Oxymorphone-Involved Fatalities: A Report of Two Cases

Iain M. McIntyre*, James L. Sherrard, and Craig L. Nelson
County of San Diego Medical Examiner’s Office, San Diego, California 92123

Abstract
There has been an increased awareness of illicit opiate abusers using the narcotic oxymorphone (Opana®) by inhalation. Many laboratory screening techniques currently in use cannot detect oxymorphone in blood or urine. Consequently, biological specimens containing low to moderate concentrations of oxymorphone will likely go undetected. The circumstances, pathology findings, and toxicology results of two fatalities involving oxymorphone are presented. An opiate confirmation gas chromatography–mass spectrometry (GC–MS) procedure, described in detail was able to detected, confirm, and quantify oxymorphone in both subjects. The blood concentrations were 0.05 mg/L (50 µg/L) and 0.12 mg/L (120 µg/L).

Introduction
Oxymorphone (available as Opana and Numorphin®) is a semi-synthetic narcotic analgesic derived from thebaine. It has been used for the relief of moderate to severe pain since 1956 and has about 6–8 times the analgesic potency of morphine (1). Oxymorphone is generally supplied as the hydrochloride salt in 5–10 mg normal-release and 5–40 mg extended-release tablets for oral administration, although it is also available in a 1 mg/mL solution. Adult oral doses are normally 5–20 mg every 4–6 h for the normal release tablets or 5–20 mg every 12 h for the extended-release form.

Single oral doses up to 20 mg of the normal release tablets produce peak plasma concentrations up to 4.4 µg/L at 0.5–1.5 h. Elimination half-lives range from 7.3 to 9.4 h (2). The oral bioavailability of oxymorphone averages 10% (3). The nasal bioavailability determined in rats was 43%, and the intravenous and nasal elimination profiles were similar (4).

Oxymorphone (also a biological metabolite of oxycodone) is metabolized principally by reduction and conjugation. The principal metabolite, 6-oxymorphol has approximately the same analgesic potency as its parent (5).

In addition to the better known opiates including heroin, oxycodone, and hydrocodone, oxymorphone has a high abuse potential. Recently, in San Diego, there has been an increased awareness of illicit opiate abusers using oxymorphone (Opana) by inhalation (personal communication with law enforcement agencies).

In overdose, oxymorphone causes hypotension, bradycardia, apnea, circulatory collapse, cardiac arrest, and coma (1).

Analytically, the detection of oxymorphone can produce problems for the forensic toxicology laboratory. Many screening techniques currently in use cannot detect oxymorphone in blood or urine. Consequently, biological specimens containing low to moderate concentrations of oxymorphone will likely go undetected (6). In a recent report, however, by Garside and co-workers (7), described oxymorphone detection by a oxycodone/oxymorphone enzyme immunoassay and confirmation by gas chromatography–mass spectrometry (GC–MS) in 33 postmortem cases. The mean peripheral blood concentrations in 23 of these cases was 0.15 mg/L (range 0.017–0.82 mg/L).

Case Histories and Scene and Circumstances of Death

A 48-year-old man and a 47-year-old woman were found dead in an apartment where the man had been living as a squatter. The pair was discovered by acquaintances, who entered the apartment and nudged each decedent before leaving and calling emergency services. Death was confirmed without medical intervention. Responding firefighters detected no carbon monoxide or toxic gases in the apartment.

Although the scene had no evidence of violence, ransack, or foul play, responding deputies summoned homicide investigators because of the presence of two decedents in one location. No prescription medications or evidence of drug use was found at the scene. The reporting party told responding deputies that the pair shared a history of heroin use but later told homicide detectives that they only used alcohol, which raised sus-
picion that the scene may have been altered by the reporting party. The decedents had last been seen alive approximately 28 h before they were found and were reported to be “extremely intoxicated.”

Medical histories
Medical history for the male was limited to drug and alcohol use. Medical history for the female included bipolar disorder and chronic alcoholism.

Materials and Methods

Initial toxicology testing
Routine toxicological testing included a simple volatile screen (ethanol, methanol, acetone, and isopropanol), an ELISA drugs of abuse screen performed on central blood (cocaaine metabolites, opiates, amphetamines, benzodiazepines, fentanyl, and cannabinoids, Immunalysis, Pomona, CA), and a basic drug screen performed on peripheral blood (GC–MS).

Additional toxicity testing
A specific opiate confirmation (GC–MS) procedure in peripheral blood and a urine screen (GC–MS) were subsequently performed.

Opiate confirmation (GC–MS)
Morphine, codeine, 6-monoacetylmorphine, hydrocodone, oxycodone, oxymorphine, dihydrocodeine, and hydromorphone were isolated from the biological samples using a solid-phase extraction (SPE) procedure and derivatization with MSTFA with 1% TMCS. The extracts were analyzed by GC–MS using a selected ion monitoring (SIM) method.

Materials
All drug stock standard compounds (morphine, morphine-d₃, codeine, codeine-d₃, 6-acetylmorphine, 6-acetylmorphine-d₆, hydrocodone, hydrocodone-d₃, dihydrocodeine, hydromorphone, hydromorphone-d₃, oxycodone, oxycodone-d₃, oxymorphone, and oxymorphine-d₃) were purchased from Cerilliant (Round Rock, TX). All solvents and chemicals were obtained from VWR International (Allison Park, PA). MSTFA with TMCS derivatizing solutions were purchased from Thermo Fisher Scientific (Hanover Park, IL).

Procedures
Specimen setup was conducted as follows: calibration standards were prepared in water; whole blood controls and specimens (2.0 mL) were added to screw-cap culture tubes; and 0.5 mL of the working internal standards (appropriate deuterated standards) were then added and tubes mixed.

SPE using SPEware Polychrom Clin II Columns (SPEware, San Pedro, CA) was carried out with 5.0 mL of a 5% zinc sulfate-methanol solution, made by dissolving 50 g zinc sulfate in 500 mL of deionized water in a 1-L volumetric flask and diluting to 1000 mL with OmniSolv methanol, was added to each tube and mixed well by vortex mixing. All tubes were centrifuged for 10 min at 3000 rpm. The extraction columns were prepared for each specimen by passing through each column sequentially first 2.0 mL methanol and then 2.0 mL pH 6 buffer, made by adding 27.2 g sodium acetate to about 1000 mL deionized water in a 1-L volumetric flask and adjusting to pH 6.00 with concentrated acetic acid, then diluting to 2000 mL with deionized water. The supernatant was then poured into the corresponding numbered column reservoir, and 2.0 mL pH 6 buffer was added to each reservoir. Each column was sequentially washed with 2.0 mL deionized water, 2.0 mL pH 4.0 sodium acetate buffer, made by adding 5.7 mL concentrated acetic acid to 800 mL deionized water in a 1-L volumetric flask, adjusting the pH to 4.0 with 1.0 M sodium hydroxide, and bringing volume up to 1000 mL with deionized water, and 2.0 mL methanol. The columns were then dried under full vacuum for 2 min. Each column was eluted with 2.0 mL elution solvent, made by mixing 98 mL ethyl acetate with 2 mL of concentrated ammonium hydroxide. The eluate was then evaporated under nitrogen in a 37°C water bath or heating block. A 50 µL 1% hydroxylamine in pyridine solution was then added; tubes capped tightly, vortex mixed, and incubated at 45°C for 30 min. At this time, 50 µL MSTFA with 1% TMCS was added followed by incubation at 65°C for 20 min. All tubes were finally reconstituted with approximately 200 µL ethyl acetate and injected on GC–MS.

Instrumentation
A series no. 6890 GC (Hewlett-Packard, Agilent Technologies, Santa Clara, CA) was coupled with a series no. 5973 mass selective detector (Hewlett-Packard, Palo Alto, CA).

Operating parameters
The inlet temperature was set at 220°C, and the oven temperatures were set at 100°C, 1.0 min, 20°C/min, 270°C, 4.0 min, 40°C/min, 300°C, 0.75 min. The mass detector was set on SIM mode with a solvent delay of 6.00 min. The ions monitored were 373, 358, and 315 for dihydrocodeine; 371, 343, and 234 for codeine; 429, 401, and 428 for morphine; 399, 400, and 340 for 6-monoacetylmorphine; 355, 444, and 429 for hydrocodeine; 297, 386, and 371 for hydrocodone; 474, 459, and 385 for oxycodone; and 532, 517, and 533 for oxymorphone. Ions monitored for internal standards were 374 and 346 for codeine-d₃; 432 and 417 for morphine-d₃; 405 and 406 for 6-monoacetylmorphine-d₆; 358 and 447 for hydromorphone-d₃; 300 and 389 for hydrocodeine-d₃; 477 and 488 for oxycodone-d₃; and 535 and 520 for oxymorphone-d₃.

The analytical column was an HP-1 capillary (15 m × 0.25-mm i.d., 0.25-µm film thickness, Hewlett-Packard). Six-point calibration curves (0.02–1.0 mg/L) were established for each compound. The limit of detection was determined to be 0.01 mg/L, and the reporting limit of quantitation was 0.02 mg/L. Coefficients of variation for a 0.10 mg/L whole blood control samples (for each analyte) were less than 20% in over 50 assays over a 12-month period. No known interfering substances were found. A 0.10 mg/L calibration standard for oxymorphone is shown in Figure 1.
Figure 1. Oxymorphone calibration standard (0.10 mg/L).
Results

Autopsy findings

Autopsies were performed on the day after the discovery of the bodies. Postmortem changes including rigor, lividity, and formation of Tardieu spots were similar in both cases, consistent with times of death in relative proximity. Trauma for both was limited to only a few minor contusions and abrasions. In the male, natural disease was limited to mild left ventricular hypertrophy and moderate coronary artery atherosclerosis. His lungs were congested (right lung, 540 g; left lung, 870 g). His bladder contained 225 mL of urine. Natural disease in the female was limited to micronodular cirrhosis. Her lungs were also congested (right lung, 570 g; left lung, 590 g). Her bladder contained 200 mL of urine.

As a tableside drug screen at the pathologists’ discretion, the San Diego County Medical Examiner’s Office routinely uses OnTrak TesTstiks™ (Varian, Palo Alto, CA) for morphine, cocaine, or methamphetamine. These immunoassay urine dipsticks provide a rapid, non-quantitative result prior to Toxicology’s ELISA screening and may be used in deciding to give a pending death certificate or to sign a death certificate the day of the autopsy. Although the circumstances and findings of both cases indicated that a pending death certificate was most appropriate anyway, the urine of both cases was tested with these dipsticks for morphine, cocaine, and methamphetamine. The urine of the male was positive only for morphine while that of the female was positive for morphine and methamphetamine. Pending death certificates were issued. At that time, the pathologist suspected that both decedents had used heroin and that the reporting party may have taken the evidence, either for their own use or to protect the decedents.

Toxicology findings

Initial toxicology results for the male detected ethanol (0.31% w/v in peripheral blood; 0.37% w/v in vitreous), fluoxetine (0.18 mg/L in peripheral blood), and chlordiazepoxide and metabolites (trace detected in peripheral blood). Initial results for the female detected ethanol (0.17% w/v in peripheral blood), methamphetamine (trace detected < 0.02 mg/L in peripheral blood), fluoxetine/norfluoxetine (0.63/0.94 mg/L in peripheral blood), sertraline (0.24 mg/L in peripheral blood), and bupropion (trace detected in peripheral blood). However, in contrast to the urine dipstick screens in both cases, the central blood ELISA opiate screens were negative. The ELISA crossreactivity for oxymorphone is 20% at 125 ng/mL (Immunalysis Opiate ELISA opiate screens were negative. The ELISA crossreactivity may be used in deciding to Toxicology’s ELISA screening and may be used in deciding to give a pending death certificate or to sign a death certificate the day of the autopsy. Although the circumstances and findings of both cases indicated that a pending death certificate was most appropriate anyway, the urine of both cases was tested with these dipsticks for morphine, cocaine, and methamphetamine. The urine of the male was positive only for morphine while that of the female was positive for morphine and methamphetamine. Pending death certificates were issued. At that time, the pathologist suspected that both decedents had used heroin and that the reporting party may have taken the evidence, either for their own use or to protect the decedents.

Results of additional toxicology testing

The urine testing confirmed fluoxetine, chlordiazepoxide metabolites, and oxymorphone in the male. In the female, methamphetamine, amphetamine, fluoxetine/norfluoxetine, sertraline, trazodone, bupropion, trimethoprim, and chlorpheniramine were all confirmed. Oxymorphone was not detected.

The previously described opiate confirmation (GC–MS) procedure detected, confirmed, and quantified oxymorphone in both subjects. In peripheral blood, the male had a concentration of 0.05 mg/L (50 µg/L) and the female 0.12 mg/L (120 µg/L). Urine specimens from the two individuals were later screened by the ELISA opiate assay and were negative for opiates.

Discussion and Conclusions

Based on the final results, the cause of death for the male was listed as acute alcohol, oxymorphone, fluoxetine, and chlordiazepoxide intoxication. The cause listed for the female was acute alcohol, oxymorphone, methamphetamine, trazodone, fluoxetine, sertraline, and bupropion intoxication. The manner for both cases was classified as accident.

The cases described earlier illustrate several important points. Oxymorphone is known to be abused, and therefore likely at some point to be encountered in a forensic setting. However, current toxicological screening methods are not likely to detect this substance, leading to an incomplete toxicology profile or allowing the actual cause of death to be overlooked. If enough natural disease were present to explain a death, missing the presence of oxymorphone may result in misclassification of cause and manner of death. Missing its presence in the setting of an in-custody death or alleged homicide could obviously have more dire consequences.

The potential of not detecting oxymorphone in screening indicates a need for improvement of these screening methods. If doing so is not immediately feasible, specific analysis for this medication should be kept in mind if an apparent overdose death is unsatisfactorily explained by initial results or if scene evidence (lacking in these cases) suggests its presence.

Merely supplementing the laboratory’s ELISA screen with an immunoassay dipstick of the type used in these cases may provide sufficient input as to whether to explore the presence of oxymorphone in a case. However, there is no evidence from the data packet supplied with the dipstick to suggest that there is significant cross-reactivity with oxymorphone on the “morphine” strip. It is possible that there was some other opiate (i.e., products of heroin) still present in these individuals’ urine specimens that could not be detected with ELISA routine screening but was detected on the urine OnTrak TesTstiks.

Data on potentially fatal postmortem concentrations of oxymorphone are scant. Although ethanol and other medications were detected in the cases described herein, these results may serve as a starting point in assessing potentially fatal postmortem peripheral blood concentrations of oxymorphone. The peripheral blood concentrations reported herein are in accordance with the data recently reported by Garside and co-workers (7).
References


Manuscript received March 19, 2009; revision received July 13, 2009.