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Nefopam Hydrochloride: A fatal overdose

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ABSTRACT

Nefopam is a non-opiate analgesic commonly used for the treatment of moderate to severe pain. A case of a 37-year-old male who was found dead in the morning is presented. An autopsy was performed and femoral venous blood, heart blood, urine, and vitreous humour were submitted for toxicological analysis. A general drug screen detected the presence of nefopam, caffeine, nicotine, citalopram, gabapentin, amitriptyline, diazepam and paracetamol in cardiac blood. Nefopam was quantitated by HPLC-DAD. Nefopam was found at the following concentrations: 13.6 mg/L in unpreserved femoral blood; 14.7 mg/L in preserved (fluoride-oxalate) femoral blood; 21.2 mg/L in unpreserved cardiac blood; 4.5 mg/L in preserved vitreous. Citalopram was present at a concentration of 0.7mg/L (femoral blood) and 0.9mg/L (cardiac blood). Ethanol analysed by headspace gas chromatography (GC-FID) was detected in preserved (fluoride-oxalate) vitreous (14 mg/ 100 mL) and preserved (fluoride-oxalate) urine 50 mg/ 100mL. Death was attributed to atherosclerotic coronary artery disease and therapeutic drug toxicity.

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Introduction

To date, there have previously been 6 reports of fatal overdoses of nefopam mainly in the UK (1-4), but also in France (5) and New Zealand (6). This study is the first to quantify nefopam in vitreous humour as well as in unpreserved femoral and cardiac blood. This study is also only the second study to report the levels of nefopam in unpreserved femoral blood. Femoral blood is generally regarded as the sample in which the concentration of drugs changes the least between the time of death and the postmortem period. The femoral blood is therefore the best sample in which to accurately determine the amount of drug present at the time of death (7).

This paper describes the autopsy and toxicological findings of a nefopam poisoning fatality. Nefopam was detected and quantitated in unpreserved and preserved femoral blood, unpreserved cardiac blood and we report for the first time the detection and quantitation of nefopam in vitreous humour. The detection and quantitation of nefopam was carried out by a validated method using high-performance liquid chromatography with diode-array detection (HPLC-DAD).

Case report

A 37 year old male was found at home lying on his stomach with no sign of life. He suffered from chronic pain and had a history of depression with a previous attempt at suicide via overdose. There was no expression by the deceased that he was intending to take his own life in the period before the death. Various medications were recovered from the scene and included naproxen, citalopram, gabapentin, omeprazole, paracetamol and diazepam. Two months prior to his death he was prescribed Nefopam Hydrochloride.

Internal examination at autopsy revealed marked degenerative narrowing and hardening of the arteries supplying blood to the muscle of the heart (atherosclerotic coronary artery disease). There was no evidence of either recent or old heart attack (no acute infraction or myocardial fibrosis). Both lungs were heavy and congested with a large amount of fluid within them (pulmonary oedema). No tablets or tablet residue was discovered within the stomach or first part of the intestine. Histopathological examination of the retained tissues confirmed their macroscopic appearances at autopsy. There were small areas of scaring in the heart muscle in keeping with old injury due to poor flow (myocardial fibrosis) and evidence of narrowing of the vessels (atherosclerosis).

Experimental

Postmortem Samples

As part of routine autopsy procedures unpreserved femoral and cardiac blood were collected. Preserved samples (2.5% Fluoride/Oxalate) of vitreous humour, femoral blood and urine were also collected to help prevent postmortem drug degradation and/or ethanol formation.

Analytical materials and methods

A stock solution of Nefopam (LGC standards, Teddington, UK) was prepared at a concentration of 1mg/ml in methanol (Fisher Scientific, Loughborough, U.K) and stored at 4°C in an amber vial. This stock solution was used to prepare a seven point calibration curve (0.156, 0.312, 0.625, 1.25, 2.5, 5 and 10 mg/L) in blank equine plasma (TCS Biosciences, Buckingham, U.K). A separate stock solution of the drug was used to prepare quality control standards of 0.5 mg/L and 5.0 mg/L. Calibrator and control samples were prepared prior to each extraction.

The extraction method for the HPLC-DAD was adapted from a previously published method for basic drugs (8). In brief, 500 µL of the standard/biological sample was added to a polypropylene test tube, and spiked with 500 µL of internal standard (5 mg/L Desipramine (Sigma-Aldrich-Fluka, Poole, U.K) in 0.2M Na_2CO_3 solution at pH 10) and followed by extraction with 5 ml of 1-chlorobutane (Fisher Scientific, Loughborough, U.K.). After 5 minutes of rotary mixing the sample was centrifuged at 5000 rpm for 10 minutes and the supernatant solvent layer was transferred to a second polypropylene test tube. A back-extraction was carried out with 100µL of 0.05M H_2SO_4 (Sigma-Aldrich-Fluka, Poole, U.K). The extract was transferred to a vial for HPLC analysis. The injection volume was 10 µL.

HPLC-DAD analyses were carried out using an UltiMate® 3000 UHPLC Dionex HPLC system (Camberley, U.K.) consisting of a DAD-3000 diode array detector, WPS-3000SL autosampler, LPG-3400SD low pressure quaternary pump and TCC-3000SD thermostated column compartment. Data acquisition was by the Chromeleon software (version 6.8) package with the DAD recording spectral data between 200 and 595 nm.

The column used for qualitative analysis was a Phenomenex Synergi Fusion column (150 X 2.0 mm, 4 µm) protected by a 4mm x 3mm Phenomenex Synergi Fusion guard column (column temperature 25 °C). HPLC screening used a 4-70% acetonitrile gradient ramp in 15 minutes with 70% acetonitrile, a hold for 3 minutes and a flow of 0.63 ml/min producing a

total run time with equilibration of 18 minutes. The peak detected was compared with a toxicological library that had been updated in house from the certified reference standard.

Quantitative HPLC-DAD analysis was performed on a Waters XSelect C18 Column, (2.1 mm X 150 mm, 3.5 μm) and protected by a 4mm x 3mm Phenomenex Synergi Fusion guard column. The mobile phase used was 25 mM triethylammonium phosphate buffer (Sigma-Aldrich-Fluka, Poole, U.K) and far UV-grade acetonitrile (Fisher Scientific, Loughborough, U.K). The quantitative analysis utilised an isocratic elution with 35% acetonitrile. The total run time was 5 minutes and flow rate was 0.6 ml/min with a column temperature of 25℃. Data acquired at 230 nm wavelength was used for all quantitation

Method Validation

The Nefopam quantification method was validated to meet ISO17025 standard requirement and the parameters assessed were as described previously (9): linearity (r^2=0.999) (Figure 1), limit of detection (LOD = 0.01 mg/L), limit of quantification (LOQ 0.11 mg/L), precision and accuracy. All parameters were within acceptable limits (table 1). The intra-day precision of Nefopam quantitation was 10% or better, with accuracy within 95 % of low and high quality controls. The method showed no interfering peaks at the retention time of Nefopam when investigating this fatality and a calibration model using a linear fit and weighting of 1/x gave less than 5 % deviation from the target concentration within the linear range set between 0.156 and 10 mg/L. None of the analytes detected in this case co-eluted with Nefopam.

Results

A general drug screen detected the presence of nefopam, caffeine, nicotine, citalopram, gabapentin, amitriptyline, diazepam and paracetamol in cardiac blood. Nefopam was quantitated by HPLC-DAD. Nefopam was found at the following concentrations: 13.6 mg/L in unpreserved femoral blood; 14.7 mg/L in preserved (fluoride-oxalate) femoral blood; 21.2 mg/L in unpreserved cardiac blood; 4.5 mg/L in preserved vitreous. Citalopram was present at a concentration of 0.7mg/L (femoral blood) and 0.9mg/L (cardiac blood). Gabapentin (below 1 mg/L), amitriptyline (below 0.15 mg/L) and diazepam (below 0.15 mg/L) were all detected below our quantitation limit. Ethanol analysed by headspace gas chromatography (GC-FID) was detected in preserved (fluoride-oxalate) vitreous (14 mg/ 100 mL) and preserved (fluoride-oxalate) urine 50 mg/ 100mL.).

Discussion

Nefopam (Fig 1A) (Acupan, Silentan, Nefadol, Ajan, fenazoxine) is a benzoxazocine known as 5-methyl-1-phenyl-1,3,4,6-tetrahydro-2,5-benzoxazocine ($C_{17}H_{19}NO$) and is a cyclic analogue of diphenhydramine ($C_{17}H_{21}NO$) (Fig 1B). Nefopam was initially developed over 30 years ago as a muscle relaxant (3) and antidepressant (1), but it eventually found clinical use as a non-opioid centrally acting analgesic drug used for relief of moderate acute and chronic pain (10). Unlike other analgesics, its mechanism of action is unique. Its analgesic activity has shown to involve inhibition of the reuptake of serotonin, noradrenaline and dopamine (11-14). More recent in vitro and in vivo studies in rodents have shown interactions with the glutamatergic system (15, 16) but the exact mechanism of action is currently unclear. Nefopam is sold as a racemic mixture (+/- isomers) of 30mg tablets and also in an injectable form (10, 17). The oral dose is initially 60 mg (elderly 30 mg) 3 times daily, adjusted according to response and the usual range is 30–90 mg 3 times daily. It can be administered by injection either intravenously or intramuscularly in 20mg doses (17). Two studies have been published describing the side effects of nefopam based on analysis of pharmacovigilance databases in France (18) and New Zealand (19) over many years. Side effects include nausea, vomiting, malaise, sedation, somnolence, palpitations, tachycardia and vertigo. More serious side effects reported are hallucinations, convulsions, confusion, hypotension and anaphylactic reactions (18, 19). Pharmacologically, the analgesic effect of nefopam has been found to be 10 times more potent than aspirin (20) and approximately 2-3 times less potent than morphine. Nefopam does not exhibit the respiratory depressant effects of morphine (10). The individual isomers have differing potencies of antinociceptive actions with (+) nefopam > (±) nefopam > (-) nefopam. (+) nefopam being around 7 – 30 times more potent than (-) nefopam (13). Based on early studies it was not expected that nefopam would have abuse potential but in France there have been reports of intramuscular abuse by patients mainly for its psychostimulant effects (21-23), but to the best of the authors knowledge there have been no reports of oral abuse. Human pharmacokinetic studies have shown a peak plasma concentration of between 1 and 3 hours (90mg dose(20)) 1.63-1.73 h (30mg dose, (24)) and 1.83h (20mg dose (25)). Nefopam undergoes significant first pass metabolism as the bioavailability (F) is 0.36 ± 0.13 (25, 26). The peak plasma concentration (T_{max}) has been reported as 0.073 – 0.155 mg/L (90mg dose, (20)) 0.067 ± 0.002 mg/L (30mg dose, (24) and 0.012 ± 0.004 mg/L (20mg dose, (25)) When given intravenously (20mg) the peak plasma concentration observed was 0.046 ± 0.014 mg/L (25) and 0.072 ± 0.014 mg/L (27). Studies have shown similar oral half-life's (t½) in human studies 5.1 ± 1.3 (25), 4.41 ± 0.16 h; 4.80 ± 0.13 h (24) and 3.8 ± 0.70 h; 4.1 ±

0.8 h (27), and between 3 − 8 h in both oral and intravenous studies (20). The drug distributes throughout the body with estimated volumes of distribution (Vd) of 410 ± 115 L; 447 ± 98 L (27) and 535 ± 139 L (25). Nefopam is metabolised mainly to n-desmethylnefopam, with nefopam glucuronide and nefopam-N-oxide being minor metabolites, all are thought to be inactive (5). Based on human trials of a dose of 20mg n-desmethylnefopam has a t½ of 10.6 ± 3.0 h (oral) and 15.0 ± 2.4 h (i.v.), a T_{max} of 2.54 h (oral) 5.10 h (i.v.) with peak plasma concentrations of 0.011 ± 0.004 mg/L (oral) and 0.007 ± 0.002 mg/L (25). Nefopam is mainly eliminated by metabolism with only 5% of the dose being excreted unchanged in urine (20).

There have been 6 previously reported cases of deaths involving toxicity of nefopam (1-6). These cases are detailed in table 2. Based on data from animal studies (28), human non-fatal cases (2) and fatal cases it is possible to discern the clinical pattern in nefopam overdose. These symptoms are generalised seizures, tachycardia, generalised limb flaccidity, fever, acute renal failure, cerebral oedema, and finally cardiac arrest. More serious side effects reported are hallucinations, convulsions, confusion, hypotension and anaphylactic reactions. The unpreserved femoral concentration of nefopam in our case was 13.6 mg/L is around 87 times higher the peak plasma concentration (0.155 mg/L) reported in human pharmacokinetic studies (20). It is also above the only other fatal concentration of nefopam reported in femoral blood (6.2 mg/L, (6)). The unpreserved cardiac blood concentration of nefopam in this case (21.2 mg/L) was also above the previously reported concentration of 4.38 mg/L in another fatal case involving the injection of nefopam (5). The other drug that was detected and quantitated in this case was citalopram with an unpreserved femoral blood concentration of 0.7mg/L and an unpreserved cardiac blood concentration of 0.9mg/L. This is in the range of drug concentrations of citalopram found in 12 autopsy in deaths unrelated to citalopram usage (0.1 − 1.1 mg/L) (29). Postmortem redistribution has been described as a "toxicological nightmare" where drug concentrations in postmortem blood may change after death (7). Drugs with a volume of distribution > 3 L/Kg are though more likely to redistribute after death with the cardiac to femoral ratio of >1 showing a likely distribution (7). The ratio of nefopam concentration in unpreserved cardiac and femoral blood was 1.6 raising the possibility that nefopam may undergo post-mortem redistribution. The volume of distribution in the literature has only been given in litres however it is possible to get an estimate using the data from the study by Aymard *et al.* (25) were the mean Vd is 535 l and the mean weight of the subjects is 74 kg. This gives a ~Vd of 7 L/Kg. It may be that none or limited postmortem redistribution has occurred in this case as the citalopram cardiac:femoral ratio is 1.3 and citalopram has a Vd of 12-16 L/Kg (30) above the value of 3 L/Kg for drugs which are likely to undergo postmortem redistribution and has

been shown in 10 case to have a mean cardiac:femoral ratio of 2.5 (range 0.7-10) (30). This also indicates that nefopam may undergo postmortem redistribution. Unfortunately to date there are no publish studies with both postmortem cardiac and femoral blood concentrations of nefopam in which to confirm the possible postmortem redistribution of nefopam.

The nefopam concentration in preserved femoral blood was higher than in unpreserved femoral blood samples by 7.4%. Although this is within the variability of analysis of analytes in biological matrices, it may also be the result of nefopam instability in blood as a consequence of the fact that benzoxazocine may be easily oxidised. Furthermore Nefopam is known to be unstable under acidic conditions (31). The unstable nature of nefopam becomes problematic post-mortem, as the pH decreases rapidly from 7.3 to 6 in the first hour and then further decreases to pH 5.0 by 96 hours (32). Consequently between case comparisons of nefopam concentrations in fatalities may prove difficult due to drug instability and postmortem blood concentration changes of drugs.).

Acknowledgments

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Table 1: Validation data for quantitation of Nefopam in plasma, vitreous, blood and urine*

Matrix		Mean Concentration (mg/L) (± SD)	RSD (%)	Accuracy (%)
Plasma Intra-day (*n* = 5)	0.5 mg/L	0.49± 0.03	6.1	98.0
	5 mg/L	4.97± 0.19	3.8	99.4
Plasma Inter-day (*n* = 15)	0.5 mg/L	0.48± 0.02	4.2	96.0
	5 mg/L	0.52± 0.02	3.8	104
Blood Intra-day (*n* = 5)	0.5 mg/L	5.12± 0.13	2.5	102.4
	5 mg/L	4.99± 0.10	2.0	99.8
Blood Inter-day (*n* = 15)	0.5 mg/L	0.52± 0.05	9.6	104
	5 mg/L	5.02± 0.09	1.8	100.4
Vitreous Intra-day (*n* = 5)	0.5 mg/L	0.53± 0.02	3.8	106
	5 mg/L	4.90± 0.07	1.4	98
Vitreous Inter-day (*n* = 15)	0.5 mg/L	0.52± 0.02	3.8	104
	5 mg/L	4.91± 0.08	1.6	98.2

* Equine plasma from TCS Biosciences; human SAGM blood from Blood Transfusion Service, Ninewells Hospital, Dundee—with ethical approval; porcine vitreous from a local butcher; human urine donated by laboratory staff.


Table 2: Reported cases of fatal nefopam overdose

Year	Gender, Age	Circumstances of death	Other Drugs Detected	Nefopam Concentration (mg/L or mg/Kg)	Ref
1981	Female (30)	Suicidal Ingestion	None	Postmortem "serum" – 11.9	(2)
1999	Female (38)	Suicidal Ingestion	Dihydrocodeine (5.9 mg/L)	Antemortem admission serum – 4.3	(1)
2001	Female (37)	Suicidal injection (i.v.)	None	PM Cardiac Blood - 4.38 Liver – 59.12 Kidney – 14.57 Lung – 44.07 Myocardium – 14.87	(5)
2005	Male (23)	Suicidal Ingestion	Venlafaxine (0.7mg/L) Codeine (0.3mg/L) Paracetamol (64.0 mg/L) Morphine (0.02mg/L)	Postmortem Blood – 35.8	(4)
2006	Female (50)	Not Given	None	PM Femoral blood – 6.2 Liver - 57	(6)
2009	Male (19)	Oral ingestion 60x30mg	Diclofenac	Postmortem "Serum" - 7.45	(3)

		nefopam, 14x50mg diclofenac	(0.069mg/L)		

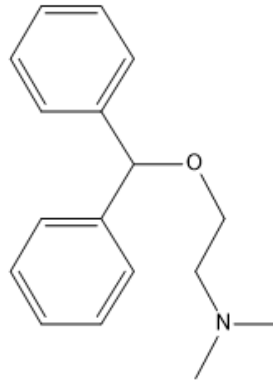Figure 1: The chemical structure of A) nefopam and B) diphenhydramine

A)
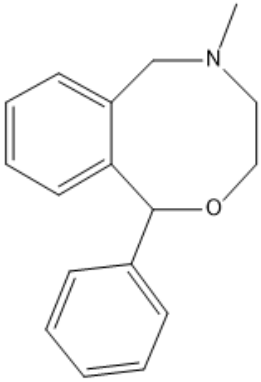
B)

Figure 2: Calibration curve and UV-Vis spectra for Nefopam