Retrospective Study

Identifying Levorphanol Ingestion Using Urine Biomarkers in Health Care Patients

Amber R. Watson, PharmD[1] and Ali Roberts, PharmD[1,2]

From: [1]Aegis Sciences Corporation, Nashville, TN; [2]Belmont University College of Pharmacy, Nashville, TN

Address Correspondence:
Amber R. Watson, PharmD
axialHealthcare
209 10th Avenue South,
Suite 332
Nashville, TN 37203
E-mail:
awatson@axialhealthcare.com

Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 07-03-2017
Revised manuscript received: 09-19-2017
Accepted for publication: 09-25-2017

Free full manuscript: www.painphysicianjournal.com

Background: Levorphanol is a long-acting opioid analgesic that is an optical isomer of dextrorphan, a metabolite of the over-the-counter cough suppressant dextromethorphan. Providers prescribing levorphanol for pain management may need to assess compliance through urine drug testing, as this agent is subject to abuse. Therefore, it is important to differentiate between dextromethorphan and levorphanol ingestion.

Objectives: This article is the first to report urine concentrations of levorphanol/dextrorphan and 3-hydroxymorphinan in human urine and assesses the need for an enantiomeric analysis to distinguish between dextromethorphan and levorphanol ingestion.

Study Design: Retrospective data review.

Methods: Medication compliance test results were reviewed for 521 urine samples submitted to Aegis Sciences Corporation between July 2014 and July 2016. Samples were included in this analysis if dextromethorphan or levorphanol testing was requested by the ordering provider. Urine samples were hydrolyzed with β-glucuronidase and analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS). An enantiomeric analysis to distinguish levorphanol from dextrorphan and (-)-3-hydroxymorphinan (norlevorphanol) from (+)-3-hydroxymorphinan was not performed.

Results: Nineteen urine samples with levorphanol listed as prescribed had median levorphanol/dextrorphan and 3-hydroxymorphinan concentrations of 1,881 ng/mL and 141 ng/mL, respectively. One-quarter of the urine samples with dextromethorphan listed as prescribed did not have any detectable dextromethorphan or 3-methoxymorphinan.

Limitations: An enantiomeric analysis was not utilized with the LC-MS/MS testing method; therefore, levorphanol could not be differentiated from dextrorphan, and (-)-3-hydroxymorphinan could not be differentiated from (+)-3-hydroxymorphinan. The hepatic and renal function for these patients was unknown; however, both could impact the metabolism, distribution, and excretion of levorphanol biomarkers in urine. The dextromethorphan and/or levorphanol dose and timing of last ingestion was also not assessed.

Conclusions: It may be impossible to distinguish between levorphanol and dextromethorphan ingestion based on urine biomarkers, unless dextromethorphan or 3-methoxymorphinan is present or an enantiomeric analysis is performed. Therefore, the potential exists for patients prescribed levorphanol to ingest dextromethorphan and appear compliant with levorphanol therapy. This should prompt clinicians to consider the parameters of their laboratory's testing method when interpreting levorphanol drug test results.

Key words: Levorphanol, dextrorphan, dextromethorphan, 3-hydroxymorphinan, urine testing, urine concentration, drug testing, medication compliance testing

Pain Physician 2018; 21:E167-E171

Levorphanol is a long-acting opioid analgesic that binds mu, delta, and kappa opioid receptors; additionally, it appears to decrease activity at N-methyl-D-aspartate (NMDA) receptors and block uptake of serotonin and norepinephrine (1). It is an optical isomer (enantiomer) of dextrorphan, which is a metabolite of the over-the-counter (OTC) cough suppressant dextromethorphan. Enantiomers have the same molecular formula with a different structural arrangement of atoms, bearing a nonsuperimposable mirror image relationship. Conventional analytical techniques do not permit separation or differentiation of enantiomers. Dextromethorphan metabolizes to dextrorphan, 3-methoxymorphinan, and (+)-3-hydroxymorphinan. Levorphanol metabolizes primarily to levorphanol-3-glucuronide and norlevorphanol, or (-)-3-hydroxymorphinan (2-4). The metabolism of dextromethorphan and levorphanol is detailed in Fig. 1.

Levorphanol was developed in 1949 as an alternative to morphine for chronic pain (5,6). Its use declined after the introduction of extended-release preparations of morphine, fentanyl, and oxycodone (5). It is now only commercially available in the United States as a 2 mg oral tablet (5,7). In more recent years, providers have expressed a renewed interest in utilizing levorphanol after a clinical trial examined its use for neuropathic pain, and a study based on retrospective chart reviews evaluated patient response to the drug in both chronic nonmalignant and cancer pain (5,8). Multiple review articles have since advocated for providers to consider its clinical utility as an alternative to other opioids (1,6,9-14). As a result, there is an increased demand for levorphanol toxicology testing to assess treatment compliance (1).

The practice of urine drug testing for the purpose of opioid prescription compliance assessment is recommended in multiple pain management treatment guidelines (15-18). Medication compliance testing provides an objective tool for clinicians to assess the presence of prescribed medications and ensure the absence of illicit and nonprescribed medications (19,20). Because a portion of the metabolic pathway of dextromethorphan is shared with that of levorphanol, it may be difficult for providers to distinguish between dextromethorphan and levorphanol ingestion when assessing levorphanol compliance. This is concerning given that levorphanol is a schedule II controlled substance with abuse potential (7). Following levorphanol consumption, dextromethorphan-specific markers should not be present; thus, the presence of dextromethorphan or 3-methoxymorphinan should strictly indicate dextromethorphan consumption. However, this has not been

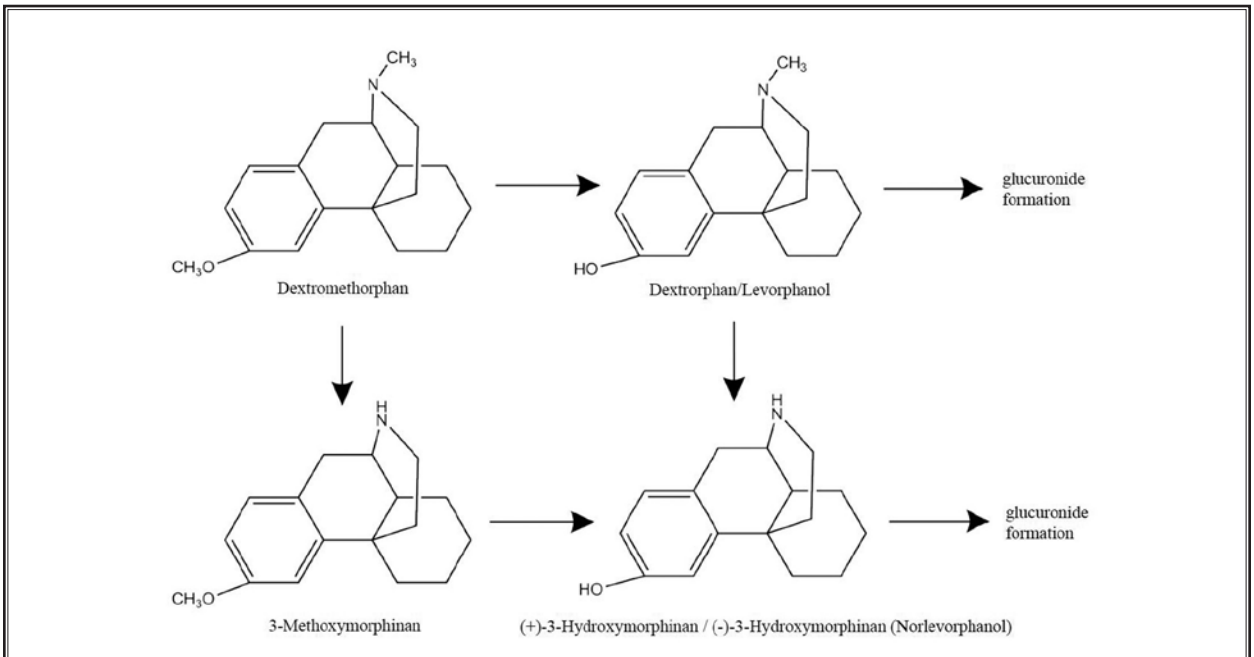

Fig. 1. *Dextromethorphan and levorphanol metabolism.*

demonstrated in the literature to date, and anticipated urine concentrations of levorphanol/dextrorphan and 3-hydroxymorphinan following human levorphanol consumption has not been published. It is therefore unknown if urine concentrations of levorphanol/dextrorphan and 3-hydroxymorphinan lend interpretive guidance regarding which medication has been consumed.

The objectives of this retrospective data review were to investigate urine concentrations of levorphanol/dextrorphan and 3-hydroxymorphinan in healthcare patients, to characterize cases of potential levorphanol ingestion based on detection of relevant urine biomarkers, and to assess the need for an enantiomeric analysis to distinguish between dextromethorphan and levorphanol ingestion.

Methods

Medication compliance test results for 521 urine samples submitted to Aegis between July 2014 and July 2016 were evaluated for the presence of dextromethorphan, 3-methoxymorphinan, levorphanol/dextrorphan, and 3-hydroxymorphinan by liquid chromatography-tandem mass spectrometry (LC-MS/MS) above the limit of quantitation (LOQ) of 10 ng/mL. All samples for which either dextromethorphan or levorphanol testing was requested on the laboratory requisition form were included in this data review. When provided, prescription information was obtained from the ordering physician as indicated on the laboratory requisition form. An enantiomeric analysis was not performed during laboratory testing; therefore, levorphanol was not differentiated from dextrorphan, and (-)-3-hydroxymorphinan (norlevorphanol) was not differentiated from (+)-3-hydroxymorphinan. Urine specimens underwent hydrolysis with β-glucuronidase.

Results

Urine concentrations and parent to metabolite ratios for levorphanol/dextrorphan and 3-hydroxymorphinan are provided in Table 1. Of the 521 urine test results evaluated, 463 were from different sample donors (median age 49 years) in 112 physician practices across 33 states.

All samples with levorphanol listed as a prescribed medication had both levorphanol/dextrorphan and 3-hydroxymorphinan present. Dextromethorphan and 3-methoxymorphinan were also identified in one of these samples, indicating ingestion of dextromethorphan. Twenty-two samples with dextromethorphan listed as a prescribed medication did not have any detectable dextromethorphan or 3-methoxymorphinan present above the LOQ. Median concentrations of levorphanol/dextrorphan and 3-hydroxymorphinan for these samples were 125 ng/mL and 135 ng/mL, respectively. Of the samples without prescribed levorphanol or dextromethorphan indicated, 95 did not have dextromethorphan or 3-methoxymorphinan present above the LOQ. The median concentrations of levorphanol/dextrorphan and 3-hydroxmorphinan for these samples were 128 ng/mL and 86 ng/mL, respectively.

Discussion

Urinary excretion of levorphanol in animals and levorphanol plasma concentrations in humans have been described elsewhere (3,4,21). To our knowledge, this is the first report identifying concentrations of levorphanol/dextrorphan and 3-hydroxymorphinan in human urine.

Metabolite concentrations are typically expected to exceed parent drug concentrations in urine, often resulting in a parent to metabolite ratio of less than one. A study in rats demonstrated that 45% of a levorphanol dose is excreted into the urine as glucuronide metabolites, while only 7% of the drug is excreted unchanged (3). If this excretion pattern holds true in humans, this data further supports an anticipated levorphanol to 3-hydroxymorphinan ratio of less than one. However, the median parent to metabolite ra-

Table 1. *Levorphanol/dextrorphan and urinary marker concentrations.*

Prescription Information	n	Urine Concentrations (ng/mL)				Parent to Metabolite Ratio	
		Levorphanol/Dextrorphan		3-hydroxymorphinan			
		Range	Median	Range	Median	Range	Median
Levorphanol	19	68–12,070	1,881	13–1,277	141	0.8–21.4	10.6
Dextromethorphan	83	< 10–35,862	2,154	< 10–32,749	1,334	0–4.5	1.4
No prescription indicated	419	< 10–325,789	903	< 10–237,625	613	0–22	1.5
Total	521	< 10–325,789	1,051	< 10–237,625	621	0–22	1.5

tio for all samples evaluated in this data review was greater than one. This observation may be attributed to the hydrolysis of glucuronide metabolites in the laboratory testing method, which converts levorphanol glucuronide back to free levorphanol. It has also been proposed that some hydrolysis of conjugated levorphanol occurs in vivo (1,4,22).

Of the 83 samples with dextromethorphan listed as a prescribed medication, 22 (26.5%) did not have any detectable dextromethorphan or 3-methoxymorphinan, suggesting the potential exists for patients prescribed levorphanol to ingest dextromethorphan and appear compliant with levorphanol therapy on a urine drug test. No prescription was indicated for either dextromethorphan or levorphanol for 419 samples. Neither dextromethorphan nor 3-methoxymorphinan was present above the LOQ for 95 (22.7%) of these samples; however, these patients were more likely to have ingested dextromethorphan since it is available without a prescription. These observations further suggest the potential for feigned levorphanol compliance on a urine drug test following dextromethorphan use. Though, illicit use of levorphanol cannot be ruled out for these samples, as it is a schedule II controlled substance with abuse potential (7). Dextromethorphan and 3-methoxymorphinan were detected in one sample with levorphanol listed as a prescribed medication. Detection of these dextormethorphan-specific markers indicates the patient either ingested dextromethorphan alone or in combination with levorphanol.

Since an enantiomeric analysis was not utilized with the LC-MS/MS testing method, levorphanol could not be differentiated from dextrorphan, and neither could (-)-3-hydroxymorphinan from (+)-3-hydroxymorphinan. The information presented in this study was derived from a retrospective data review, and hepatic and renal function of patients was not assessed. However, hepatic and renal function could impact the metabolism, excretion, and distribution of levorphanol biomarkers in urine. Furthermore, the dosage amount of levorphanol and/or dextromethorphan and time from last ingestion was not provided. Given these limitations, further investigation of levorphanol in human urine is warranted.

In conclusion, it may be impossible to distinguish between levorphanol and dextromethorphan ingestion based on urine biomarkers, unless dextromethorphan or 3-methoxymorphinan is present or an enantiomeric analysis is performed. Providers should consider the parameters of their laboratory's testing method when interpreting levorphanol urine drug test results.

References

1. Gudin J, Fudin J, Nalamachu S. Levorphanol use: Past, present, and future. *Postgrad Med* 2016; 128:46-53.
2. Baselt RC. Disposition of toxic drugs and chemicals in man, 10th ed. Biomedical Publications, Seal Beach, CA. 2014.
4. Misra AL, Vadlamani NL, Bloch R, Mule SJ. Differential pharmacokinetic and metabolic profiles of the stereoisomers of 3-hydroxy-n-methyl morphinan. *Res Commun Chem Pathol Pharmacol* 1974; 7:1-16.
5. Dixon R, Crews T, Inturrisi C, Foley K. Levorphanol: Pharmacokinetics and steady-state plasma concentrations in patients with pain. *Res Commun Chem Pathol Pharmacol* 1983; 41:3-17.
6. McNulty JP. Can levorphanol be used like methadone for intractable refractory pain? *J Palliative Med* 2007; 10:293-296.
7. Prommer E. Levorphanol: Revisiting an underutilized analgesic. *Palliat Care* 2014; 8:7-10.
8. Levorphanol [package insert]. Solana Beach, CA: Sentynl Therapeutics; Dec 2016.
9. Rowbotham MD, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med* 2003; 348:1223-1232.
10. Prommer E. Levorphanol: The forgotten opioid. *Support Care Cancer* 2007; 15:259-264.
11. Foley KM. Opioids and chronic neuropathic pain. *N Engl J Med* 2003; 384:1279-1281.
12. Zorn KE, Fudin J. Treatment of neuropathic pain: The role of unique opioid agents. *Pract Pain Manag* 2011; 11:26-33,119.
13. Atkinson TJ, Fudin J, Pandula A, Mirza M. Medication pain management in the elderly: Unique and underutilized analgesic treatment options. *Clin Ther* 2013; 35:1669-1689.
14. Pham TC, Fudin J, Raffa RB. Is levorphanol a better option than methadone? *Pain Med* 2015; 16:1673-1679.
15. Nalamachu SR, Gudin JA. Levorphanol: An optimal choice for opioid rotation. *Pract Pain Manag* 2016; 16:20-23.
16. Chou R, Fanicullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskog A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* 2009; 10:113-130.
17. Manchikanti L, Kaye AM, Knezevic NN, McAnally H, Slavin KV, Trescot AM, Blank S, Pampati V, Abdi S, Grider JS, Kaye AD, Manchikanti KN, Cordner HJ, Gharibo CG, Harned ME, Albers SL, Atluri S, Aydin SM, Bakshi S, Barkin R, Benyamin RM, Boswell MV, Buenaventura RM, Calodney AK, Cedeno DL, Datta S, Deer TR, Fellows B, Galan V, Grami

V, Hansen H, Helm S, Justiz R, Koyyalagunta D, Malla Y, Navani A, Nouri K, Pasupuleti R, Sehgal N, Silverman SM, Simopoulos TT, Singh V, Solanki DR, Staats PS, Vallejo R, Wargo BW, Watanabe A, Hirsch JA. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2017; 20:S3-S92.

18. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain — United States, 2016. *MMWR Recomm Rep* 2016; 65(No. RR-1):1-49.
19. Department of Veterans Affairs / Department of Defense (VA/DoD). *Clinical Practice Guideline for Opioid Therapy for Chronic Pain*. Washington, DC: Department of Veterans Affairs / Department of Defense (VA/DoD); 2017. www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPG022717.pdf.
20. Pergolizzi J, Pappagallo M, Stauffer J, Gharibo C, Fortner N, de Jesus MN, Brennan MJ, Richmond C, Hussey D, Integrated Drug Compliance Study Group (IDCSG). The role of urine drug testing for patients on opioid therapy. *Pain Pract* 2010; 10:497-507.
21. Peppin J, Passik S, Couto JE, Fine PG, Christo PJ, Argoff C, Aronoff GM, Bennett D, Cheatle MD, Slevin KA, Goldfarb NI. Recommendations for urine drug monitoring as a component of opioid therapy in the treatment of chronic pain. *Pain Med* 2012; 13:886-896.
22. Woods LA, Mellett LB, Andersen KS. The synthesis and estimation of N-C14-methyl labeled levorphanol and its biological disposition in the monkey, dog and rat. *J Pharmacol Exp Ther* 1958; 124:1-8.
23. Schulz R, Goldstein A. Inactivity of narcotic glucuronides as analgesics and on guinea-pig ileum. *J Pharm Exp Ther* 1972; 183:404-410.