CASE REPORT

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A Fatality Due to Flurazepam

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ABSTRACT: A fatality attributed to suicidal ingestion of up to 2.2 grams of flurazepam is described. The deceased was a 52-year old female with a history of depression and suicidal attempts. No significant pathology was found at autopsy. Full toxicological analyses detected only flurazepam and metabolites in her tissues. The concentrations of flurazepam in femoral blood, liver, bile, vitreous humor and urine were 5.5 mg/L, 130 mg/kg, 33 mg/L, 1.3 mg/L and 3.3 mg/L, respectively. Analysis of gastric contents showed 600 mg of flurazepam. Desalkylflurazepam was also detected in blood, liver, bile and vitreous, but at much lower concentrations than the parent compound.

KEYWORDS: toxicology, pathology and biology, flurazepam

Flurazepam, 7-chloro-1-(diethylaminoethyl)-5-(fluorophenyl)-1, 3-dihydro-2 H-1, 4-benzodiazepine-2-one, is a benzodiazepine which was synthesized in 1965 and introduced onto the market in 1970. It is used clinically for the treatment of insomnia, anxiety and depression as well as epilepsy in association with other drugs [*1*].

Although flurazepam has a short terminal elimination half-life of 1 to 3 h, the major active metabolite N-1-desalkyl flurazepam, exhibits a much longer half-life of about 70 h [*2*]. For this reason toxicological analyses of flurazepam should usually consider both the parent drug and the desalkyl metabolite.

Fatalities resulting from flurazepam toxicity have been seldom reported. One report described a poisoning with flurazepam alone [*3*], and some have been reported in association with other significant drugs [*1,4*]. We describe here the death of a woman following deliberate overdosage with flurazepam (Dalmane) as the sole drug.

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Case History

The deceased was a 52-year-old woman who was in a depressed suicidal state following a breakup with her boyfriend. She went into her bedroom one night with the intention of smoking cannabis. The following morning she was found dead lying across the bed. Several medications were located in the room including flurazepam (Dalmane), alprazolam (Xanax), and a mixture of natural estrogens (Premarin). Dalmane 30 mg (100 tablets) had been prescribed to her 2 days prior to her death, and only 28 tablets remained. A plastic bag and bottle were also found in the room, both containing green vegetable matter.

Autopsy Findings

An autopsy was performed the day following death. This included a complete macroscopic and microscopic examination. The autopsy disclosed no pre-existing natural disease. Patchy mild to moderate pulmonary edema and congestion were the only significant findings. Specimens of femoral blood, bile, liver, urine, vitreous humor and gastric contents were taken for toxicological analysis.

Toxicological Analyses

Toxicological analyses were conducted on blood, urine, and bile and used a combination enzyme-multiplied immunoassay (EMIT) for illicit drugs, gradient liquid chromatography (HPLC) with photodiode array detection for acid/neutral substances, and capillary gas chromatography (GLC) for basic/neutral substances and alcohol analyses [*5,6*].

Flurazepam and Desalkyl Flurazepam Analyses

Flurazepam and desalkyl flurazepam were measured essentially as previously described [*7*].

Drug stock solutions of flurazepam and desalkyl flurazepam (1 mg/mL) were prepared in methanol and stored at −20°C until use. Drugs were obtained from the Australian Government Analytical Laboratories (AGAL, Pymble, N.S.W., Australia). Working standards were prepared from stock solutions in the appropriate matrix to give concentrations from 0.05 to 2.5 mg/L for blood, urine and vitreous. Concentrations were increased, without loss of linearity, to 20 mg/L for bile and liver. The case specimens were diluted to a level required to fall within the appropriate calibration curve range.

Liver homogenates were also extracted with the described method. A liver homogenate was prepared by homogenizing 10 g of freshly minced liver in 10 mL of water. The pH was adjusted to 10 using 1M NaOH and 10 mg subtilisin (Sigma, St. Louis, MO,) added. The homogenate was incubated for 60 min at 55°C. The pH was finally adjusted to 7.0 ± 0.5 with dilute mineral acid. Homogenates were stored at −20°C until analysis.

Flurazepam eluted at 37.4 min, with a relative retention time (RRT) of 0.87 compared with the internal standard clobazam, and desalkyl flurazepam eluted at 34.9 min (RRT 0.80).

Results and Discussion

Flurazepam and desmethyl flurazepam concentrations in tissues are shown in Table 1. Flurazepam was detected in high concentrations in blood, liver, bile, vitreous, and urine while the equivalent of twenty 30 mg tablets were detected in the gastric contents. Desalkyl flurazepam was detected in blood, liver, bile, and vitreous, but not in urine and gastric contents. No evidence of poisons other than flurazepam and its metabolites were detected. Neither cannabinoids in urine (less than 20 ng/mL) nor alprazolam in blood (limit of detection 0.05 mg/L) were detected.

TABLE 1—*Flurazepam and N-1-desalkyl flurazepam concentrations in postmortem specimens.*

Specimen	Flurazepam	N-1-desalkyl flurazepam
Blood (femoral)	5.5 mg/L	0.73 mg/L
Liver	130 mg/kg	3.2 mg/kg
Bile	33 mg/L	19 mg/L
Vitreous	1.3 mg/L	0.04 mg/L
Urine	3.3 mg/L	N.D.
Gastric contents	600 mg	N.D.

NOTE: N.D. = Not Detected.

The green vegetable matter found in the plastic bag and bottle (analyzed by gas chromatography-mass spectrometry), was identified as cannabis.

There has been only one death previously reported as being due solely to flurazepam [*3*]. In this case the blood flurazepam concentration was 1.8 mg/L. The desalkyl flurazepam concentration was not measured. Other deaths in which flurazepam was detected have involved mixed drug toxicity. Pounder and Jones [*4*] reported a case of mixed drug toxicity from a combination of chloral hydrate, clomipramine and flurazepam. Blood flurazepam concentrations ranged from 0.15 to 0.99 mg/L depending on the site of sampling, with mixed cardiac blood containing 0.51 mg/L. The lowest concentrations were found in the subclavian and femoral veins. Desalkyl flurazepam was not measured. A review of five cases of combined flurazepam and phenobarbitone toxicity found flurazepam blood concentrations ranging from undetectable to 3.2 mg/L (mean 1.1 mg/L), with desalkyl flurazepam ranging from 0.4 to 1.9 mg/L (mean 1.2 mg/L) [*1*].

Therapeutic blood concentrations of flurazepam and desalkyl flurazepam are considerably lower than those observed in drug-related deaths. Single dose administration of 90 mg flurazepam produced average blood concentrations of flurazepam at 0.013 mg/L, and the desalkyl metabolite at 0.05 mg/L [*8*]. Chronic daily administration of 30 mg flurazepam produced steady-state blood concentrations of desalkyl flurazepam ranging from 0.033 to 0.114 mg/L, while the parent drug was below the limit of detection [*9*].

Comparison of these pharmacokinetic data with cases involving ingestion of a flurazepam overdose, suggest a relatively high blood concentration of the parent compound compared with the metabolite in cases associated with an acute ingestion of a large amount of flurazepam [*10*]. This is reinforced by our observations including a high ratio of parent drug to metabolite concentration.

In summary, we report the death of an otherwise healthy woman from the toxic effects of flurazepam. We also show the presence of flurazepam and its desalkyl metabolite in a number of tissues including vitreous humour in concentrations greatly exceeding those expected from therapeutic use.

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