Tissue Distribution of Xylazine in a Suicide by Hanging

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Abstract

Xylazine (Rompun®, Sedazine®, AnaSed®) is currently the most commonly used sedative-analgesic in veterinary medicine. There are nine published cases of xylazine's involvement in human drug-related deaths and impairment. However, blood concentrations were reported in only four of these cases. Three of these nine cases were fatalities involving xylazine, two of which involved xylazine alone but did not report blood concentrations because of extensive decomposition of the bodies. This report documents a case in which xylazine alone was identified in a suicide by hanging. The following xylazine concentrations were found: 2.3 mg/L in heart blood; 2.9 mg/L in peripheral (subclavian) blood; 6.3 mg/L in bile; 0.01 mg/L in urine; 6.1 mg/kg in liver; and 7.8 mg/kg in kidney.

Introduction

Kroneberg et al. (1) developed xylazine in the mid 1960s for use in veterinary medicine for restraint, facilitation of minor surgical procedures, and preanesthesia. It was also investigated for use in humans as a sedative-hypnotic/analgesic/anesthetic premedication, but was rejected because of its frequent association with severe hypotension.

Xylazine acts centrally as an α2-adrenergic agonist with inhibitory effects on the brain stem vasomotor center resulting in bradycardia and transient hypertension followed by sustained hypotension (2). It also has peripheral autonomic effects, reducing the centrally mediated sympathetic tone by interneural blockade of norepinephrine release, resulting in bradycardia, hypotension, and reduced cardiac output. More recently, it has also been found to have an affinity for cholinergic, serotonergic, dopaminergic α1-adrenergic, H2-histaminergic, and possibly opiate receptors (3,4).

Because of the relative lack of blood concentrations in toxicological case report data, this case report presents a suicide by hanging where xylazine most likely was used to sedate the victim and perhaps facilitate his fall from the tree from which he was found hanging.

Case History

The police responded to a phone call from a woman who reported her husband missing and finding a suicide note. The note stated that she could "...find [him] at the gravel pit past the second no trespassing sign...". After a brief search, a neighbor advised that he had found the deceased hanging from a tree just inside the tree line near an abandoned gravel quarry. The deceased was a 42-year-old Caucasian male who was a practicing veterinarian and had a history of depression. A used 3-cc syringe, clamps, and a tourniquet were found on the ground below the body.

At autopsy, the body presented with a rope around the neck. There was an underlying ligature furrow mark on the anterior aspect of the neck, and it extended upwards behind the ears to the occipital area. Rare petechiae were identified on the conjunctiva bilaterally. There were no other significant autopsy findings. Specimens were submitted for toxicological analysis.

Experimental

Materials

Xylazine hydrochloride standard was obtained from Sigma-Aldrich Corp. (St. Louis, MO). Mepivacaine (internal 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.

Extraction and instrumentation

Xylazine analysis was performed using an alkaline drug extraction as described in a previous publication (5).

Analysis was performed on a Hewlett-Packard (Wilmington, DE) 5890 gas chromatograph (GC) equipped with a nitrogen-phosphorus detector (NPD). The column was a J&W Scientific (Folsom, CA) DB-5 5% phenyl-methyl-silicone fused capillary column (15 m x 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. Xylazine was quantitated from a matrix-based calibration curve using calibrators of 0.5, 1.0, 2.0, and 4.0 mg/L. Appropriate tissue dilu-
When used intramuscularly or subcutaneously, the manufacturer with ketamine, it induces neuroleptic-type anesthesia and amnesia, leading to sedation, coma, and death.

Pathognomonic signs of xylazine use, including hypotension, bradycardia, decreased cardiac output, and respiratory depression, are produced in horses and analgesia/sedation in dogs and cats (6). Pharmacologically, in addition to the above effects, xylazine also produces bradycardia and hypotension in a mechanism similar to clonidine (Catapres, a potent antihypertensive drug), which is usually maintained for 1-2 h, and analgesia that lasts for 15-30 min.

Xylazine (Rompun, Sedazine, AnaSed), whose chemical structure closely resembles the phenothiazine tranquilizers and tricyclic antidepressants, is a non-narcotic sedative used exclusively in veterinary medicine. It is also used as a weak analgesic, muscle relaxant, and an emetic. When used in combination with ketamine, it induces neuroleptic-type anesthesia and ameliorates the "emergence reactions" commonly associated with the use of ketamine alone. In the United States, xylazine is available in 20 mg/mL and 100 mg/mL injectable solutions.

Pharmacologically, in addition to the above effects, xylazine also produces bradycardia and hypotension in a mechanism similar to clonidine (Catapres), a potent antihypertensive agent, to which xylazine also bears a structural resemblance. These effects are mediated via stimulation of $\alpha_2$-receptors and depression of norepinephrine release from peripheral nerve terminals (4). The central $\alpha_2$-receptor stimulation produces inhibitory effects via interneural blockade producing the pathognomonic signs of xylazine use, including hypotension, bradycardia, decreased cardiac output, and respiratory depression, leading to sedation, coma, and death.

Therapeutic doses vary from $\leq 0.2$ mg/kg intramuscularly (IM) for Caesarean sections in cattle up to 5 mg/kg for anesthesia in horses and analgesia/sedation in dogs and cats (6). When used intramuscularly or subcutaneously, the manufacturer recommends a dose of 0.5 mg/kg. These dosages produce sedation, which is usually maintained for 1-2 h, and analgesia that lasts for 15-30 min.

The manufacturer recommended intravenous dosage for all animals is 0.2 mg/kg. As with most sedative analgesics/ anesthetics, xylazine distributes rapidly after intravenous administration, primarily to the central nervous system and kidneys (2). After intravenous administration, systemic $t_1/2$ ranges between 22 min for sheep, and 50 min for horses (7). Peak plasma concentrations are reached in 12-14 min in all species. Xylazine bioavailability (intramuscular to intravenous) ranges from 52 to 90% in the dog, 17 to 73% in sheep and 40 to 48% in the horse. The effective $t_1/2$ is approximately 2-3 h. This drug has a very wide therapeutic index with an LD$_{50}$ in animals ranging from 47 to 70 mg/kg (8).

Total excretion occurs within 10-15 h, 70% of which is accomplished via the kidneys (2). Only about 8% is excreted as unchanged drug.

A number of fatal and non-fatal intoxication cases from xylazine have been reported. Poklis et al. (9) reported a blood xylazine concentration of 0.2 mg/L in a 36-year-old veterinarian who had been self-administering xylazine for at least one month prior to death. The victim's blood also had an ethanol concentration of 0.38 g/dL and a nordiazepam concentration of 2.5 mg/L. Mittleman et al. (10) reported two fatalities in which xylazine was detected. Both cases were badly decomposed. One death was attributed to head injuries; the liver xylazine concentration in this case was 0.26 mg/kg. The other case had no obvious cause of death, but had a liver xylazine concentration of 42 mg/kg. Hoffman et al. (4) presented a non-fatal case of a farmer who attempted to commit suicide by intramuscular injection of xylazine. He was comatose, hypotensive, bradycardic, and mildly hypoglycemic. The highest plasma concentration measured was 4.6 mg/L. Supportive therapy led to a full recovery.

This case is unique because we report blood concentrations of xylazine when no other drugs were detected and xylazine was not the cause of death. Although the exact amount administered was unknown, the maximum amount that could have been administered is 300 mg because a 3-cc syringe was found, and the highest concentration available is 100 mg/mL. Assuming the maximum possible dose, this equates to a dose of $\sim 3.5$ mg/kg in this 89-kg individual. This is well within the range of non-fatal doses reported elsewhere (10). As stated, xylazine is extensively metabolized (only 8% excreted unchanged) and primarily excreted in the urine. Therefore, the detection of a significant amount of parent drug in the bile and a small amount in the urine may indicate a period of survival before his death, which was ultimately by strangulation.

The medical examiner reported the cause of death as hanging, the manner of death was suicide. Although "xylazine intoxication" was listed in the "Pathologic Diagnoses" section of the autopsy report, it was not listed as "contributory" on the death certificate. It was theorized the victim self-administered the xylazine to sedate/anaesthetize himself and/or to assist his fall from the tree from which he was found hanging.

References

1. G. Kroneberg, A. Oberdorf, F. Hofmeister, and W. Wirth. On the pharmacology of 2-(2,6-dimethylphenylamino)-4H-5,6-dihydro-1,3-thiazine (Bayer 1470), a substance inhibitory for adrenergic and...


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