

## Case Report

# Usefulness of venoarterial extracorporeal membranous oxygenation for fatal cibenzoline succinate poisoning

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**Background:** The effect of venoarterial extracorporeal membranous oxygenation (V-A ECMO), plasma exchange (PE), and direct hemoperfusion (DHP) for fatal cibenzoline succinate poisoning is unclear. We report a rare case of severe cibenzoline succinate poisoning along with cardiac arrest, wherein the patient was managed with V-A ECMO, PE, and DHP. We also measured the blood levels of cibenzoline succinate frequently.

**Case Presentation:** A 51-year-old woman had a refractory cardiac arrest after cibenzoline succinate ingestion. We initiated V-A ECMO, PE, and DHP. Plasma exchange did not improve clinical manifestations. Her clinical condition improved during DHP, but there was no evidence about removal of drugs. On day 3, DHP and ECMO were terminated. On day 9, she was transferred to another hospital without arrhythmia recurrence.

**Conclusion:** Venarterial ECMO is effective in cases of cibenzoline succinate poisoning-related cardiac dysfunction or cardiac arrest. No evidence was obtained for the effects of PE and DHP.

**Key words:** Cardiopulmonary arrest, cibenzoline succinate, direct hemoperfusion, extracorporeal membranous oxygenation, poisoning

## INTRODUCTION

CIBENZOLINE SUCCINATE IS an antiarrhythmic agent with properties such as those of Vaughan Williams class Ia, Ic, and III agents. Cibenzoline succinate causes severe side-effects, including proarrhythmia, hemodynamic effects, hypoglycemia, and liver and renal dysfunction due to Na<sup>+</sup> and Ca<sup>2+</sup> channel block. Direct hemoperfusion (DHP) and plasma exchange (PE) have been found effective in the management of these cases.<sup>1–3</sup> However, there are limited data on the plasma cibenzoline succinate concentration during treatment with extracorporeal cardiopulmonary resuscitation (ECPR), PE, or DHP. Herein, we report a rare case of severe cibenzoline succinate

poisoning along with cardiac arrest, wherein the patient was managed with ECPR, PE, and DHP. Informed consent was obtained from the patient before the publication of this case report.

## CASE REPORT

A 51-YEAR-OLD WOMAN ingested cibenzoline succinate (6,900 mg) with alcohol during a suicide attempt. Approximately 75 min after ingestion, she was brought to our emergency department. Physical examination at arrival revealed the following: respiratory rate, 17 breaths/min; pulse rate, 20–30 b.p.m.; blood pressure, 84/50 mmHg; tympanic temperature, 35.5°C; and Glasgow Coma Scale score, 7 (E1V1M5). Her electrocardiogram showed a wide QRS (0.36 ms). Blood examination revealed mild liver dysfunction.

Echocardiography revealed dyssynchrony in left ventricle wall motion, with 30% left ventricular ejection fraction. Considering her worsening clinical condition, including hypotension and bradycardia, she was intubated and placed on mechanical ventilation. Treatment with noradrenaline (0.2 µg/kg/min) and transcutaneous pacing were ineffective.

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Received 18 Oct, 2019; accepted 3 Mar, 2020

### Funding Information

The funding source had no role in the design, practice, or analysis of this study.

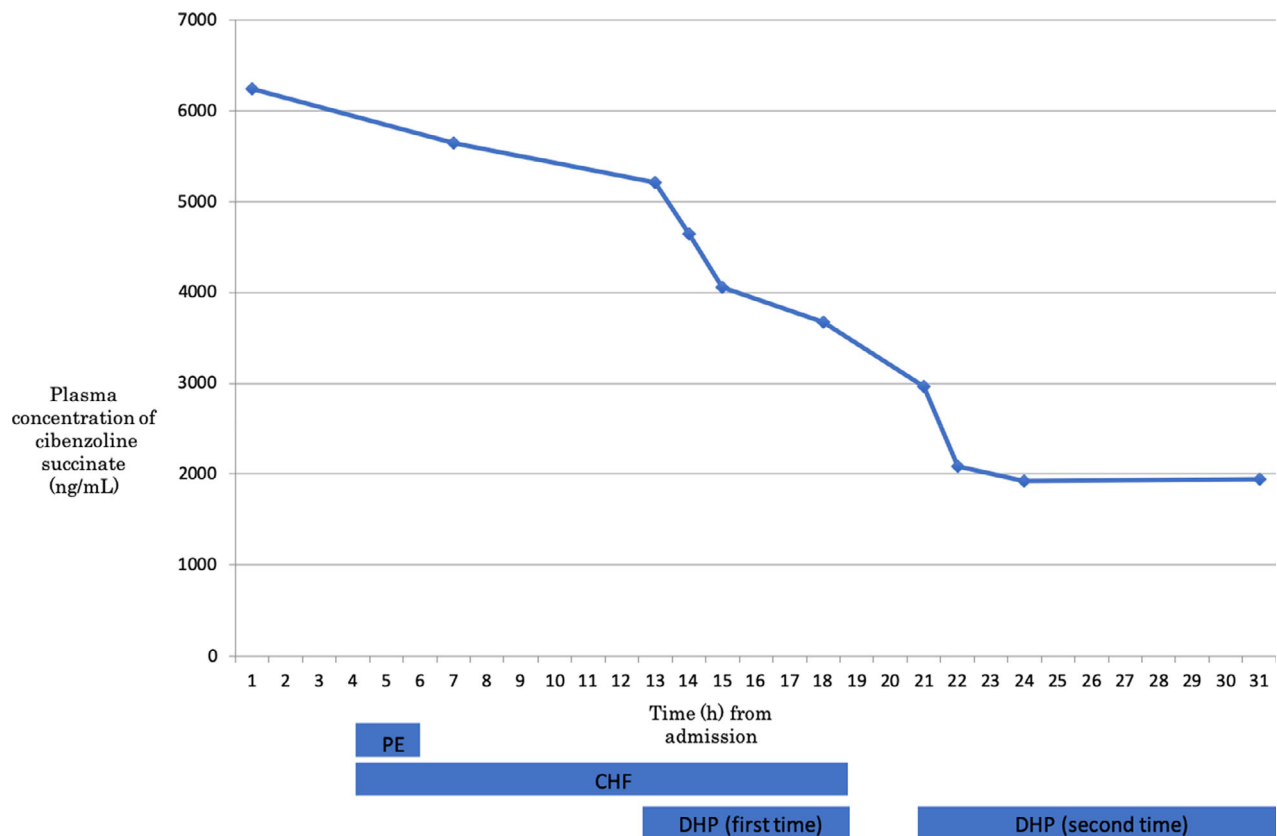
Approximately 26 min after admission, her electrocardiogram indicated ventricular fibrillation (VF). Twenty minutes later, venoarterial extracorporeal membranous oxygenation (V-A ECMO) treatment was started for cardiac arrest with VF. She developed alternating bradycardia and VF during V-A ECMO. Changes in plasma her cibenzoline succinate levels were observed during treatment (Fig. 1).

Plasma exchange was carried out for 2 h using Plasmaflo (Asahi Kasei Medical, Tokyo, Japan) at quantity of blood flow rate of 100 mL/min and quantity of plasma flow rate of 25 mL/min to reduce her plasma cibenzoline succinate concentration; however, her hemodynamics did not improve. Continuous hemofiltration (CHF) was undertaken to treat acute kidney injury with anuria using AEF (Asahi Kasei Medical) at quantity of blood flow rate of 180 mL/min and quantity of filtration rate of 2000 mL/h.

Due to continuous arrhythmias and lack of improvement in her hemodynamics, approximately 15 h after cibenzoline ingestion, DHP was carried out using Hemosorba CHS-350, which included an activated charcoal-coated hemoperfusion

column (Asahi Kasei Medical). After DHP, her electrocardiogram showed a change from a wide QRS to a narrow QRS, hemodynamics improved, and she no longer had anuria; therefore, CHF and DHP were terminated after 4.5 h. However, 40 min after withdrawal, her electrocardiogram showed a wide QRS and ventricular tachycardia, indicating clinical deterioration.

Her clinical condition immediately improved following a second DHP, and her electrocardiogram showed a sinus rhythm within a normal QRS range (Fig. 2). We decided there was no need to resume CHF, because her renal function had been gradually improving. On day 3, her hemodynamics stabilized and the left ventricular dyssynchrony disappeared. Hence, we decided to withdraw DHP; her hemodynamics were monitored carefully for a few hours, after which ECMO was safely withdrawn. On day 5, mechanical ventilation was successfully withdrawn. On day 9, she was transferred to another hospital for treatment of her psychological disorder, without arrhythmia recurrence.



**Fig. 1.** Plasma concentration of cibenzoline succinate from admission of a 51-year-old woman who suffered cardiopulmonary arrest due to fatal cibenzoline succinate poisoning. CHF, continuous hemofiltration; DHP, direct hemoperfusion; PE, plasma exchange.



**Fig. 2.** Electrocardiogram 40 min after weaning from direct hemoperfusion (DHP) (A) and 30 min after running DHP again (B) of a 51-year-old-woman who suffered cardiopulmonary arrest due to fatal cibenzoline succinate poisoning.

## DISCUSSION

**I**N THIS CASE, renal dysfunction was observed and hence we could not expect cibenzoline succinate excretion in the urine. Therefore, PE and DHP were undertaken with reference to previous published reports. We frequently measured the plasma cibenzoline succinate concentration to assess the removal efficiency of cibenzoline succinate with PE and DHP. We found that PE did not effectively decrease the plasma cibenzoline succinate concentration or improve the hemodynamics. Kashiwagi *et al.* reported limited efficiency of PE because their case did not involve renal

dysfunction.<sup>3</sup> However, we observed the same result with PE in our case involving renal dysfunction.

After DHP was run twice, the patient's clinical condition and electrocardiogram improved. Therefore, we initially speculated that DHP could effectively remove cibenzoline succinate. However, as shown in Figure 1, DHP did not effectively decrease plasma concentration of cibenzoline succinate. There was no increase in plasma cibenzoline succinate concentration after DHP completion, and the improvement in clinical symptoms before and after the start of DHP was likely transient. We think that the clinical condition of a fatal cibenzoline succinate poisoning is easy to

**Table 1.** Reported cibenzoline succinate poisoning treated with venoarterial extracorporeal membranous oxygenation

Primary author, year	Sex	Age (years)	Plasma concentration (ng/mL)	Outcome
Kashiwagi, 2016	Male	Teen	6,150	Survived
Ohata, 2010	Male	46	6,336	Dead
Nakamura, 2019	Male	38	4,095	Survived

change unless decreasing the plasma concentration, so we should be careful.

Extracorporeal cardiopulmonary resuscitation has been effective in the management of severe cibenzoline succinate poisoning (Table 1).<sup>3–5</sup> Apart from this patient, two other patients with cibenzoline succinate poisoning survived after management and were discharged. Recently, ECPR has been used for the management of poisoning by other drugs, with similar effectiveness.<sup>6,7</sup> In this case, our patient was discharged without any neurological and cardiac complications. Because V-A ECMO makes hemodynamics stable until the blood level of drugs decreases, ECPR is recommended for the effective management of acute fatal poisoning cases involving severe cardiac dysfunction and cardiac arrest.

In the reported cases, V-A ECMO was withdrawn safely after improvements in electrocardiogram in addition to stable hemodynamics, which indicate these improvements as an important parameter for withdrawing V-A ECMO.

In our case, there was temporary left ventricular dyssynchrony on echocardiography, Fujioka *et al.* reported a similar observation.<sup>8</sup> Although the mechanism of left ventricular dyssynchrony is not exactly clear, it can cause hemodynamic failure. Therefore, it might be important to confirm dyssynchrony recovery in the management of these patients.

With regard to limitations, many emergency departments cannot measure plasma concentrations of cibenzoline succinate and cannot accurately predict symptoms or drug concentrations after the rebound effect. Therefore, in cases of a high cibenzoline succinate concentration on admission and presentation of severe symptoms, it is preferable to monitor clinical conditions under V-A ECMO.

## CONCLUSION

POTENTIALLY FATAL CIBENZOLINE succinate poisoning along with cardiac dysfunction or cardiac arrest should be considered an indication of ECPR. Our patient's clinical condition appears to have improved following DHP,

but the effect of DHP on cibenzoline succinate poisoning could be transient. It is necessary to observe hemodynamics carefully until decreasing the plasma concentration of cibenzoline succinate.

Withdrawal of treatments or devices could be undertaken after confirming cardiac stability by electrocardiogram and echocardiography. This careful monitoring can be considered an important factor for successfully treating potentially fatal cibenzoline succinate poisoning.

## ACKNOWLEDGEMENTS

WE WOULD LIKE to thank Editage for providing assistance in English language editing.

## DISCLOSURE

Approval of the protocol: N/A.

Informed consent: Informed consent was obtained from the patient.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Data sharing and accessibility: N/A.

Conflict of interest: None.

## REFERENCES

- 1 Aoyama N, Sasaki T, Yoshida M *et al* Effect of charcoal hemoperfusion on clearance of cibenzoline succinate (Cifenline) poisoning. *J. Toxicol. Clin. Toxicol.* 1999; 37: 505–8.
- 2 Kurokawa Y, Watanabe T, Sano K *et al* Hemoadsorption and hemodiafiltration for cibenzoline poisoning; a case report (in Japanese). *J. Jpn. Soc. Dial. Ther.* 2003; 36: 1457–9.
- 3 Kashiwagi Y, Suzuki A, Tampo A *et al* A case of cardiac arrest caused by overdose of cibenzoline that was successfully treated with extracorporeal life support and plasma exchange therapy (in Japanese). *J. Jpn. Soc. Intensive. Care. Med.* 2016; 23: 43–7.
- 4 Ohata T, Ueda H, Yamada Y. Cibenzoline intoxication necessitating implantation of a biventricular assist system in a patient with severe cardiomyopathy. *Interact. Cardiovasc. Thorac. Surg.* 2010; 11: 95–7.
- 5 Nakamura T, Seki T, Nomura Y *et al* A case of cardiopulmonary arrest caused by overdose of cibenzoline that was successfully treated with extracorporeal membrane oxygenator (in Japanese). *J. Jpn. Assoc. Acute. Med.* 2019; 30: 50–6.
- 6 Wang GS, Levitan R, Wiegand TJ *et al* Extracorporeal membrane oxygenation (ECMO) for severe toxicological exposures: review of the Toxicology Investigators Consortium (Toxic). *J. Med. Toxicol.* 2016; 12: 95–9.

- 7 Lewis J, Zarate M, Tran S, Albertson T. The recommendation and use of extracorporeal membrane oxygenation (ECMO) in cases reported to the California Poison Control System. *J. Med. Toxicol.* 2019; 15: 169–77.
- 8 Fujioka K, Hayashi K, Tada H *et al* A case of cibenzoline toxicosis resulted in cardiopulmonary arrest showing remarkable left ventricular dyssynchrony (in Japanese). *Heart* 2011; 43: 87–92.