Physostigmine use in clozapine intoxication from adulterated heroin: an atypical toxidrome with an effective antidote

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ABSTRACT
Anticholinergic toxicity results from a multitude of toxins and other agents. Clozapine is an uncommon cause. We describe a case of anticholinergic toxicity secondary to acute clozapine overdose from adulterated heroin with successful reversal by physostigmine. We highlight how the case presented, unique departures from the typical anticholinergic toxidrome in clozapine overdose and the benefits of using physostigmine in our patient.

KEYWORDS
Clozapine intoxication; physostigmine; heroin adulteration; emergency medicine; antipsychotic overdose; anticholinergic toxicity

Introduction
Anticholinergic toxicity is responsible for up to 40% of poisoning admissions to medical intensive care units [1]. Clozapine is a rare cause of such toxicity. Physostigmine is a recognized antidote for central and peripheral signs and symptoms of the anticholinergic toxidrome, though it remains underused. Herein, we report successful reversal of anticholinergic toxicity from clozapine overdose from adulterated heroin. The last similar case appeared almost 40 years ago [2]. A physostigmine given in the emergency department may avoid intubation and medical intensive care unit admission in a patient with anticholinergic toxicity [3]. Thus, we submit that physostigmine is an appropriate antidote for anticholinergic toxicity from clozapine overdose.

Case 1
A 37-year-old man with a history of major depression, chronic hepatitis C, and polysubstance abuse (coca in, benzodiazepine, heroin, opioids, and alcohol) was unresponsive on the street. Paramedics observed coarse breath sounds and “dry heaving,” and they found a pink powder nearby. He received naloxone 0.5 mg intramuscularly, then 1 mg intravenously without effect and promptly transported to the emergency department for further evaluation and treatment.

Initial vital signs showed tachycardia to 124 beats per minute, blood pressure of 122/78 mmHg, respiratory rate of 10 breaths/min, temperature of 96.8°F, and oxygen saturation of 93% on 15 L/min by non-rebreather mask. He moved but did not withdraw to noxious stimuli. He had no signs of trauma on examination. Cardiac, pulmonary, and abdominal examinations were benign. His skin was warm and dry, his muscle tone normal, and he displayed no clonus.

He underwent endotracheal intubation for airway protection in the emergency department. He required no sedation after intubation. Laboratory investigations showed CK of 978 U/L, lactate of 2.3 mmol/L, and mild elevation of aspartate transaminase and alanine transaminase of 87 and 73, respectively. Urine immunoassay was positive for benzodiazepines but was negative for amphetamines, tetrahydrocannabinol, cocaine, and opiates. Non-contrast computed tomography of the head showed no acute intracranial abnormality. The medical ICU accepted the patient for further care.

The toxicology service evaluated the patient in the ICU on hospital day 1 and noted miosis bilaterally, mouth secretions requiring repeated suctioning, minimal bowel sounds, and relaxed muscle tone. His mental status improved over the next 24 h and he was extubated without complication on hospital day 2. He was transferred to the medicine/psychiatry unit that day.
Discussion

The primary mechanism underlying anticholinergic toxicity is competitive acetylcholine receptor antagonism. Most common anticholinergic toxins act primarily on muscarinic receptors, moreso than nicotinic receptors. The delirium results from blockade of the M1 receptors found in the CNS [1,4]. Other muscarinic receptors include the M2 receptors in the brain and heart, M3 in the salivary glands, and M4 in the brain and lungs [1].

Signs and symptoms of anticholinergic toxicity stem from antagonism of peripheral and central muscarinic receptors. Peripheral signs and symptoms include dry mouth, dysphagia, blurry vision, photophobia, dry skin, decreased or absent bowel sounds, urinary retention, sinus tachycardia, and fever. Central signs and symptoms include agitation, delirium, incoherent speech, visual and/or auditory hallucinations and a characteristic picking behavior in which a patient often picks at objects that may or may not actually be present in their vicinity [1]. Our patient displayed small pupils, which may have been “spiked” with benzodiazepines. His vital signs normalized and his mental status continued to improve over the next two days and he was discharged on hospital day 4.

Physostigmine is a short-acting acetylcholinesterase inhibitor, which increases synaptic concentrations of acetylcholine for competition with the toxic muscarinic antagonist for the acetylcholine receptor. It is a tertiary amine, allowing for crossing of the blood brain barrier for reversal of central antimuscarinic effects [1,11]. Its first documented use for reversing anticholinergic delirium was in 1864 by Kleinwachter, who treated patients that had mistakenly consumed atropine [1,12,13]. Physostigmine has successfully reversed agitation in a procyclidine overdose [14], postanesthetic delirium attributed to atropine premedication [15], and anticholinergic toxicity in a massive ingestion of atropine eye drops after which the use of physostigmine apparently obviated the need for intubation [3]. A retrospective study of 52 patients referred to a toxicology consulting service found physostigmine to be more effective and safer than benzodiazepines for treatment of anticholinergic poisoning [16–18]. Consensus panel guidelines recommend hospitals that provide emergency care stock physostigmine [1]. When dosed appropriately, however, most patients who receive physostigmine in the ED require only a single dose [11]. To avoid toxicity and prevent unnecessary redosing, recent recommendations suggest a single dose of 0.5 to 1 mg of physostigmine given intravenously with a minimum delay of 10–15 min before redosing [1].

In 1977, Schuster et al. reported the use of physostigmine in two cases of clozapine overdose [2]. The first involved a 25-year-old woman with mania who developed delirium, hypersalivation, and tachycardia while receiving clozapine for sedation. The second involved a 26-year-old male who ingested 3 g of clozapine in a suicide attempt. He also developed delirium, was agitated and displayed hypersalivation and tachycardia. Both patients received 2 mg of physostigmine by slow intravenous injection with rapid reversal of delirium. Both had recurrence of delirium, and the first patient received subsequent doses of physostigmine that resolved her anticholinergic toxicity [2].
Our patient displayed both central and peripheral signs of antimuscarinic toxicity from clozapine. These symptoms persisted for days after initial resuscitation and extubation and, not surprisingly, did not improve with the use of benzodiazepines. Clozapine was likely an adulterant or co-ingestant, as comprehensive drug screening later confirmed. He responded rapidly to physostigmine administration with rapid reversal of delirium and agitation without side effects. Had he received physostigmine in the ED, he may have avoided intubation and intensive care unit admission.

In a large series of 1197 patients treated with physostigmine, Rasimas et al. observed isolated seizures in two patients [21]. One patient received physostigmine for anticholinergic symptoms after overdose of clozapine and trifluhenazine, had a favorable response to physostigmine before having a brief seizure lasting 25 sec. The other patient had a history of epilepsy with sub-therapeutic concentrations of prescribed anti-epileptic medication. He had an overdose of quetiapine, had a favorable response to physostigmine before having a single, brief seizure lasting 20 sec. Neither patient had received a benzodiazepine before physostigmine. Patients with overdoses of epileptogenic drugs should receive lorazepam prior to physostigmine [21].

Clozapine is a rare but potentially significant cause of anticholinergic toxicity. This case illustrates that physostigmine is an appropriate antidote for anticholinergic toxicity from clozapine overdose. If used early in the course of intoxication, physostigmine may prevent need for intubation and intensive care unit admission.

Disclosure statement
Nothing to report.

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