they reported that the half-lives of plasma phenobarbital levels individually were 7.7, 12.7, 11.8, 14.1, and 11.0 hours. Amitai and Degani (31) observed the effect of the combined use of urinary alkalinization and MDAC on a 28-day-old infant in whom lethargy, hypotonia, and hypothermia developed after a phenobarbital overdose secondary to a pharmacist's mistake. The half-life of phenobarbital resulting from this combination was found to be 11.2 hours.

It was expected that the combined use of MDAC and urinary alkalinization would be more effective than either one of them alone in enhancing phenobarbital elimination. However, this combination was significantly superior and more effective than the sole use of urinary alkalinization in enhancing the elimination of phenobarbital, but it was significantly less effective when compared with the sole use of MDAC. This unexpected result may be explained by either ion trapping of phenobarbital molecules or trapping of the drug molecules through protein binding as a result of the increased pH of the blood. The pH of the blood is increased above normal as a result of $NaHCO_3$ infusion; consequently, ionization of phenobarbital in the blood is also increased. This decreases the nonionized fraction of the drug and consequently decreases the chance for phenobarbital molecules to pass to the gut lumen across the blood–gastrointestinal tract barrier. They are trapped in the compartment in which they are ionized, and therefore only a small amount of phenobarbital molecules can reach the gut lumen to be trapped by the activated charcoal that is already present there (3). Also, as the pH of the plasma increases, the ability of albumin to bind free drug molecules increases, because although a higher pH drives phenobarbital from the tissues into the systemic circulation (32), it also increases the number of charged drug molecules. When the numbers of the charged groups increase, the ability of albumin to bind drug molecules is increased. Bound drug molecules cannot cross the blood–gastrointestinal tract barrier to the gut lumen to be trapped by the activated charcoal (33,34).

In conclusion, the management of drug overdose in the case of weak acidic drugs with a small volume of distribution should include the sole use of MDAC and supportive care without urinary alkalinization. Using urinary alkalinization alone with supportive care produced a significant longer elimination half-life and smaller clearance compared with MDAC alone. Also, the addition of urinary alkalinization to MDAC significantly reduced the efficacy of MDAC in enhancing drug elimination.

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