Case study: The highest reported Nefopam overdose

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Introduction

Nefopam is a centrally acting non-opioid analgesic, known under trade names Acupan, Fenazoxxine and Ajan, is a racemic mixture of two enantiomers.

Nefopam interacts with tricyclic antidepressants, monoamine-oxidase inhibitors (MAOIs) and antimuscarinic drugs by enhancing the side effects of these drugs.

Case History

A 23 year old man, a prison inmate, fell from his top bunk following convulsions. Attempts to resuscitate him at the scene were unsuccessful. The autopsy examination revealed swelling of the brain, bite marks on the tongue and bruising to the face. He was allowed to keep his medications in his cell.

Post mortem blood and urine samples were sent to the Analytical Unit, Forensic Toxicology Service for analysis.

Extracted nefopam was identified in both blood and urine specimens. The concentration in blood was 35.8mg/L. Venlafaxine, codeine and paracetamol were also found at blood concentrations of 0.7mg/L, 0.3mg/L and 64.0mg/L respectively. Morphone, a metabolite of codeine, was also detected at a low blood concentration (0.02mg/L).

Nefopam interacts with tricyclic antidepressants, monoamine-oxidase inhibitors (MAOIs) and antimuscarinic drugs by enhancing the side effects of these drugs.

Nefopam was obtained from MP Biomedicals, LLC (Ohio, USA) and pyribenzamine (internal standard) was obtained from Sigma (Poole, Dorset, England). Methyl-tert-butylether (MTBE) was purchased from Rathburns Chemicals Limited (Walkerburn, Scotland). Sodium hydroxide (40%) and phosphoric acid (85%) solution were obtained from BDH (Poole, Dorset, England). Deionised water was prepared on site (ELGA Limited).

Method

The GC/MS system consisted of a Shimadzu GCMS-QP 2010 and Shimadzu AOC-20s autosampler. HP-5MS column (30m x 0.25mm, 0.5 µm film thickness) was used for the separation and helium as a the carrier gas. The injector port was held at 225° C. The initial column temperature was set at 150°C and held for 2 minutes. It was ramped by 30° C per minute up to 290°C and held for further 1.5 minute. 1µL of extract was injected in split mode and the total run time was 8 minutes. The method was run in positive electron impact ionisation mode (EI) and the following ions were monitored m/z: 225 for nefopam and m/z: 91 for pyribenzamine. (Fig. 3)

Chemicals and Reagents

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It is used for the treatment of acute and chronic pain, including musculo-skeletal, post-operative, cancer and dental pain. Nefopam is a unique drug that is both chemically and pharmacologically distinct from any presently known analgesics.1 It is structurally related to diphenhydramine and phenothiazine, although it does not have antihistamnine or antiparkinsonian properties. Its mechanisms of action are not fully understood, but in vivo analysis has revealed inhibition of serotonin, norepinephrine and dopamine reuptake in animal models.2 The drug is known to act centrally by activating opioid descending pain modulating pathways in the spinal cord.3

Nefopam is approximately 10 times more potent than aspirin and 2 to 3 times less potent than morphine. It is generally well tolerated, acts rapidly and has low potential for dependence. Adverse reactions to overdose concentrations of nefopam affect the central nervous system (convulsions, dizziness and hallucinations), the cardiovascular system (tachycardia) and the kidneys (oliguria and renal failure). Nefopam has been administered intravenously and orally in Europe since 1976, being available as the hydrochloride salt in 60 mg tablets, taken three times a day, with a limit of 300 mg per day. Following a single oral dose of 90 mg, peak blood concentrations of 0.07 to 0.15 mg/L were reported at 1 to 3 hours following ingestion.1

References:

8. Present result