症 例 報 告

Benzalkonium chloride intoxication caused by intravenous self-injection

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——Summary——(Jpn J Clin Toxicol 2014；27：327-332)

Background：Benzalkonium chloride (BZK) is widely used as a germicide in hospitals and other places. Although several cases of accidental oral intake of BZK have been reported, there have been few reported cases of BZK toxicity due to intravenous injection.

Case report：A male nurse in his 40 s injected 15 mL of 10% BZK (Osvan S) directly into his left antebrachial vein while at home, as a suicide attempt. The patient was admitted to our hospital 1 hour later. Acute respiratory distress syndrome (ARDS) was diagnosed by blood gas analysis, chest X-ray, and CT scan. Due to extracorporeal blood purification therapy, including hemoperfusion and plasma exchange, serum BZK became undetectable. However, the ARDS was not improved. Extracorporeal blood purification therapy consisting of continuous hemodiafiltration (CHDF) was continued to treat the ARDS. After performing CHDF for the next 36 hours, improvement of both the PaO_2/FiO_2 ratio and chest X-ray findings was noted. Tracheal extubation was performed on day 9 and no further complications occurred after this period, he was discharged on day 21.

Conclusion：Extracorporeal blood purification therapy is probably effective for treatment of BZK intoxication by intravenous injection.

Key words：benzalkonium chloride, acute respiratory distress syndrome, extracorporeal blood purification therapy, plasma exchange, continuous hemodiafiltration

Introduction

Benzalkonium chloride (BZK) is a cationic detergent, like other quaternary ammonium compounds, and is widely used as a germicide and preservative in hospitals and other places. In Japan, many pharmaceutical products containing BZK can be purchased over-the-counter. BZK is also used as a disinfectant for hospital utensils and other environmental surfaces and for the disinfection and storage of catheters in critical care settings[1)]. Many cases of poisoning due to accidental or intentional intake of household products containing significant amounts of BZK have been reported[2)3)]. However, reported cases of intoxication due to intravenous injection of BZK are rare[4)]. *In vivo* toxicity studies have demonstrated that BZK is 10 to 20 times more toxic when given intravenously than orally[5)]. In the critical care setting, there have been many cases involving the use of germicides, including BZK. For successful treatment of patients intoxicated with BZK, it is important to understand the usual clinical course. To our knowledge, this is the

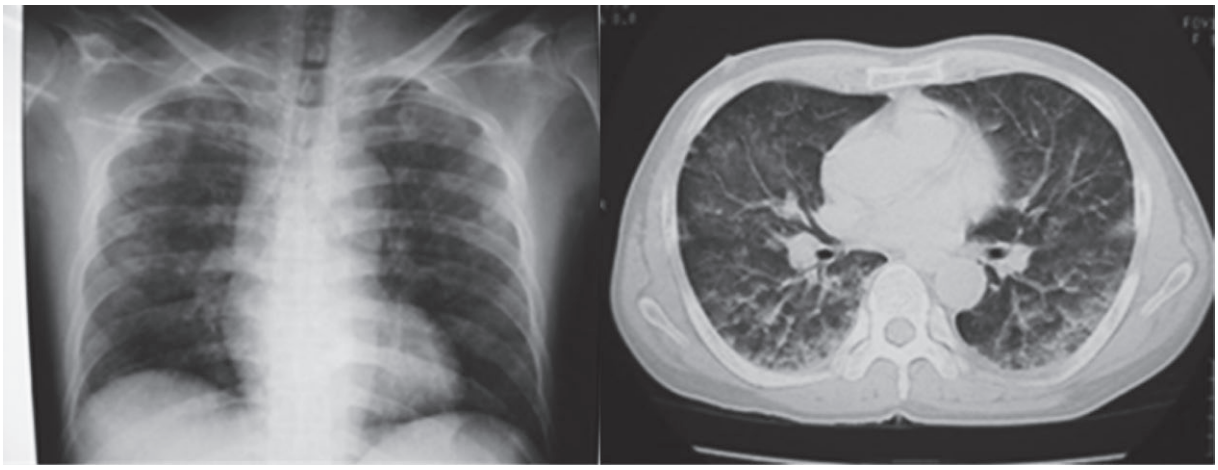

Fig. 1 Chest X-ray (left) shows ground-glass opacity and CT (right) shows ground-glass opacity with bronchial dilatation

first report to present in detail the clinical course of, and treatment for, intravenous BZK intoxication.

Case report

A male nurse in his 40 s injected 15 mL of 10% BZK (Osvan S；Nihon Pharmaceutical Co., Ltd., Tokyo, Japan) directly into his left antebrachial vein while at home. He had a history of depressive illness. After BZK injection, there was immediate shortness of breath. One hour after the injection, he was transferred to our emergency department by ambulance. On arrival, the chief complaint was shortness of breath. Vital signs were as follows：blood pressure 160/126 mmHg, heart rate 82 beats per minute, respiratory rate 18 breaths per minute, and temperature 36.2℃. The initial blood gas analysis showed a pH of 7.413, $PaCO_2$ of 41.9 mmHg, and PaO_2 of 109 mmHg on 100% oxygen. The Glasgow Coma Scale score was 15. Physical examination revealed no heart murmurs. An injection puncture wound was identified over the left antebrachial vein. The urine was brownish in color, and urinalysis revealed hemoglobinuria. The chest X-ray showed bilateral ground-glass opacity and chest CT showed bilateral ground-glass opacity with bronchial dilatation, indicating acute respiratory distress syndrome (ARDS)[6] (**Fig. 1**). Neither renal nor heart failure was detected. Laboratory data included normal creatine phosphokinase and creatinine levels, which suggested normal renal function. The plasma BZK level at admission was 1.1 μg/mL, as measured by high performance liquid chromatography[7]. The patient was admitted to the intensive care unit. At the time of his admission, it was unknown whether extracorporeal blood purification therapy would effectively remove the BZK, but because the level far exceeded the presumed lethal dose, we thought that there was no other treatment option. After obtaining informed consent, we attempted to reduce the concentration of BZK through the use of extracorporeal blood purification therapy. As the first step, direct charcoal hemoperfusion was performed for 1 hour. The plasma BZK concentration declined to 0.11 μg/mL (**Fig. 2**). However, the shortness of breath continued and the patient's PaO_2 and chest X-ray findings worsened (**Fig. 3B**). Moreover, despite the charcoal hemoperfusion, the ARDS continued, necessitating tracheal intubation. Bilevel positive airway pressure was administered. Following the charcoal hemoperfusion, the patient underwent plasma exchange for approximately 4 hours. The BZK level in the plasma waste was 5.38 μg/mL, with a total BZK amount of 20.4 mg. Although plasma BZK became undetectable after the plasma exchange, the PaO_2/FiO_2 ratio (P/F ra-

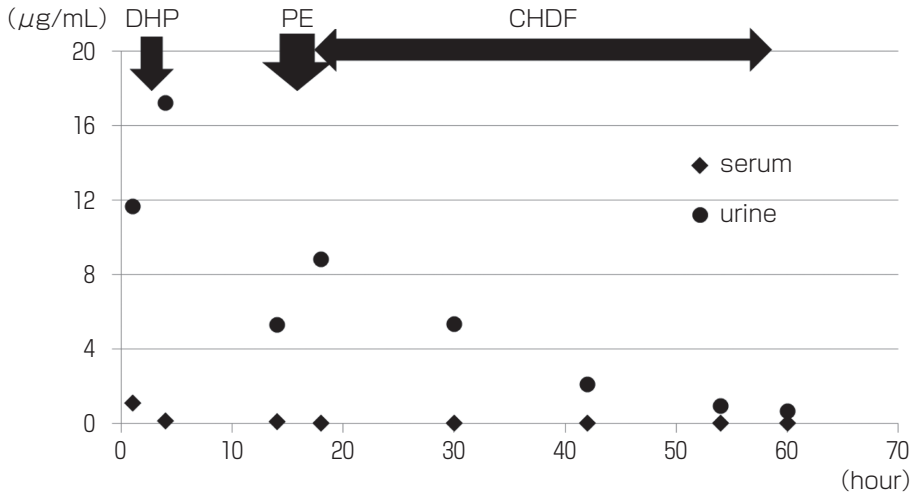

Fig. 2 Changes in BZK concentrations in serum and urine samples after intravenous injection of BZK

DHP：direct charcoal hemoperfusion, PE：plasma exchange, CHDF：continuous hemodiafiltration

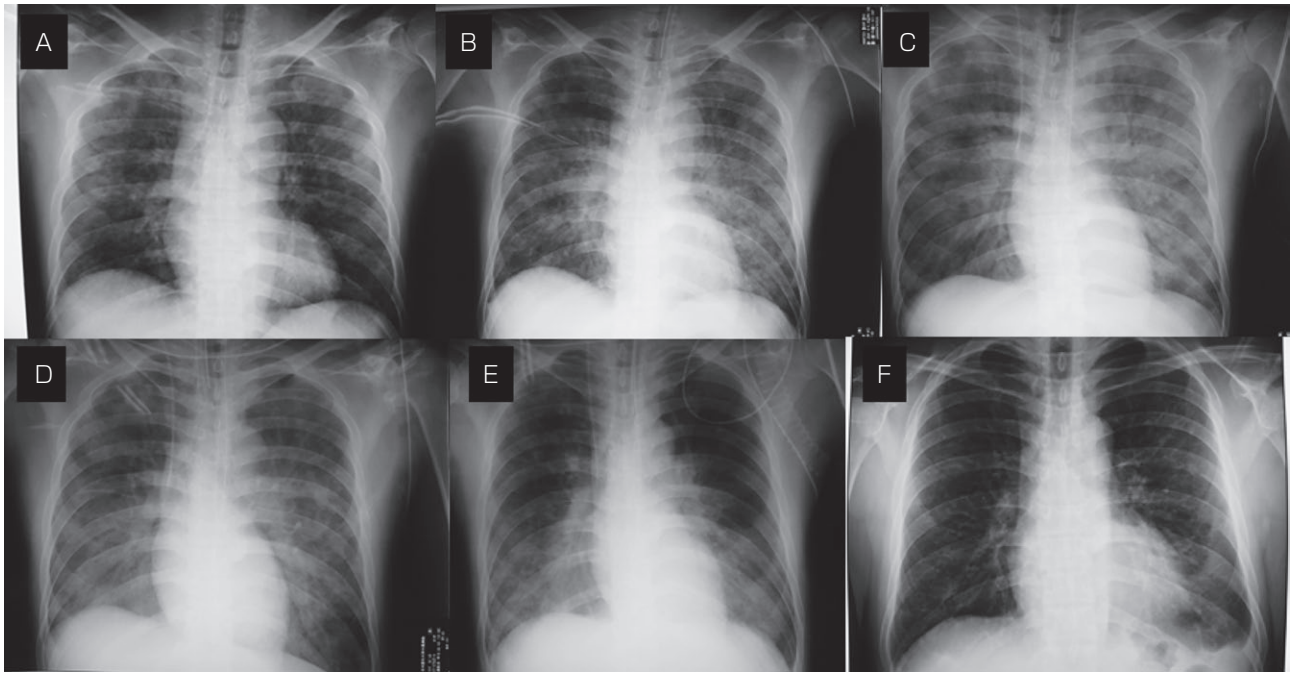

Fig. 3

A：Chest X-ray on admission shows the presence of pulmonary nodules with ground-glass opacity
B：Chest X-ray after direct charcoal hemoperfusion shows increased ground-glass opacity
C：Chest X-ray after plasma exchange shows the ground-glass opacity has increased further
D：Chest X-ray after continuous hemodiafiltration shows slight improvement
E：Chest X-ray obtained on day 4 shows reduction of the ground-glass opacity
F：Chest X-ray on day 9 shows further improvement

tio) remained low (**Fig. 4**) and the chest X-ray findings worsened (**Fig. 3C**). Approximately 18 hours after BZK self-injection, continuous hemodiafiltration (CHDF), using a cytokine-adsorbing hemofilter with a membrane made of polymethyl methacrylate (PMMA), was begun. During the CHDF, the BZK level in the CHDF waste was 0.12 μg/mL at 7 hours and 0.26 μg/mL at 18 hours. After 42 hours of CHDF, the chest X-ray findings (**Fig. 3D**) and P/F ratio improved, so the extracorporeal blood purifica-

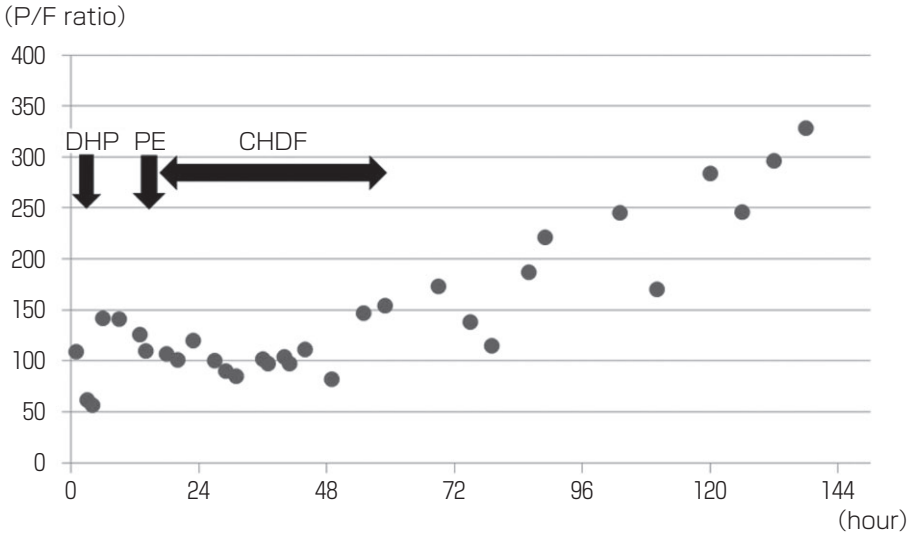

Fig. 4 Time course of changes in the P/F ratio following extracorporeal blood purification therapy for intravenous injection of BZK

DHP：direct charcoal hemoperfusion, PE：plasma exchange, CHDF：continuous hemodiafiltration

tion therapy was discontinued. Other therapeutic measures were employed, including mechanical ventilatory support, management to maintain appropriate fluid balance, and administration of anti-inflammatory agents such as the neutrophil elastase inhibitor sivelestat. On day 4, improvement was observed in both the P/F ratio and chest X-ray findings, the P/F ratio was＞300 (**Fig. 3E**). No complications, such as pneumonia, renal dysfunction or multiple organ failure, occurred during treatment of this patient. Tracheal extubation was performed on day 9 (**Fig. 3F**), and no further complications occurred after this period, he was discharged on day 21.

Discussion

It is well known that BZK is considerably harmful to biological membranes. BZK may change the permeability of the cellular membrane[8] and stimulate chemotaxis and chemokinesis of human neutrophils[9]. As a result, BZK can cause cytolysis that may lead to organ destruction and subsequent death[10]. Acute toxicity studies in mice and rats have demonstrated that intravenously administered BZK is 10 to 20 times more toxic when compared with orally administered BZK. The LD_{50} of oral and intravenous BZK in rats was reported to be 234–525 mg/kg and 14 mg/kg, respectively. In humans, both an oral dose of 100–400 mg/kg and a parenteral dose of 5–15 mg/kg are thought to be fatal[11]. The current patient, 60 kg in weight, injected 1,500 mg BZK, far exceeding the presumed lethal dose.

Current treatments for BZK poisoning are based on information that has been obtained from cases of oral intake, but not intravenous injection. The toxic effects of BZK have been shown to depend on the route of administration[12]. Rapid fatality was observed in rats when BZK was injected into the jugular vein, while delayed fatality occurred soon after intrafemoral arterial injection or oral administration. It has also been reported that BZK rapidly accumulated in the lungs after intravenous administration of the compound to rats[7]. In the current case, shortness of breath occurred immediately after intravenous injection of BZK, which may have been due to accumulation in the lungs. On admission, the patient's chest X-ray revealed signs presumably due to BZK toxicity within the lungs. This toxicity may have been associated with impairment of endothelial function in the pulmonary vascular bed, which would result in vascular permeability and inflammation. The therapeutic

options for severe acute respiratory failure include mechanical ventilation, recruitment maneuvers, supportive treatment, pharmacologic agents, and extracorporeal techniques[13]. It has been reported that CHDF using a cytokine-adsorbing hemofilter with a membrane made of PMMA was effective in treating a patient with ARDS[14]. However, the best method for effectively removing BZK remains unknown. In the present case, we could not determine whether the charcoal hemoperfusion was effective because BZK was excreted at high concentrations in the urine (**Fig. 4**). However, the extracorporeal blood purification therapy, including plasma exchange, was probably effective in removing the BZK, because a substantial amount was detected in the plasma. During the CHDF, BZK was detected in the waste material, although the plasma BZK was not detectable. In addition, the BZK level in the CHDF waste was low compared with the plasma exchange level. These results indicate that the volume of distribution of BZK and the rate of BZK binding to protein were probably high；there have been no previous reports regarding the volume of distribution and protein binding of BZK. On the other hand, we believe that the combination of therapies used (CHDF using PMMA, mechanical ventilatory support, attention to fluid balance, and administration of the anti-inflammatory agent) were effective for treatment of the ARDS. Extracorporeal blood purification therapy is probably effective not only for BZK removal, but also for treatment of the ensuing respiratory failure. Intravenous infusion of BZK can cause severe respiratory failure and even death. The current case report may be of help to others during attempts to treat similar cases in the future.

Conclusion

The use of extracorporeal blood purification therapy was probably effective in this case of BZK intoxication by intravenous injection. Extracorporeal blood purification therapy is likely to be effective not only for BZK removal, but also for treatment of the ensuing ARDS.

Disclosure

The authors declare no conflicts of interest.

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要 旨

背景：塩化ベンザルコニウム（BZK）は病院内を含め消毒液として広く使用されている。誤飲による症例報告は多いが，静脈内注射による中毒例はほとんどみられない。

症例：40歳代，男性看護師。自宅で10% BZK（オスバンS®）を15 mL，自殺企図にて左前腕から静脈注射し，呼吸困難にて自ら救急車要請した。来院時BZK注射から1時間経過していた。血液ガス分析，胸部X線，CTなどより急性呼吸促迫症候群（ARDS）と診断された。来院後血液吸着，血漿交換などの体外循環による血液浄化法により血中のBZKは検出されなくなったが，ARDSの改善は認められず，続いて持続的血液濾過透析（CHDF）を施行した。CHDF開始36時間後よりPaO_2/FiO_2，胸部X線は改善傾向となった。第9病日に抜管，合併症もなく第21病日退院となった。

結論：静脈注射によるBZK中毒に対して，体外循環による血液浄化法は有効である可能性がある。