American Journal of Emergency Medicine (2006) **24**, 440–443

ELSEVIER

The American Journal of Emergency Medicine

www.elsevier.com/locate/ajem

Original Contribution

Influence of activated charcoal on the pharmacokinetics and the clinical features of carbamazepine poisoning

Nozha Brahmi MD*, Nadia Kouraichi MD, Hafedh Thabet MD, Mouldi Amamou MD

Intensive Care Unit, Centre d'Assistance Médicale Urgente, 1008 Montfleury, Tunis-Tunisia

Received 1 December 2005; revised 29 December 2005; accepted 30 December 2005

Abstract Carbamazepine (CBZ) poisoning has been associated with cases of severe toxicity and death. Multiple-dose activated charcoal was proposed to enhance the clearance of CBZ elimination, but there are no prospective controlled studies that demonstrated a change in clinical outcome after the use of multiple-dose activated charcoal. The aim of this study was to determine the CBZ elimination kinetics and the evolution of clinical features according to the dose of activated charcoal in acute poisoning patients. It is a prospective study for 6 months, from January to June 2004, including all pure acute CBZ-poisoned patients. Twelve patients were randomized to receive a multiple-dose activated charcoal (G1) or a simple dose of 1g/kg (G2). Their mean age was 27.6 ± 12.2 years; the Simplified Acute Physiology Score (SAPS II), 16.37 ± 8.46; and the Acute Physiology and Chronic Health Evaluation (APACHE II), 8 ± 3.96. They were 8 men and 4 women. The mean concentration of blood CBZ at hospital admission was of 29.42 ± 6.68 mg/L. Each group includes 6 patients. The peak value of blood CBZ was comparable in the 2 groups: 33 ± 3.46 mg/L (G1) vs 32.6 ± 5.63 (G2) (P = .5); the requirement of mechanical ventilation was similar also (3 in each group). The duration of both coma and mechanical ventilation was significantly decreased in the first group compared with the second: 20.33 ± 3.05 vs 29.33 ± 4.11 hours for coma (P = .02) and 24.1 ± 4.2 vs 36.4 ± 3.6 hours for mechanical ventilation (P = .001). The length of stay was also significantly decreased in the first group: 30.3 ± 3.4 vs 39.7 ± 7.3 hours in the second group (P = .000006). Concurrently, we have noted a significant constant reduction of the half-life of CBZ from serum in the first group: 12.56 ± 3.5 hours after multiple dose vs 27.88 ± 7.36 hours after a simple dose (P = .0004). This decrease was correlated to the dose of charcoal. In summary, we can conclude that multiple-dose activated charcoal is more efficient than simple-dose; it permits a constant decrease of the half-life of blood CBZ without any rebound effect and could improve the prognosis by reducing the duration of coma and the length of stay.

1. Introduction

Carbamazepine (CBZ) poisoning is associated with cases of severe toxicity and death [1]. The frequency of CBZ poisoning is increasing during these last years. It represents about 8.4% of all drug intoxications in our unit. The degree of toxicity depends on the dose and the quality of the substance. Pharmacokinetic studies have demonstrated a discrepancy between absorption of solid and suspension formulations. A substantial interindividual variability of the half-life of CBZ has also been reported. This variability may be explained by some factors such as age, sex, coingestion of others substances, and administration of charcoal [2-5].

* Corresponding author. Department of Intensive Care and Emergency, Centre d'Assistance Médicale Urgente, 1008 Montfleury, Tunis-Tunisia. Tel.: +216 71341665; fax: +216 71341180.

E-mail address: nozha_brahmi@yahoo.fr (N. Brahmi).

0735-6757/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.ajem.2005.12.025

Table 1 Influence of charcoal administration modality on the elimination of CBZ serum

	Multiple dose (n = 6)	Simple dose (n = 6)	*P*
SAPS II	24 ± 11	13 ± 7.8	NS
APACHE II	10.33 ± 3.5	6.5 ± 3	NS
Glasgow Coma Scale	10 ± 7.8	12.3 ± 8.5	NS
CBZ concentration at admission (mg/L)	29.33 ± 5.03	31 ± 6.08	NS
Peak value of blood CBZ (mg/L)	33 ± 3.46	32.6 ± 5.63	NS
Total dose of charcoal (g)	166.6 ± 28.8	61.7 ± 6.8	.000002
Half-life of blood CBZ (h)	12.56 ± 3.5	27.88 ± 7.36	.0005

NS, non significant.

The aim of this study was to determine the CBZ elimination kinetics according to the modality of activated charcoal administration in acute CBZ-poisoning patients.

2. Materials and methods

2.1. Patients

We prospectively included all patients admitted for CBZ poisoning on a period of 6 months from January to June 2004 in a 16-bed intensive care and toxicological unit.

The diagnosis of CBZ poisoning was based on a history of CBZ ingestion, clinical features of poisoning, and laboratory findings. The determination of CBZ blood level was performed using gas chromatography (therapeutic value ranges between 5 to 12 mg/L).

Children and mixed poisoning were excluded.

2.2. Methods

Once CBZ poisoning was retained, no gastric lavage was done, and patients were randomized in 2 groups.

The first group (G1) received multiple doses of activated charcoal (50 g every 6 hours), administrated via a nasogastric tube until a return to a CBZ blood concentration less than 12 mg/L.

The second group (G2) received a simple-dose charcoal of 1g/kg.

Symptomatic treatment as the need of mechanical ventilation or supportive treatment was the same in the 2 groups.

Carbamazepine blood level was measured successively at admission (CBZH0) every 3 hours until the peak then every 6 hours until annulation of CBZ blood level.

The half-life of CBZ in blood was calculated using the following equation: CBZ $t_{1/2}$ = (t2 − t1) × ln (2)/ln (CBZ t1/CBZ t2), where CBZ $t_{1/2}$ is the half-life CBZ in blood, t2 − t1 denotes the times between the 2 CBZ measurements, and ln, the natural logarithm.

The criteria for judgment were the duration of coma, mechanical ventilation, and the length of stay. This protocol was approved by the hospital ethics committee.

2.3. Statistics

Statistical analysis was performed with SPSS 11.0 (SPSS Inc, Chicago, Ill).

Continuous variables were expressed as means (±SD) and subgroups evaluated by the χ^2 test; a 2-tailed test was used in the statistical analysis. A P value less than .05 was considered statistically significant.

Correlations were determined using both Pearson and Spearman rank methods.

3. Results

Twelve patients were included in the study for acute CBZ poisoning in a suicidal attempt. Their mean age was 27.6 ± 12.2 years; the SAPS II, 16.37 ± 8.46; and the APACHE II, 8 ± 3.96. They were 8 men and 4 women. The mean concentration of blood CBZ at hospital admission (CBZH0) was of 29.42 ± 6.68 mg/L.

Six of them were comatous, requiring mechanical ventilation with a mean Glasgow Coma Scale of 8.28 ± 1.60. The analysis of the CBZ blood elimination showed that the concentration (y) in the blood at given time is expressed by the following equation: $y = -10.56 \ln(x) + 32.436$, where y is in mg/L and x is in hours. Each group includes 6 patients. The peak value of blood CBZ was comparable in the 2 groups: 33 ± 3.46 mg/L (G1) vs 32.6 ± 5.63 (G2) (P = .5). The requirement of mechanical ventilation was similar also (3 in each group). The duration of both coma and mechanical ventilation was significantly decreased in the first group compared with the second:

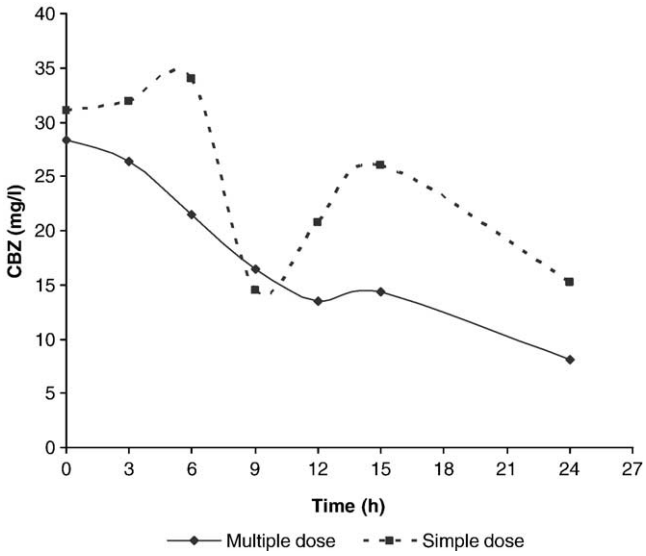

Fig. 1 Kinetics of CBZ according to the dose of activated charcoal.

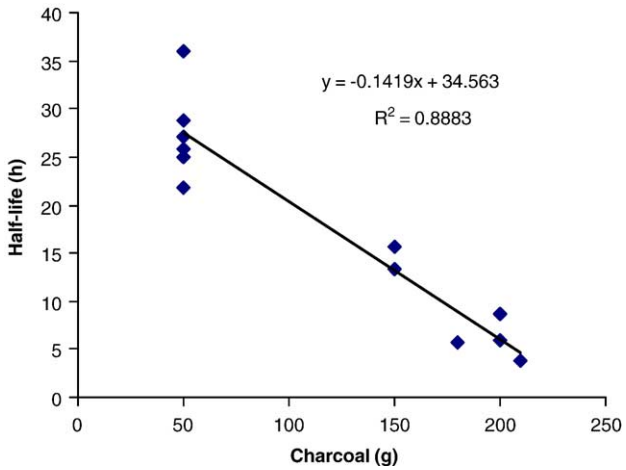

Fig. 2 Relationship between the half-life of CBZ and the dose of charcoal.

20.33 ± 3.05 vs 29.33 ± 4.11 hours for coma (P = .02) and 24.1 ± 4.2 vs 36.4 ± 3.6 hours for mechanical ventilation (P = .001). The length of stay was significantly decreased also in the first group: 30.3 ± 3.4 vs 39.7 ± 7.3 hours in the second group (P = .000006). Concurrently, we have noted a significant reduction of the half-life of CBZ from serum in the first group: 12.56 ± 3.5 hours after a multiple dose vs 27.88 ± 7.36 hours after a single dose (P = .0004) (Table 1). We have noted also a constant decrease of the CBZ blood concentration without any rebound effect in the first group (Fig. 1). A linear correlation was also found between the half-time of blood CBZ (y) and the dose of charcoal (x) ($r = -0.93$; P = .01), expressed by the following equation: $y = 35.279 - 0.1458x$, where y is in hours and x is in grams (Fig. 2).

4. Discussion

Carbamazepine distribution and metabolism is complex. Carbamazepine is reasonably bioavailable and rapidly absorbed from the gastrointestinal tract. It is highly bound to plasma proteins (75%-80%) with a moderately large volume of distribution (V_d = 1.0-2.0 L/kg) [2-4]. Because of these characteristics (prolonged elimination and a small volume of distribution), several modalities have been proposed to enhance drug clearance of CBZ using multiple doses of activated charcoal and hemoperfusion [4,6]. Multiple-dose activated charcoal has been recommended by the American Association of Poison Centres and Clinical Toxicologists and the European Association of Poison Centres and Clinical Toxicologists in a consensus position statement as useful in enhancing systemic clearance of CBZ in severe or life-threatening cases of poisoning. However, it should be noted that currently, there are no prospective controlled studies that demonstrated a change in clinical outcome after the use of multiple-dose activated charcoal in CBZ poisoning [4,7]. In our study, we try to demonstrate the influence of multiple-dose activated charcoal on elimination of CBZ and the clinical features.

In fact, the biologic half-life of CBZ in humans shows substantial interindividual variability. It averages 35 hours after the administration of a simple dose and 20 hours after a multiple dose [3]. Multiple-dose activated charcoal is thought to produce its beneficial effect by interrupting the enteroenteric and, in some cases, the enterohepatic and the enterogastric circulation of drugs. In addition, any unabsorbed drug still present in the gut will be adsorbed to activated charcoal, thereby reducing drug absorption. It should be used if no contraindication exists [2,4,7]. A few series have studied the impact of charcoal on the elimination of CBZ and demonstrated a significant decrease of the half-life in those who have received charcoal compared with supportive measures [4]. In 1987, Boldy et al [7] have demonstrated that the half-life of CBZ after a total dose of 203 ± 58 g of activated charcoal decreased to 8.6 ± 2.4 hours in 15 acute poisoned patients. Montoya-Cabrera et al [8] also found approximately the same results as those of Boldy et al with a decrease of the half-life to 9.5 ± 1.9 hours after multiple doses of charcoal (386 ± 72 g). The decrease of the half-life was remarkable if compared with the half-life with only supportive treatment, as it is the case in the studies of Hundt et al [9] and Vree et al [10], who evaluated the half-life of the blood CBZ at approximately 19 hours and in the study of Wason et al [11], at 23.3 hours. In our study, the dose-activated charcoal has been found to influence the duration of both coma and mechanical ventilation, and, consequently, the length of stay. The beneficial effect of charcoal may be explained by the decrease of the blood CBZ half-life, which was in correlation with the dose of activated charcoal. We have demonstrated also that the metabolic clearance of CBZ depends on the activated charcoal dose in favor of multiple dose, and that with a simple dose, we can observe a distribution of CBZ from tissue stores. This rebound phenomenon was reported with simple dose and hemoperfusion [1]. In fact, metabolic clearance has been reported to increase from 20 mL/kg per hour after a single dose to 55 mL/kg per hour after multiple-dose [1]. As a result, multiple-dose activated charcoal seems to be as efficient as hemoperfusion, which has been reported to reduce serum concentrations by 25% to 50% and the half-life to 6 to 8 hours, and could be proposed instead of hemoperfusion in severe patients with hemodynamic disturbance because charcoal hemoperfusion is an invasive method of CBZ purifying [1,4,12,13]. They are also interesting because they showed that a simple dose of charcoal (1g/kg) was less efficient than multiple dose and could be compared with supportive measures. The same result was reported by Winnicka et al [3] who do not demonstrate any in fluency of 30 to 70 g of charcoal on the half-life of CBZ. In summary, in spite of the little number of patients, we can conclude that multiple-dose activated charcoal is more efficient than simple dose; it permits a

constant decrease of the half-life of blood CBZ without any rebound effect and could improve the prognosis by reducing the duration of coma and the length of stay.

References

[1] Low C, Haqqie S, Desai R, et al. Treatment of acute carbamazepine poisoning by hemoperfusion. Am J Emerg Med 1996;14:540-1.

[2] Perez A, Wiley JF. Pediatric carbamazepine suspension overdose—clinical manifestations and toxicokinetics. Pediatr Emerg Care 2005;21:252-4.

[3] Winnicka R, Lopacinski B, Szymczak W, et al. Carbamazepine poisoning: elimination kinetics and quantitative relationship with carbamazepine 10,11-epoxide. J Toxicol Clin Toxicol 2002;40:759-65.

[4] AAMT, EAPCCT. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. J Toxicol Clin Toxicol 1999;37:731-51.

[5] Bertilsson L, Tomson T. Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine-10,11-epoxide. An update. Clin Pharmacokinet 1986;11:177-98.

[6] Askenazi D, Goldstein S, Chang IF, et al. Management of a severe carbamazepine overdose using albumin-enhanced continuous veno-venous hemodialysis. Pediatrics 2004;113:406-9.

[7] Boldy D, Heath A, Ruddock S, et al. Activated charcoal for carbamazepine poisoning. Lancet 1987;1:1027.

[8] Montoya-Cabrera MA, Sauceda-Garcia JM, Escalante-Galindo P, et al. Carbamazepine poisoning in adolescent suicide attempters. Effectiveness of multiple-dose activated charcoal in enhancing carbamazepine elimination. Arch Med Res 1996;27:485-9.

[9] Hundt HKL, Aucamp AK, Müller FO. Pharmacokinetic aspects of carbamazepine and its two major metabolites in plasma during overdosage. Hum Toxicol 1983;2:607-14.

[10] Vree TB, Janssen TJ, Hekster YA, et al. Clinical Pharmacokinetics of carbamazepine and its epoxy and hydroxy metabolites in humans after an overdose. Ther Drug Monit 1986;8:297-304.

[11] Wason S, Baker RC, Carolan P, et al. Carbamazepine overdose—the effects of multiple dose activated charcoal. J Toxicol Clin Toxicol 1992;30:39-48.

[12] Spiller H. Management of carbamazepine overdose. Pediatr Emerg Care 2001;17:452-6.

[13] Graudins A, Peden G, Dowsett RP. Massive overdose with controlled-release carbamazepine resulting in delayed peak serum concentrations and life-threatening toxicity. Emerg Med 2002;14:89-94.