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CASE REPORT

TOXICOLOGY

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Accidental Death from Hydromorphone Ingestion

ABSTRACT: A 15-year-old male orally consumed an unknown but fatal amount of sustained release hydromorphone. He was naïve to opioid use. No other drugs or alcohol were involved. The cause of death was acute aspiration-related bronchopneumonia, secondary to hydromorphone ingestion; the manner of death was accidental. Hydromorphone and hydromorphone-3-glucuronide were quantified in postmortem fluids by tandem liquid chromatography–mass spectrometry. The hydromorphone concentrations in the peripheral blood, urine, and vitreous humor were 57, 4460, and 31 ng/mL, respectively. The hydromorphone-3-glucuronide concentrations in the corresponding three fluids were 459, 36,400, and 40 ng/mL. Hydromorphone-3-glucuronide accumulation probably did not contribute significantly to the opiate toxicity. The proposed minimum lethal hydromorphone blood concentration in the nontolerant user is in the vicinity of 60 ng/mL.

KEYWORDS: forensic science, fatality, hydromorphone, hydromorphone-3-glucuronide, tandem liquid chromatography–mass spectrometry, blood

Hydromorphone is a narcotic, which is used in the management of acute and chronic pain. Like other opioids, it has a propensity for abuse and addiction. Analgesia is achieved over the short term with equilibrium plasma concentrations in the 1–2 ng/mL range (1). Following prolonged use, drug tolerance builds, such that higher doses are needed to produce the same effects. Consequently, the plasma "therapeutic" concentration proportionately increases.

Postmortem blood hydromorphone concentrations cover a wide range. Elevated blood concentrations can be attributed to incomplete distribution to tissue sites and to postmortem redistribution following a prolonged postmortem interval. Most often, other drugs are present, confounding blood level interpretations. Consequently, establishing the lower lethal blood limit has been elusive. Nevertheless, the lower limit is a fundamental reference point when interpreting a postmortem blood hydromorphone concentration.

The straightforward case presented herein is that of a healthy young man, naïve to opiates, who orally consumed a lethal quantity of sustained release hydromorphone. Because of the slow drug absorption, there was time for tissue distribution to occur before he expired. No other drugs or alcohol were taken. The postmortem interval was 27 h, thus minimizing any postmortem redistribution.

Hydromorphone-3-glucuronide is the major hydromorphone metabolite (2). This is the first time hydromorphone-3-glucuronide has been reported in postmortem fluids following a fatal hydromorphone overdose. There are four other minor metabolites: dihydromorphine, dihydroisomorphine, and their respective 3-glucuronides (2). They were not measured because of the unavailability of the reference compounds.

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Case History

The decedent (DS) was a healthy 15-year-old boy. He and his friend had stolen up to 30 Hydromorph Contin® (Purdue Pharma, Pickering, Ontario, Canada) capsules from a family member of a mutual acquaintance. Each capsule contained 24 mg of controlled release hydromorphone. At about 2030 h, they each consumed three or four capsules. The decedent returned home at about 21:30 h. He was last seen alive by his father at 23:00 h. During the evening, three email messages were sent to his friend, the last at 23:50 h. He described feeling itchy, a side effect of opiate overdose.

He was found unresponsive in bed the next morning. His pupils were fixed and dilated. Brown foamy emesis covered his face. Resuscitation efforts by Emergency Medical Services personnel and by hospital Emergency Department personnel were unsuccessful. Treatment included intubation and administration of epinephrine, atropine, ipratropium, and salbutamol. He remained asystolic throughout and was pronounced dead at 08:00 h. His rectal temperature was 36.8°C and some stiffness was noted, suggesting he had died around 05:00 h. He had no prior medical history and was on no prescribed medication. He had no history of depression or thoughts of suicide. When questioned by police, his friends stated that he had been occasionally experimenting with alcohol and marijuana within the past year. It is not known how many capsules DS or his friend consumed. However, four capsules were discovered in the decedent's bedroom after his death. His friend was ill during the night; he was treated at hospital the following day and then released.

The autopsy was performed 27 h after death. His height and weight were 184 cm and 100 kg. There was no evidence of any injury. Aspirated gastric material was evident in the larynx, trachea, and large bronchi. The lungs were heavy; the left and right lung weighed 930 and 795 g, respectively. The stomach contained 100 mL of partially digested food matter without obvious pill fragments. On microscopy, the lungs showed diffuse pulmonary edema

and widespread acute aspiration-related bronchopneumonia. The liver showed mild fatty change, and the brain showed early hypoxic–ischemic injury.

Materials and Methods

Peripheral blood, urine, and vitreous humor were submitted for toxicology analyses. The urine was screened for basic drugs by gas chromatography–mass spectrometry (GC–MS) using a modification of the method described by Foerster et al. (3). Acidic and neutral drugs were screened by GC–MS after extracting and derivatizing the urine sample with ethyl iodide (4). The KIMS method was used on an Integra (Roche Diagnostics, Laval, QC) instrument to screen the urine for benzoylecgonine, opiates, and cannabinoids, whereas the CEDIA (Microgenics, Freemont, CA) method on a Modular (Roche) instrument was use to screen for benzodiazepines. A modified dual column method, described by Brown and Long (5), was used to screen and quantitate samples for alcohols by static headspace gas chromatography.

Hydromorphone and hydromorphone-glucuronide were quantitated in all three postmortem fluids by tandem liquid chromatography–mass spectrometry (LC–MS–MS) using electrospray positive ionization, using a modified method of that described by Al-Asmari and Anderson (6). Fluid-matched calibrators and unknown samples (100 μL) were prepared for analysis by solid-phase extraction as described (6). The eluates were dried to residue, reconstituted in 500 μL of mobile phase and 10 μL injected. All stock standards were purchased from Cerilliant (Round Rock, TX). Hydromorphone-d6 was used as the internal standard for hydromorphone, whereas morphine-3-glucuronide-d3 was used as the internal standard for hydromorphone-3-glucuronide. Six standards between zero and 4000 ng/mL were prepared in drug-free fluids. Calibration curves were linear with coefficients of variation greater than 0.999. The assayed values for in-house blood quality control samples containing hydromorphone at 75 ng/mL and 500 ng/mL were within 10% of the spiked values. The case urine aliquot was diluted 10-fold to bring the target compounds within the confines of the calibration. Analysis was performed on a 1200 HPLC (Agilent, Mississauga, ON, Canada) connected to a 3200 Q-Trap (Applied Biosystems, Concord, ON, Canada). As the published LC–MS–MS method (6) was developed with the Finnigan LCQ DECA XP Plus ion trap, it was necessary to optimize the acquisition parameters for the 3200 Q-Trap. The optimized turbospray conditions were as follows: ion spray voltage 2000 V, heater 550°C, curtain gas 12 psi, collision gas 7 psi, ion source 1 gas 60 psi, ion source 2 gas 40 psi. The collision cell conditions for all analytes were as follows: collision energy 40 V, declustering potential 66 V, entrance potential 10 V, cell exit potential 2 V, dwell time 100 ms. The retention time (min), precursor ion (*m/z*), and product ion (*m/z*) for the four target compounds were as follows: hydromorphone 3.0 286 185, hydromorphone-d6 3.0 292 185, hydromorphone-3-glucuronide 1.0 462 286 and morphine-3-glucuronide-d3 0.9 465 289. Separation was performed by reverse phase chromatography on an Allure PFP propyl column (Restek, Bellefonte, PA), 50 × 2.1 mm. Mobile phase A was made with water containing 0.2% formic acid and 2 mM ammonium formate, while mobile phase B was made with acetonitrile containing 0.2% formic acid and 2 mM ammonium formate. A gradient consisting of 10% B for 1.5 min, then changing to 50% B over 0.5 min and held for a further 2.5 min at constant flow of 0.5 mL/min was used. Re-equilibration time was 3 min. Figure 1 shows the extracted ion chromatogram, the four multiple reaction monitoring (MRM) product ion spectra and the four full-scan product ion spectra for the case blood sample.

The postmortem fluids were also analyzed for opiates by GC–MS (7,8). Analyses were performed with and without enzymatic hydrolysis with E-coli β-glucuronidase to give free and total hydromorphone concentrations. The hydromorphone conjugated to glucuronide was determined by subtraction. From this value, the hydromorphone-3-glucuronide concentration was calculated by multiplying by the molecular weight of hydromorphone-3-glucuronide and dividing by the molecular weight of hydromphone (461.5/285.3).

Results and Discussion

Adverse effects from high-dose administration of hydromorphone are primarily respiratory depression, nausea, and vomiting (9). The cause of death of DS was attributed to aspiration of vomitus secondary to hydromorphone overdose. The manner of death was accidental. Respiratory depression was a likely contributory factor but cannot be substantiated.

No alcohols were detected in any of the three postmortem fluids. Hydromorphone, nicotine, cotinine, and caffeine were detected in the urine by GC–MS screening. The immunoassay screen for opiates was positive using a 300 ng/mL cut-off. The urine creatinine was upper normal at 16 mM (181 mg/dL).

The case postmortem fluid hydromorphone concentrations appear in Table 1. The hydromorphone blood concentration was 57 ng/mL by LC–MS–MS and 65 ng/mL by GC-MS. The hydromorphone-3-glucuronide blood concentrations were almost identical, 459 and 461 ng/mL, respectively, by the two methods. The fact that all corresponding values in the table agree favorably with each other supports the validity of the two analytical methods.

For both the blood and the urine, the hydromorphone-3-glucuronide concentration was eight times higher than the free hydromorphone concentration. Also, the hydromorphone concentration in the urine (4460 ng/mL) was 78 times higher than in the blood (57 ng/mL). Similarly, the hydromorphone-3-glucuronide concentration in the urine (36,400 ng/mL) was 79 times higher than in the blood (459 ng/mL). In contrast, the hydromorphone and the hydrormorphone-3-glucuronide concentrations in the vitreous humor were somewhat similar: 31 and 40 ng/mL, respectively.

Wallage and Palmentier (10) reviewed 251 hydromorphone-related fatalities within a 19-year span, in which postmortem blood hydromorphone measurements were performed at their facility. In four cases, hydromorphone was the sole cause of death. The blood hydromorphone concentrations were 77, 141, 569, and 2684 ng/mL. In six other cases, ethanol was the only other substance found. Here, the blood hydromorphone concentrations were 65, 72, 102, 138, 154, and 163 ng/mL; the blood alcohol concentrations were 0.123, 0.065, 0.02, 0.284, 0.267, and 0.147 g/100 mL, respectively. Incidental drug findings were reported in two additional cases. In the first, the blood hydromorphone concentration was 51 ng/mL, with a citalopram of 260 ng/mL. In the second, the blood hydromorphone concentration was 70 ng/mL, with trace amounts of morphine, diazepam, and nordiazepam. These lower blood hydromorphone concentrations agree with the value of 57 ng/mL in our case.

The minimum lethal concentration in an opiate naïve individual would appear to be in the vicinity of 60 ng/mL. Higher postmortem blood concentrations appeared in opiate-tolerant subjects (10). Patients dying from cancer, not hydromorphone administration, had blood hydromorphone concentrations in the 75–423 ng/mL range. Also, high-dose hydromorphone consumption, either by injection or by ingestion, causing immediate death would result in a superficially high blood hydromorphone concentration because the short

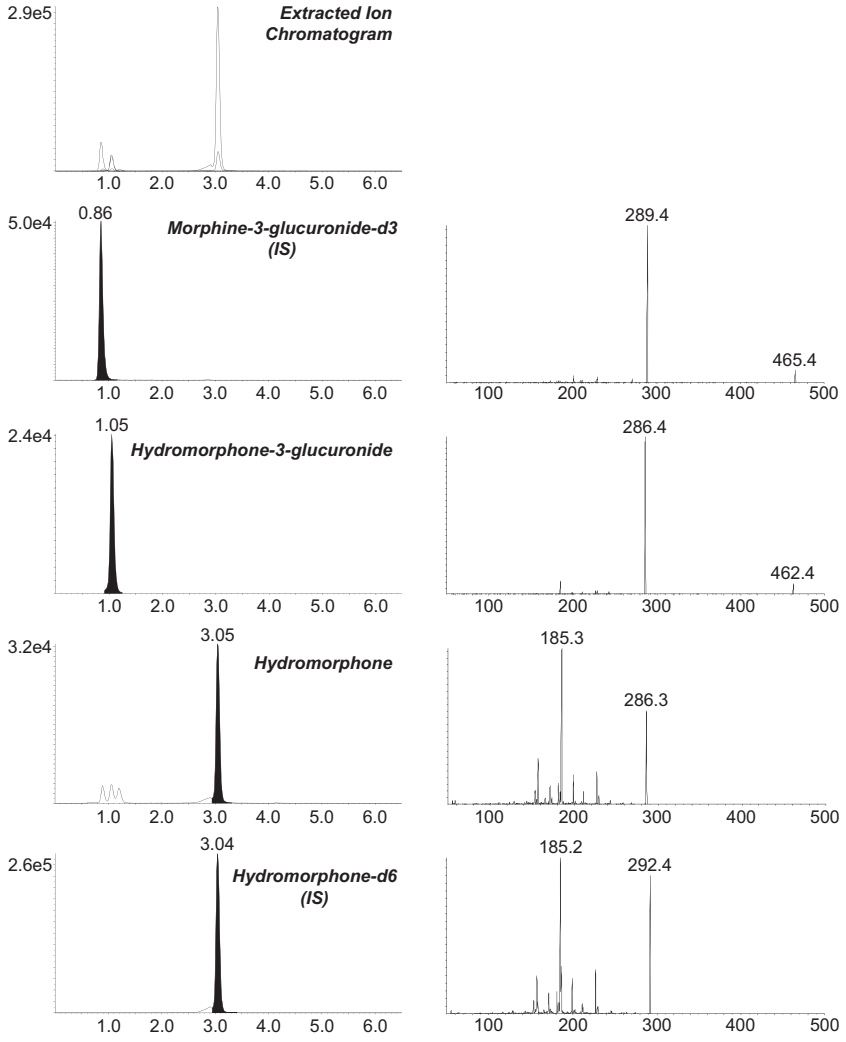

FIG. 1—*Top: Extracted ion chromatogram of the case blood sample showing the four MRM transitions. Bottom: Retention times and integrated areas of the four product ions peaks (left) alongside the full scan mass spectrum from Q3 (right). The precursor and product ions masses are indicated.*

TABLE 1—*Postmortem concentrations of hydromorphone and hydromorphone-3-glucuronide.*

	LC–MS–MS		GC–MS	
	Hydromorphone ng/mL	Hydromorphone-g (Hydromorphone)* ng/mL	Hydromorphone ng/mL	Hydromorphone-g (Hydromorphone)* ng/mL
Peripheral blood	57	459 (284)	65	461 (285)
Urine	4460	36,400 (22,495)	4800	38,139 (23,570)
Vitreous humor	31	40 (25)	26	32 (20)

*Hydromorphone content = hydromorphone-3-glucuronide ×285.3/461.5.
g, glucuronide; GC–MS, gas chromatography–mass spectrometry; LC–MS–MS, tandem liquid chromatography–mass spectrometry.

survival time does not allow for complete drug distribution between the vascular space and the peripheral tissue.

Hagen et al. (11) measured plasma free and total hydromorphone from 18 cancer patients receiving multiple daily doses of either immediate release (q 4 h) or controlled release formulations (q 12 h) in a two-way cross-over study. The dose was individualized to the patient's needs and ranged from 6 to 216 mg per day. Blood was collected after 7 days of dosing. The quantitations were performed by radioimmunoassay with and without enzymatic hydrolysis. Hydromorphone content of the glucuronide conjugate was calculated by subtracting the free concentration from the total concentration. When patients received the controlled release formulation, the average trough steady-state free and total hydromorphone content in the conjugate were 6.04 ± 1.01 and 171.85 ± 38.05 (SEM) ng/mL, whereas the average peak steady-state values were 17.76 ± 3.07 and 401.69 ± 78.22 (SEM) ng/mL, respectively.

There was no significant difference between the respective values when hydromorphone was administered as an immediate release formulation. The free hydromorphone in the case blood sample, 57 ng/mL, is 9.5 and 3.2 times higher than the average steady-state plasma trough and peak study values, respectively. In contrast, the hydromorphone content in the conjugate of the case blood sample, 284 ng/mL, is similar, 1.6 and 0.7 times that of the average steady-state plasma trough and average peak study values, respectively. It is not known if hydromorphone-3-glucuronide possesses any pharmacological activity in humans (9). If so, the effect would be the same in our case as in the study patients because the concentrations are comparable. Although Hagen et al. (11) did not focus on the clinical aspects of hydromorphone treatment for cancer pain, no untoward adverse effects were mentioned. Others (12,13) have speculated that hydromorphone-3-glucuronide would have similar properties to morphine-3-glucuronide, that being, neuroexcitatory, but void of antinociceptive properties. Wright et al. (13) attributed the myoclonus, seizures, and allodynia observed in a few patients on high-dose hydromorphone to the accumulation of hydromorphone-3-glucuronide in the central nervous system. Hagen and Swanson (14) reported severe multifocal myoclonus in one patient and seizures in two cancer patients taking high doses of hydromorphone. One of the seizuring patients died. No blood hydromophone or metabolites were quantified.

Al-Asmari and Anderson reported a postmortem blood hydromorphone of 5 ng/mL and a hydromorphone-3-glucuronide of 183 ng/mL as an incidental case finding (6). The values are consistent with ingestion of therapeutic doses of hydromorphone.

To estimate a rapid versus a delayed death from morphine ingestion, Staub et al. (15) calculated the ratio of free morphine to total morphine in blood. A result higher than 50% indicated a rapid death, with a survival time <3 h, whereas a result lower than 40% indicated a delayed death. If their proposed formula is applied to our hydromorphone case, the calculated ratio is $57/(57 + 284) \times 100 = 17\%$. The value implies a delayed death, in keeping with the ingestion of sustained release hydromorphone formulation.

Conflict of interest: The authors have no relevant conflicts of interest to declare.

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