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Early hemoperfusion for emergency treatment of carbamazepine poisoning

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ABSTRACT

Objectives: To investigate the clinical value of early hemoperfusion (HP) in emergency treatment of carbamazepine (CBZ) poisoning.
Methods: 104 patients with acute CBZ poisoning treated from August 2004 to October 2015 in the Emergency Department were reviewed. Patients were categorized into three groups: group A, who received HP treatment in the Emergency Department; group B, who received HP treatment in the blood purification room; and group C, who did not received HP treatment. Pharmacokinetic parameters of CBZ and remission of complications were compared among the three groups.
Results: Both groups A and B had lower time to peak, area under curve and maximum concentration values than group C ($P < 0.05$), and these kinetics indexes were significantly lower in group A than in group B ($P < 0.05$). The mean retention times were 0.85 ± 0.08, 1.20 ± 0.15 and 2.52 ± 0.29 days in the three groups, respectively, and were significantly lower value in group A than in group B ($P < 0.05$). The incidences of respiratory depression and seizure in group A were significantly lower than those of groups B and C ($P < 0.05$). Group A had significantly higher Glasgow coma scale (GCS) scores at 4 h after admission than the other two groups ($P < 0.05$), and group B had significantly higher GCS scores than group C at 6 h after admission ($P < 0.05$).
Conclusions: Initiation of HP in the early treatment stage of CBZ poisoning upon admission to an emergency department can significantly reduce the plasma concentration and retention period of CBZ, relieve the symptoms and shorten the overall treatment period.

1. Introduction

Presently, with rapid development of the society, people have increased mental stress due to their life and work, which has caused a significant increase in suicide events. Patients with poisoning due to suicide attempts treated in emergency departments have been increasing yearly. Recently, the poisoning spectrum of suicides has changed from chemical ingestions, such as organophosphorus, rodenticides and paraquat, to routinely available clinical drugs.

Carbamazepine (CBZ), approved in 1974, is the first classic anticonvulsant and antiepileptic drug [1]. CBZ has a bioavailability of 58–85% and a high protein binding rate of approximately 80–85%. In addition, it is distributed extensively (volume of distribution ranges from 1.0 to 2.0 L/kg). Due to its stable performance, especially its clear effectiveness in patients with epilepsy, it is used worldwide [2,3].

According to some foreign reports, CBZ has been the most frequently ingested antidepressant in suicide events [4,5]. Recently, patients with CBZ poisoning have increased in China, especially in urban areas where cases of young people with oral intoxication have significantly increased. Clinical manifestations of CBZ overdose include coma, seizures, combativeness, hallucinations, choreiform movements, drowsiness, ataxia, respiratory depression, apnea or pulmonary edema and other fatal complications [6].

Currently, there is no specific antidote for CBZ poisoning, and it is difficult to eliminate the drug. Blood purification therapy is an effective method for treating drugs poisonings, which has been developed rapidly in recent years. Hemoperfusion (HP) mainly eliminates toxins with a high molecular weight, high lipid solubility and a large volume of distribution. So, it is suitable for rescuing patients with CBZ poisoning. In previous studies, HP was recommended for patients with severe CBZ poisoning [7,8].

In this study, we reviewed the records of patients with CBZ poisoning who presented to the Emergency Department of Shengjing Hospital of China Medical University from August 2004 to October 2015. We compared pharmacokinetic parameters of CBZ and clinical symptoms

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after early HP in the Emergency Department, with those following HP performed in hemopurification room and those not receiving HP. This is the first study of the pharmacokinetic changes after emergency HP treatment for CBZ poisoning in an emergency department.

2. Materials and methods

2.1. General information

This study identified 104 patients with CBZ poisoning who were treated in the Emergency Department of Shengjing Hospital of China Medical University from August 2004 to October 2015. According to the treatment strategies adopted, the patients were categorized into three groups: group A, who received early HP treatment in emergency department; group B, who received HP treatment in the hemopurification room; and group C, who did not received HP treatment.

Patients who were exposed to multiple toxins, pregnant or <18 years old, or with indefinite doses of drugs were excluded.

The design of this study was approved by the Ethics Committee of Shengjing Hospital of China Medical University, and all treatment regimens were initiated after obtaining informed consent and signed informed consent forms from the patients. If the patient was in a coma or unable to sign, the immediate family was informed and signed informed consent forms.

2.2. Treatment methods

Every patient with CBZ poisoning received routine gastrolavage, oral activated charcoal and symptomatic supportive treatments upon admission to the Emergency Department. Once consent was obtained from the patients in group A, central venous catheterization followed by HP treatment was performed independently by emergency care physicians. The Jianfan 800-A HP machine (Zhuhai Lizhu Medical Biomaterials Co., Ltd., Guangdong) and HA230 resin HP columns (Zhuhai Lizhu Medical Biomaterials Co., Ltd., Guangdong) were used. Before the procedure, 2500–3750 IU of unfractionated heparin was administered as a single dose i.v. bolus. During the procedure, heparin and 5% glucose were used alternately to flush the infusion tube. The speed of blood flow was 120–180 mL/min. The HP lasted for 90 min. After the procedure, coagulation markers were monitored. For those with prolonged coagulation times, 10–15 mg protamine was given to neutralize the effect of heparin. For patients with bleeding tendency, low molecular weight heparin was chosen or the dose of heparin was appropriately reduced.

Similar to group A, patients in group B received routine treatment in the emergency department. The patients were then transferred to the hemopurification room for HP. Central venous catheterization and HP treatment were performed in hemopurification room. The HP protocol was the same as that described above for group A. These patients received HP in the hemopurification room because, in that time period, HP could not be independently performed by emergency physicians in our hospital. This common practice existed in most hospitals in China.

Group C patients received routine treatments upon admission to the Emergency Department. These patients were fully informed but refused to receive HP treatment.

2.3. Study design

The age, gender, dose of CBZ ingested, time interval from drug intake to hospital visit, body temperature, blood pressure, heart rate and respiratory rate at the time of admission, the time when HP was initiated, clinical symptoms, state of consciousness, mortality rate, duration of hospitalization and other data were recorded for the three groups of patients. Plasma CBZ concentrations of each patient were measured at time of arrival, time after HP (4 h after arrival for C group), 1 days, 2 days, 3 days, up to day of departure. CBZ pharmacokinetic parameters peaktime (T_{max}), area under curve (AUC), maximum concentration (C_{max}) and mean retention time (MRT) were calculated by 3P97 software. Incidence of clinical symptoms and Glasgow coma scale (GCS) score were analyzed. Because no system has been standardized to evaluate the progression of manifestations after CBZ, comparing how the groups improved was challenging. Manifestations of CBZ poisoning are strongly affected by dose ingested, time interval between ingestions and initiation of therapy and personal sensitivity. So, we compared the effect of different treatments using only total incidence of manifestations after CBZ poisoning.

2.4. Glasgow coma scale

The degree of coma was assessed using the GCS score. We compared the GCS of the three groups at the time of admission and at 2 h, 4 h, 6 h, 24 h, 2 days and 3 days after admission.

2.5. Statistical analysis

Continuous variables were summarized as mean ± SD. Variables that were not distributed normally (poisoning duration, dose of CBZ and AUC) were summarized by median. One-way analysis of variance was used to compare the mean values among the three groups. Data with equal variance were compared in pairs using the Least Significant Difference (LSD) method. Data with unequal variance were compared in pairs using the Games-Howells method. Non-normally distributed data were compared using non-parametric tests. A non-compartment model was adopted to analyze the pharmacokinetic feature of CBZ in different groups. Pharmacokinetic parameters T_{max}, AUC, C_{max} and MRT were calculated by software 3P97. A $P < 0.05$ was defined as statistical significance. SPSS16.0 software was used for statistical analysis.

3. Results

3.1. General information

The records of 104 patients with acute CBZ poisoning admitted to the Emergency Department were reviewed. There were 51 patients in Group A, 34 patients in group B and 19 patients in group C. The three groups did not differ significantly in age, gender ratio, body temperature, respiratory rate, heart rate, systolic blood pressure and diastolic blood pressure at the time of admission. The doses of CBZ ingested were 75.3 (median, range 14.2–342.5) mg/kg, 77.2 (range 11.6–255) mg/kg and 79.2 (range 12.9–328.1) mg/kg, respectively ($P > 0.05$). The time intervals from CBZ intake to hospital visit were 7.1 (range 0.5–21) h, 5.8 (range 0.3–26) h and 6.4 (range 0.3–28) h, respectively ($P > 0.05$). The levels of consciousness at admission, assessed by GCS score,

Table 1
General condition of three groups when admission.

	Group A	Group B	Group C
No.	51	34	19
Age (yrs)	29 ± 5	28 ± 6	31 ± 5
Male (%)	22 (43.14)	13 (38.24)	9 (47.37)
CBZ intake (mg/kg)	75.3 (range 14.2–342.5)	77.2 (range 11.6–255)	79.2 (range 12.9–328.1)
Time interval to hospital (h)	7.1 (range 0.5–21)	5.8 (range 0.3–26)	6.4 (range 0.3–28)
T (°C)	37.4 ± 0.5	37.2 ± 0.4	37.3 ± 0.4
RR (times/min)	14 ± 2	14 ± 1	14 ± 2
HR (r/min)	105 ± 5	110 ± 6	103 ± 4
SP (mm Hg)	130 ± 5	129 ± 4	119 ± 6
DP (mm Hg)	65 ± 6	64 ± 7	66 ± 5
GCS	7.3 ± 3.2	6.7 ± 3.3	7.2 ± 3.8

CBZ, carbamazepine; T, temperature; RR, respiration rate; HR, heart rate; SP, systolic pressure; DP, diastolic pressure; GCS, Glasgow coma scale.

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7.3 ± 3.2, 6.7 ± 3.3 and 7.2 ± 3.8, respectively, did not differ significantly (P > 0.05). Therefore, at the time of admission, the clinical manifestations of the three groups were not significantly different (see Table 1).

3.2. Laboratory test results

Each patient underwent laboratory tests of liver function, kidney function, cardiac enzymes and initial CBZ concentration. The laboratory test results are displayed in Table 2. These biochemical indexes did not differ significantly among the three groups (P > 0.05). The plasma CBZ concentrations of the three groups at admission were 19.9 ± 8.2, 20.6 ± 10.8 and 19.5 ± 7.6 mg/L, respectively (P > 0.05).

3.3. Analysis of CBZ pharmacokinetics

Pharmacokinetics of CBZ is complex with wide individual variation, so we adopted a non-compartment model to analyze the pharmacokinetics of CBZ. The pharmacokinetic parameters of CBZ are displayed Table 3. According to analysis, group A and group B had lower T_{max}, AUC and C_{max} than group C, and the values were significantly lower in group A than in group B. The MRT of the drug in the body were 0.85 ± 0.08, 1.20 ± 0.15 and 2.52 ± 0.29 day, respectively in the three groups. Group A had the lowest MRT values, and both group A and group B had lower values than group C (P < 0.05). These data suggested that after HP treatment, the retention time of CBZ in the body was significantly shortened, with decreased C_{max} and shortened T_{max}, and accelerated drug elimination.

3.4. Improvement of clinical symptoms

After CBZ poisoning, the patients primarily presented with respiratory depression, altered consciousness, seizure, hypotension and dysrhythmias; most clinical manifestations occurred within 1–3 h after poisoning. We observed that improvements in respiratory depression and seizure in group A were significantly greater than in group B and C. In addition a lower occurrence rate of hypotension and dysrhythmias was observed in group A, although not statistically different (Table 4).

3.5. Change in consciousness after admission

Change in consciousness is the most common and most prominent clinical manifestation after CBZ poisoning and the only manifestation that can be evaluated using a rating scale. No significant difference was seen in the GCS score at the time of admission among the three groups (see Table 1). However, a significant difference in the state of consciousness was seen at 4 h after admission: GCS scores in group A were significantly higher than those of groups B and C (P < 0.05). At 6 h, group B had higher GCS scores than group C (P < 0.05). At 3 days, the GCS score was higher in group A and B than that in group C, and group A had the highest score (Fig. 1).

Table 2
Laboratory results of three groups when admission.

	References	Group A	Group B	Group C
ALT (U/L)	0–40	30.6 ± 3.5	32.5 ± 4.2	29.6 ± 3.8
AST (U/L)	5–34	20.3 ± 4.1	21.4 ± 3.2	19.8 ± 3.1
ALB (g/L)	35–53	31.7 ± 3.0	32.0 ± 4.1	28.7 ± 3.6
CK (U/L)	29–200	3465 ± 103	3652 ± 123	3132 ± 112
CK-MB (U/L)	0–24	52 ± 5.1	61 ± 5.6	49 ± 4.8
Cr (μmol/L)	53–115	98.6 ± 8.2	88.6 ± 7.1	90.2 ± 7.7
BUN (mmol/L)	3–9.2	6.2 ± 1.1	6.7 ± 1.2	5.6 ± 0.9
CBZ (mg/L)	4–12	19.9 ± 8.2	20.6 ± 10.8	19.5 ± 7.6

ALT, alanine transaminase; AST, aspartate aminotransferase; ALB, albumin; CK, creatine kinase; CK-MB, creatine kinase-MB; Cr, creatinine; BUN, blood urea nitrogen; CBZ, carbamazepine.

Table 3
Pharmacokinetics parameters of CBZ in three groups.

Groups	MRT (d)	Tmax (d)	Cmax (mg/L)	$AUC_{(0 \to \infty)}$ (mg/L*d)
Group A	0.85 ± 0.08*,†	0.56 ± 0.12*,†	26.4 ± 11.8*,†	86.4 (47.2–214.2)*,†
Group B	1.20 ± 0.15*	0.61 ± 0.15*	30.6 ± 7.2*	109.74 (50.2–258.4)*
Group C	2.52 ± 0.29	0.64 ± 0.21	33.8 ± 10.4	163.93 (79.2–270.2)

MRT, mean retention time; Tmax, time to peak; Cmax, peak concentration; AUC, area under curve.
* P < 0.05, V.S. C group.
† P < 0.05, V.S. B group.

3.6. Adverse effects and length of hospitalization

The invasive procedures of HP may induce adverse effects, such as bleeding, infection, reduction of platelets and leukocytes, hypotension and hypoglycemia. The adverse effects that occurred in group A and group B during HP were recorded. One case of transient hypoglycemia was seen in group A, which normalized after a bolus injection of glucose. In group B, one case of transient thrombocytopenia occurred, which returned to normal after 3 days, and one patient experienced a hematoma at the puncture site. No patients in either group experienced severe adverse effects. The adverse effects were effectively relieved after timely treatment. Group A did not experience more adverse effects than group B. In group C, 2 patients died during their treatment; the mortality rate of that group was 10.5%. All patients in groups A and B recovered and were discharged.

The average lengths of hospitalization were 3.12 ± 0.98 days in group A, 4.16 ± 0.74 days in group B and 5.84 ± 1.32 days in group C. Hospital stay was significantly shorter in group A than in groups B and C.

4. Discussion

Recently, patients with acute poisoning have increased significantly, and the spectrum of toxins has changed to drugs commonly used in clinical settings. Moreover, most toxins have no specific antidotes. Therefore, to rescue patients with poisoning more effectively, some hospitals in China implemented blood purification technologies in their emergency departments. Before hemopurification became a standard practice performed by emergency physician independently, HP was only available in hemopurification rooms; we needed to transfer patients to the hemoperfusion room causing delays in the initiation of HP for patients. In this study, we compared the treatment effect of emergency HP with that of traditional hemopurification treatment and routine treatment. We observed a better treatment effect after emergency HP on CBZ pharmacokinetic metabolism and clinical manifestations. Beginning hemopurification as early as possible in the emergency department is critical for optimal treatment, especially for patients with poisoning.

CBZ is highly bound to proteins (80–85%) and is distributed extensively (volume of distribution ranges from 1.0 to 2.0 L/kg). Theoretically, HP is better than hemodialysis because of the high protein binding rate [9,10]. Presently, the primarily extracorporeal treatment methods adopted for CBZ poisoning include hemodialysis, HP, continuous renal replacement therapy and HP-hemodialysis. The high cost of continuous renal replacement therapy and HP-hemodialysis limited use of these

Table 4
Symptoms after CBZ poisoning in three groups.

Symptoms	Group A	Group B	Group C	Sig.
Respiratory depression % (n)	23.5 (12)	50 (17)*	63.2 (12)*	0.003
Seizure % (n)	64.7 (22)	47.1 (24)*	94.7 (18)*,†	0.000
Hypotension % (n)	17.6 (9)	20.6 (7)	26.3 (5)	0.832
Dysrhythmias % (n)	11.7 (6)	14.7 (5)	15.8 (3)	0.656

* P < 0.017, V.S. group A.
† P < 0.017, V.S. group B.

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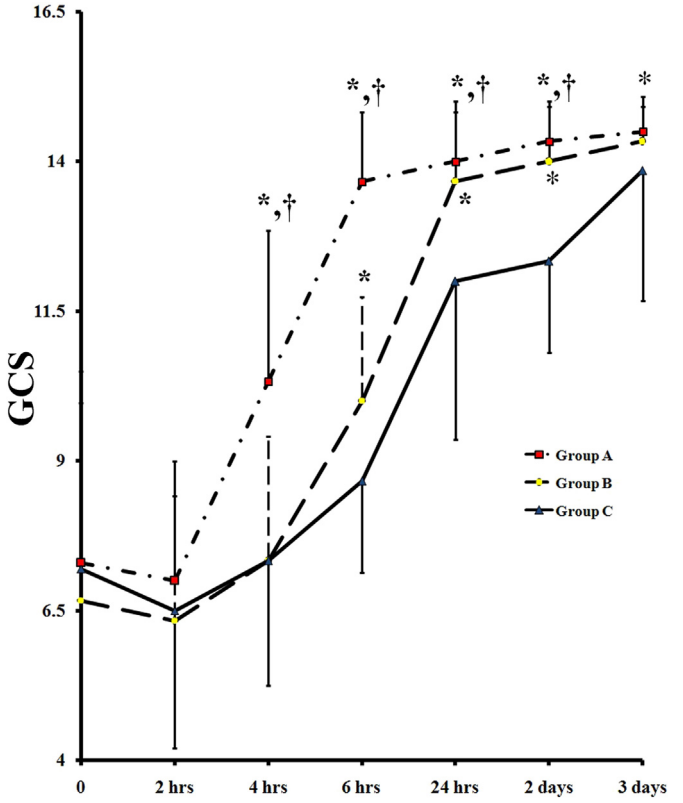

Fig. 1. Continuous monitoring of GCS in three groups. GCS of group A was higher significantly than group B and C since 4 h after CBZ intake, while group B was higher significantly than group C since 6 h after CBZ intake. *, $P < 0.05$, V.S. group C; †, $P < 0.05$, V.S. group B.

two methods for CBZ poisoning. Until now, no evidence appeared to support the benefit of HP-hemodialysis from studies by others [8]. Patients also received less favorable clinical parameters after continuous renal replacement therapies [6,8]. According to the Extracorporeal Treatments in Poisoning workgroup, hemodialysis and hemofiltration are not commonly suggested to remove CBZ because of it is highly protein-bound. The mean clearance for hemodialysis was inferior to that for HP [8]. Some reports suggest that high blood flow hemodialysis (exceeding 100 mL/min) has clearance comparable with HP [11]. However, a recent report by Shah et al. showed an effectiveness of high volume continuous veno-venous hemofiltration with dialysis in a massive CBZ overdose [12]. As a result, HP is the only definitely effective extracorporeal treatment of CBZ poisoning. So, HP is the first choice for emergency hemopurification of CBZ poisoning if conditions support its use.

In our study, we selected early HP for CBZ poisoning in emergency department. During the early phase of poisoning, the absorption of oral CBZ is slow and irregular. The peak plasma drug concentration is generally reached within 2–6 h, and the half-life is 12–14 h. Therefore, timely and effective blood purification treatment should be given within 6 h after acute poisoning, which is the best timing for blood purification. In this study, we observed that patients who received emergency HP treatment performed by emergency doctors had shorter MRT, and reduced T_{max}, C_{max} and AUC compared with the other two groups. Moreover, with the elimination of CBZ, we observed that consciousness recovered faster after HP treatment in group A than in group B and C. Therefore, HP treatment decided and administered by emergency care physicians is more expeditious than that performed by doctors in hemopurification rooms. Early HP can effectively decrease plasma CBZ concentration, reduce the accumulation of CBZ in fat tissues, reduce the reabsorption of CBZ and thereby relieve the symptoms of this toxin.

In this study, we also observed individual differences in the treatment effect of HP, which might be related to the great individual differences in CBZ metabolism. Furthermore, there was no strict correlation between plasma CBZ concentration and clinical manifestations. Improvement of plasma CBZ concentration was not necessarily accompanied by improvement of manifestations, especially in patients with severe conditions. These results were consistent with previous reports on CBZ [13,14]. The metabolism differences after CBZ ingestion maybe related to dosage form, genetic differences or contemporaneous food intake. However, a temporal trend of overall relief of clinical symptoms that paralleled the decrease in CBZ concentration was confirmed, especially the rapid relief of impaired consciousness and seizure that followed decreases in CBZ concentration.

Our study has some limitations. First, due to the laboratory facilities in our hospital, we only examined the plasma concentration of CBZ. However, major active metabolites of CBZ (CM-E, CM-D, for example), which maybe more related to poisoning effect of CBZ, were not assessed. Second, the dose of CBZ ingested by each patient was collected by inquiry. However, due to different factories, different production lots, or memory errors the dose of CBZ may have been inaccurate. The inaccurate dose of CBZ could produce error in our calculation of pharmacologic parameters. This may also lead to a deviation from other countries. Therefore, to decrease possible errors, we selected patients with a definite dose of drugs. Finally, we used resin HP for elimination of CBZ. However, some other studies adopted active charcoal HP. These two kinds of column were not compared in our study, but such a comparison is an interesting topic for evaluating determinants of HP effects in a future study.

5. Conclusion

In summary, early HP administered directly by emergency doctors to patients with CBZ poisoning can significantly reduce plasma CBZ concentration and accelerate the elimination of CBZ from the body. In addition, HP treatment can significantly relieve impaired consciousness, respiratory depression and seizure after CBZ poisoning. Therefore, early HP by emergency care physicians is recommended for patients with CBZ poisoning.

Declaration of interest

The authors report no declarations of interest.

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