Iran Red Crescent Med J. 2019 December; 21(12):e86590. doi: 10.5812/ircmj.86590.

Published online 2019 December 25. **Case Report**

# Use of Charcoal Hemoperfusion and High-Flux Hemodialysis in Carbamazepine Intoxication: Two Case Reports

Sibel Yucel Kocak [1, *], Aysegul Kudu [1], Ceren Gumusel [2], Arzu Ozdemir Kayalar [1] and Murvet Yilmaz [1]

[1] Department of Nephrology, University of Health Sciences Bakırkoy Dr. Sadi Konuk Educational and Research Hospital, Istanbul, Turkey
[2] Department of Internal Medicine, University of Health Science Bakırkoy Dr. Sadi Konuk Educational and Research Hospital, Istanbul, Turkey

[*] *Corresponding author*: Department of Nephrology, University of Health Sciences Bakırkoy Dr. Sadi Konuk Educational and Research Hospital, No. 11, Tevfik Sağlam St., Bakırköy, Istanbul, Turkey. Tel: +90-5055830860, Email: fsibelkocak@yahoo.com

**Received** 2018 November 20; **Revised** 2019 May 13; **Accepted** 2019 June 02.

## Abstract

**Introduction:** Carbamazepine (CBZ) is a drug used in the treatment of neurological and psychiatric disorders. Intoxication with CBZ is a serious condition that can result in coma, hemodynamic instability and death. Urgent management of CBZ intoxication is life saving and extracorporeal methods are used for removal of CBZ. It is also known that CBZ is highly protein-bound and charcoal hemoperfusion is the most effective extracorporeal elimination. We know that hemodialysis is also a technique for management of this drug.

**Case Presentation:** We present two cases of CBZ intoxication, treated with two different methods, charcoal hemoperfusion and high-flux hemodialysis. The first patient who was receiving CBZ treatment for anxiety disorder was admitted to Bakırköy Dr. Sadi Konuk Educational and Research Hospital, Istanbul, Turkey on 11th of December 2017, with complaints of dizziness and blurred vision. Vital signs were stable. Laboratory tests were normal. Serum CBZ level was 56 $\mu$g/mL (reference 4 - 12 $\mu$g/mL). The CBZ level was 15.6 $\mu$g/mL after charcoal hemoperfusion for 3 hours. The second patient was admitted to the emergency room on the 5th of February 2015, with blurred consciousness. The patient had taken CBZ for suicide. The CBZ level was 33 $\mu$g/mL and was 14.86 $\mu$g/mL after hemodialysis with high-flux membrane for 4 hours. Serum CBZ level decreased by 73% in the first patient who received charcoal hemoperfusion and by 55% in the second patient who received high-flux hemodialysis.

**Conclusions:** In presenting these cases, we aimed to show the decrease of CBZ serum levels by using two different hemodialysis modalities in CBZ intoxication.

*Keywords:* Carbamazepine, Dialysis, Hemoperfusion

## 1. Introduction

Carbamazepine (CBZ) is a drug commonly used in the treatment of neurological and psychiatric disorders such as epilepsy, schizophrenia, mood disorders, trigeminal neuralgia, and neuropathic pain. This medication has anticholinergic, antidepressant, antiarrhythmic, sedative and neuromuscular blocking properties. According to data from the American Association of Poison Control Center, 3447 cases of CBZ overdose were reported in 2017. Fifty nine of these cases were severely poisoned and one of them had died. The mortality rate due to CBZ intoxication has been reported to range from 2% to 13% (1).

Oral CBZ is absorbed approximately 70% - 95% but absorption is slow due to the gastrointestinal motility inhibition by the drug. It is metabolized mainly by the cytochrome p450 system in liver and forms into the active metabolite (carbamazepine-10,11-epoxide). It is lipophilic and has a large distribution volume, highly bound (70% - 80%) to plasma proteins and reaches the highest level in 4 - 8 hours in plasma. The therapeutic level of CBZ is narrow and the targeted level is between 4 - 12 $\mu$g/mL. The treatment dose is determined to be 15 - 25 mg/kg. Intoxication with CBZ is a serious condition that can result in coma, respiratory depression, arrhythmia, hemodynamic instability and death. Life-threatening symptoms such as loss of consciousness, coma, and seizures are seen especially at doses above 50 mg/kg. In CBZ intoxication, removal of the drug is very important and urgent (2).

There is no specific antidote for the treatment of CBZ intoxication and supportive therapy is generally recommended. Multiple-dose activated charcoal is given to reduce gastrointestinal system absorption. Multiple-dose activated charcoal may enhance its clearance, but the effect is incomplete and often limited by ileus or concerns of pulmonary aspiration in an unprotected airway. CBZ is not removed through conventional hemodialysis (HD) as it highly binds to proteins. Therefore, charcoal hemoperfusion, continuous hemodiafiltration and plasma exchange

are applied (3-5). Conventional HD, especially high-flux HD is also found to be effective in removing CBZ in some case reports (6-8). The recommended procedure for removal of the drug is usually charcoal hemoperfusion (9).

In this article, we present two cases with CBZ intoxication and show the efficiency of two removal modalities. In the first patient charcoal hemoperfusion was used, whereas the other patient underwent high-flux HD.

## 2. Case Presentation

### 2.1. Case 1

A 19-year-old male patient was admitted to the Emergency Department of Bakırköy Dr. Sadi Konuk Educational and Research Hospital, Istanbul, Turkey the on 11th of December 2017 with symptoms of gait disturbance, dizziness, blurred vision and speech disorders one week after the beginning of CBZ treatment, due to anxiety disorder by the psychiatric clinic. He was also using escitalopram and risperidone. The blood pressure was 105/60 mmHg, pulse rate was 125/min, oxygen saturation was 98% and body temperature was 36.80°C. On physical examination, the Glasgow Coma Scale (GCS) was 10/15. Pupils were isochoric, bilateral pupillary light reflex was positive, no neuromuscular examination pathology was detected. Other system examinations were normal.

In laboratory tests, leucocytes 6000 /$mm^3$, hemoglobin 13 gr/dL, platelet 263000 /$mm^3$, urea 29 mg/dL, creatinine 0.8 mg/dL, sodium 139 mmol/L, potassium 4.25 mmol/L, calcium 9.11 mg/dL. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were normal (13 mEq/L and 8 mEq/L, respectively). In arterial blood gas analysis pH 7.42, partial pressure of carbondioxide ($paCO_2$, 43.8 mmHg; reference range, 40 - 50 mmHg), partial pressure of arterial oxygen ($paO_2$, 76.2 mmHg; reference range, > 80 mmHg), bicarbonate 27.1 mmol/L (reference range, 21 - 27 mmol/L), oxyhemoglobin saturation ($SaO_2$, 96%; reference range > 95) were detected. Serum CBZ level was 56 $\mu$g/mL (reference 4 - 12 $\mu$g/mL) and measured by using a latex particle enhanced immunoturbidimetric assay. Laboratory tests are shown in Table 1.

Activated charcoal was applied to the patient with a nasogastric catheter. Approximately 3000 cc isotonic solution (%0.9 NaCL) and 1000 cc 5% dextrose were administered to the patient in the emergency care unit. After 6 hours from admission, charcoal hemoperfusion (Adsorba 150 C, Gambro) was performed at a blood flow rate of 200 mL/min for 3 hours as the CBZ level was in toxic range and the patient had a clouding of consciousness. After one session of charcoal hemoperfusion, the controlled CBZ level was 15.6 $\mu$g/mL. The consciousness of the patient was recovered after hemoperfusion. The administration of 50 grams of active charcoal continued every 4 hours. Hypocalcemia or hypokalemia was not detected. Platelet count was 128.000 /$mm^3$ and thrombocytopenia resolved spontaneously. After 24 hours, the patient was discharged with a CBZ level of 8 $\mu$g/mL and his general condition improved rapidly.

**Table 1.** Laboratory Parameters of Patients

| Test | First Patient | Second Patient | Reference Value |
|---|---|---|---|
| **Glucose (mg/dL)** | 96 | 152 | 74 - 106 |
| **Hemoglobin (g/dL)** | 13 | 10.3 | 12.9 - 15.9 |
| **Leucocytes (cells $\times$ $10^9$/L)** | 6.0 | 15.1 | 3.7 - 10.1 |
| **Platelets (cells $\times$ $10^9$/L)** | 263 | 256 | 155 - 366 |
| **Urea (mg/dL)** | 21 | 21 | 16 - 48 |
| **Creatinine (mg/dL)** | 0.8 | 0.5 | 0.7 - 1.2 |
| **Potassium (mmol/L)** | 4.25 | 3.5 | 3.3 - 5.1 |
| **Sodium (mmol/L)** | 139 | 136 | 136 - 145 |
| **Calcium (mg/dL)** | 9.1 | 8.4 | 8.6 - 10.6 |
| **AST (IU/L)** | 13 | 13 | 0 - 32 |
| **ALT (IU/L)** | 8 | 11 | 0 - 32 |
| **LDH (IU/L)** | 159 | 130 | 135 - 214 |
| **Total protein (g/dL)** | 7.4 | 6.3 | 6.4 - 8.3 |
| **Albumins (g/dL)** | 4.9 | 3.5 | 3.5 - 5.2 |
| **Prothrombin time (sn)** | 11.8 | 13.7 | 10 - 15 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

### 2.2. Case 2

A 20-year-old female patient with no chronic disease was admitted to the Emergency Room of Bakırköy Dr. Sadi Konuk Educational and Research Hospital, Istanbul, Turkey on 5th of February 2015 with clouding of consciousness. The patient had taken an unknown amount of CBZ tablets (each CBZ tablet was 400 mg) to commit suicide.

On physical examination, the blood pressure was 130/80 mmHg, pulse rate was 126 /min. She was in coma and the Glasgow Coma Scale (GCS) was 3/15 so she was intubated in the emergency room. Pupils were anisocoric, bilateral pupillary light reflex was negative. Other system examinations were normal. Activated charcoal was applied to the patient with nasogastric catheter in emergency department.

In laboratory tests, leucocyte 15100 /$mm^3$, hemoglobin 10.3 gr/dL, platelet 256000 /$mm^3$, urea 21 mg/dL, creatinine 0.5 mg/dL, sodium 136 mmol/L, potassium 3.5 mmol/L, calcium 8.4 mg/dL. AST and ALT were normal (13 mEq/L and 11 mEq/L, respectively). In arterial blood gas analysis, pH 7.33, $paCO_2$ 41.4 mm/Hg, $paO_2$ 84, bicarbonate 20.7 mmol/L, $SaO_2$ 95.4% were detected. Serum CBZ level was 33 $\mu$g/mL (reference 4 - 12 $\mu$g/mL) and measured by using a latex particle enhanced immunoturbidimetric assay. The clinical laboratory findings are shown in Table 1.

A gastric lavage was performed and an activated charcoal was given in the emergency room. Intravenous iso-

tonic solution (%0.9 NaCl) was administered. Extracorporeal treatment was planned as the CBZ level was in toxic range and the patient was in coma.

We had no charcoal hemoperfusion opportunity, so 12 hours from admission, high-flux HD was performed with a highly permeable 1.8 $m^2$ membrane at a blood flow rate of 300 mL/min for 4 hours. The CBZ level decreased to 14.86 $\mu$g/mL afterwards. The patient was followed by intensive care unit. In follow-up the patient did not need any other HD session. The CBZ level was 4.93 $\mu$g/mL after 48 hours from admission and she was discharged. The decrease of CBZ levels in two patients with two different methods can be seen in Figure 1.

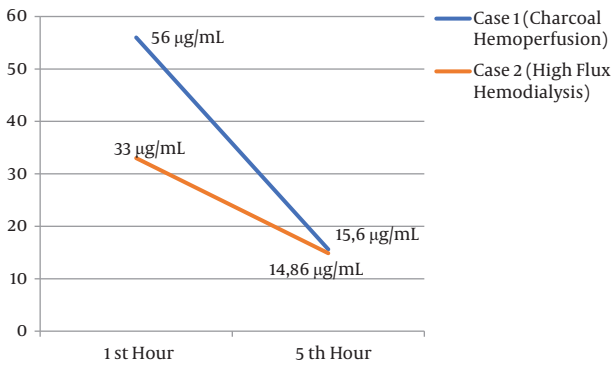


**Figure 1.** Graph showing plasma carbamazepine levels before and after charcoal hemoperfusion and high-flux hemodialysis

## 3. Discussion

CBZ intoxication may results in seizures, coma, arrhythmia, respiratory depression and death. Clinical findings of CBZ intoxication are related to the dose and serum CBZ level. Clinical findings are mostly neurological. In acute intoxication with CBZ, ataxia, nystagmus, mydriasis, ophthalmoplegia, sinus tachycardia, atrioventricular block, convulsion, myoclonus, hyperthermia, coma and respiratory arrest may be seen. In chronic poisoning, hyponatremia and hypokalemia, hepatitis, neutropenia, thrombocytopenia, agranulocytosis, aplastic anemia, exfoliative dermatitis might be seen. Neurological findings were significant in our cases because they were acute (10, 11).

Carbamazepine is metabolized by cytochrome P450 system in the liver. Only 1% - 3% of the drug is excreted unchanged in the urine. It has a wide distribution volume due to its lipophilic nature. Central nervous system and cardiac side effects occur as a result of blockade of sodium channels and anticholinergic effects. The drug itself and the active epoxide metabolite are responsible for the toxic effects. The primary metabolite, carbamazepine-10,11-epoxide, binds to proteins at 50% (12).

The drug and its active metabolite have an anticonvulsant and toxic effect on an equal level. Therefore, total CBZ plasma concentration was measured. The therapeutic level of CBZ is 4 - 12 $\mu$g/mL. Severe toxicity usually occurs at 40 $\mu$g/mL. In our cases, the CBZ level was 56 $\mu$g/mL and 33 $\mu$g/mL. There is no direct correlation between serum levels and the clinical severity of the poisoning. The severity of toxicity is measured by the evaluation of the clinical findings of the patient rather than the serum level (9). As can be seen in the second case, although the plasma CBZ level was lower, the clinical findings were more severe.

There is no specific antidote. At 4 - 6 hour intervals, active charcoal can be used to reduce the half-life of CBZ and to prevent enterohepatic circulation. However, this procedure is difficult in patients with intubation and mechanical ventilation and is not possible in cases of ileus due to anticholinergic effects of CBZ. The urgent removal of the drug is only achieved with extracorporeal treatment methods. Carbamazepine is a highly protein-bound molecule and therefore not easily removed by conventional HD. In several studies, the hemoperfusion clearance of CBZ was reported to be 96.9 mL/min, while the HD clearance was 59.8 mL/min cleansing with HD or hemofiltration, even if the protein binding rate is high (13). The effectiveness of extracorporeal treatments on mortality is limited but it is beneficial because it reduces short-term morbidity, respiratory failure and coma, and shortens the length of hospitalization. In our cases the length of hospitalization was short, since extracorporeal treatment was done early (9).

Charcoal hemoperfusion is the golden standard treatment for acute CBZ intoxication and many case reports have shown that its efficacy is superior to HD (10). It is reported that charcoal hemoperfusion can decrease serum CBZ levels by 45% - 50% (14). However, it is also known that other methods, such as HD, hemodiafiltration and plasma exchange can be used in treatment of CBZ intoxication (5, 12).

In our cases, serum CBZ level was decreased by 73% in the first patient who received charcoal hemoperfusion and by 55% in the second patient who received high-flux HD. The characteristics of our case were compared with previously published case reports (Table 2) (7, 8, 14). There are studies showing that while doing both hemoperfusion and HD, the level can be reduced up to 50% (15). However, since charcoal hemoperfusion is a relatively expensive method and is not available at all centers, high-flux HD is still one of the first treatment options for CBZ intoxication. The advantages of HD are that it has no side effects such as hypokalemia, thrombocytopenia, coagulopathy and hypothermia that can be seen in charcoal hemoperfusion.

The Extracorporeal Treatments in Poisoning Workgroup (EXTRIP) was created to provide standardized clin-

**Table 2.** The Compared Blood Carbamazepine Levels of Our Cases with Previously Published Case Reports

| | Method | Before Treatment ($\mu$g/mL) | After Treatment ($\mu$g/mL) | Carbamazepine Reduction Ratio[a] |
|---|---|---|---|---|
| **First patient** | HP | 56 | 15.6 | 73 |
| **Second patient** | HD | 33 | 14.86 | 55 |
| **Mochizuki et al., 2015 (14)** | HP | 31.8 | 17.3 | 46 |
| **Drick et al., 2015 (7)** | HD | 47 | 25 | 47 |
| **Sikma et al., 2012 (8)** | HD | 27.4 | 13 | 52.6 |

[a](Before-After)/Before × 100 (%).

ical recommendations based on a review of all available evidence. According to the EXTRIP recommendations, in CBZ intoxication, intermittent HD is the preferred modality suggested in cases of prolonged coma, seizures, life-threatening dysrhythmias and if the CBZ concentrations are over 45 $\mu$g/mL. If HD is not available, charcoal hemoperfusion and continuous renal replacement therapy should be performed (16).

### 3.1. Conclusions

High-flux HD and charcoal hemoperfusion are effective and safe in life-threatening CBZ intoxications. Early initiation of treatment reduces hospital stay and morbidity.

## Footnotes

**Conflict of Interests:** The authors declare that they have no conflicts of interest.

**Funding/Support:** It is not declared by the authors.

**Patient Consent:** Written informed consent was obtained from the patients for the publication.

## References

1. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. *Clin Toxicol (Phila)*. 2018;**56**(12):1213–415. doi: 10.1080/15563650.2018.1533727. [PubMed: 30576252].
2. Ram Prabahar M, Raja Karthik K, Singh M, Singh RB, Singh S, Dhamodharan J. Successful treatment of carbamazepine poisoning with hemodialysis: A case report and review of the literature. *Hemodial Int*. 2011;**15**(3):407–11. doi: 10.1111/j.1542-4758.2011.00559.x. [PubMed: 21624045].
3. Isik Y, Soyoral L, Karadas S, Emre H, Cegin MB, Goktas U. Effectivity of one session charcoal hemoperfusion treatment in severe carbamazepine poisoning. *Iran Red Crescent Med J*. 2013;**15**(8):749–51. doi: 10.5812/ircmj.7516. [PubMed: 24578847]. [PubMed Central: PMC3918204].
4. Choi JS, Kim CS, Bae EH, Ma SK, Kee SJ, Woo YJ, et al. Enhanced clearance of carbamazepine using albumin-containing dialysate during CVVHDF. *Intensive Care Med*. 2013;**39**(1):159–60. doi: 10.1007/s00134-012-2717-7. [PubMed: 23096427].
5. Kozanoglu I, Kahveci S, Asma S, Yeral M, Noyan A, Boga C, et al. Plasma-exchange treatment for severe carbamazepine intoxication: A case study. *J Clin Apher*. 2014;**29**(3):178–80. doi: 10.1002/jca.21305. [PubMed: 24136443].
6. Azak A, Kocak G, Huddam B, Duranay M. Is conventional hemodialysis enough to manage carbamazepine intoxication? *Blood Purif*. 2012;**33**(4):225–6. doi: 10.1159/000335608. [PubMed: 22286972].
7. Drick N, Patecki M, Arelin V, Schmidt JJ, Wahl O, Kielstein JT. [Successful hemodialysis for life-threatening carbamazepine drug overdose: Case-based introduction of new guidelines]. *Med Klin Intensivmed Notfmed*. 2015;**110**(7):551–4. German. doi: 10.1007/s00063-015-0010-6. [PubMed: 25801374].
8. Sikma MA, van den Broek MP, Meulenbelt J. Increased unbound drug fraction in acute carbamazepine intoxication: Suitability and effectiveness of high-flux haemodialysis. *Intensive Care Med*. 2012;**38**(5):916–7. doi: 10.1007/s00134-012-2501-8. [PubMed: 22327559]. [PubMed Central: PMC3332384].
9. Yang X, Xin S, Zhang Y, Li T. Early hemoperfusion for emergency treatment of carbamazepine poisoning. *Am J Emerg Med*. 2018;**36**(6):926–30. doi: 10.1016/j.ajem.2017.10.048. [PubMed: 29066188].
10. Li TG, Yan Y, Wang NN, Zhao M. Acute carbamazepine poisoning treated with resin hemoperfusion successfully. *Am J Emerg Med*. 2011;**29**(5):518–22. doi: 10.1016/j.ajem.2009.12.006. [PubMed: 20825822].
11. Yaylaci S, Demir MV, Acar B, Sipahi S, Tamer A. Successful treatment of excessive dose of carbamazepine. *Indian J Pharmacol*. 2012;**44**(3):417–8. doi: 10.4103/0253-7613.96353. [PubMed: 22701260]. [PubMed Central: PMC3371473].
12. Harder JL, Heung M, Vilay AM, Mueller BA, Segal JH. Carbamazepine and the active epoxide metabolite are effectively cleared by hemodialysis followed by continuous venovenous hemodialysis in an acute overdose. *Hemodial Int*. 2011;**15**(3):412–5. doi: 10.1111/j.1542-4758.2011.00563.x. [PubMed: 21676154].
13. Ghannoum M, Bouchard J, Nolin TD, Ouellet G, Roberts DM. Hemoperfusion for the treatment of poisoning: technology, determinants of poison clearance, and application in clinical practice. *Semin Dial*. 2014;**27**(4):350–61. doi: 10.1111/sdi.12246. [PubMed: 24823936].
14. Mochizuki K, Hamano Y, Miyama H, Arakawa K, Kobayashi T, Imamura H. Successful treatment of a case with concurrent ingestion of carbamazepine overdose and grapefruit juice. *Acute Med Surg*. 2016;**3**(1):36–8. doi: 10.1002/ams2.117. [PubMed: 29123746]. [PubMed Central: PMC5667222].
15. Vallianou N, Giannopoulou M, Trigkidis K, Bei E, Margellou E, Apostolou T. A case of severe carbamazepine overdose treated successfully with combined hemoperfusion and hemodialysis technique. *Saudi J Kidney Dis Transpl*. 2017;**28**(4):906–8. [PubMed: 28748895].
16. Ghannoum M, Yates C, Galvao TF, Sowinski KM, Vo TH, Coogan A, et al. Extracorporeal treatment for carbamazepine poisoning: Systematic review and recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)*. 2014;**52**(10):993–1004. doi: 10.3109/15563650.2014.973572. [PubMed: 25355482]. [PubMed Central: PMC4782683].