FALSE-POSITIVE METHADONE URINE DRUG SCREEN IN A PATIENT TREATED WITH QUETIAPINE*

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SUMMARY – We present a case of T.M. admitted to University Department of Psychiatry, Split University Hospital Center, in Croatia, because of the acute psychotic reaction (F23.9). The patient's urine tested positive for methadone without a history of methadone ingestion. Urine drug screen was performed with the COBAS Integra Methadone II test kit (kinetic interaction of microparticles in solution /KIMS/ methodology) by Roche. Drugs that have been shown to cross-react with methadone feature a tricyclic structure with a sulfur and nitrogen atom in the middle ring, which is common for both quetiapine and methadone. Therefore, it is plausible that this structural similarity between quetiapine and methadone could underlie the cross-reactivity on methadone drug screen. Besides quetiapine, a number of routinely prescribed medications have been associated with triggering false-positive urine drug screen results. Verification of the test results with a different screening test or additional analytical tests should be performed to avoid adverse consequences for the patients.

Key words: *Quetiapine; Methadone; False-positive urine drug screen*

Introduction

Quetiapine is a dibenzothiazepine atypical antipsychotic. It has been proposed that this drug's antipsychotic activity is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5\text{-}HT_2$) antagonism. It is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5\text{-}HT_{1A}$ and $5\text{-}HT_2$, dopamine D_1 and D_2, histamine H_1, and adrenergic $alpha_1$- and $alpha_2$-receptors, but appears to have no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors. Norquetiapine, an active metabolite, differs from its parent molecule by exhibiting high affinity for muscarinic M1 receptors[1].

Methadone is a synthetic opioid, used medically as an analgesic and a maintenance anti-addictive for use in patients with opioid dependency. It was developed in Germany in 1937. Although chemically unlike morphine or heroin, methadone acts on the same opioid receptors as these drugs, and thus has many of the same effects. Methadone is also used in managing severe chronic pain, owing to its long duration of action, extremely powerful effects, and very low cost. Methadone is a partial μ-opioid agonist. Methadone also binds to the glutamatergic NMDA (N-methyl-D-aspartate) receptor, and thus acts as a receptor antagonist against glutamate[1].

Drug screening through urinalysis is a widely accepted method for rapid detection of the potential drug abuse. The most commonly used tests to screen urine for drugs of abuse are immunoassays, even though false-positive results for drugs of abuse have been reported with a number of these rapid-screening products[2]. Confirmation of presumptive positive urine

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drug screens, necessary to minimize the reporting of false-positive results, can be costly and time-consuming[3].

Interference in immunoassay is one of the factors that contribute to the uncertainty of medical testing. Cross-reactivity has been reported in the methods of drug misuse screening[4]. Cross-reactivity is the most common interference in immunoassays, but mostly in competitive ones. It is a nonspecific influence of substances in a sample that structurally resembles the analyte (carries similar or the same epitopes like the analyte) and competes for the binding site on the antibody[5]. The interference grade caused by cross-reactivity depends on three factors: antibody specificity, method, and sample preparation[6]. Cross-reactivity of structurally similar substances is a problem associated with immunoassay methodologies, resulting in false-positive or false-negative results. Screening technologies are predominantly immunoassay techniques which may prove high sensitivity but are of limited specificity.

In immunoassays, an antibody used as a reagent detects the analyte (antigen) of interest. Although the noncovalent bond between the analyte and the complementary antibody is specific, false-positive and false-negative interferences are possible. Some interferences are similar to those in chemical analyses and some are typical only for immunoassays. One should suspect interferences in the following cases: upon receiving an unacceptable result, if there is non-linearity during dilution, if there is no agreement with other test results or clinical data, or if different immunoassays in determination of the same analyte provide significantly different results[4].

Drugs that have been shown to cross-react with methadone feature a tricyclic structure with a sulfur and nitrogen atom in the middle ring, which is common to both quetiapine and methadone. Therefore, it is plausible that this structural similarity between quetiapine and methadone could underlie cross-reactivity on methadone drug screen. Besides quetiapine, a number of routinely prescribed medications have been associated with triggering false-positive urine drug screen results.

We present a case of T.M., admitted to the Department of Psychiatry, Split University Hospital Center, in Croatia, because of the acute psychotic reaction (F23). Urine sample obtained from the patient tested positive for methadone without a history of methadone ingestion.

Urine drug screen was performed with the COBAS INTEGRA Methadone II test kit (kinetic interaction of microparticles in solution /KIMS/ methodology) by Roche. The COBAS INTEGRA Methadone II assay is based on the kinetic interaction of microparticles in a solution (KIMS) as measured by changes in light transmission. In the absence of sample drug, soluble drug polymer conjugates bind to antibody-bound microparticles, causing the formation of particle aggregates.

When a urine sample containing the drug in question is present, this drug competes with the conjugate-bound drug derivative for microparticle-bound antibody. Antibody bound to sample drug is no longer available to promote particle aggregation, and subsequent particle lattice formation is inhibited. As the aggregation reaction proceeds in the absence of sample drug, the absorbance increases. Conversely, the presence of sample drug diminishes the increasing absorbance in proportion to the concentration of drug in the sample. Sample drug content is determined relative to the value obtained for a known cutoff concentration of drug[7,8].

Case Report

We report a case of T.M., a 30-year-old male patient, who was admitted to University Department of Psychiatry, Split University Hospital Center in Split, Croatia, for acute psychotic exacerbation (F 23.9), paranoid-hallucinatory features. The patient had experienced the first psychotic episode two months before and the episode we report was his second exacerbation.

Table 1. Reports of false-positive results of urine drug screens for commonly used antipsychotics

Antipsychotic	Methadone	Amphetamine or methamphetamine
Chlorpromazine	X	X
Promethazine	X	
Quetiapine		X
Thioridazine		X

During the examination, the patient stated that he had consumed different psychostimulative drugs of abuse (amphetamines) several days before hospital admission. Therefore, as part of the routine laboratory diagnostic work-up, the urine drug screen was made, which showed a positive amphetamine result.

We started antipsychotic treatment with quetiapine (900 mg/24 h) and risperidone (6 mg/24 h) and achieved substantial improvement within 2 weeks. Two weeks after admission, as part of the routine laboratory diagnostic work-up, the urine drug screen was repeated and showed methadone-positive result. Since the patient was persistently denying consumption of any drugs of abuse during his hospital stay, and because of the internal organization of the Department, it was not possible to come in contact with drugs of abuse, the urine drug screen result was interpreted as false-positive.

In fact, because of the structural similarity between quetiapine and methadone, the guidelines of the urine drug screen test kit used (COBAS INTEGRA Methadone II test kit, Roche Diagnostics; semiquantitive detection) admit the possible cross-reactivity with quetiapine.

The additional test with gas chromatography (GC) was performed to exclude methadone abuse.

Discussion

Awareness of the potential for false-positive results and confirmatory follow-up information are particularly important for both the clinicians and the patients because the false-positive urine drug screen results may affect the clinician-patient relationship by raising issues of trust.

Reports of false-positive results were found for the following formulary and nonprescription medications: brompheniramine, bupropion, chlorpromazine, clomipramine, dextromethorphan, diphenhydramine, doxylamine, ibuprofen, naproxen, promethazine, quetiapine, quinolones (ofloxacin and gatifloxacin), ranitidine, sertraline, thioridazine, trazodone, venlafaxine, verapamil, and for the nonprescription nasal inhaler. False-positive results for amphetamine and methamphetamine were most commonly reported. False-positive results for methadone, opioids, phencyclidine, barbiturates, cannabinoids, and benzodiazepines were also reported in patients taking commonly used medications[2].

Drugs that have been shown to cross-react with methadone feature a tricyclic structure with a sulfur and nitrogen atom in the middle ring, which is common to both quetiapine and methadone. Therefore, it is plausible that this structural similarity between quetiapine and methadone could underlie cross-reactivity on methadone drug screen.

Several authors have reported cases of patients treated with quetiapine who showed methadone-positive urine drug screens[9-11].

Besides quetiapine, a number of routinely prescribed medications have been associated with triggering false-positive urine drug screen results. Verification of test results with a different screening test or additional analytical tests such as high-performance liquid chromatography or liquid chromatography-mass spectrometry should be performed to avoid adverse consequences for the patients[12].

Processes need to be in place to make both laboratories and physicians aware of the potential for immunoassay interference, which can lead to clinical misinterpretation. The processes include on-going education, review of patient results in the clinical setting, protocols for testing of suspected interference, and notification of interferences both to the physician and to the diagnostic manufacturer. To minimize the reporting of false-positive or false-negative results, a constant dialogue is required between physician and laboratory about unexpected immunoassay results[13,14].

Conclusion

Drug screening through urinalysis is a widely accepted method for rapid detection of the potential drug abuse. Cross-reactivity of structurally similar substances is a problem associated with immunoassay methodologies, resulting in false-positive or false-negative results. Verification of test results with a different screening test or additional analytical tests should be performed to avoid adverse consequences for the patients. To minimize the reporting of false-positive or false-negative results, a constant dialogue is required between physician and laboratory about unexpected immunoassay results. It is recommended to review patient results in the clinical setting, protocols for testing of suspected interference, and notification of interferences both to the physician and to the diagnostic manufacturer.

References

1. SADOCK BJ, SADOCK VA. Kaplan & Sadock's Comprehensive textbook of psychiatry, 8th ed. New York: Lippincott Williams & Wilkins, 2005.
2. BRAHM NC, YEAGER LL, FOX MD, FARMER KC, PALMER TA. Commonly prescribed medications and potential false-positive urine drug screens. Am J Health Syst Pharm 2010;67:1344-50.
3. SPIEHLER VR, O'DONNELL CM, GOKHALE DV. Confirmation and certainty in toxicology screening. Clin Chem 1988;34:1535-9.
4. DODIG S. Interferences in quantitative immunochemical methods. Biochemia Medica 2008;19:50-62.
5. WU JT. Quantitative immunoassay: a practical guide for assay establishment, troubleshooting, and clinical application. Washington, DC: AACC Press, 2000.
6. GOSLING JP. Immunoassays. A practical approach. Oxford: Oxford University Press, 2000.
7. Roche Diagnostics Corp. ONLINE methadone II [Package Insert] 2003 Roche Diagnostics Corp. Indianapolis, IN.
8. FELDMAN M, KUNTZ D, BOTELHO K, ANANIAS DC, GNEZDA M, *et al*. Evaluation of Roche Diagnostics ONLINE DAT II, a new generation of assays for the detection of drugs of abuse. J Anal Toxicol 2004;28:593-8.
9. WIDSCHWENDTER CG, ZERNIG G, HOFER A. Quetiapine cross reactivity with urine methadone immunoassays. Am J Psychiatry 2007;164:172.
10. CHERWINSKI K, PETTI TA, JEKELIS A. False methadone-positive urine drug screens in patients treated with quetiapine. J Am Acad Child Adolesc Psychiatry 2007;46:435-6.
11. FISCHER M, REIF A, POLAK T, PFUHLMANN B, FALLGATTER AJ. False-positive methadone drug screens during quetiapine treatment. J Clin Psychiatry 2010;71:1696.
12. LANCELIN F, KRAOUL L, FLATISCHLER N, BROVEDANI-ROUSSET S, PIKETTY ML. False-positive results in the detection of methadone in urines of patients treated with psychotropic substances. Clin Chem 2005;51:2176-7.
13. SLOAN KL, HAVER VM, SAXON AJ. Quetiapine and false-positive urine drug testing for tricyclic antidepressants. Am J Psychiatry 2000;157:148-9.
14. TATE J, WARD G. Interferences in immunoassay. Clin Biochem Rev 2004;25:105-20.

Sažetak

LAŽNO POZITIVNI NALAZ METADONA U MOKRAĆI BOLESNIKA LIJEČENOG KVETIAPINOM

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Testovi probira mokraće široko su prihvaćena metoda brzog otkrivanja moguće zloporabe psihoaktivnih supstanca. Najčešće korišteni testovi analize mokraće na droge su imunokemijske metode, unatoč činjenici da su prijavljeni brojni slučajevi lažno-pozitivnih rezultata za mnoge od testova za brzo otkrivanje. Potvrda mogućih pozitivnih probira mokraće na lijekove, koja je neophodna kako bi se smanjio broj prijava lažno pozitivnih rezultata, može biti skupa i zahtijevati veći utrošak vremena za analizu. Prikazuje se slučaj bolesnika T.M. zaprimljenog u Kliniku za psihijatriju Kliničkog bolničkog centra Split poradi akutne psihotične reakcije (F23). U mokraći bolesnika testiranog na metadon isti je otkriven, ali bez potvrde konzumacije istog. Analiza mokraće provedena je testom COBAS Integra Methadone II (kinetička interakcija mikročestica u otopini, metoda KIMS) tvrtke Roche. Lijekovi koji su pokazali križnu reaktivnost s metadonom sadrže triciklični strukturu s atomima sumpora i dušika u srednjem prstenu, što je zajedničko i kvetiapinu i metadonu. Stoga je za pretpostaviti da je strukturna sličnost kvetiapina i metadona uzrokom križne reaktivnosti u testu probira na metadon. Uz kvetiapin, velik broj rutinski propisivanih lijekova pokazao je povezanost s pojavom lažno-pozitivnih rezultata u testovima mokraće. Kako bi se izbjegle neželjene posljedice za bolesnike potrebna je verifikacija rezultata dodatnim metodama potvrde.

Ključne riječi: *Kvetiapin; Metadon; Lažno-pozitivni test probira mokraće*