CASE REPORT

Phlebitis as a consequence of peripheral intravenous administration of cisatracurium besylate in critically ill patients

Annelijn M Meeder, Marijke S van der Steen, Annemieke Rozendaal, Arthur R H van Zanten

Department of Intensive Care, Gelderse Vallei Hospital, Ede, The Netherlands

Correspondence to
Dr Arthur RH van Zanten,
ZantenA@zgv.nl

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SUMMARY

This case report series describes 3 cases of cisatracurium besylate associated phlebitis after an infusion period of 14–20 hours. No similar cases have been reported in the literature. Association of phlebitis with another neuromuscular blocking agent, atracurium, has been described in the literature. The acidity of atracurium is thought to be the main cause. It is recommended that atracurium is administered only via central venous catheters when indicated to infuse over prolonged periods of time due to the acidity. Cisatracurium is a stereoisomer of atracurium and as such has the same molecular weight. Although cisatracurium also has a similar acidity as atracurium, a recommendation concerning infusion via a central venous catheter is lacking. We suggest prolonged administration of cisatracurium besylate only via centrally placed venous catheters or if not possible to carefully monitor relevant peripheral intravenous sites to diminish the risks of phlebitis and associated complications or other cutaneous reactions.

BACKGROUND

Cisatracurium besylate, a non-depolarising neuromuscular blocking agent, is frequently used in the intensive care unit (ICU). It is administered in order to induce muscle relaxation to facilitate mechanical ventilation in critically ill patients not sufficiently responding to sedatives and analgesics alone. Clinical indications include acute respiratory distress syndrome, therapeutic hypothermia, increased intracranial pressure and high intra-abdominal pressure.^{1 2} Several side effects of cisatracurium besylate have been reported, including bradycardia, bronchospasm, tachyphylaxis and new-onset critical illness polyneuropathy. In a comprehensive literature review on use of the cisatracurium in critically ill patients the overall incidence of cisatracurium besylate-related adverse events was 2.4%.³ Few studies have reported adverse skin reactions.^{2 4} At present phlebitis after the infusion of cisatracurium besylate has not specifically been reported. Phlebitis is a clinical diagnosis that denotes the presence of inflammation involving a vein, with clinical symptoms as pain, tenderness, warmth, erythema and induration. Although infusion phlebitis is generally benign and self-limiting, propagation into a deep vein thrombosis or bloodstream infection may occur.⁵ Recently we encountered several cases of cisatracurium

besylate-associated phlebitis within 48 hours of ICU admission, while on admission new intravenous catheters had been placed.

CASE PRESENTATION

Case 1

A 73-year-old man was admitted to the ICU and invasively mechanically ventilated for an exacerbation of chronic obstructive pulmonary disease (COPD) and hypercapnic respiratory failure. Despite deep sedation and medication to reduce bronchospasm the patient was difficult to ventilate. Continuous infusion of cisatracurium besylate was administered through a peripheral intravenous catheter with an infusion rate up to a maximum rate of 3.0 µg/kg/min. Phlebitis was clinically diagnosed after 14 hours of continuous infusion (depicted in [figure 1](#)). No other medications were infused through this cannula, except for NaCl 0.9% continuously infused at a rate of 5 mL/hour. After the clinical diagnosis of phlebitis the intravenous catheter was removed and the phlebitis disappeared spontaneously within 4–5 days, without any other sequelae.

Case 2

A 74-year-old woman was admitted to our ICU for haemorrhagic shock after a ruptured abdominal aortic aneurysm. After open surgical repair this patient developed abdominal compartment syndrome. Cisatracurium besylate was started in order

Figure 1 Photograph of the first intensive care unit patient showing signs of phlebitis after the administration of cisatracurium besylate. A 73-year-old man showing signs of phlebitis on his left arm after 14 hours of administration of cisatracurium besylate.

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Figure 2 Photograph of the second intensive care unit patient showing signs of phlebitis after the administration of cisatracurium besylate. A 73-year-old woman showing signs of phlebitis on her left arm after 20 hours of administration of cisatracurium besylate.

to lower abdominal pressures and to facilitate mechanical ventilation. Cisatracurium besylate was infused through a peripheral intravenous catheter. After an initial bolus dose of 4 mg, the infusion rate was set at 1.0 µg/kg/min. Phlebitis was diagnosed after 20 hours of cisatracurium infusion (depicted in [figure 2](#)). Before this, only insulin was administered through this cannula without any clinical signs of phlebitis. After the removal of the cannula the phlebitis disappeared spontaneously within 5 days, without any complications.

Case 3

A 77-year-old woman was admitted to the ICU for respiratory failure due to exacerbation of COPD. To facilitate slow normalisation of hypercapnia complicated by persistent respiratory drive, despite deep sedation cisatracurium besylate was added. The infusion rate on a peripheral intravenous catheter varied from 1.5 to 3.0 µg/kg/min. Phlebitis was clinically diagnosed after 18 hours of cisatracurium besylate infusion (depicted in [figure 3](#)). No other medications were infused through this intravenous catheter. After the removal of the intravenous catheter the phlebitis disappeared spontaneously within 5 days.

Figure 3 Photograph of the third intensive care unit patient showing signs of phlebitis after the administration of cisatracurium besylate. A 77-year-old woman showing signs of phlebitis on his left arm after 18 hours of administration of cisatracurium besylate.

INVESTIGATIONS

The intravenous catheters were cultured. No peripheral intravenous catheter-related bacteraemia was found in any of the cultures.

DIFFERENTIAL DIAGNOSIS

Phlebitis is a common complication of the insertion of a peripheral intravenous catheter. The inflammation of the vein could be of mechanical, chemical or bacterial origin. The incidence of peripheral venous catheter-related phlebitis varies between 1.5% and 60%.⁶ The intravenous catheters were placed on admission of the patients to the ICU. First signs of phlebitis were shown within 48 hours of admission.

TREATMENT

Infusion of cisatracurium besylate was stopped. The intravenous catheter was removed and the site of phlebitis was carefully monitored during the following days.

OUTCOME AND FOLLOW-UP

In all cases, after the removal of the intravenous catheter the phlebitis disappeared spontaneously within a few days.

DISCUSSION

To the best of our knowledge, these are the first cases documenting the association of continuous infusion of the neuromuscular blocker cisatracurium besylate through a peripheral venous access and local phlebitis. Cutaneous reactions have only been reported in few studies, and frequently the exact nature of the skin reactions is not described.^{2 4}

Factors such as pH and osmolarity of dissolved intravenous drugs may confer significant effects on the incidence of phlebitis.⁷ Common causative agents of chemical phlebitis include potassium chloride, diazepam, antibiotics (eg, vancomycin and oxacillin), chemotherapy agents, and hypotonic (<250 mOsm/kg) or hypertonic (>350 mOsm/kg) electrolyte solutions.⁸

Association of phlebitis with the neuromuscular blocking agent atracurium has been reported earlier. In a study of 33 patients requiring neuromuscular blockade for ventilation in the ICU, using atracurium via a peripheral vein, phlebitis was observed in two patients.⁹ Both atracurium and cisatracurium are non-depolarising muscle relaxants from the benzylisoquinoline family that undergo degradation in plasma at physiological pH and temperature by organ-independent Hofmann elimination.¹⁰ Cisatracurium is a stereoisomer of atracurium and as such has the same molecular weight.¹¹ As the pH of dissolved atracurium is 3.5, the acidity of atracurium is thought to be the main cause of phlebitis of peripheral veins. Therefore, it is recommended to administer atracurium only via central venous catheters when indicated to infuse over prolonged periods of time.⁹ However, with respect to cisatracurium besylate this recommendation is lacking, although cisatracurium has a similar acidity (pH of 3.25–3.65).¹²

All intravenous catheters were placed in the upper extremity. According to several studies phlebitis is more common when the catheter is inserted in the lower extremities. No statistically significant differences were observed between the specific anatomical site used on the upper extremity, for example, hand, forearm or wrist.

Furthermore, typical sizes (18–20 gauge) of intravenous cannulas were used. A larger size of catheter has been implicated as a risk factor in the pathogenesis of phlebitis, although several studies did not find a significant relationship between size and phlebitis.^{13 14}

The occurrence of three cases of cisatracurium besylate-associated phlebitis was reported to the pharmaceutical company that supplies the cisatracurium besylate and to the relevant healthcare authorities. The batch numbers of the medication were checked for quality control, but no abnormalities were noticed in these particular batches. Therefore, it is unlikely that the phlebitis was a result of a problem in the manufacturing process of cisatracurium besylate.

In two of the cases the only drug that was administered through the intravenous catheter was the cisatracurium besylate. In case 2 also only insulin had been infused through the intravenous catheter; however, clinical signs and symptoms of phlebitis only started after the infusion of cisatracurium besylate.

Learning points

- ▶ Cisatracurium besylate is a non-depolarising neuromuscular blocking agent that is frequently used in the intensive care unit.
- ▶ Peripheral intravenous administration of cisatracurium besylate in critically ill patients may be associated with phlebitis.
- ▶ The use of centrally placed venous catheters in case of prolonged administration of cisatracurium besylate should be considered and careful monitoring of relevant peripheral intravenous sites is recommended to diminish the risks of phlebitis and associated complications or other cutaneous reactions.

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