Unexpected Urine Drug Testing Results in a Hospice Patient on High-Dose Morphine Therapy

Gary M. Reisfield,1 Chris W. Chronister,2 Bruce A. Goldberger,2,3 and Roger L. Bertholf4*

CASE DESCRIPTION
A 41-year-old African-American woman was admitted to an inpatient hospice facility with advanced, inoperable cervical cancer. The patient was experiencing severe pain secondary to extensive local tumor invasion, osseous pelvic metastases, and sacral decubitus ulcers. Her pain was treated with an escalating-dose schedule of morphine sulfate until satisfactory analgesia was achieved with stable doses of a combination of controlled-release morphine sulfate (MSContin®️, Purdue Pharma LP) 400 mg orally every 8 h, and immediate-release morphine sulfate (MSIR®, Purdue Pharma LP), 180 mg orally every 4 h, as needed for breakthrough pain (average 2 to 3 doses per day). The patient experienced several episodes of life-threatening vaginal bleeding for which she was hospitalized for red blood cell transfusions and bilateral hypogastric artery embolizations. She spent the final 12 weeks of her life exclusively on the inpatient hospice unit. Approximately 3 weeks before her death, the patient underwent urine specimen collection and analysis of morphine and metabolites. GC-MS analysis revealed the presence of morphine as well as small quantities of hydromorphone.

DISCUSSION
During the past 2 decades, chronic opioid analgesic therapy (COAT) for chronic nonmalignant pain has gained increasing clinical acceptance. An unintended consequence of more liberal opioid prescription practices has been a dramatic increase in the abuse and diversion of these drugs.

According to the most recent National Survey on Drug Abuse and Health (1), the number of new, past-year abusers of prescription opioids was 2 147 000—more than the number of new abusers of any other single class of prescription or illicit drugs. Furthermore, most of these opioids originated with valid physician prescriptions. By 2002, prescription opioids surpassed cocaine and heroin as the leading cause of drug poisoning reported on death certificates (2).

This potential for opioid abuse and diversion is a concern for physicians who prescribe these drugs. Consequently, urine drug testing is becoming an increasingly common part of the management plan of patients treated with COAT for chronic pain.

Knowledge of opioid metabolism is critical to the correct interpretation of opioid-positive urine drug tests in patients on COAT. Several prescription opioids produce metabolites that are themselves prescription opioids, so the presence of a metabolite in the urine may reflect either the in vivo conversion of the prescribed opioid or the unauthorized use of a second opioid (Figure 1). Alternatively, some drugs, such as heroin, are not detectable in urine owing to their rapid metabolism; heroin administration is determined solely by the detection of metabolites, 6-acetylmorphine and morphine. Because the presence of metabolites can be interpreted as unauthorized use of prescription opioids and may result in punitive actions, including loss of opioid privileges and dismissal from medical practice, it is essential that clinicians correctly interpret urine drug-testing results. Surveys of physicians who order urine drug tests in their patients on COAT reveal, however, that relatively few clinicians are aware of these metabolic conversions (3).

The most prevalent morphine metabolites of opioid analgesics include the UGT2B7-catalyzed, pharmacologically active 3- and 6-glucuronides, with several inactive metabolites occurring in smaller quantities. The possible metabolism of morphine to hydromorphone...
phone was first reported in 2006 by Cone et al., who performed a study in which hydromorphone was detected in 10 of 13 outpatients who had been prescribed morphine (hydromorphone:morphine ratio range 0.015–0.024) (4). Recently, the same group again demonstrated this metabolic conversion in 34 of 34 outpatients administered unspecified “high-dose” morphine therapy (urine hydromorphone:morphine ratio range 0.002–0.020) (5). In addition, Wasan et al. (6) recently reported data on a retrospective study involving 32 outpatients prescribed morphine therapy. These investigators tested urine specimens for hydromorphone by using GC-MS with a detection limit of 50 μg/L. Of the 32 outpatients, 21 produced hydromorphone (urine hydromorphone:morphine ratio range 0.01–0.06) (Ajay Wasan, personal communication, October 17, 2008). In addition, the investigators tested solutions with morphine concentrations up to 25 000 μg/L to determine whether hydromorphone could be formed during the chromatographic separation process. In these solutions, hydromorphone was not detected. Both groups, however, noted the provisional nature of their findings because of the possibility that urinary hydromorphone was attributable to unauthorized use of the opioid.

**RESOLUTION OF CASE**

This patient’s opioid analgesic regimen was managed entirely—in both the hospice and hospital settings—by one of the authors (GMR). During at least the final 6 months of the patient’s life she received no opioids other than morphine sulfate. She also was administered no known inhibitors or substrates of cytochrome P450 2D6 or UGT2B7. It should be noted that our patient required high-dose opioid analgesic therapy—in excess of 1500 mg/day of morphine. Although there is no “typical” morphine analgesic requirement, particularly in the context of end-of-life care, one study of hospice patients found that 90% were managed with ≤300 mg/day of oral morphine equivalents (7).

Approximately 3 weeks before the patient’s death, a urine specimen was collected from one of her bilateral nephrostomy tubes for determination of morphine and hydromorphone concentrations. The urine was collected in a standard specimen cup with no preservative, and was stored at 2–4 °C before analysis. At the time the urine specimen was collected, serum indices of renal and hepatic function were within reference intervals.

An aliquot of the urine specimen was subjected to solid-phase extraction without enzymatic or acid hydrolysis, followed by GC-MS analysis. Morphine and hydromorphone were quantified by use of deuterated internal standards and a 5-point calibration curve. The mass spectrometer was operated in selected ion-monitoring mode, and identification of morphine and hydromorphone was based on ion ratios (8). The morphine concentration in the urine specimen was...
171 000 µg/L, and the hydromorphone concentration was 104 µg/L. The hydromorphone:morphine ratio was 0.0006. Dilution of the urine specimen (500×) was required for the concentration of morphine to fall within the range of linearity.

In this patient the possibility remained that the urinary hydromorphone was a contaminant in the pharmaceutical manufacture of the morphine sulfate rather than a product of the in vivo metabolic conversion of morphine to hydromorphone. To determine the purity of the drug being administered, tablets of MSContin® (morphine sulfate, controlled release) and MSIR® (morphine sulfate, immediate release) were dissolved in 0.9% saline, and we reextracted and analyzed the drug by using the same procedure as for the urine specimen. It should be noted that in the presence of very large amounts of morphine, as found in these pills, quantifying trace amounts of hydromorphone is difficult owing to chromatographic overload and its impact on analyte resolution and identification. The limit of detection for hydromorphone confirmed that the morphine sulfate immediate release (30-mg tablet) contained <0.0125 mg of hydromorphone, and the morphine sulfate controlled-release (100-mg tablet) contained <0.125 mg of hydromorphone. These maximum limits of hydromorphone contamination correspond to urine hydromorphone:morphine ratios of 0.00042 and 0.00125 for the immediate- and controlled-release formulations, respectively.

Although these findings do not eliminate the possibility that the hydromorphone in this patient’s urine was due to contamination of the controlled-release morphine tablet, we believe this scenario to be unlikely for the following reasons: (a) we detected no hydromorphone in either the immediate- or controlled-release morphine tablets, (b) we were unable to identify any published reports of hydromorphone contamination of pharmaceutical morphine preparations, and (c) the maximum possible hydromorphone:morphine ratio of 0.00125, although greater than the ratio found in our patient, was less than the ratio reported in all other published accounts, which comprise data from more than 60 individuals.

CONCLUSIONS

This case illustrates the appearance of hydromorphone as a minor metabolic product of morphine in the urine of a sequestered patient on chronic, high-dose morphine therapy with no access to hydromorphone. Our findings in this case confirm the findings of Cone et al. (4, 5) and Wasan et al. (6) In patients administered chronic morphine therapy, urine drug tests that yield morphine as well as small quantities of hydromorphone should be interpreted with caution, because the hydromorphone may be a morphine metabolic product rather than an indicator of unauthorized use of the opioid.

POINTS TO REMEMBER

- Patients administered morphine may produce small amounts of hydromorphone, unlikely to exceed 6% of the urinary morphine concentration. Higher concentrations likely reflect hydromorphone administration.
- Similar metabolic conversions have been reported for other opioids, such as:
  - codeine → morphine,
  - codeine → hydrocodone (9),
  - hydrocodone → hydromorphone,
  - oxycodone → oxymorphone.
- Poppy seeds contain small amounts of opiates and may yield opiate-positive urine drug screen results and positive confirmations for morphine and codeine.
- Heroin (diacetylmorphine) is rapidly metabolized to 6-acetylmorphine and then to morphine. Morphine may be the only opioid detected in the urine of heroin abusers, although screening tests exist for 6-acetylmorphine, as well.
- Many physicians who order urine drug tests have insufficient understanding of opioid metabolism to correctly interpret urine drug testing results. Lack of awareness of opioid metabolic conversion may result in false accusations of opioid abuse.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: None authors declared any potential conflicts of interest.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References

4. Cone EJ, Heit HA, Caplan YH, Gourlay D. Evidence of morphine metabolism to 6-acetylmorphine as a minor metabolic product of morphine in the urine of a sequestered patient on chronic, high-dose morphine therapy with no access to hydromorphone. Our findings in this case confirm the findings of Cone et al. (4, 5) and Wasan et al. (6) In patients administered chronic morphine therapy, urine drug tests that yield morphine as well as small quantities of hydromorphone should be interpreted with caution, because the hydromorphone may be a morphine metabolic product rather than an indicator of unauthorized use of the opioid. Clinical Chemistry 55:10 (2009) 1767
The role of the laboratory in pain management combines aspects of clinical and workplace toxicology (detection of drugs in urine) and therapeutic drug monitoring (measuring drug concentrations in atypical patients, explaining unusual results, and so forth). Recommendations contained in guidelines from the American Pain Society, the American Academy of Pain Medicine, and the American Society of Interventional Pain Physicians include the use of urine drug testing to monitor patients to both confirm compliance and detect the use of illicit or unprescribed drugs (1, 2). The laboratory scientist can play a key role in the development and choice of drug panels. Considerations include the medication taken (opioids/opiates), potentially abused unprescribed medications (methadone, oxycodone, fentanyl, benzodiazepines, barbiturates), illicit drugs (amphetamine, cannabinoids, cocaine, phencyclidine), masking agents, available methodologies (immunoassay screening, chromatographic confirmation), and technical considerations (analytical sensitivity and specificity, interferences, cutoff concentrations). To address these issues, laboratories may offer several different panels for pain-management drugs.

Interpretation of drug-testing results is another key role of the laboratory scientist in pain management. Interpretation often requires knowledge of drug metabolism, as illustrated in the case presented by Reisfield et al., in which they demonstrated the apparent metabolic conversion of morphine to hydromorphone, a minor metabolite. An example of the type of critical analytical thinking that the laboratory scientist can contribute to pain management in this case is the elimination of 2 potential alternative sources of hydromorphone: contamination of the ingested morphine and generation during the extraction/detection processes. Knowledge of pharmacokinetics, pharmacodynamics, pharmacogenetics, and the analytical parameters of laboratory-testing methods are all important tools that are used when interpreting results.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest: Employment or Leadership: None declared. Consultant or Advisory Role: None declared. Stock Ownership: None declared. Honoraria: None declared. Research Funding: None declared. Expert Testimony: L.A. Broussard, Southern Nuclear, Birmingham, AL.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References

Commentary

Douglas Gourlay1,2* and Howard A. Heit3

This case raises several interesting questions about the clinical role of urine drug testing. First, it is important to distinguish between clinical, patient-centered drug testing, which is done for the patient with informed consent, and regulated or forensic drug testing, which is rarely performed in the best interests of the patient. Clearly, the testing strategy is different in these 2 situations.

This case discussion addresses the all too familiar challenges of end-of-life care that come to bear on the case of a young woman with end-stage cervical cancer. Although her case history is incomplete, it is clear that she had been on an escalating schedule of controlled- and immediate-release morphine to control pain. The reason for conducting the drug test is unclear, however, and traces of hydromorphone in the urine sample appear to conflict with the palliative treatment plan in place.

The presence of unsprescribed hydromorphone in the patient’s urine may well have created some concern for her treatment team. The differential diagnosis that may account for such results includes medication error, interpatient medication diversion, and illicit drug smuggling by family or friends who believe they are assisting their dying loved one. Although the authors are likely correct in their interpretation of this finding as a minor metabolite of morphine, an occurrence first reported by Cone et al. in 2006 (1), the authors also raise important questions about the ethical challenges of drug testing in general and testing at the end of life in particular.

Unfortunately, a lack of information about the patient’s personal and family history precludes an assessment of risk of drug misuse and addiction. Even in the context of palliative care these issues remain important. A “universal precautions” approach to risk management may have answered many of these questions (2). For example, a drug misuse history, particularly involving drugs in the opioid class, would have made the interpretation of the urine drug testing results more challenging. It is important to remember that drug misuse and addiction can and do occur in the palliative care setting, even in the relatively controlled context of a hospice. Although such behavior may pose ethical challenges regarding the use of controlled substances, even at the end of life, these issues are often overlooked.

Had the case involved chronic noncancer pain, this urine drug testing result might well have led to discontinuation of opioid medication at best or discharge of the patient from the practice, actions largely based on a failure to appreciate basic opioid metabolic pathways. The revelation that a minor metabolic pathway may have accounted for the presence of trace amounts of hydromorphone could be discerned only through a careful examination of the clinical context, thus illustrating the importance of a patient-centered, team approach to problem solving. We would encourage readers to approach urine drug testing in a patient-centered fashion (3).

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: D. Gourlay, Pharmacofor; H.A. Heit, Purdue Pharma, Abbott Laboratories, King Pharmaceuticals, Ortho-McNeil-Jansen, Cephalon, and Endo Pharmaceuticals.
Stock Ownership: None declared.
Honoraria: D. Gourlay, King Pharmaceuticals, Cephalon, and Purdue; H.A. Heit, Purdue Pharma, Abbott Laboratories, King Pharmaceuticals, Ortho-McNeil-Jansen, Cephalon, and Endo Pharmaceuticals.
Research Funding: None declared.
Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References