Letter to the Editors

Instantaneous rigor after fatal pholcodine intoxication

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Introduction

Pholcodine is a commonly used antitussive medication. In France, its use is limited because of the risk of an allergic cross-reaction with curare. Here we report the case of a 52-year-old man who ingested 750 mg of pholcodine syrup. An emergency medical team found him at home in nonshockable cardiac arrest. Orotracheal intubation was impossible because of instantaneous rigor associated with trismus, so an emergency cricothyrotomy was performed. Return of spontaneous circulation was obtained 5 min later. Cardiac arrest recurred upon arrival at the intensive care unit, leading to death. Toxicological analysis showed a pholcodine blood level of 2500 ng mL⁻¹ (a lethal dose is >1000 ng mL⁻¹, extrapolated from animal studies). Pholcodine is an opioid derivate with a central antitussive effect that is indicated for unproductive cough in adults. No case of fatal intoxication has ever been reported. We hypothesize that cardiac arrest was the result of hypoxia due to respiratory arrest connected to the opioid nature of pholcodine. Interestingly, instantaneous rigor occurred, which should be not confused with rigor mortis. Instantaneous rigor is a rarely reported condition that persists until rigor mortis and disappears in the stage of secondary flaccidity. Instantaneous rigor can lead to trismus, making orotracheal intubation impossible and necessitating emergency cricothyrotomy. This case shows that pholcodine overdose can be lethal and can lead to instantaneous rigor.

Case report

Pholcodine is one of the most commonly used antitussive medications [1]. In France, its use is limited due to the risk of allergic cross-reaction with curare [2–4]. Here we report the first fatal case of pholcodine overdose. The overdose resulted in instantaneous rigor (IR) that necessitated emergency cricothyrotomy.

A 52-year-old male patient with a past medical history of hypertension and dyslipidaemia was treated with antitussive syrup for viral bronchitis. His family reported that

he drank three bottles of antitussive syrup, each containing 250 mg of pholcodine, in 2 h. One hour after the last bottle, he felt uncomfortable and complained of dyspnoea. His wife called the emergency medical system, and upon arrival, the emergency medical team found the patient in nonshockable cardiac arrest (asystole). Cardiopulmonary resuscitation (CPR) was started immediately, with an estimated no-flow duration of ~10 min. Orotracheal intubation was impossible because of generalized rigidity associated with trismus. Despite the use of 90 mg of succinylcholine followed by 12 mg of vecuronium, the rigidity remained. An emergency cricothyrotomy was performed 8 min after the start of CPR, and return of spontaneous circulation occurred 5 min later. A total of 5 mg of epinephrine was used. The patient was transferred to an intensive care unit. On arrival, the patient was haemodynamically unstable, with a mean arterial pressure of 50 mmHg despite 10 mg h⁻¹ epinephrine. Forty minutes later, cardiac arrest occurred again and resulted in the patient's death despite advanced life support measures. After agreement of the next of kin, a forensic autopsy was performed that confirmed pholcodine intoxication. Toxicological analysis showed a pholcodine blood level of 2500 ng mL⁻¹. Notably, therapeutic doses are 20–80 ng mL⁻¹, toxic doses are >100 ng mL⁻¹ and lethal doses are >1000 ng mL⁻¹ (extrapolated from animal studies) [1, 5].

Pholcodine is an opioid derivate with a central antitussive effect that is indicated for unproductive coughs in adults. In France, pholcodine became available only by prescription in 2011, and prescriptions of pholcodine are limited [2]. Indeed, recent data suggest that pholcodine may increase the occurrence of allergic reactions to curare due to cross IgE sensitization [3, 4]. However, no cases of fatal intoxication have ever been reported. We hypothesize that the cardiac arrest in this patient was hypoxia related, due to respiratory arrest connected to the opioid nature of the drug, because opioids can lead to respiratory depression. Previous human studies have never shown pholcodine to have opioid-like side-effects, although some studies demonstrate that 0.5–1% of the ingested pholcodine dose is metabolized to morphine via

cytochrome P450 (CYP) 2D6 [6, 7]. In this case, we cannot formally exclude a CYP2D6 overexpression leading to an overproduction of morphine (>1%) causing the cardiac arrest. However, a direct effect of pholcodine is the most likely mechanism. This mechanism has not yet been described in humans, but dosage studies in animals show that higher doses of pholcodine can have the same adverse effects as morphine, including reductions in respiratory rate and tidal volume that lead to respiratory depression and hypoxia [1, 8].

In addition to causing respiratory arrest, in this case pholcodine overdose also led to IR, which is not to be confused with rigor mortis (RM). The exact pathophysiology of IR remains unknown but seems to be similar that RM, i.e. adenosine triphosphate depletion in muscles, with actin and myosin complexes entering into a nonmoveable state, causes stiffening of all the muscles in the body. Instantaneous rigor differs from RM in that it is a rarely reported condition that occurs at the time of cardiac arrest and most often in cases of violent death. Rigor mortis begins 2–6 h after death. The reason that this condition should not be confused with RM is that return of spontaneous circulation is still possible after CPR, as in the present case and in another reported case [9]. Rigor mortis is one of the signs of irreversible death that contraindicates CPR [10]. Here, IR did not disappear after the use of depolarizing curare or after the use of intermediate-acting nondepolarizing curare, probably because curares do not act directly on actin and myosin complexes [9]. Instantaneous rigor can lead to trismus by affecting the temporomandibular joint, which makes orotracheal intubation impossible. According to the French guidelines, an emergency cricothyrotomy must be performed as soon as possible when intubation is impossible in order to oxygenate the patient [11].

In conclusion, this case has two interesting features. First, it shows that pholcodine must be used carefully, because massive overdose can be lethal. Second, it illustrates that IR, while a rare condition, should not be confused with RM; in the event of IR, CPR must be started as soon as possible and may require emergency cricothyrotomy.

Competing Interest

There are no competing interests to declare.

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RECEIVED

6 February 2013

ACCEPTED

4 June 2013

ACCEPTED ARTICLE PUBLISHED ONLINE

17 June 2013

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