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Opioid-positive urine drug screen during treatment with oral naltrexone and the clinical implications

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Abstract

Introduction: Naltrexone is an opioid antagonist that is FDA approved to treat alcohol dependence and opioid dependence. It is available as an oral tablet and an extended-release injectable suspension. Naltrexone is metabolized to the primary metabolite, 6-β-naltrexol, and to 2 minor metabolites, 2-hydroxy-3-methoxy-6-β-naltrexol and 2-hydroxy-3-methyl-naltrexone. One of the lesser-known metabolites of naltrexone is noroxymorphone.

Methods: A 27-year-old man taking oral naltrexone seen in the outpatient setting for alcohol use disorder and cannabis use disorder was found to have multiple positive urine drug screens (UDSs) for oxycodone. Confirmatory urine drug testing was completed and noroxymorphone was detected. A naloxone challenge test was conducted with negative results and the patient tolerated the transition from oral naltrexone to the extended-release injectable suspension of naltrexone.

Results: This case illustrates that it is possible for a patient stabilized on oral naltrexone to have a false-positive oxycodone UDS. Confirmatory urine drug testing was used to substantiate that the metabolite of naltrexone, noroxymorphone, was the cause of the false-positive oxycodone UDS.

Conclusions: One of the lesser-known metabolites of naltrexone, noroxymorphone, can cause a positive oxycodone UDS during treatment with oral naltrexone. Confirmatory urine drug testing should be conducted to confirm the presence of noroxymorphone and rule out alternative opioids.

Keywords: naltrexone, urine drug screen, oxycodone, noroxymorphone, false-positive

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Background

Naltrexone is an opioid antagonist that blocks the effects of opioids by competitively binding to the opioid receptors.[1–3] Naltrexone is FDA approved to treat alcohol dependence and opioid dependence, and it is available as an oral tablet and an extended-release injectable suspension (XR-NTX).[1–3] Naltrexone is metabolized to the primary metabolite, 6-β-naltrexol, by dihydrodiol dehydrogenase.[2,3] Two minor metabolites of naltrexone are 2-hydroxy-3-methoxy-6-β-naltrexol and 2-hydroxy-3-methyl-naltrexone, and 1 lesser-known metabolite is noroxymorphone.[2–4] Contraindications for naltrexone include those receiving opioid analgesics, those with current physiologic opioid dependence, those in acute opioid withdrawal, any individual who has failed the naloxone challenge test or has a positive urine screen for opioids, and those who have previously exhibited hypersensitivity to naltrexone.[2,3] For patients who have a positive urine drug screen (UDS) for opioids, the naloxone challenge test can be used to assess for a lack of physical opioid dependence.[2,3] The package insert for naltrexone and the Substance Abuse and Mental Health

Services Administration provide guidance on the naloxone challenge test.[2,3,5]

Urine drug monitoring (UDM) is widely used in health care, particularly for those with substance use disorders (SUDs).[6] Because individuals with SUDs are at risk of stigma and potential negative consequences associated with positive UDM, it is important for providers to understand the different types, limitations, and interpretation of UDM to facilitate safe and effective treatment.[6,7] There are 2 main types of UDM: UDSs and confirmatory urine drug tests (UDTs).[6,7] Urine drug screens are laboratory-based immunoassays that are easy to use, sensitive, and produce rapid results, which has led them to become the most common method for urine analysis.[8,9] Since false-positive and false-negative results can occur with UDSs because of their lack of specificity, a confirmatory UDT would be recommended if the results of a UDS were unexpected.[8,9] Confirmatory UDTs have high specificity and use techniques like liquid or gas chromatography–mass spectrometry to detect the presence of specific drugs and metabolites.[8,9]

Case Report

A 27-year-old man was seen in the outpatient setting for substance use disorder (SUD) treatment. He had a past medical history of low back pain, urinary frequency, constipation, insomnia, depression, alcohol use disorder, severe, and cannabis use disorder, moderate to severe. His medications included bupropion 150 mg daily, cholecalciferol 50 µg daily, fluticasone nasal spray daily, methocarbamol 500 mg daily, naloxone nasal spray 4 mg as needed for opioid overdose, naltrexone 50 mg daily, pregabalin 100 mg twice daily, sertraline 50 mg daily, tolterodine 2 mg daily, and trazodone 150 mg at bedtime as needed for insomnia.

At the initial visit with the SUD provider, the patient endorsed he had been abstinent from alcohol for about 6 months, and he had been taking oral naltrexone daily for about 2 months with occasional missed doses. His refill history supported adherence to oral naltrexone. He reported using cannabis daily but declined to report the exact quantity. A routine UDS, oxycodone UDS, fentanyl confirmatory UDT, and norfentanyl confirmatory UDT were completed 12 days prior to the initial visit. The results of the UDM are presented in the Table. The positive oxycodone UDS was discussed with the patient, and he denied any opioid use. No opioid medications were found in the prescription drug monitoring program query completed on the date of the initial visit, and none of the patient's reported medications were expected to cause a false-positive oxycodone UDS. The patient was interested in transitioning from oral naltrexone to XR-NTX. However, because the patient had a positive opioid UDS, which is listed a contradiction for naltrexone, and because XR-NTX cannot be removed once injected, it was determined that repeat UDM should be completed.[2]

The patient agreed to complete UDM on the date of the initial visit and a routine UDS and oxycodone UDS were obtained. The results of the repeat UDM presented in the Table were identical to the results of the UDSs collected 12 days prior and were reviewed with the patient.

The SUD provider discussed the patient case with the SUD pharmacist, and it was recommended that an opioid confirmatory UDT and a general toxicology confirmatory UDT be ordered. A general toxicology confirmatory UDT was suggested because the opioid confirmatory UDT does not test for all opioids and corresponding metabolites. A routine UDS, oxycodone UDS, heroin metabolite confirmatory UDT, general toxicology confirmatory UDT, and opioid confirmatory UDT were obtained. The Table shows the results of the UDM collected 7 days after the initial visit. No oxycodone was detected in the opioid confirmatory UDT, nor were either of its primary metabolites, noroxycodone or oxymorphone, but noroxymorphone was shown in the general toxicology confirmatory UDT. Because the oxycodone UDS was positive and the confirmatory UDT detected noroxymorphone, it was determined that a naloxone challenge test should be conducted prior to administration of the XR-NTX because XR-NTX can be administered if an individual has a positive UDS for opioids but does not fail the naloxone challenge test.[2] The naloxone challenge test was completed at an outpatient visit 14 days after the initial visit. Verbal education on the naloxone challenge test was provided. A baseline Clinical Opiate Withdrawal Scale (COWS) was completed, and the score was 0. Naloxone 0.8 mg was administered subcutaneously, and the patient was monitored for 30 minutes following the naloxone injection. The naloxone challenge test was negative because the repeat COWS score was 0. The XR-NTX was administered intramuscularly into the gluteal muscle without adverse reaction. Presented in the Table are the 2 routine UDSs collected at subsequent follow-up visits while the patient was maintained XR-NTX, 28 days and 56 days following the initial XR-NTX injection. An oxycodone UDS was not collected during treatment with XR-NTX because the results would not impact clinical care.

Discussion

A literature review was completed using PubMed to search for case reports of opioid-positive UDM with naltrexone, and 1 case report was found. Keywords included naltrexone, oxycodone, noroxymorphone, and oxymorphone. The case report describes a 28-year-old woman admitted to an inpatient facility who had a positive oxycodone UDS and a detectable level of noroxymorphone with multiple confirmatory UDTs while taking oral naltrexone.[10] After discontinuation

TABLE: Urine drug screen and urine confirmation test results

Time Frame, Test Name, Substance	Reference Range	Result
Twelve days prior to initial SUD visit		
Routine UDS		
Ethanol	>50 mg/dL	Negative
Cocaine metabolite	>300 ng/mL	Negative
Opioids	>300 ng/mL	Negative
Phencyclidine	>25 ng/mL	Negative
Amphetamines	>1000 ng/mL	Negative
Cannabinoids	>50 ng/mL	Positive
Barbiturates	>200 ng/mL	Negative
Benzodiazepines	>200 ng/mL	Negative
Methadone	>150 ng/mL	Negative
Creatinine	>20 mg/dL	50 mg/dL
Oxycodone UDS[13]	>100 ng/mL	Positive
Fentanyl confirmatory UDT	<0.5 ng/mL	Negative
Norfentanyl confirmatory UDT	<0.5 ng/mL	Negative
Initial SUD visit		
Routine UDS		
Ethanol	>50 mg/dL	Negative
Cocaine metabolite	>300 ng/mL	Negative
Opioids	>300 ng/mL	Negative
Phencyclidine	>25 ng/mL	Negative
Amphetamines	>1000 ng/mL	Negative
Cannabinoids	>50 ng/mL	Positive
Barbiturates	>200 ng/mL	Negative
Benzodiazepines	>200 ng/mL	Negative
Methadone	>150 ng/mL	Negative
Creatinine	>20 mg/dL	111 mg/dL
Oxycodone UDS[13]	>100 ng/mL	Positive
Seven days after initial SUD visit		
Routine UDS		
Ethanol	>50 mg/dL	Negative
Cocaine metabolite	>300 ng/mL	Negative
Opioids	>300 ng/mL	Negative
Phencyclidine	>25 ng/mL	Negative
Amphetamines	>1000 ng/mL	Negative
Cannabinoids	>50 ng/mL	Positive
Barbiturates	>200 ng/mL	Negative
Benzodiazepines	>200 ng/mL	Negative
Methadone	>150 ng/mL	Negative
Creatinine	>20 mg/dL	218 mg/dL
Oxycodone UDS[13]	>100 ng/mL	Positive
Heroin metabolite confirmatory UDT; 6-acteylmorphine (6-MAM)	<10 ng/mL	Negative
General toxicology confirmatory UDT		
Noroxymorphone	Not provided	Detected
Pregabalin	Not provided	Detected
Caffeine	Not provided	Detected
Hydroxybupropion	Not provided	Detected
Methocarbamol	Not provided	Detected
Sertraline	Not provided	Detected
THC-COOH	Not provided	Detected
Opioid confirmatory UDT		
Codeine	<50 ng/mL	Negative
Hydrocodone	<50 ng/mL	Negative
Hydromorphone	<50 ng/mL	Negative
Morphine	<50 ng/mL	Negative
Norhydrocodone	<50 ng/mL	Negative
Noroxycodone	<50 ng/mL	Negative
Oxycodone	<50 ng/mL	Negative
Oxymorphone	<50 ng/mL	Negative

TABLE: Urine drug screen and urine confirmation test results (continued)

Time Frame, Test Name, Substance	Reference Range	Result
Ten weeks after initial SUD visit		
Routine UDS		
Ethanol	>50 mg/dL	Negative
Cocaine metabolite	>300 ng/mL	Negative
Opioids	>300 ng/mL	Negative
Phencyclidine	>25 ng/mL	Negative
Amphetamines	>1000 ng/mL	Negative
Cannabinoids	>50 ng/mL	Positive
Barbiturates	>200 ng/mL	Negative
Benzodiazepines	>200 ng/mL	Negative
Methadone	>150 ng/mL	Negative
Creatinine	>20 mg/dL	94 mg/dL
Fourteen weeks after initial SUD visit		
Routine UDS		
Ethanol	>50 mg/dL	Negative
Cocaine metabolite	>300 ng/mL	Negative
Opioids	>300 ng/mL	Negative
Phencyclidine	>25 ng/mL	Negative
Amphetamines	>1000 ng/mL	Negative
Cannabinoids	>50 ng/mL	Positive
Barbiturates	>200 ng/mL	Negative
Benzodiazepines	>200 ng/mL	Negative
Methadone	>150 ng/mL	Negative
Creatinine	>20 mg/dL	62 mg/dL

of the oral naltrexone, the subsequent urine drug toxicology screen was negative for all, including oxycodone.[10]

We present a similar patient case with a clinical concern for potential opioid use in the outpatient setting. Based on the patient-reported cannabis use, there was some concern that the cannabis may have contained opioids because the oxycodone UDS was positive on 3 separate occasions. The metabolism of oxycodone and completion of multiple opioid confirmatory UDTs helped to determine the potential cause of the positive oxycodone UDSs.

The Figure shows the metabolism of oxycodone, which is metabolized to 2 primary metabolites, noroxycodone and oxymorphone, and to the secondary metabolite noroxymorphone.[11]

It is unlikely that the initial positive oxycodone UDS was a result of recent substance use because the subsequent oxycodone UDSs yielded the same results and only the secondary metabolite of oxycodone was detected with confirmatory testing. Because the opioid confirmatory UDT was negative for oxycodone and both its primary metabolites, we do not believe that oxycodone was the cause of the positive oxycodone UDSs. Rather, we suspect that the lesser-known noroxymorphone metabolite from naltrexone, outlined in the Figure, was responsible for the positive oxycodone UDS.[4] Confirmatory UDTs were negative for fentanyl, norfentanyl, and heroin metabolite. A positive oxycodone UDS during treatment with oral naltrexone without confirmatory UDTs could be interpreted as opioid use. This case highlights that UDM should be carefully interpreted and that oral naltrexone can cause a

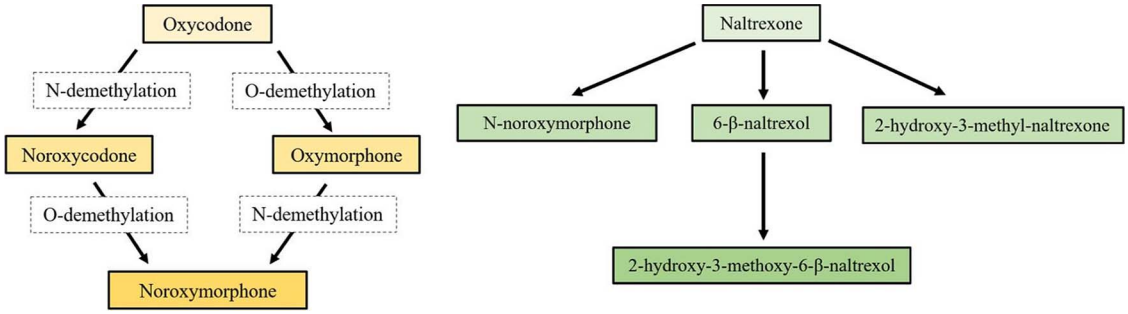

FIGURE: Metabolism of oxycodone and naltrexone to noroxymorphone[4,11]

false-positive oxycodone UDS, which can be substantiated with confirmatory urine drug testing.

An early study examining the metabolism and elimination of naltrexone following oral and intravenous administration was unable to show the presence of noroxymorphone by gas chromatography–mass spectrometry.[12] However, the more recent case report that was previously mentioned was able to illustrate that the noroxymorphone metabolite from naltrexone can cause a false-positive oxycodone UDS.[10,12]

Because multiple UDSs were positive for oxycodone in this case, a naloxone challenge test could have been considered to help mitigate the risk for precipitated opioid withdrawal. However, because the cause of the positive oxycodone UDSs was suspected to be due to the metabolite of naltrexone, and the multiple positive oxycodone UDSs with a confirmatory UDT for noroxymorphone supported the conclusion that the patient was adherent to oral naltrexone, the naloxone challenge test would not have been clinically indicated for this patient stabilized on oral naltrexone. Despite this, the naloxone challenge test was completed in an abundance of caution because an opioid-positive UDS is listed as a contraindication in the FDA package insert for XR-NTX.[2,3]

Conclusion

It is important for providers to be aware that one of the lesser-known metabolites of naltrexone, noroxymorphone, may cause a positive oxycodone UDS. Confirmatory urine drug testing should be conducted to confirm the presence of noroxymorphone and rule out alternative opioids. Interpretations of positive UDSs without confirmatory urine drug testing can negatively impact patient care and lead to inappropriate treatment consequences.

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