K4 Fatal Overdose With the Anti-Diarrheal Medication Loperamide

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After attending this presentation, attendees will be briefed on an apparent suicidal overdose involving loperamide, including analytical parameters used for confirmation and quantitation.

This presentation will impact the forensic science community by describing lethal loperamide concentrations and autopsy observations. This case also highlights the importance of scene investigation and communication between the toxicology laboratory and medical examiners.

Loperamide is a Piperidine Opioid (PO) found in several over-the-counter anti-diarrheal preparations. Doses range from 2 – 4mg PO in adults, not to exceed 16mg daily and expected plasma concentrations are <0.01mg/L. At therapeutic doses, loperamide does not produce typical opioid effects on the central nervous system because of low systemic availability, high protein binding, and poor accumulation in the brain. Loperamide and its primary, inactive metabolite desmethylloperamide are almost immediately pumped out of the brain by P-glycoproteins. Adverse effects are rare, but can include cramps, nausea, drowsiness, dizziness, headache, and dry mouth. Overdoses are usually accidental, nonfatal, and occur in children under age three. Here is reported an apparent suicidal overdose involving loperamide.

A 20-year-old White male with a history of pain and depression was found dead at home along with eight empty 72-count bottles of 2mg loperamide hydrochloride tablets and a receipt of purchase dated one day prior. No suicide note was found. Significant autopsy findings included clear, frothy fluid at the lips and slight vomitus on the face. Biological tissues and fluids collected at autopsy were submitted for toxicological analysis with loperamide noted as a suspected factor in death.

Femoral blood and urine were negative for ethanol, methanol, acetone, and isopropanol. Enzyme-linked immunosorbent assay screening for cocaine metabolite, opiates, methamphetamine/MDMA, phencyclidine, barbiturates, carisoprodol/meprobamate, fentanyl, methadone, zolpidem, amphetamine/phentermine, acetaminophen, and salicylate was negative in femoral blood. HPLC-UV analysis tentatively identified 7-aminoclonazepam, but was not confirmed by mass spectrometry. Alkali-extractable drug screening by liquid-liquid extraction and GC/MS was also negative.

Given the numerous empty bottles on scene and autopsy findings suggesting overdose, it was assumed that loperamide may be present in this case but instrument settings precluded identification as loperamide and desmethylloperamide are reportedly late eluters. As hypothesized, loperamide fortified into drug-free blood, extracted and analyzed by a normal GC/MS screen was not detected. By extending the final hold time, loperamide eluted with substantial tailing. Modifying the temperature ramp further improved peak shape and loperamide was confirmed in femoral blood and urine. Desmethylloperamide was tentatively identified by spectral library match in both matrices, but a reference standard is not commercially available for comparison.

This study successfully quantitated loperamide by GC/NPD using a less polar column and the optimized GC/MS chromatographic conditions. The linear dynamic range was from 0.1 – 6mg/L and accuracy was greater than 85%. Loperamide results obtained in blood, urine, liver, and gastric contents were 0.4mg/L, present, 7mg/kg, and 30mg/kg, respectively; urine was evaluated qualitatively per department policy.

The medical examiner ruled the death a suicidal overdose of loperamide. Two suicidal loperamide overdoses are reported with loperamide concentrations of 2.6mg/L (blood), 12.5mg/kg (liver), and 3mg/kg (gastric contents) in one case and 0.084mg/kg (blood) and 0.87mg/kg (liver) in the other. Blood concentrations in this case and the literature greatly exceed expected therapeutic concentrations. Presumably in overdose, the P-glycoprotein efflux mechanism is overwhelmed, allowing loperamide to exert typical opioid CNS effects leading to euphoria and ultimately death.

Internet-user forums debate the effectiveness of high-dose loperamide to achieve euphoria, ward off withdrawals, and potentiate other opioid receptor agonists. If euphoria is achieved, the high is reportedly not as intense as other prescription opiates/opioids and does not justify the cost or gastrointestinal side effects. Still, since loperamide is easily accessible, the potential for abuse exists and laboratories should evaluate whether their basic drug screens are capable of detecting this late-eluting compound.

Loperamide, Suicide, Death Investigation

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