

## Fatal nefopam overdose

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Nefopam is a non-opioid analgesic agent with a central mode of action involving activation of descending pain-modulating pathways and inhibition of synaptosomal uptake of hydroxytryptamine, norepinephrine and dopamine. Adverse effects during therapeutic use and after overdose of nefopam are known to involve the central nervous system (confusion and convulsions), the cardiovascular system (tachycardia and palpitations) and the kidneys (oliguria and renal failure). We report a death after nefopam overdose in a young woman who exhibited many of these features. It is only the second case of death after nefopam overdose in the literature.

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We report the death of a previously healthy 38-yr-old woman after an intentional overdose of nefopam. Nefopam is a centrally acting non-opioid analgesic agent which is structurally related to the antihistamine diphenhydramine and the anti-parkinsonian drug orphenadrine. It has a unique mode of action distinct from non-steroidal anti-inflammatory drugs and opioids. In rat brain, it inhibits synaptosomal uptake of hydroxytryptamine, norepinephrine and dopamine,<sup>1</sup> and has been shown to activate the descending pain-modulating pathways in the spinal cord.<sup>2</sup>

Originally investigated 30 yr ago as an antidepressant or centrally acting muscle relaxant for use in spastic disorders, nefopam then found a role as an analgesic agent. It is advocated for the treatment of both acute and chronic pain and appears to have a low potential for dependence. It has an appreciable analgesic effect but is less potent than opioids. Adverse reactions to nefopam include confusion, hallucinations, convulsions, dizziness, headache, sweating, urinary retention, nausea and vomiting, tachycardia and palpitations, which could be predicted from its proposed mode of action.<sup>3,4</sup> There is one previous report of death associated with nefopam overdose.<sup>4</sup>

### Case report

A 38-yr-old woman was admitted to the accident and emergency department after ingesting an unknown quantity of nefopam and dihydrocodeine 1 h previously. The patient became unconscious in transit to the hospital, presumably because of the central depressant effects of dihydrocodeine. On arrival in the accident and emergency department, she had a Glasgow coma score of 3 with fixed, dilated pupils.

She rapidly became apnoeic and had a generalized convulsion which was followed by cardiac arrest. Ventricular tachycardia and electromechanical dissociation were noted during the arrest. Cardiac massage was commenced and the lungs ventilated with 100% oxygen after tracheal intubation. Restoration of cardiac output took 12 min, during which time two DC shocks, atropine 3 mg and epinephrine 2 mg were administered. She remained apnoeic and unresponsive. Flumazenil and naloxone had no effect.

She was transferred to the intensive care unit after receiving gastric lavage and nasogastric charcoal 50 g, and mechanical ventilation was continued. She remained unresponsive with fixed, dilated pupils and was having frequent myoclonic seizures. A sinus tachycardia of 120 beat min<sup>-1</sup> and right bundle branch block were initially evident on the electrocardiogram, but the latter resolved over 48 h. At no time did she have impaired gas exchange or x-ray changes to suggest aspiration of stomach contents.

During the first 24 h after admission, she developed widespread rigidity, despite sedation with propofol and alfentanil, which resolved by 48 h. She had absence of deep tendon reflexes and left conjugate deviation of the eyes. Urine output was low at 0.5 ml kg<sup>-1</sup> h<sup>-1</sup> despite crystalloid and colloid infusions to maintain an adequate central venous pressure and furosemide infusion at a rate of 5 mg h<sup>-1</sup>. Serum concentrations of creatinine increased to 331 µmol litre<sup>-1</sup> and she developed metabolic acidosis, presumably as a result of acute renal failure. Serum bicarbonate concentration was 16.6 mmol litre<sup>-1</sup>, 24 h after admission and 18.9 mmol litre<sup>-1</sup> at 48 h, with corresponding base deficit values of –6.9 and –8.3, respectively. Lactate

concentrations were not measured. Liver function tests were normal.

Forty-eight hours after admission, there was an acute deterioration in her condition with tachycardia, hypotension, pyrexia of 38.5°C and generalized limb flaccidity. Arterial pressure was supported with an infusion of norepinephrine 0.1–0.2 µg kg<sup>-1</sup> min<sup>-1</sup> without the use of a pulmonary artery catheter. Computerized tomography scan showed widespread cerebral oedema. Neurosurgical opinion was sought and, as the scan appearance and clinical course suggested brain-stem coning, only supportive therapy was advised. Tests for brain-stem death, performed the next day, showed no evidence of brain-stem activity and mechanical ventilation was withdrawn after discussion with the family.

Post mortem examination revealed no evidence of natural disease, but cerebral oedema was present. Toxicological examination confirmed that both nefopam and dihydrocodeine overdose had occurred, although the results were not available until after death. Plasma concentration of nefopam on admission was 4.3 mg litre<sup>-1</sup> and dihydrocodeine concentration was 5.9 mg litre<sup>-1</sup> (both 30–100 times therapeutic concentrations). Concentrations of both drugs in specimens obtained the following day were markedly reduced (nefopam 0.6 mg litre<sup>-1</sup> and dihydrocodeine 1.7 mg litre<sup>-1</sup>).

## Discussion

This is only the second reported death after nefopam overdose, although the drug manufacturer has three other non-reported deaths on its records. Adverse reactions after nefopam overdose include effects on: the cardiovascular system (tachycardia, bundle branch block and cardiac arrest); central nervous system (convulsions, hallucinations, pupil abnormalities and cerebral oedema); peripheral

nervous system (hypo- and hyperreflexia); and the kidneys (oliguria and biochemical renal failure).<sup>3,4</sup>

This case was complicated by concomitant dihydrocodeine overdose and reduction in conscious level before arrival in hospital. It is likely that the significant overdose of dihydrocodeine caused this early deterioration in conscious level by a central depressant effect. This, together with cardiac arrest after arrival in the accident and emergency department, may have caused hypoxic brain injury. Abnormal pupil responses, eye deviation and cerebral oedema could be attributed to hypoxic brain injury, but the previous reported case of fatal nefopam overdose showed similar features.<sup>4</sup> This suggests that the central nervous system findings in these patients could be a direct consequence of nefopam overdose. In addition, this patient showed many other features consistent with nefopam overdose, as detailed above.

Treatment of such overdose is supportive. As nefopam has no affinity for opioid receptors it is not antagonized by naloxone. Gastric lavage and activated charcoal 50–100 g are recommended. Treatment of the complications of overdose includes the use of benzodiazepines for convulsions. Beta-blockade is recommended for tachycardia after nefopam overdose but was not felt to be appropriate in this patient because of hypotension and pyrexia.

## References

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