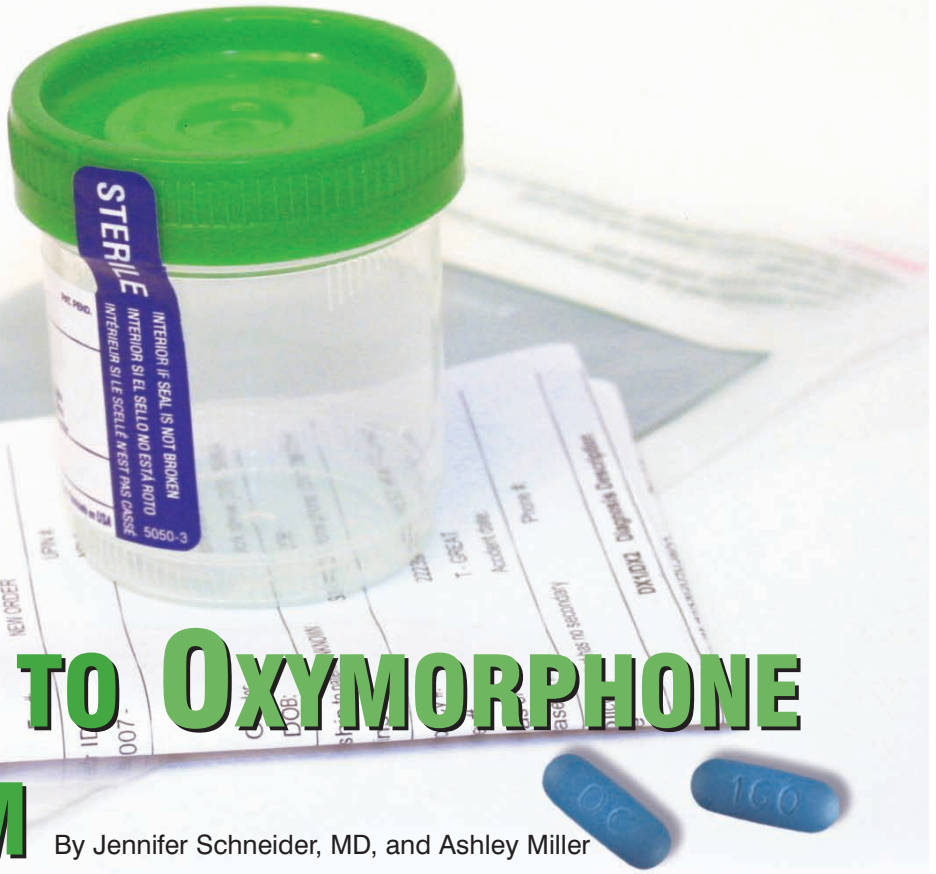
Interpreting urine drug tests in pain patients treated with oxycodone requires an understanding that oxymorphone, although considered a minor metabolite, can sometimes equal or exceed urine concentrations of oxycodone.



Oxycodone to Oxymorphone Metabolism

By Jennifer Schneider, MD, and Ashley Miller

Primary care physicians, as well as pain specialists, are increasingly ordering urine drug tests as part of the initial evaluation and follow-up of patients with chronic pain when opioid therapy is being used or is under consideration. Physicians should know that ordering a urine drug test (UDT) carries with it an obligation to understand the results and to act on them accordingly, instituting changes in treatment plan if indicated.

Interpreting UDT results can be confusing unless physicians understand the metabolism of opioids. For example, it is well recognized that codeine is a prodrug, with its analgesic effect resulting from conversion of codeine to morphine by the cytochrome P450 2D6.[1,2] Thus, patients on codeine frequently test positive for both codeine and morphine. When patients who lack the cytochrome P450 2D6 enzyme necessary to convert codeine to morphine are treated with codeine, their urine may show only codeine.[2] On the other hand, a finding of codeine in the urine of a patient being treated with morphine implies that the patient was also obtaining codeine from another source. Similarly, hydrocodone is metabolized to hydromorphone, so that both may legitimately be found in the urine of a patient who is being prescribed hydrocodone (Vicodin, Lorcet, etc.)[3,4] But again, the reverse is not true; a patient prescribed hydromorphone (Dilaudid) should not have hydrocodone in the urine. Recently, Cone et al[5] reported that in some patients chronically treated with morphine, hydromorphone can appear in the urine as a result of a minor metabolic pathway.

An extended-release oxymorphone (OpanaER) and an immediate-release oxymorphone (Opana) have recently become available. The question then arises, what is the explanation for a finding of oxymorphone in the urine of a patient who is not being prescribed this drug? Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone, which represents less than 15% of the total administered dose.[6] However, oxymorphone has a significantly longer half life (7-9 hours)[7] than does oxycodone, whose mean elimination half-life following a single, oral dose is 3.51 ± 1.43 hours.[8] It is therefore plausible that in oxycodone-using patients, serum and urine levels of oxymorphone may be significantly more than 15% those of oxycodone. Large numbers of patients consume oxycodone, either as the extended-release form (OxyContin) or as immediate-release Percocet, Percodan, or its generic equivalents. The present study was designed to obtain information on the frequency and concentration (in ng/mL) of oxymorphone in the urine of patients prescribed oxycodone.

Methods

Over a two-month period (March and April 2007), all 175 patients in a chronic pain practice were asked without advance notice to submit a urine specimen. The patients were being treated for various types of chronic non-cancer pain, with back pain being the most common diagnosis. Eighty-eight patients who were being prescribed oxycodone (extended-release and/or immediate-release) were tested for oxycodone and oxymorphone by an enzyme immunoassay (EIA). Because the usual immunoassay screen for opiates will not pick up oxycodone and oxymorphone, the order was written as "Routine urine drug test plus oxycodone and oxymorphone." Each patient's daily dose and time of last dose were recorded by the medical assistant, who also checked the temperature of the urine immediate-

Table 1. Daily Oxycodone doses in the 86 patients

Dose qd	N (total 86)	% of 86
15-100 mg	45	52.3%
101-200 mg	17	19.8%
201-300 mg	12	13.9%
301-400 mg	7	8.1%
>400 mg	5	5.8%

Table 2. Percent urine oxymorphone/oxycodone by CG/MS testing in 48 patients on oxycodone

Dose qd	N=48	%	Percent oxymorphone/oxycodone
15-50mg	17	35.4%	0. 2.5, 3.3,3.5, 4.6, 9.8, 10.0, 10.6, 11.7, 14.3, 15.2, 25.2, 34.1, 36.5, 41.1, 99.5, 138.9
51-100mg	11	22.9%	0.67, 7.6, 12.8, 13.2, 14.6, 14.6, 37.3, 71.9, 96.5, 96.9, 147.4
101-200mg	7	14.6%	4.8, 5.8, 6.7, 13.7, 18.5, 19.4, 28.5
201-300 mg	6	12.5%	10.5, 11.6, 11.6, 19.1, 19.8, 184.1
>301 mg	7	14.6%	5.2, 5.5, 10.0, 14.7, 17.8 26.0, 45.8

Table 3. Results in patients with high percent urine oxymorphone

Oxycodone dose qd	oxymorphone (ng/ml)	Oxycodone (ng/ml)	%OM/OC
40 mg	916	912	99.5%
50 mg	450	324	138.9
80 mg	2,406	2,482	96.9
80 mg	4,634	4,802	96.5
240 mg	4,436	2,410	184.1

ly after voiding to be sure it fell within the range of 90-100 ºF. Two of the patients had UDT results that were negative on immunoassay for oxycodone. They were excluded from the remainder of this study. For 48 of the remaining 86 patients who tested positive for oxycodone on immunoassay, the urine concentration of oxycodone and oxymorphone was determined quantitatively using gas chromatography/mass spectrometry (GC/MS). The cut-off level for a "Positive" oxycodone or oxymorphone result was 100 ng/mL.

Results

Of eighty-six patients whose urines were positive for oxycodone by EIA screen, 80 (93%) were also positive for oxymorphone. The cut-off for the immunoassay screens was 100 ng/ml of oxycodone and 100 ng/ml of oxymorphone. The six patients who were negative for oxymorphone on immunoassay screen were receiving only relatively small doses of oxycodone ranging from 15 to 45 mg per day. Two of these patients were also tested by GC/MS, and one of the two was positive at a low level by this more sensitive test, which showed a urine level of oxymorphone of 66 ng/ml, below the cutoff of 100 ng/mL of the immunoassay. It was also noted that 22 other patients on the same dose range of oxycodone screened positive for both oxycodone and oxymorphone by immunoassay.

Table 1 summarizes the daily doses of oxycodone (sustained-release and/or immediate release) of the 86 patients.

As expected, the results for the quantitative GC/MS testing (in ng/mL) were widely variable because of the different doses as well as variable relationship between the time of the last dose and the time of urine collection. Accordingly, the results are presented as a percentage of ng/ml oxymorphone to oxycodone in the urine (see Table 2).

Table 2 clearly shows that there is tremendous variation in the relative amount of oxymorphone in the urine, as compared with oxycodone. It does not appear as if higher doses are associated with a relatively greater percent of oxymorphone. For the reader's interest, the results for the five highest ratios are presented in Table 3.

Discussion

Physicians who obtain urine drug tests for their chronic patients need to be able to interpret the results and act on them when the results are unexpected. If this is not done, the physician may fail to recognize drug misuse in the patient or, alternatively, may unfairly accuse the patient of obtaining prescription opioids from other sources.

To understand urine drug testing, physicians must have a basic understanding of the different types of tests. Standard screening tests, usually done by immunoassay, test only for the presence of classes of drugs (such as opiates and benzodiazepines.) The usual immunoassay for "opiates" reacts only with natural opiates (morphine, hydrocodone, hydromorphone, and codeine). Oxycodone and oxymorphone can be identified by immunoassay, but only if those drugs are specifically requested. To identify specific drugs and their concentration in the urine, labs offer gas chromatography/mass spectrometry (GC/MS) or high-performance liquid chromatography (HPLC). Unexpected positive and negative results should be confirmed by one of these quantitative techniques.

Given the fact that various prescribed opioids can be metabolized to other opioids, urine drug test results can be confusing. The physician needs to be familiar with the various metabolic pathways, and be willing to contact laboratory personnel or more knowledgeable colleagues if unexpected results are found. Because of the recent availability of oxymorphone as medication, it behooves physicians to understand the significance of finding oxymorphone in urine drug testing. Patients who are being prescribed oxycodone can be expected to have oxymorphone in the urine and, as this study shows, the amount of oxymorphone in the urine is highly variable. Even when the

ratio of oxymorphone to oxycodonewas very high, the author had no reason to suspect that any of the patients were surreptitiously using oxymorphone in addition to their prescribed oxycodone.

Conclusion

Chronic pain patients treated with sustained- and/or immediate-release oxycodone (dosage range 15-730 mg/day), were tested for both oxycodone and oxymorphone by urine drug testing (UDT). None of the patients were being treated with oxymorphone. Among urines which tested positive for oxycodone by enzyme immunoassay (EIA), 80 out of 86 (93%) were also positive for oxymorphone. Among 48 urine specimens subjected to quantitative analysis by gas chromatography/mass spectrometry (GC/MS), the ratio of oxymorphone to oxycodone in the urine ranged from 0% to 184%. There was no correlation between the dose of oxycodone and the ratio of oxymorphone to oxycodone.

Although oxymorphone is considered a minor metabolite of oxycodone, immunoassay urine drug screening of patients treated with oxycodone can be expected to be positive for oxymorphone. Further, the quantity of oxymorphone (determined by GC/MS) can at times equal or exceed that of oxycodone. On the other hand, patients who are prescribed oxymorphone but not oxycodone would not be expected to have any oxycodone in their urine.

Knowledge of these facts should enable oxycodone and oxymorphone prescribers to more correctly interpret the results of urine drug screens of oxycodone patients. ■

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