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Reliability of urine drug testing among patients on buprenorphine transdermal patch

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Case Report

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Abstract

Background. Urine drug testing (UDT) plays a significant role in monitoring patients on chronic opioid therapy (COT) for non-medical opioid use (NMOU). UDT, at times, can be inconsistent and misleading. We present a case where a patient on a buprenorphine patch had false negative results.

Case description. A female in her 70s with metastatic breast cancer presented with uncontrolled pain from a T6 compression fracture. She had no relief with tramadol 50 mg every 6 hours as needed. Due to an allergic reaction to hydromorphone, our team prescribed a buprenorphine patch of 5 μg/h. Subsequently, she expressed excellent pain control, and the clinician confirmed the patch placement on examination. She underwent a UDT during the visit. The UDT was negative for both buprenorphine and its metabolites. The literature review showed that false negative UDT results are relatively common among patients with low-dose buprenorphine patches. The combination of a thorough physical examination, a review of the Prescription Drug Monitoring Program, and reassuring scores on screening tools placed her at low risk for NMOU.

Discussion. Buprenorphine has a ceiling effect on respiratory depression and a lower risk for addiction. However, when used in low doses, the drug might not have enough metabolites in the urine, leading to a false negative UDT. Such results might affect patient–physician relationships.

Conclusion. In addition to the UDT, a thorough history, screening for NMOU, physical exam, a review of PDMP, and a good understanding of opioid metabolism are necessary to help guide pain management.

Introduction

Opioids are the gold standard for treating cancer pain (Amaram-Davila et al. 2020; 2021; ASCO 2021). There is strong support for universal screening for all patients before initiating opioids using assessment tools such as Cut Down, Annoyed, Guilty, and Eye Opener – Adapted to Include Drugs (CAGE-AID) and Screener and Opioid Assessment for Patients with Pain (SOAPP) questionnaires to determine the baseline risk for nonmedical opioid use (NMOU) (Amaram-Davila et al. 2021; Arthur and Bruera 2019). Similarly, ongoing monitoring with urine drug tests (UDTs) and Prescription Drug Monitoring Programs (PDMPs) is essential to identify patients adherence to prescribed opioids (Amaram-Davila et al. 2021; Arthur and Bruera 2019; Arthur et al. 2020; Reddy and de la Cruz 2019).

Growing evidence also shows that UDTs effectively monitor for compliance and NMOU in patients receiving chronic opioid therapy (COT; Arthur et al. 2020; Reddy and de la Cruz 2019; Yennurajalingam et al. 2021). In a study by Arthur et al., 1 in 4 patients with cancer who underwent random UDT had 1 or more abnormal results. Patients were randomly assigned to undergo UDT, in contrast with to targeted UDT, which is conducted among patients exhibiting high-risk behaviors for NMOU. The abnormal UDTs were commonly identified among younger male patients, those with a history of CAGE-AID positivity, and high expression of anxiety on the Edmonton Symptom Assessment System (ESAS). The most frequently observed abnormality was the absence of the prescribed opioid in the UDT, which may indicate nonadherence or diversion of the opioid. Random UDT successfully detected abnormalities much earlier than the targeted tests (Arthur et al. 2020).

However, routine testing might sometimes fail to detect all opioids, especially those not excreted in the urine, such as buprenorphine and methadone (Jamshidi et al. 2021; Keary et al. 2012). Buprenorphine has become popular recently owing to its pharmacokinetics, such as a lower risk for respiratory depression, dependency, and the development of tolerance (Pergolizzi et al. 2010). In addition, buprenorphine is available in sublingual

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tablets, transdermal (TD), and buccal patches with variable bioavailability. Only 10–30% of the drug is excreted in the urine, which can lead to false-negative results on a routine UDT (Davis et al. 2023).

A false-negative UDT can create conflict and mistrust between patients, and health-care providers (HCP) due to the inaccurate suspicion of NMOU. The potentially inaccurate results from UDT among patients on buprenorphine can make it challenging for HCP to monitor compliance (Markman et al. 2015; Pergolizzi et al. 2010). One such example is the case presented below.

Case report

A woman in her 70s with metastatic breast cancer was referred to our supportive care clinic for uncontrolled pain. During the initial consultation, the patient expressed mid to lower back pain, with an intensity of 8/10 on the ESAS scale. The pain was constant and radiating to bilateral lower extremities. Radiology imaging was consistent with a pathological compression fracture at the T6 vertebra. Her CAGE-AID and SOAPP total scores were 0, indicating a low risk for NMOU. A review of the PDMP database was consistent with prescribed medications, including tramadol 50 mg every 6 hours for pain and temazepam 15 mg as needed for insomnia. She took tramadol 50 mg every 6 hours without adequate relief. She was initially transitioned to hydromorphone 2 mg tablet every 4 hours as needed for pain. The patient, unfortunately, developed hives and itching, leading to the discontinuation of hydromorphone and resumption of tramadol 50 mg every 6 hours around-the-clock with minimal relief. Other traditional mu-opioid agonists were not considered because of her allergy to hydromorphone.

The patient was initiated on buprenorphine TD patch 5 μg/h every 7 days and tramadol 50 mg every 6 hours as needed for breakthrough pain. During a follow-up, on a follow-up telemedicine visit 1 week later, she reported marked improvement in her pain (2/10 on the ESAS scale) and did not require any breakthrough tramadol. At her subsequent in-person follow-up visit, the patient continued to express satisfaction with her pain control, and buprenorphine patch of 5 μg/hr was continued. The accurate placement of the patch was confirmed by both the nurse and the physician seeing her in the clinic that day. The patient was randomly selected to undergo UDT on that day as a part of our clinic procedure. Surprisingly, the UDT results did not detect buprenorphine or its byproducts (norbuprenorphine and norbuprenorphine glucuronide). The other parameters in the urine sample, including temperature, pH, specific gravity, oxidants, and creatinine, were all within normal limits. After an extensive literature review and discussions with our supportive care clinical pharmacist, we realized discrepancies in the UDT results were likely associated with low-dose buprenorphine TD use. A definitive determination of patient nonadherence could not be made based on the results.

Discussion

The above case reports a false-negative UDT result in a patient compliant with opioids. The false-negative result with the absence of buprenorphine metabolites in the urine sample can be explained by its low dose (Markman et al. 2015). A retrospective study by Markam et al. reported that the existing types of UDT currently available, including liquid chromatography–tandem mass spectroscopy-based assays, might not be sensitive enough to detect buprenorphine metabolites in the urine. Nearly 40% of the patients on buprenorphine TD had no buprenorphine metabolites in the urine, suggesting the test was falsely negative. However, all metabolites were detected in 100% of the patients using the sublingual formation of buprenorphine (Markman et al. 2015).

The UDT performed in this patient follows a testing algorithm set by the Mayo Clinic Laboratories. All samples start with an adulterant survey. Samples with no adulterants proceed for further analysis. If an immunoassay screen is positive, confirmation is performed either with gas chromatography–mass spectrometry or liquid chromatography–tandem mass spectrometry, high-resolution accurate Mass (Mayo Clinic Laboratories).

HCP should be aware that the lower strength of the buprenorphine TD formulation might not have enough metabolite concentration in the urine samples (Markman et al. 2015; Pergolizzi et al. 2010). Moreover, the metabolite concentration might be less on day 7 of the patch vs. a mid-week sample (Markman et al. 2015; Pergolizzi et al. 2010). HCP should be cautious when making significant changes to the treatment plan based on the UDT results, especially if the patient's buprenorphine TD is confirmed on the physical examination, and the review of PDMP is appropriate (Markman et al. 2015). In such cases, UDT might not be a reliable tool to monitor compliance but can still detect NMOU or substance use disorder (SUD) (Arthur and Bruera 2019; Markman et al. 2015).

The National Comprehensive Cancer Network guidelines recommend that UDTs be utilized to monitor compliance among patients with aberrant use of opioids (Swarm et al. 2023). In a previous case report where a patient reported stolen opioids and requested early refills, the targeted UDT successfully detected SUD with cocaine, cannabis, and unprescribed tramadol. UDT results guided the HCP to take necessary steps to counsel and initiate an opioid stewardship program for continued safe prescription of opioids and management of cancer pain (Amaram-Davila et al. 2021).

During the opioid crisis engulfing many parts of the United States, HCP may prefer buprenorphine over other opioids for treating cancer-related pain due to its unique properties and decreased potential for abuse. It is an effective option for chronic noncancer and cancer pain (Case et al. 2021; Davis et al. 2018). Its high affinity for mu receptors and slower dissociation property lead to a longer action duration with good analgesic qualities (Volpe et al. 2011). Also, its low intrinsic activity has a ceiling effect on respiratory depression, making it an ideal choice for COT with fewer adverse events (Volpe et al. 2011). Moreover, its kappa antagonist property does not cause craving (Khanna and Pillarisetti 2015). While using buprenorphine, a patient can continue to use small doses of other immediate-release opioids for breakthrough pain without increased risk of opioid overdose (Khanna and Pillarisetti 2015). Buprenorphine undergoes metabolism through the cytochrome 450 (CYP 450) pathway into norbuprenorphine. Both buprenorphine and norbuprenorphine undergo glucuronidation via uridine 5′-diphosphate-glucuronosyltransferase and get excreted through feces. Buprenorphine is, therefore, safe in mild-to-moderate hepatic and renal insufficiency. Buprenorphine and its metabolites do not inhibit CYP 450 pathway at therapeutic doses, meaning it can be used concomitantly with other CYP450 inhibitors and inducers, especially in patients with hepatic impairment (Davis et al. 2023).

HCP need to be aware that relying only on screening tools such as CAGE-AID or SOAPP or performing UDTs may not be sufficient, and one must obtain a detailed history, perform a thorough examination, monitor PDMP, and also have a thorough understanding of opioid metabolism and interpretation of UDT to successfully detect NMOU.

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Conclusion

Our case report highlights the importance of understanding opioid metabolism and accurate interpretation of UDT. Relying on UDT alone to detect nonadherence and NMOU in patients on buprenorphine TD might not be ideal due to the possibility of false-negative results. Clinicians must therefore conduct a more comprehensive patient assessment when monitoring for NMOU behaviors.

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Competing interests. None.

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