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Mixed drug intoxication involving zaleplon (“Sonata®”)

Karla A. Moore*, Tasha L. Zemrus, Vera Ramcharitar, Barry Levine, David R. Fowler

Office of the Chief Medical Examiner, State of Maryland, 111 Penn Street, Baltimore, MD 21201, USA

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Abstract

Zaleplon (“Sonata®”) is a pyrazolopyrimidine derivative approved for use in the United States for the treatment of insomnia. To date, there has been little data in the toxicological literature where zaleplon has been implicated as causing a fatal intoxication, either alone or in combination with other drugs. This report documents a case where zaleplon was identified in a suicide by multiple drug ingestion. The following zaleplon concentrations were found: heart blood 2.2 mg/l; bile 8.6 mg/l and urine 1.4 mg/l. Zaleplon was also detected but not quantitated in the kidney and liver.

Keywords: Zaleplon; Suicide; Fatality; Forensic science; Drug overdose

1. Introduction

Zaleplon (“Sonata®”) is a pyrazolopyrimidine derivative approved for use in the United States as a Drug Enforcement Administration (DEA) Schedule IV compound for the treatment of insomnia in August 1999. It is structurally unrelated to the barbiturates and benzodiazepines, but is structurally similar to zolpidem (Fig. 1). Like zolpidem, it is a selective agonist at the benzodiazepine type I receptor subtype on the $GABA_A$ receptor complex in the brain. The recommended use for zaleplon is the short term (less than 1 month) management of insomnia. The recommended dose is from 5 to 20 mg per night [1].

Zaleplon undergoes significant first pass metabolism when taken orally; bioavailability was reported to be about 30% [2]. Peak plasma concentrations increase linearly with dose, with a peak concentration of 0.05 mg/l being reported after a 20 mg dose [3]. It has an elimination half-life of approximately 1 h. The liver enzyme “aldehyde oxidase” extensively metabolizes the drug to 5-oxo-zaleplon. Zaleplon and 5-oxo-zaleplon are further metabolized by demethylation (CYP3A4) to desmethylzaleplon and 5-oxo-desmethylzaleplon, respectively [4].

To date, there has been little data in the toxicological literature implicating zaleplon in a fatal intoxication, either alone or in combination with other drugs. The following is a case investigated by the Office of the Chief Medical Examiner, State of Maryland, where intoxication with zaleplon was suspected.

2. Case history

The deceased was a 41-year-old, Caucasian female. She was reported to be very depressed and upset about the recent loss of her job. There was no available medical history, however she had been prescribed alprazolam, zaleplon and butalbital at various different times. She was found on the floor next to the sofa surrounded by multiple empty pill vials. She had no prior suicide attempts and had not left a suicide note.

There were no significant autopsy findings. Routine specimens, including bile, urine, liver and kidney, were submitted for toxicological analysis.

3. Experimental

3.1. Materials

Zaleplon standard was obtained from Wyeth-Ayerst Laboratories (Philadelphia, PA). Ethylmorphine (internal

* Corresponding author. Tel.: +1-410-333-3240; fax: +1-410-333-3248.
E-mail address: kamoore2@juno.com (K.A. Moore).

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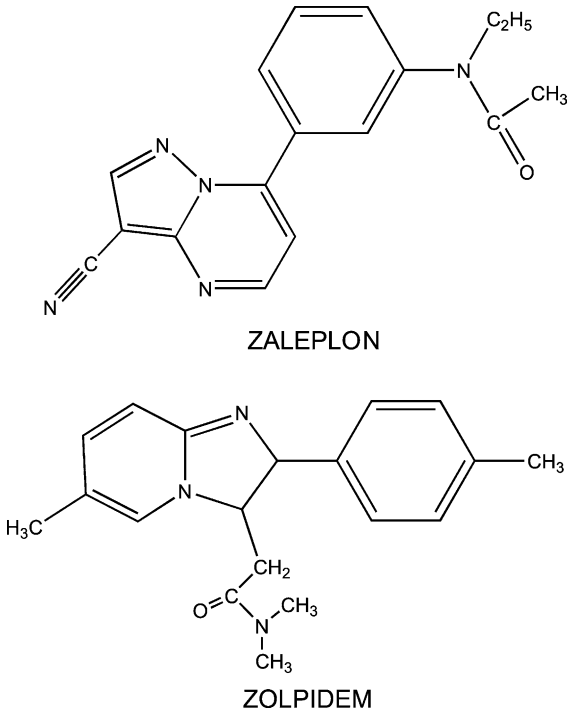

Fig. 1. Structures of zaleplon and zolpidem.

standard) was obtained from Alltech-Applied Science Labs (State College, PA). All reagents were J.T. Baker reagent grade and solvents were Fisher Optima grade.

3.2. Extraction and instrumentation

Zaleplon analysis was performed using a single-step alkaline drug extraction. Specifically, 2 ml 0.1N sodium hydroxide, 50 µl of a 100 mg/l internal standard solution and 10 ml *n*-butyl chloride were added to 2 ml of calibrator or specimen. After mechanical shaking and centrifugation, the organic layer was removed and evaporated to dryness at 40 °C. The residue was reconstituted in 100 µl isopropanol and injected into the gas chromatograph.

Analysis was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a nitrogen–phosphorus detector (NPD). The column was a J&W DB-5 5% phenyl-methyl-silicone fused capillary column (15 m × 0.25 mm i.d. × 0.25 µm film thickness). The oven temperature began at 100 °C for 1 min, increased by 30 °C/min to 200 °C, and increased by 15 °C/min to 300 °C, holding for 6 min. Total analysis time was 17 min. Zaleplon was quantitated from a matrix based calibration curve using calibrators of 0.5, 1.0, 2.0, and 4.0 mg/l. Appropriate dilutions were made to ensure area ratios were within the range of the standard curve. Under these conditions, the retention time of zaleplon was ~10.9 min and the retention time of the internal standard (ethylmorphine) was ~8.1 min.

The presence of zaleplon was confirmed by full scan electron ionization gas chromatography/mass spectrometry. The mass spectrum of zaleplon has a base peak of $m/z = 248$, with other prominent ions at $m/z = 263$, 305 and 219.

4. Results and discussion

Postmortem cases received in the Forensic Toxicology Laboratory routinely receive a gas chromatography/headspace analysis for volatile substances, a radioimmunoassay screen for morphine and gas chromatograph/nitrogen–phosphorus detector screens for acidic drugs and 12 classes of alkaline drugs. Table 1 lists the drugs identified and quantitated in the blood.

Since the case history suggested an intoxication of zaleplon, a 1 mg/l zaleplon standard was prepared. No peak corresponding to zaleplon was identified. The alkaline drug testing procedure involved an initial alkaline extraction at pH 14 into *n*-butylchloride. This was followed by a back extraction into 1.0N sulfuric acid and re-extraction after alkalinization. Subsequent work indicated that a single-step extraction was required to identify zaleplon by gas chromatography. Zaleplon elutes late from a DB-5 column under the oven temperature program used in this laboratory. It elutes after the common antidepressants, benzodiazepines and zolpidem but just prior to thioridazine and verapamil. The concentrations of zaleplon in the submitted specimens are listed in Table 2.

The blood zaleplon concentration in this case (2.2 mg/l) is approximately 40 times greater than what is reported in serum following therapeutic use. Since zaleplon has a half-life of approximately 1 h, accumulation of drug following chronic therapeutic use is unlikely. Therefore, this concentration represents the acute administration of a large amount of drug. The central nervous system (CNS) depression caused by zaleplon would be exacerbated by the presence of a potentially toxic amount of butalbital, another CNS depressant. The medical examiner reported the cause of

Table 1
Routine toxicologic findings in the presented case

Blood		Urine
Promethazine	0.8 mg/l	Promethazine "+"
Butalbital	9.9 mg/l	Butalbital "+"
		Alprazolam "+"

Table 2
Zaleplon distribution in the presented case

Specimen	Concentration (mg/l)
Blood	2.2
Bile	8.6
Urine	1.4

death as multiple drug intoxication; the manner of death was suicide.

Zaleplon was also quantitated in the bile and urine submitted with this case. The bile zaleplon concentration was significantly higher than the urine concentration indicating that bile would be preferable to urine for screening for zaleplon use in postmortem specimens.

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