Xylazine in Human Tissues and Fluids in a Case of Fatal Drug Abuse

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Abstract
A fatal case of multiple drug abuse in a 36-year-old veterinarian involving injection of xylazine and ingestion of alcohol and clorazepate is presented. Quantitative analysis of xylazine was by gas liquid chromatography with a nitrogen detector. Xylazine concentrations (mg/L or mg/kg) were: blood, 0.2; brain, 0.4; kidney, 0.6; liver, 0.9; lung, 1.1; omentum adipose 0.05; and urine, 7.0. Blood ethanol and nordiazepam concentrations were 380 mg/dL and 2.5 mg/L, respectively.

Introduction
Xylazine (5,6-dihydro-2-(2,6 xylidino)-4H-1,3 thiazine) is a sedative, analgesic, and skeletal muscle relaxant veterinary drug effective in a wide range of domestic and wild animals (1). In the United States, the drug is marketed under the trade name Rompun (Bayvet) and is available in a 50-mL vial of 100-mg/mL xylazine hydrochloride intended for either intravenous or intramuscular injection. Xylazine shares certain pharmacological properties with a number of structurally related drugs: phenothiazines, tricyclic antidepressants, and clonidine (Figure 1) (2). Although xylazine is not indicated for human administration, three cases of non-fatal xylazine poisoning in man have been reported (2-4). Xylazine concentrations in body fluids were reported in only one of these cases (3).

A fatal case of multiple drug abuse in which xylazine was determined in body fluids and tissues is presented.

Case History
The decedent was a 36-year-old white male veterinarian. On the evening prior to death he was drinking alcohol to excess before retiring to bed at midnight. At 7:00 a.m. he awoke to use the bathroom and drank some orange juice before returning to bed until 3:00 p.m. He then ate some food. His wife left the house on an errand at 4:00 p.m. Upon returning at 8:00 p.m. she found the decedent lying unresponsive on the kitchen floor. In the kitchen were two syringes and a 50-mL vial of xylazine only one-quarter full. Emergency medical personnel were immediately summoned but resuscitation efforts were unsuccessful.

The decedent had a five-year history of alcoholism and was known to have been self-administering xylazine for at least one month prior to death. He had been prescribed clorazepate (7.5 mg, three times daily) by his psychiatrist, but was known to routinely take larger doses of the drug. Although, his substance abuse resulted in personal and financial problems, he had never been institutionalized for treatment nor was he considered to be suicidal.

Autopsy
The body was that of a well-developed white male measuring 5 ft 11 in. tall (178 cm) and weighing 200 lb (91 kg), who appeared his stated age of 36 yr. An intravenous line was present in the left antecubital fossa and, on removal, there were three fresh puncture sites in that area. Additionally, there were three fresh injection sites in the right antecubital fossa. Only one of these puncture sites could be accounted for by therapeutic procedure. There were several fresh rib fractures related to resuscitation efforts. The lungs weighed 1350 g and were markedly congested and edematous. All other organs were normal. Specimens were collected and submitted for toxicological analysis.

Analytical Methods
Chemicals and Reagents
Inorganic chemicals were analytical reagent grade. Solutions were prepared with deionized water and stored in glass. Organic chemicals were distilled in glass. All glassware was washed with 15% nitric acid and silanized with Prosil-28 (PCR).

Xylazine Standards
A stock standard of 100 mg/L of xylazine was prepared by dissolving 10 mg of the drug in 100 mL of absolute ethanol. Prior to analysis, 1.0 mL of the stock standard was diluted to 10.0 mL with absolute ethanol. Working standards of 0.1, 0.25, 0.50, and 1.0 mg/L of xylazine were prepared by adding 10, 25,
by the method of Freimuth and subjected to ultraviolet (UV)
ing systems A, B, and C, respectively. Visualization was by potas-
sium iodoplatinate. Xylazine spots were eluted from TLC plates
lyzed by TLC, displayed R_f values of 0.78, 0.62, and 0.20 in develop-
ments A, B, and C, respectively. Visualization was by potassium
eluted spots displayed a UV maximum at 212 nm. General screening procedures applied in the
spectrophotometric analysis in 0.1N sulfuric acid (8). Reference
sols were dried by shaking with anhydrous sodium
sulfate, transferred to a concentration tube, and evaporated to
dryness under a stream of nitrogen. The resultant residues were
redissolved in methanol and aliquots were injected in the gas
cromatograph. Typical chromatograms of tissue extracts are
presented in Figure 2. The precision of the assay was determined
by multiple analysis of each specimen (N = 3). The observed
coefficients of variation (CV) ranged from 4% (liver, 0.9 mg/kg)
to 16% (blood, 0.2 mg/L). The absolute recovery of xylazine
was not determined. The sensitivity of the assay (a peak twice
the baseline) was approximately 0.02 mg/L.

Results and Discussion

The results of the toxicological analysis are presented in Table
1. Xylazine was detected in all specimens analyzed. Based upon
these findings, death was attributed to the combined depressant
effects of alcohol, nordiazepam, and xylazine. The nordiazepam
blood concentration exceeded the expected value if the decedent
had ingested clorazepate as prescribed (22.5 mg/day). The concen-
tration, 2.5 mg/L, is consistent with a doubling of the daily dose
(50 mg/day) which the decedent had been known to do (10).

Three cases of xylazine overdose in man have been previously
reported. Carruthers et al. reported a case of a 34-year-old male
who had been self-medicating for insomnia with intramuscular
injections of xylazine (4). Within 30 min of apparently injecting
as much as 1 g of xylazine, he was found comatose, apneic,
and areflexic. During his hospitalization, he displayed hypergly-
cemia, various electrocardiograph (ECG) abnormalities and ele-

Figure 1. Structural formulas of xylazine and related drugs (with permission of Marcel Dekker, Inc. from Reference 2).
vated cardiac enzymes. Sinus tachycardia and premature ventricular contractions (PVC) were successfully treated with lidocaine. The patient recovered and was discharged. No toxicological analysis was performed. Carruthers et al. stated that "the patient would have died had he not been found shortly after the xylazine was administered since respiratory depression was marked" (4).

Gallanosa et al. reported the attempted suicide of a 20-year-old female horse trainer who drank 0.4 g of xylazine (2). When found 2 hr after ingestion, she was drowsy, incontinent of urine, difficult to arouse, and complaining of dizziness and weakness. On admission to the hospital, she displayed signs of central nervous system (CNS) depression (drowsiness, disorientation, hyporeflexia) but responded to painful stimuli. Bradycardia, hyperglycemia, apneic spells, hypotensive episodes, and PVCs were also noted during her two-day hospitalization. Analysis by GLC/mass spectrometry detected the presence of xylazine in her urine; however, with a detection limit of 0.1 mg/mL, no xylazine was detected in blood.

Lewis et al. reported the case of a 39-year-old veterinary surgeon’s wife who, like the decedent in the authors’ case, was an alcoholic supplementing her drinking with injections of xylazine (3). Hospitalized for drowsiness and slurred speech, she displayed on admission a sinus bradycardia of 35/min. Analysis of serum and urine (procedure not reported) revealed xylazine concentrations of 0.03 mg/L and 1.7 mg/L, respectively.

Little is known of xylazine effects in man; however, these three cases provide a consistent picture of overdose symptoms: pronounced initial bradycardia, significant CNS and respiratory depression, ECG abnormalities including possible ventricular arrhythmias, and transient hyperglycemia. Additionally, the intravenous injection of 7 mg of xylazine in a volunteer induced anesthesia and a bradycardia of 44/min (11). Gallanosa et al. noted these findings and compared the toxicity of xylazine overdose to that of structurally similar drugs; phenothiazines, tricyclic antidepressants, and clonidine (Figure 1) (2). All four drugs may produce bradycardia, CNS depression, and ECG abnormalities. Transient hypoglycemia is associated with clonidine overdose (2).

The pharmacokinetics of xylazine have been studied in the dog, sheep, horse, and cattle (12). In all four species the drug displayed a typical second order plasma decay curve with a rapid alpha distribution phase, half-life of 1.2 min (cattle) to 5.9 min (horse), and a beta elimination half-life of 22 min (sheep) to 50 min (horse). Both the onset and duration of xylazine-induced analgesia correlated well with xylazine pharmacokinetics in the dog, sheep, and horses. However, sustained xylazine-induced sedation, hyperthermia, and hyperglycemia were not correlated with xylazine plasma concentrations in cattle (12). This suggests the possible production of one or more active xylazine metabolites in cattle. In all four species the drug was characterized by a very large apparent volume of distribution and an intensive, rapid biotransformation. In rats, 70% of the drug is eliminated in urine within 2 to 3 hr of administration; however, only 8% is eliminated as the parent drug (13). Likewise, cattle excrute only 1% of the dose unchanged in urine (7).

While the dose and time of injection were not known in the authors’ case, if it is assumed the decedent injected only several hundred milligrams (2 to 3 mL) of xylazine shortly before death, the low concentrations of xylazine in blood and tissues support the hypothesis that in man as well as domestic animals, xylazine is rapidly biotransformed. The relative concentrations of the drug in tissues compared to blood are consistent with second order pharmacokinetics in which the drug is rapidly biotransformed and distributed to visceral organs and skeletal muscle. Significant concentrations of xylazine have been detected in skeletal muscle distal to the site of xylazine injection in sheep (7). Unfortunately, skeletal muscle was not collected in the authors’ case; however, this tissue may be expected to contain a significant percentage of an administered dose of xylazine. The authors’ recommend that this tissue be collected in future cases of xylazine overdose.

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References


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