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CASE REPORT

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Zaleplon and Driving Impairment

ABSTRACT: Zaleplon, a sedative-hypnotic, was identified in the blood of a subject arrested for impaired driving. Symptoms reported were those of central nervous system (CNS) depression. The zaleplon concentration was determined to be 0.13 μg/mL. Symptoms included slow movements and reactions, poor coordination, and lack of balance. Although no quantitative relationship between blood concentrations and degree of driving impairment is currently possible, it is reasonable to conclude that because of its specific activity as a sedative-hypnotic, blood concentrations consistent with doses exceeding therapeutic concentrations of zaleplon have the potential to cause impairment of psychomotor function, and would impair a person's level of consciousness and driving ability.

KEYWORDS: forensic science, sonata, driving, impairment

The arrest of a subject for driving under the influence after taking the sleep inducer zaleplon (Sonata®) prompted a review of the literature on the pharmacology and performance effects of this drug to assist with the evaluation of future cases.

Case Histories

A 20-year-old male was the causing driver in a two-car collision, having hit another vehicle at an intersection. The subject was observed to be unsteady on his feet. He had slow movements and reactions, poor coordination, lack of balance, and poor attention. The subject admitted inhaling three crushed Sonata® 10 mg tablets and ingesting three Sonata® 10 mg tablets. The time of inhalation and ingestion was not determined. Blood was drawn about an hour after driving. His toxicology results indicated a blood zaleplon concentration of 0.13 μg/mL, chlorpheniramine of 0.03 μg/mL and dextromethorphan of 0.08 μg/mL. No alcohol was present and bupropion metabolite was detected.

Material and Methods

Cases of suspected drug-impaired driving in Oklahoma are submitted to the Oklahoma State Bureau of Investigation's Toxicology Laboratory by law enforcement agencies for alcohol and/or drug testing. Cases where the alcohol concentration cannot reasonably account for the degree of impairment observed in the subject are screened by comprehensive procedures using modified protocols from previously published methods described elsewhere (1,8) and analyzed by gas chromatography (GC) and gas chromatography-mass spectrometry (GC/MS) for drugs with weakly acidic, neutral and basic characteristics.

Zaleplon (Fig. 1) is isolated in a simple procedure utilizing Chem Elut™ columns for the extraction of weak acid and neutral drugs (1). It has the mass spectrum shown in Fig. 2. When identified in the subject's blood, zaleplon was quantitated by GC/MS using a four-point calibration curve (0.00, 0.10, 0.20, 0.40, 0.80 μg/mL) by means of the following procedure.

One μg of internal standard (Hexobarbital, Cerilliant, Corporation, Round Rock, TX), blood (2.5 mL) and 0.5M, pH 5.5 phosphate buffer (2.5 mL) were mixed in a 15 mL culture tube. The mixture was poured into a 10 mL capacity (#1010) Chem Elut™ column and allowed to stand for 2 min after the last of the sample had entered the frit. Ten milliliters of dichloromethane were added to the column and allowed to stand for 2 min after the last of the solvent had entered the frit. Approximately 5 mL of dichloromethane eluted from the column at this stage. This first eluant and the subsequent one were collected in a single 15 mL culture tube. A second elution was continued with the addition of another 15 mL of dichloromethane to the column. The collected solvent was evaporated under nitrogen stream to approximately 3 mL, transferred to a 5 mL conical tube and 1 mL of acetonitrile was added, mixed and evaporated to approximately 100 μL. The sample was partitioned with 0.5 mL hexanes previously saturated with acetonitrile. The sample was centrifuged and the hexanes aspirated. The partitioning procedure was repeated twice (1). The sample was transferred to a glass sample vial, sealed with a snap cap, and a 2-μL aliquot was injected into the chromatograph. GC/MS analysis was performed in the scan mode. Calibration was determined to be linear over the range 0.10 to 0.80 μg/mL, and the correlation coefficient was 0.996.

Results and Discussion

The collection of symptoms associated with use of zaleplon with respect to this case after inhalation and ingestion were characteristic of a CNS depressant, and the associated effects on complex tasks resembled those of alcohol.

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Structurally, zaleplon is a pyrazolopyrimidine (Fig. 1), and is unrelated to the benzodiazepines. It acts as an agonist at the omega-1 receptor subtype (6), resulting in sedative/hypnotic effects, anxiolysis, anticonvulsant, and muscle relaxation properties (4,11). It is prescribed for the short-term treatment of insomnia and other sleep disorders (3). The drug is normally prescribed in 5 to 20 mg doses, to be taken before going to bed. Its rapid absorption after oral ingestion (average peak plasma concentrations are achieved in 0.9–1.5 h), and short blood half-life (~1 to 1.2 h) make it very effective as a sleep inducer, promoting a short-lasting sleep with rapid onset, and limited potential for hangover effects (3,6,10). Following administration of a single 5 mg oral dose of zaleplon, Rosen et al. (7) reported peak serum zaleplon concentrations of 0.015 μg/mL at 0.8 h, declining to 0.003 μg/mL by 4 h (3).

Zaleplon is primarily metabolized by aldehyde oxidase to form 5-oxo-zaleplon. Zaleplon is metabolized to a lesser extent to form desethylzaleplon, which is quickly converted to 5-oxo-desethylzaleplon. All of zaleplon's metabolites are pharmacologically inactive (2). Zaleplon has an abuse potential similar to benzodiazepines and benzodiazepine-like hypnotics that cause impairment of psychomotor function. Following administration of a 60 mg dose of zaleplon, peak plasma zaleplon concentrations of 0.109 μg/mL were reported by Beer et al. (9). The most frequent signs of impairment at elevated concentrations include drowsiness, dizziness, impaired concentration, impaired coordination and nystagmus (2,3,9).

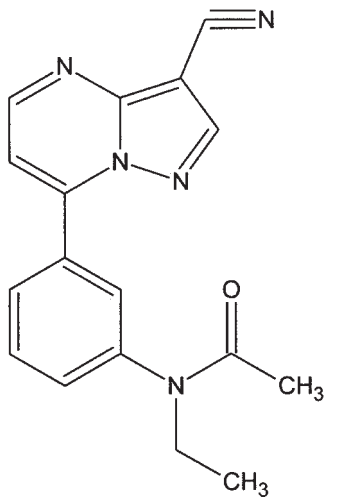

FIG. 1—*Structure of zaleplon.*

Chlorpheniramine and dextromethorphan were the only other drugs identified that have been shown capable of impairing psychomotor abilities (3,12). Chlorpheniramine can produce symptoms of central nervous system depression in overdosage and may enhance the decremental effects in an additive manner (3,12). Dextromethorphan can produce sedation in overdosage (12). It is believed by the author, that the concentration of zaleplon alone in the absence of any other drug would reasonably attributed to impairment. The chlorpheniramine concentration could possibly have an additive effect but was within therapeutic range (13). The dextromethorphan concentration was determined to be insignificant to psychomotor performance (13). The zaleplon concentration was determined and found to be sufficient to result in sedation and sleepiness (9).

Information from the manufacturer (2) indicates that the drug should not be taken before driving. Given the short half-life of the drug, when properly managed, hangover or residual effects should be unlikely, but risk of subjective feelings of sedation increases with an increasing dose (6). The *Physicians Desk Reference* (2) notes that patients taking zaleplon may experience effects similar to those associated with alcohol, and recommends that zaleplon not be taken with alcohol, since the effects would be additive. Given the specific role of zaleplon as a sleep inducer, its simple pharmacokinetics, and the known relationship between fatigue, sleepiness, and decrements in driver performance and the associated increased accident risk, it appears reasonable to conclude that doses of zaleplon exceeding therapeutic concentrations have the potential to affect driving in a negative way (3,9).

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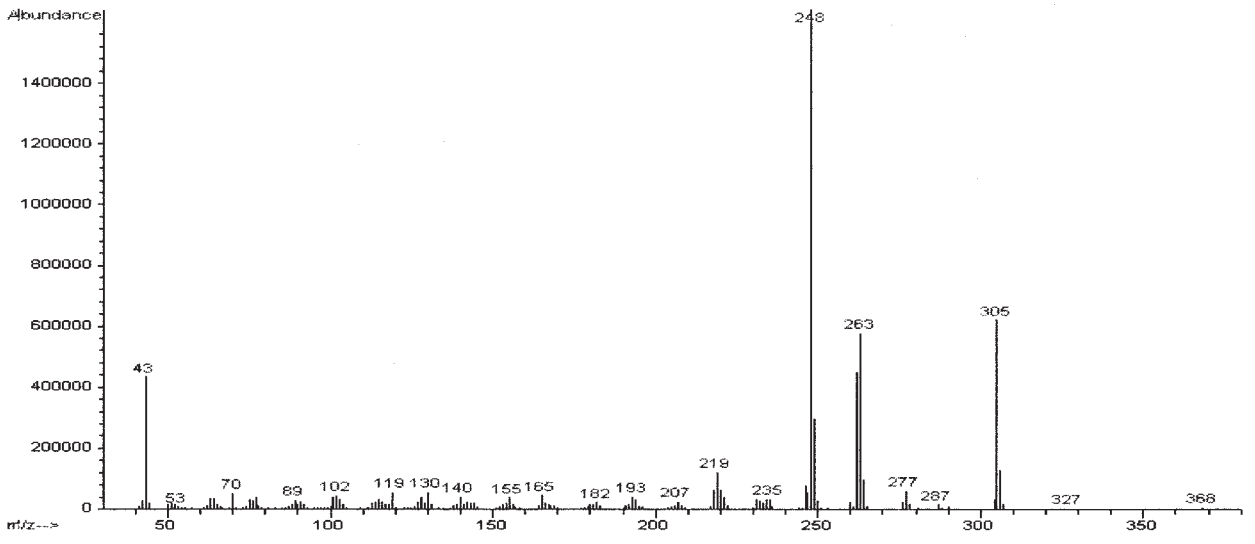

FIG. 2—*Electron impact mass spectrum of zaleplon.*

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