CASE REPORT

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A Hydromorphone and Ethanol Fatality

REFERENCE: Levine, B., Saady, J., Fierro, M., and Valentour, J., **"A Hydromorphone and Ethanol Fatality,"** *Journal of Forensic Sciences*, JFSCA, Vol. 29, No. 2, April 1984, pp. 655–659.

ABSTRACT: A case report is presented of a fatality where death is attributed to the combined central nervous system-depressing effects of ethanol and hydromorphone. Blood and tissue levels of hydromorphone are reported and the concentrations are compared to previously reported data.

KEYWORDS: toxicology, pathology and biology, alcohol, hydromorphone

Hydromorphone (Dilaudid®) is a semisynthetic narcotic that is approximately five to ten times more potent than morphine as an analgesic [*1*]. It may be administered orally, parenterally, or rectally and is prescribed for its antitussive as well as its analgesic effects. Like morphine, it is subject to physical dependence and abuse. This paper presents a case report in which hydromorphone, in conjunction with ethanol, is implicated in a death.

Case History

A 29-year-old white male house painter was found dead on a couch at 8:00 a.m. by friends. During the early evening before his death, he had been drinking ethanol. Upon arriving at a friend's house at 7:30 p.m. he immediately went to sleep on the couch. Snoring was noted at 3:30 a.m. when he was checked by a friend.

Past medical history included labile severe hypertension for which propranolol had been prescribed. He also had complained of cold symptoms the day before his death. Family members reported that he used unspecified street drugs and drank excessively episodically. No drugs were found at the scene. Moreover, there was no history of seizure disorders, faint-

Received for publication 18 April 1983; revised manuscript received 29 June 1983; accepted for publication 2 July 1983.

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ing spells, episodes of arrhythmia, or other complaints associated with sudden unexpected death. Also there was no family history of sudden unexpected deaths.

Autopsy Findings

External examination disclosed an 80-kg, 170-cm muscular male who showed no evidence of injury. He did not exhibit any old or recent needle tracts, skin popping scars, or nasal septal ulcerations. The pupils were 4 mm. Visceral examination revealed no abnormalities except for marked congestion and edema of the lungs, which weighed 1560 g, and marginal edema of the brain manifested by mild flattening of the gyri and symmetrical narrowing of the ventricles. The brain weighed 1610 g.

Microscopy of heart, coronary arteries, brain, and gastric mucosa showed them to be normal. The lungs were congested and the alveoli distended by pink pulmonary edema fluid. The liver sections disclosed diffuse moderate microvesicular and macrovesicular fatty change of the central and midzones of the lobules. Portal fibrous tissue was slightly increased and densely infiltrated by lymphocytes and plasma cells and a few eosinophils. No crystals or fibrosis were demonstrable in lung, liver, or brain. The kidney exhibited mild concentric medial hypertrophy of medium sized arteries and rare shrunken sclerotic glomeruli, consistent with a history of hypertension. No etiology for labile hypertension was discovered.

Experimental Procedure

Materials

The standards used were hydromorphone hydrochloride in a 100-mg/L methanolic solution (as free base), prepared from pharmaceutical Tubex preparations (Wyeth Laboratories) and nalorphine hydrochloride in a 1-mg/mL methanolic solution (as free base), donated by the Medical College of Virginia Department of Pharmacology and Toxicology.

The reagents included as solvents were toluene (Fisher high-performance liquid chromatography [HPLC] grade), hexane (Fisher pesticide grade), isoamyl alcohol (Baker reagent grade), and methanol (Fisher HPLC grade); the extraction solvent was toluene:hexane:isoamyl alcohol (78:20:2). The buffer was a pH 9.9 carbonate buffer 0.5*M* sodium bicarbonate (Fisher S-233) adjusted to pH 9.9 with 0.1*M* sodium hydroxide. *N*-methyl-*bis*-trifluoroacetamide (MBTFA) (Regis Chemical Co.) was used as the derivatizing agent.

Ethanol Analysis

Ethanol was quantitated by using a Perkin-Elmer F-45 gas chromatograph for headspace analysis. The procedure used was based on the method of Wallace and Dahl [*2*].

Hydromorphone Analysis

The method of Saady et al [*3*] was used for hydromorphone quantitation. The extraction procedures for blood and urine were followed directly. Tissues were also extracted at pH 9.9, but were followed by a back extraction into 0.1*N* sulfuric acid and by re-extraction after alkalinization. In each case, the residue obtained during the extraction process was reconstituted with 40 μL of MBTFA and heated at 70°C for 20 min in a water bath; 1 μL was then injected into the gas chromatograph/mass spectrometer (GC/MS). Gas chromatograph/mass spectrometer conditions were as given in the Saady et al method.

Results

Ethanol quantitations in blood, urine, and vitreous humor were performed; the results are given in Table 1. These fluids were also screened for methanol, isopropanol, and acetone; none was detected.

Hydromorphone concentrations in the fluids and tissues obtained at autopsy are listed in Table 2. Hydromorphone was detected in bile during a routine drug screen, but an insufficient amount of bile remained to permit quantitation. A drug screen on gastric contents, urine, and bile detected no other narcotics, sedatives, hypnotics, stimulants, or salicylates.

Discussion

The quantitation of hydromorphone as well as other opiates is somewhat difficult because of poor extraction efficiency and poor chromatographic properties. After considering several methods, it was decided that the method of opiate analysis developed by Saady et al [*3*] afforded the best opportunity for hydromorphone quantitation. This method involves a one-step pH 9.9 extraction followed by the preparation of the trifluoroacetyl derivative of hydromorphone and an internal standard. By using selective ion monitoring, a detection limit of 0.05 mg/L for hydromorphone was found. The analysis of tissues included an acid cleanup of the initial extraction, followed by re-extraction after alkalinization. The sensitivity for this multiple-step extraction was 0.2 mg/L. Of the fluids and tissues analyzed, only urine was hydrolyzed before analysis; hydrolysis of blood and tissues before analysis would have resulted in higher hydromorphone concentrations. For example, a brief analysis of the blood from the present case showed a greater amount of hydromorphone present after hydrolysis than without hydrolysis. Unfortunately, the insufficient specimen amount precluded greater quantitative detail. Nakamura and Way [*4*] found up to 2.5 times more morphine and up to 1.2 times more codeine from hydrolyzed blood samples than from unhydrolyzed samples. However, since only free drug can interact with its receptor to produce pharmacologic effects, it was decided that quantitation of free hydromorphone would provide more meaningful information.

TABLE 1—*Ethanol concentrations.*

Fluid	Concentration, mg/L
Blood	900
Urine	1500
Vitreous humor	1100

TABLE 2—*Hydromorphone concentrations.*

Fluid or Tissue	Concentration, (mg/kg or mg/L)
Blood	0.1
Vitreous humor	0.1
Urine	7.8[a]
Liver	0.8
Kidney	0.7
Brain	0.5

[a] Following hydrolysis.

There are few reports in the literature relating blood hydromorphone concentrations with oral or intravenous overdoses. Garriott and Baselt [5] reported five such cases with blood concentrations ranging from 0.02 to 1.2 mg/L. This sixtyfold difference in blood hydromorphone concentrations in cases attributed to drug overdose can make the interpretation of blood concentrations somewhat difficult. In the present case, the interpretation is further complicated by the presence of ethanol in the blood. In the five previously reported cases, other drugs affecting the central nervous system detected included ethanol, diazepam, propoxyphene, secobarbital, amitriptyline, morphine, phenmetrazine, and amphetamine. Although no previously published studies were found concerning the synergistic action of ethanol and hydromorphine, similar types of studies have been made for ethanol and other narcotics in animals and humans. For example, Eerola [6] found an additive type of synergism in the combined effect of sublethal and lethal doses of ethanol and morphine in mice. McCoy et al [7] found an additive interaction in mice in all ethanol-to-morphine ratios (weight-to-weight) greater than two to one, but an antagonistic interaction in ratios less than two to one. Reisch [8] recently reported an average blood morphine level of 0.4 mg/L (range 0.01 to 1.2 mg/L) and an average blood ethanol level of 1100 mg/L (range 0 to 4000 mg/L) in heroin-related deaths. Therefore, it is likely that ethanol would contribute to the adverse pharmacologic effects of hydromorphone. Given these data and the absence of any distinguishng abnormalities detected at autopsy, it seems reasonable to attribute the death in the present case to the respiratory and cardiovascular depression from the combined effects of ethanol and hydromorphone.

Garriott and Baselt [5] also included hydromorphone concentrations in blood, liver, kidney, bile, and urine. No distribution patterns were ascertained; in four of the five cases, there were greater concentrations of hydromorphone in the liver and kidney than in the blood. Liver-to-blood ratios ranged from 0.3 to 16, while kidney-to-blood ratios ranged from 1 to 25. In the present case, these two ratios were within the ranges previously reported. Reasons that may explain these wide variations in tissue-to-blood ratios include the frequency of drug use and time between exposure and death.

This wide variability in drug distribution has also been found in other narcotics. For example, Garriott and Sturner [9] found morphine concentrations greater than 1 mg/L in liver and kidney in acute heroin deaths in 16 of the 18 cases. However, morphine concentrations in addicts who died from other causes was also greater than 1 mg/L in liver and kidney, suggesting that these tissues were not good indications of recent injection. Felby et al [10] determined that in general, morphine concentration in the liver was greater than in blood and muscle. Moreover, bound morphine is greater than free morphine in the liver, but bound morphine may be greater or less than free morphine in the kidney [4]. Further, Speihler et al [11] quantitated morphine in different parts of the brain and spinal cord and found no consistencies with history or time between injection and death.

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