Case study: The highest reported Nefopam overdose

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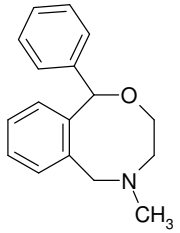
Introduction

Nefopam (Fig. 1 & 2) a centrally acting non-opioid analgesic, known under trade names Acupan, Fenazoxine and Ajan, is a racemic mixture of two enantiomers.

Figure 1. The chemical structure of Nefopam.

(3,4,5,6-tetrahydro-5-methyl-1-phenyl-1H-2,5 benzoxazocine)



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 orphenadrine, although it does not have antihistamine 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 the 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]

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. The pathologist concluded that these injuries did not contribute to his death. The deceased was prescribed nefopam, venlafaxine, co-codamol and cetirizine. 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.

Figure 2. Nefopam tablet.

Chemicals and Reagents

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% solution) and phosphoric acid (85% solution) were obtained from BDH (Poole, Dorset, England). Deionised water was prepared on site (ELGA Limited).

Extraction

Nefopam was extracted from postmortem blood using liquid-liquid extraction. 100µL of sample or calibrator was transferred to an 8 mL polypropylene tube and 50µL of 10mg/L pyribenzamine (internal standard), 500µL of 1 molar sodium hydroxide and 4 mL of methyl-tert-butylether (MTBE) were added. The sample was mixed for 15 minutes and centrifuged for 5 minutes. The organic phase was then transferred to a 4.5 mL polypropylene tube containing 250µL 0.1 molar phosphoric acid. After mixing and centrifuging the organic layer was removed and 100µL of 1 molar sodium hydroxide and 500µL of methyl-tert-butylether were added to the aqueous layer. The sample was vortex mixed and centrifuged for 5 minutes. The extract was injected onto the gas chromartography-mass spectrometry system (GC/MS).

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)

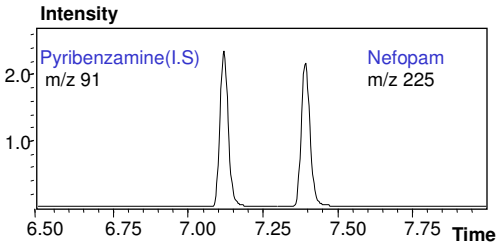


Figure 3. TIC of nefopam (7.4 min) and pyribenzamine (7.1 min).

Results

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. Morphine, a metabolite of codeine, was also detected at a low blood concentration (0.02mg/L).

Conclusion

The blood concentration of nefopam in this case (35.8mg/L) exceeds the highest therapeutic range by more than 170 times.[4] This concentration could, in part, be due to post mortem redistribution. This is only the fourth reported death due to nefopam overdose and the concentration of the drug is the highest recorded so far (Table 1). The adverse effects attributed to nefopam overdose, such as convulsions, are common to all published cases.

Table 1. Review of the reported fatal cases of nefopam.

Year	Age; gender	Circumstance of death	Concentration of nefopam in blood or plasma (mg/L)	Other drugs taken
1981	30; F	Suicidal ingestion; death 19 hours later	Post mortem blood 11.9 [5]	None
1999	38; F	Suicidal ingestion; death 3 days later	Plasma 4.3 (admission) Plasma 0.6 (day one) [6]	Dihydrocodeine
2001	37; F	Voluntary i.v injection; found dead at home	Post mortem heart blood 4.38 [7]	None
2005	23; M	Suicidal ingestion	Post mortem blood 35.8 [8]	Co-codamol, Venlafaxine

References:

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8. Present result