TOXICOLOGY: AN AUSTRALIAN PERSPECTIVE

Toxicology case of the month: carbamazepine overdose

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A 29-year-old woman presents shortly after a massive overdose of carbamazepine controlled-release tablets. In anticipation of coma, she is electively intubated to safely enable gastrointestinal decontamination with nasogastric activated charcoal. She is admitted to the intensive care unit for ongoing supportive care, and further doses of activated charcoal are prescribed to enhance elimination of carbamazepine. Carbamazepine levels remain high and haemodialysis is carried out to further enhance elimination. Her coma resolves as levels fall, but clinical progress is complicated by anticholinergic delirium, ileus and bowel obstruction from charcoal concretions. She survives to medical discharge on day 12.

This is the third in a series of cases presented by the Western Australian Toxicology Service. The cases are selected because of their relevance to emergency medicine practice and emphasise the importance of risk assessment in formulating a coherent management plan for a patient with acute poisoning (box 1). These principles were discussed in depth in the introductory article for this series.

CASE REPORT

A 29-year-old woman weighing 50 kg absconded from a nearby psychiatric hospital earlier in the day. She is brought to the emergency department by a concerned relative 1 h after ingesting 200 × 200 mg carbamazepine CR tablets. On presentation, she is alert and cooperative. Her vital signs are as follows: pulse rate 70 beats/min, blood pressure 110/70 mm Hg, respiratory rate 14/min and temperature 36.4°C.

Resuscitation

There are no immediate resuscitation issues.

Risk assessment

Carbamazepine is an anticonvulsant agent that is also increasingly prescribed as a mood stabiliser. The clinical features of toxicity after acute overdose are dose related and correlate well with serum levels. They are predominantly neurological and usually of delayed onset because of delayed and erratic absorption of the drug. Ingestions of >20 mg/kg result in levels above the normal therapeutic range (6–12 mg/l, 17–51 mmol/l) and are associated with neurological signs and symptoms including ataxia, nystagmus, mydriasis, movement disorders and the anticholinergic toxidrome. More severe neurotoxicity in the form of severe central nervous system (CNS) depression is expected to develop after ingestion of doses >50 mg/kg. Minor changes on electrocardiography are common after large ingestions, but major cardiotoxicity is rare.^{1 2}

This patient had taken a massive overdose of 20 g or 400 mg/kg of carbamazepine. We expect her to develop neurological symptoms progressing to coma requiring intubation and ventilation in the next 8 h. She may even develop more unusual complications associated with massive overdose, including seizures and cardiovascular instability.

Armed with this individualised risk assessment, we can now plan a rational management plan for our patient.

Supportive care and monitoring

This patient needs to be carefully observed for neurological deterioration in a fully monitored area with ready availability of staff and equipment to carry out rapid sequence induction of anaesthesia and endotracheal intubation. Staff must be aware of the likelihood of delayed neurological deterioration. As she is expected to develop profound coma within the next 8 h, it would be prudent to intubate her pre-emptively at the first sign of deterioration in level of consciousness. This would reduce the risk of aspiration pneumonia and permit early and safe administration of activated charcoal via a nasogastric tube.

Investigations

The routine screening investigations after deliberate self-poisoning are the 12-lead electrocardiogram and serum paracetamol level. Serial serum carbamazepine levels, ideally performed every 4 h until they peak, are useful to refine risk assessment, and monitor clinical course and response to enhanced elimination techniques. Levels >12 mg/l (50 mmol/l) are associated with ataxia and nystagmus, and levels >40 mg/l (170 mmol/l) are associated with coma, respiratory depression and seizures.^{1 3} Peak levels may be

Box 1 General approach to acute poisoning

• Resuscitation

- Airway
- Breathing
- Circulation
- Seizure control
- Correct hypoglycaemia
- Correct hyperthermia
- Resuscitation antidotes

• Risk assessment

• Supportive care and monitoring

• Investigations

- Screening—ECG, paracetamol
- Specific

• Decontamination

• Enhanced elimination

• Antidotes

• Disposition

Abbreviation: CNS, central nervous system.

Box 2 Risk assessment

A distinct cognitive step that aims to be quantitative and takes into account:

- **Agent(s)**
- **Dose(s)**
- **Time since ingestion**
- **Current clinical status**
- **Patient factors**

delayed up to 96 h after massive ingestion of controlled-release preparations.⁴

Decontamination

The prolonged absorption of carbamazepine means that administration of oral activated charcoal is likely to reduce drug absorption even when given many hours after the overdose. This potential to reduce the duration and severity of toxicity must be balanced against the risk of subsequent aspiration of charcoal associated with CNS depression. If CNS depression over the next few hours is anticipated, then it is safer to withhold treatment with activated charcoal until after the airway is secured with endotracheal intubation.^{1 5}

Whole-bowel irrigation has been advocated as a method of decontamination after carbamazepine overdose, particularly of controlled-release preparations. However, as this procedure usually takes about 6 h to complete, it can be safely carried out only if the airway is first secured. Whole-bowel irrigation is technically more difficult in the intubated and ventilated patient, and is further complicated if ileus develops as a result of the anticholinergic effects of carbamazepine.

In our patient, given the massive nature of the overdose, administration of activated charcoal is indicated, but only after the airway is first secured as development of considerable CNS depression over the next few hours is anticipated. Whole-bowel irrigation has a considerable risk of complications, without defined additional benefit.

Enhanced elimination

Administration of multidose activated charcoal enhances elimination of carbamazepine by interruption of enterohepatic circulation.⁵ This intervention has the potential to reduce the duration of toxicity. A potential major adverse effect is acute bowel obstruction from charcoal concretions, especially if anticholinergic ileus develops.

Haemoperfusion or haemodialysis also improves elimination of carbamazepine.⁶ This invasive, resource-intensive intervention is not justified unless risk assessment indicates potential for prolonged coma, seizures, cardiovascular instability or other adverse outcome not easily managed with supportive care.

In this patient in whom coma is anticipated, initiation of multidose activated charcoal is justified once the airway is secured. It should be continued until ileus develops or coma resolves. Urgent implementation of haemodialysis is not indicated but might be useful at a later time depending on clinical progress and serial serum carbamazepine levels.

Antidotes

There are no antidotes for carbamazepine toxicity.

Disposition

The patient requires admission to an intensive care for ventilation, close monitoring of vital signs, cardiac rhythm

Box 3 Carbamazepine overdose

- Absorption is delayed and erratic
- Dose >20 mg/kg: anticipate mild-moderate central nervous system and anticholinergic effects
- Dose >50 mg/kg: anticipate fluctuation in mental status with intermittent agitation followed by coma requiring intubation and ventilation within 12 h
- Cardiovascular instability may occur with very high doses
- Enhanced elimination with repeat-dose activated charcoal, haemodialysis or haemoperfusion is clinically useful in selected cases

and serial carbamazepine levels. The unit must be capable of carrying out haemodialysis, should this be required.

CLINICAL PROGRESS

This patient is closely monitored in the emergency department resuscitation area. Immediate charcoal administration is withheld because of concern about imminent decline in the level of consciousness. Over the next few hours, she becomes increasingly drowsy and her Glasgow Coma Score falls to 12/15. Rapid-sequence induction of anaesthesia and endotracheal intubation is carried out at this point rather than waiting for further decline in the level of consciousness and a risk of aspiration. Just before intubation her blood pressure is 90/60 mm Hg, but she responds to a fluid bolus of 20 ml/kg normal saline. Activated charcoal 50 g is given via the nasogastric tube and orders written for repeat doses of 25 g every 4 h. She is admitted to the intensive care unit for ventilation and supportive care. Serial carbamazepine levels are determined and peak at 41 mg/l (175 mmol/l) at 36 h. They remain >30 mg/l (128 mmol/l) over the first week, during which time the patient remains unresponsive without sedation. It appears that ongoing absorption of carbamazepine matches elimination. A small dose of norepinephrine by intravenous infusion is required to maintain an adequate blood pressure.

On day 7, bowel sounds are lost and a degree of abdominal distension is noted. Further treatment with multidose activated charcoal is discontinued. In view of the persistently raised plasma carbamazepine levels, charcoal haemoperfusion is started. The patient returns to consciousness as carbamazepine levels fall rapidly to within the normal therapeutic range. Inotropes are successfully withdrawn. An agitated delirium is controlled with titrated doses of intravenous diazepam. Progress is complicated by persisting abdominal distension with clinical and radiological evidence of complete small-bowel obstruction. Laparotomy shows a large charcoal concretion obstructing the ileum, and the patient requires an ileostomy.

Our patient is finally extubated 12 days post-overdose and transferred to the care of the general surgeons prior to definitive psychiatry evaluation.

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