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Research Article

Multiple Dose Activated Charcoal in The Management of Drug Overdose: A Pharmacokinetic Based Study

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Abstract

Activated charcoal is a useful adsorbent for gastric decontamination. Enhancement of elimination may involve multiple dosing of activated charcoal (MDAC), diuresis hemodialysis, or charcoal hemoperfusion. In the past few years, data emerged that only some patients demonstrate clinical benefit. This study aims to determine the rational use of multiple-dose-activated charcoal in different acute toxicities depending on Pharmacokinetics principles. Results show that the mean reduction in theophylline plasma conc. Was 88 % after 30 hours and total body clearance was increased by 45 %. While Paracetamol's total body clearance was increased by a reduced by 71.42 %. Carbamazepine total body clearance increased by 33.33% after 24 hours as regards 0 – 12 hours. In the salicylates group total body clearance increased after 24 hours by 43 % because of treatment of MDAC. On the other hand, valproic acid A significant reduction in elimination half-life occurred but after 54 hours by 70.76%, while the total body increased by 65 % in the period between 48 -54 hours. From these results, Theophylline, paracetamol, carbamazepine, and salicylates are all adsorbable by activated charcoal, activated charcoal barely affects the elimination of valproic acid.

Introduction

Managing acute poisoning is an essential part of emergency care and accidents. Several gastric decontamination procedures were widely used before. inhibition of absorption is the main approach for patients care who have swallowed poisons or been given an overdose of drugs (in acute poisoning after oral ingestion), by giving specific therapy, and improvement of drug elimination from the body [1].

Administration of more than 2 doses of activated charcoal is known as Multiple dose activated charcoal (MDAC) widely used in the treatment of overdoses or a given poisoning. Drugs with a long half-life, low plasma protein binding, and a small apparent volume of distribution (e.g., ≤ 0.6 L/kg) are highly eliminated after multiple doses of activated charcoal, and improvement of the clinical profile of the patient is achieved. In addition, some drugs undergo recirculation which, in the case of an overdose, may be enhanced by MDAC [2].

Nowadays, activated charcoal has been effectively absorbed gastric toxins. Improvement of elimination involve repetitive dosing of activated charcoal, charcoal hemoperfusion in addition to diuresis haemodialysis. [3].

Kinetics in human poisoning has become more important due to the evolution of qualitative techniques. Kinetic studies in acute poisoning provoke numerous difficulties: precising the dose and the delay are usually challenging. These studies improves the evaluation of treatments such as, haemodialysis, hemoperfusion, and gastric lavage, in addition to oral activated charcoal and antidotes that alter the kinetic of the toxin [4]. Lacking in clinical data failed to support or exclude the rational use of multiple doses activated charcoal, despite that volunteer studies have demonstrated its enhancement of elimination of many drugs [5].

Our study aimed to validate the efficacy of Multiple Dose Activated Charcoal as an enhanced elimination modality in different acute toxicities depending on Pharmacokinetics principles.

Methods

This prospective study was carried out on patients with different drug overdoses from those admitted to the Poison Control Centre (PCC), Faculty of Medicine, Ain Shams University. In accordance with declaration of Helsinki, the protocol for this study was approved by the Hospital (PCC) Medical Ethical Committee under number (2010P0045), and the current study was registered from ClinicalTrials.gov with registration number; (1606YAS141008).

Patients:

Forty-four adult patients (36 females and 8 males) were selected from those admitted to PCC. Patient's ages ranged between 15 to 54 years. All were suffering from drug overdose. We recruited all adult patients presenting with an oral overdose.

Inclusion criteria: Candidates of this study included patients with acute intoxication by a drug to which MDAC is one of the routine enhanced elimination procedures at the PCC.

Exclusion criteria: Patients were excluded: No history of time of administration or inability to follow for 24 hours due to patient leaving hospital or discontinuing therapy. Patients suffering from liver impairment, renal dysfunction and Comatose patients were also excluded.

Once the patients were stabilized using the intensive and supportive measures, they were classified into 5 groups according to the type of drug ingested. Theophylline group, Paracetamol, carbamazepine, salicylates and valproic acid group.

Blood Sampling:

A venous blood sample of 3ml was withdrawn from each patient on admission. The drug concentration estimated in this sample is considered an initial concentration (zero time or baseline time). Successive blood samples (3ml every 6 hours) were withdrawn from each patient until the drug concentration was lower than the therapeutic level of the drug under consideration. The samples were centrifuged directly after collection to separate the plasma fractions, then kept refrigerated at -8 OC until analysis.

Analysis of plasma drug concentration:

Theophylline, carbamazepine and valproic acid contents in plasma were estimated using Enzyme Linked Immune Sorbent Assay (ELISA) [6]. Acetylsalicylic acid analyzed by quantitatively converting it to salicylate ion, which is complexed with Fe+3. The iron-salicylate complex

absorbs green light and can be quantitated using absorption spectrometry [7].

Paracetamol drug concentration in patients' plasma samples was determined by the spectrofluorimetric method, which is based on the oxidation of the paracetamol by sodium hypochlorite (used as an oxidizing reagent) at pH 10, in presence of sodium carbonate boric acid buffer solution to give thefluorophore2,2-dihydroxy-5,5- diacetyldiaminebiphenyl [8].

Pharmacokinetics and Data Analysis: for each patient, plasma drug concentrations were plotted in normal and semi log manner as a function of time to measure pharmacokinetic parameters for each drug. By using software program (PCNONLIN; SCI Software, Lexington, KY, USA) nonlinear regression pharmacokinetic parameter were measured. The elimination rate constant (Ke) was calculated as the slope of the terminal phase of the log _linear plasma concentration – time curve.

The elimination half-life (t ½) was determined as:

$$t1/2 = 0.693/ ke$$

Considering the volume of distribution (Vd) of a drug with respect to that value of literature. Theophylline Vd = 0.5[9]. Paracetamol Vd =0.95[10]. Carbamazepine Vd = 1.4 [11, 12]. Salicylates Vd = 0.4 [13, 14]. Valproic acid Vd = 0.2 [15, 16]

Calculation of Total Body Clearance (CLT) as:

$$CLT = Ke\ Vd$$

Statistical Analysis for each group of patients, expressing the pharmacokinetic parameters as mean ± standard deviation. The pharmacokinetic parameters were compared.

Sample size:

Sample size calculation for this study was done using the comparison of Total Body Clearance (CLT) between the 5 groups as it was the primary outcome of this study. Accordingly, using the One-Way Analysis of Variance test, calculating the minimum proper sample size was ten samples in each group to detect a real difference in Total Body Clearance (CLT) with 95% power at $\alpha = 0.05$ level. Sample size calculation was done using G*Power software version (2009) for Windows, Franz Faul, Kiel University, Germany.

RESULTS

This study was carried out on 44 patients (36 females and 8 males) with different drug overdoses. Patients then grouped into 5 groups according to the type of drug ingested. Group 1: theophylline, group 2: paracetamol, group 3: carbamazepine, group 4: salicylates and group 5: valproic acid.

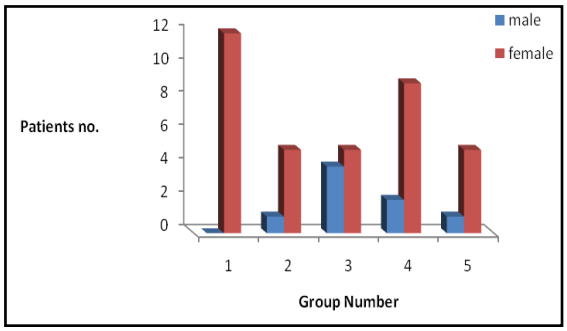

Figure 1: Sex distribution among patients enrolled in the different groups.

Table 1: Patient demographic data.

	Theophylline (Group 1)	Paracetamol (Group 2)	Carbamazepine (Group 3)	Salicylates (Group 4)	Valproic acid (Group 5)
No. of patients	12	6	9	11	6
Sex					
No. of Male	0	1	4	2	1
No. of female	12	5	5	9	5
Age (year)	23.4 ± 10.3	23.12 ± 5.52	25.7 ± 9.62	21.2 ± 5.74	23 ± 5.4
Drug ingestion					
Mode	suicidal	suicidal	suicidal	suicidal	Suicidal
Route	**Oral**	**Oral**	**Oral**	**Oral**	**Oral**

Table 2: Baseline clinical presentation of patients

Variable	Group1	Group 2	Group 3	Group 4	Group5
Initial plasma drug concentration (µg/ml)	58.90±13.20	80±16.10	21.20±6.80	55.50±10.20	160±96.80
SBP (mm Hg)	120 ± 8.50	118.3±7.50	116.60±7.07	118.18±6.02	116.60±1.50
DBP (mm Hg)	75.80±7.10	75 ± 8.30	80 ±7.07	75.45 ± 5.20	75 ± 8.36
HR (beat/min)	116.60±14.35	96.60±19.80	85.50±12.30	79.09 ± 9.43	85 ± 18.70
Respiratory Rate	17.10 ± 4.75	17.6 ± 4.20	14 ± 1.70	15.45 ± 2.50	15.3 ± 2.06
Temperature	37.03 ± 0.40	37 ± 0	36.7 ± 0.40	36.8 ± 0.40	36.6 ± 0.52
Serum sodium (mmol/L)	136.25±3.17	138.83±2.48	138.77±2.49	138.80±3.79	138.2 ±3.19
Serum potassium (mmol/L)	3.12 ± 0.54	2.63 ± 0.61	3.48 ± 0.27	3.54 ± 0.45	3.40 ±0.33
Serum creatinine (mg %)	0.83 ± 0.30	-	-	0.83 ± 0.15	-
Urea	23 ± 6.65	-	-	18.33 ± 8.50	-
Serum Glucose	154 ± 42.07	97.66±16.24	92.22±10.97	83.30±14.48	84.60±15.58
pH	7.42 ± 0.06	-	7.35 ± 0.08	7.24± 0.99	….
AST	-	28.50±11.44	34.50 ±6.36	-	33.33 ±4.93
ALT	-	19 ± 3.55	19.5 ± 3.53	-	18.33±3.07
Time between drug ingestion And	3.33 ± 1.23	2.60 ±0.84	2.28 ± 1.51	3 ± 1	3 ± 1.10

SBP: systolic blood Pressure. **DBP**: diastolic blood pressure.

AST: Asprtate transferase. **ALT:** Alanine aminotransferase.

Initial plasma drug concentration

From table 2 the initial plasma drug concentration in group 1 was 58.90 ± 13.20 which is significantly higher than the highest therapeutic drug concentration of theophylline. The mean initial plasma concentration in group 1 is higher than the higher therapeutic concentration by 66 %. While in group 2, group 3, group 4 and group 5 the initial plasma concentrations were 80 ± 16.10, 21.20 ± 6.80, 55.50 ±10.20 and 160±96.80 µg/ml, respectively. The initial drug concentration in groups 2, 3, 4 and 5 were higher than the upper therapeutic limit by 75%, 48% in 54 % and 37%, respectively.

The reported therapeutic drug concentration ranges of theophylline, paracetamol, carbamazepine, salicylates and valproic acid were 5- 20 µg/ml, 5- 20 µg/ml, 4 -12 µg/ml, 5-25 µg/ml and 50 - 100µg /ml, respectively[17, 18].

Effect of MDAC on initial drug plasma concentration

Table 3: The mean % reduction in plasma drug concentration after administration of MDAC regarding the initial plasma concentration.

Time (hr.)	Theophylline	Paracetamol	carbamazepine	Salicylates	Valproic acid
12	41.25*	41.50*	29.15	45.09*	24.13
18	61.46*	64.75*	44.81*	60.83*	21.68
24	76.16*	82.50*	60.61*	74.09*	46.25*
30	82.68*	-	59.66*	79.27*	52.95*
36	88.26 *	-	-	93.94*	58.50*
48	-	-	-	-	73.35*
52	-	-	-	-	70.31*

*Statistically significant difference (P <0.05) regarding the initial drug plasma level.

Patients discharged from hospital after the drug plasma concentration reached the normal therapeutic level.

Effect of MDAC on the pharmacokinetic parameters of the studied drugs

Elimination half-lives ($t_{½}$):

Table 4: Mean % reduction in elimination half-lives after treatment with MDAC

Time (hr)	Theophylline	Paracetamol	carbamazepin	Salicylates	Valproic acid
12-24	38.12*	55.35*	17.10*	18.30*	22.27*
24-36	48.50*	-	-	-	42.9*
36-48	-	-	-	-	77.16*
48-54	-	-	-	-	70.76*

*Statistically significant difference (P<0.05) regarding $t_{½}$ during the period between 0–12 hours.

Patients' discharge from hospital after the drug plasma concentration reached the normal therapeutic level.

Effect of MDAC on total body clearance (CL_T).

Table 5: Comparison of the mean Total Body Clearance (CL_T) after administration of MDAC.

Time (hr)	Theophylline	Paracetamol	carbamazepine	Salicylates	Valproic acid
12-24	45.00*	71.42*	33.33*	43*	21.25*
24-36	45.00*	-	-	-	42.00*
36-48	78.00*	-	-	-	75.00*
48-54	-	-	-	-	65.00*

*Statistically significant difference ($P<0.05$) regarding CL_T between the period of 0 – 12 hours.

Discussion

To establish the role of MDAC in the treatment of acute poison and to estimate the optimum dosage administration of charcoal, the present study has been carried out. Forty-four adult patients with five different drug overdoses were enrolled in this study. These five drugs were theophylline, paracetamol, carbamazepine, salicylates and valproic acid. MDAC was given orally as 50 g of activated charcoal in water every 4 hours.

Treatment with MDAC reduced the initial drug plasma concentration to the normal therapeutic range after 24 hours. From previous studies, repeated administration of activated charcoal lower free drugs concentration in the GIT. This process favors the diffusion of the drug in blood stream back into the GIT. MDAC enhanced the elimination of the already absorbed drugs such as Phenobarbital and theophylline **[19]**.

Theophylline:

Similar results have been reported by **Lim, et al.,** [20]**.** The authors reported a case of sever theophylline toxicity (peak level 85 mg/L) and was giving activated charcoal via the nasogastric tube. The patient was terminated after 15 hours of treatment, when his serum theophylline level reduced to 6 mg/L, and concluded that charcoal hemoperfusion appears to be the most effective extracorporeal therapy for severe theophylline toxicity. Charcoal hemoperfusion should be considered if plasma theophylline concentrations are greater than 100 mg/L in acute intoxication or greater than 60 mg/L in a chronic intoxication.

The treatment with MDAC successfully reduces the mean elimination $t_{½}$ of theophylline to the normal range after 24 hours. The reported elimination half-life of theophylline varies roughly from 3 to 15 hours in healthy adults **[21]**. Studies revealed that MDAC decrease the half–life and enhance clearance of theophylline in healthy volunteers.

In this study MDAC reduced the elimination half-life in first day from 11.86 ± 3.49 and to 9.15± 2.3 hours and increase total body clearance in first day from 0.031 ± 0.01ml/kg/hr and was increased to 0.04 ± 0.01ml/kg/hr in second day with 22.5 % more reduction than the first day. These results are nearly in agreement with the pervious data accessible in literature concerning the effect of MDAC on the pharmacokinetic parameters of theophylline **[22, 23].**

As a result of the observed significant decrease in theophylline elimination $t_{½}$ and the observed increase of theophylline total body clearance, oral activated charcoal can be used as an effective therapy to enhance the clearance of theophylline from in acute poisoned patients and, therefore, is the treatment of choice for theophylline toxicity.

Paracetamol:

Base-line paracetamol plasma concentration of the 6 patients included in this study was ranged from 68 to 107µg/ml with a mean value of 80±16.1µg/ml. Since the toxic dose of paracetamol is > 20µg/ml or 150 mg/kg. In view of these toxic values of paracetamol, all patients included in this study are considered severely toxic.

This study indicated that, activated charcoal given after a short interval of drug ingestion (2.60 ± 0.84 hours) reduces the initial paracetamol plasma concentration from 80±16.1µg/ml to 14 ± 13.15µg/ml after ingestion of 4 dose of activated charcoal absorption. The reduction in the initial paracetamol plasma concentration is due to the fact that, charcoal reduces paracetamol absorption. Similar results have been reported by Rutherford Rose et al. [24]. The authors found that 30g activated charcoal decrease absorption of 5g paracetamol elixir by 48, 44 and 33% when administered after 15, 30 and 120 min.

In addition, Green et al.,[25] declared that administration of activated charcoal (50 g) as 1, 2, and 3 hours after acetaminophen 4g intake to 10 volunteers was effective. The mean AUCs of acetaminophen bioavailability at 1, 2, and 3 hours were 154 ±71 mg/L/h, 206 ±67 mg/L/h, and 204 ±58 mg/L/h, respectively. Bioavailability was reduced at 1 hour of 30.5%, 2 hours 7.7% and 3 hours 6.2%. Only the reduction at 1 hour was statistically different from the control AUC (221±54; $p<0.01$). The authors stated that their results surprisingly did not support the administration of activated charcoal beyond 1 hour after the drug overdose.

In the present study, treatment with MDAC successfully reduces the mean elimination t½ paracetamol to normal ranges with only 2 patients during the period of 12 -24 hours, while after 24 hours one patient remains in the PCC with a t½ of 4.27 hours which is still above the normal t½ of paracetamol. The reported mean plasma t½ of paracetamol in normal adult subjects using therapeutic doses is ranged from 1 to 3 hours [18].

The results of this study showed that MDAC has a significant effect on elimination half-life and clearance of paracetamol. The t1/2 after 12-hour treatment with activated charcoal was 15.74 ±2.27 and was significantly reduced to 6.95 ±4.45 after 24 hours. Moreover, after 4 doses of activated charcoal, paracetamol clearance shows a great significant increase by 71 % after MDAC therapy as it was 0.04 ± 0.006 and was increased to 0.14 ± 0.10 after 24 hours.

Carbamazepine (CBZ):

Carbamazepine approved in treating simple partial, complex partial, and generalized tonic seizures. The daily therapeutic dosage is 200 mg, and the therapeutic level is 4-12 µg/ml. Carbamazepine serum level more than 40µg/ml is usually accompanied by the possibility of serious complications like coma convulsion, breathing disorder, and cardiac complication. Initial half-life values range from 25-65 hours, decreasing to 12-17 hours on repeated doses [12].

The mean plasma concentration for carbamazepine at hospital admission was 21.20± 6.8 µg/ml. After 24 hours treatment with MDAC, carbamazepine plasma concentration was significantly ($P < 0.05$) reduced to 8.35 ± 3.52 µg/ml ($n = 6$ patients). The reduction % in the initial mean carbamazepine plasma concentration due to MDAC administration was 60.60 % and 59.6% after 24 and 30 hours post admission, respectively.

The reported mean t½ of carbamazepine in normal subjects using therapeutic doses is ranged from 25 to 65 hours [18]. The treatment with MDAC successfully reduces the mean elimination t½ of carbamazepine to the normal range after 12 hours. The half-life values determined in our study are consistent with values reported previously [26].

Although there are few patients enrolled in this study, we can conclude that multiple-dose activated charcoal is efficient enough to treat patients with carbamazepine overdose poisoning. It permits constant decrease of the half-life blood carbamazepine without any rebound effect and therefore could prevent successfully different complex symptoms encounters in carbamazepine poisoning.

Salicylates:

Acute salicylate poisoning causes gastric irritation and vomiting leading to metabolic acidosis, ulceration or bleeding. Respiratory alkalosis & secondary venal bicarbonate wasting, hypokalemia and dehydration all are symptoms of acute salicylates poising. Gastric lavage, multiple dose activated charcoal, fluid and electrolyte correction, alkalinization of the urine and renal dialysis, are useful options for salicylates treatments

The volume of distribution of salicylate is small 0.4 L/kg [27]. Enhanced elimination by MDAC would also be favorable for salicylate poisoning. Hypothesis for the use of MDAC in acute poisoning situation is based on the gut dialysis theory [28].

There was a significant decrease in salicylates half-life among all patients. As it was 14.54 ± 5.72 hours and was significantly reduced to 4.22 ± 2.09 hours after 24 hours. In spite of this significant reduction in the elimination t½ of salicylates, the activated charcoal treatment does not reduce the t½ to its normal range (20 minutes to 1.7 hours).

The total body clearance of salicylates increased from 0.008 ±0.004 to 0.016±0.011 ml/kg/hr. after 24 hours. It is worth noting here, that the use of MDAC in salicylate poisoning considered in volunteers' studies but most of the studies did not support an increase in salicylate clearance with MDAC therapy [29-31]. Effectiveness of MDAC in real overdoses situation still doubtful. Besides, the major weakness of volunteer studies is that the toxic or even the fetal dose of salicylates was not studied, thus it may be challenging to utilize results into real overdose situations.

Hillman et.al. [32] studied five cases of acute oral salicylates poisoning treated with multiple dose of activated charcoal, and the authors found significant reduction of the half-life of salicylates among these patients.

While there is inadequate evidence to support the use of MDAC in salicylate poisoning for enhanced elimination by the procedure of "gut dialysis" MDAC has a special role in limiting absorption of salicylates overdoses mainly when there is a enormous ingestion with a risk of bezoar formation. Multiple doses of activated charcoal offer more binding sites and prevent additional systemic absorption of salicylates.

Additionally, breakdown of the bezoar due to mechanical action of the gut may lead to unexpected flow of salicylates absorption. By recoating the surface of bezoar fragments with activated charcoal, ongoing absorption can be reduced [33].

Although there is insufficient clinical data to support the recommendation on the use of MDAC for enhancing elimination in salicylates poisoning. MDAC should be considered as a means of GIT decontamination in moderate and sever aspirin poisoning as well.

Valproic Acid:

Valproic acid is well absorbed after oral ingestion; Vd is 0.2 L/Kg with high affinity to plasma protein (90%-95%). Valproic acid metabolized in liver and the elimination half-life ranged from 7 -15 hours in healthy volunteer [16]. Elimination by hemodialysis and MDAC may be ineffective due to small volume distribution and high protein binding. Though, unbound drug fraction could be increased due to saturation of protein binding during acute overdose. Recent data showed plasma-protein binding reduced to 35% when plasma valproic acid level was in toxic level of 300 mg/ml. Therefore, MADC and hemodialysis may be useful in certain limit to increase elimination in valproic acid toxicity [34].

In an attempt to investigate the impact effectiveness of multiple dose activated charcoal to improve elimination of acute valproic acid overdose, this forgoing study was carried out. Six patients were enrolled in this study for acute poisoning in a suicidal attempt using valproic acid and its derivative. All patients enrolled in this study were drowsy and hemodynamically stable, therefore hemodialysis might be unnecessary. Twelve hours after MADC dosing plasma valproic acid concentration decreased in all patients from 160 ± 96.8 to 137 ± 79.25 µg/ml. The half-life of valproic acid in all patients was decreased from 60 ± 36.5 to 48.1 ± 39.3 hours because of MDAC administration for 24 hours. While after 48 hours the t½ was reduced to 14.16± 4.53 hours. The reported mean t½ of valproic acid at normal therapeutic dose is ranged from 9 to 16 hours [18].

Therefore, MDAC treatment had little effect on enhanced elimination of valproic acid in comparison with effect of MDAC on elimination of theophylline and paracetamol, since the t ½ of valproic acid reached the normal value after 48 hours while the plasma t½ in the other treated groups reached the normal values after 24 hours in case of theophylline and paracetamol. This could be explained on the fact that Valproic acid is highly protein bound and did not respond to charcoal therapy. These are in good agreement with Farrar et al [35], the authors assumed that the pharmacokinetic parameter of drugs changed at higher doses, and nonlinear absorption, protein binding, metabolism, and elimination may result from saturation or adjustment of normal processes. Valproic acid is known to have high protein binding affinity and respond minimal to charcoal therapy, but an overdosed patient exhibited saturation of binding sites, rising unbound valproic acid concentrations, and possible enhanced elimination with MDAC therapy.

Multiple doses of activated charcoals are thought to produce its beneficial effect by interfering the enterogastric circulation of drugs. In addition, any unabsorbed drug found in the gut will be adsorbed to activated charcoal, thereby lowering drug absorption. It should be used if no contraindication exists [36, 37].

Conclusion

Administration of the repetitive doses of activated charcoal shall be considered, as it reduces the hospitalization period and enhances the improvement of patients and can be considered as an effective therapy and treatment of choice for theophylline toxicity. In addition to its significant effect on treatment paracetamol overdose, especially when taken few hours after ingestion of the drug.

Carbamazepine elimination is improved significantly by multiple dose activated charcoal therapy. MDAC should be considered as a means of GIT decontamination in moderate and sever salicylates poisoning as well. Activated charcoal barely affects the elimination of Valproic acid. This is due to valproic acid is highly bound to plasma protein in addition to small volume of distribution.

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