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Amphetamine-positive urine drug screens in the setting of mexiletine use: A case series

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Illicit drug use is widely accepted as an absolute contraindication to many advanced medical therapies such as transplantation. Clinical practice guidelines list active or recent illicit drug use as a class III recommendation for heart transplantation and durable mechanical circulatory support. After heart transplantation, patients with a history of substance abuse have significant increases in noncompliance (38.3% vs 6.3%, $p = 0.0001$), death because of non-compliance (27.7% vs 2.1%, $p = 0.0004$), and heart-related death (44.7% vs 24.7%, $p = 0.017$).¹ For this reason, candidates for heart transplantation are routinely screened for use of tobacco, alcohol, and illicit drugs starting with urine immunoassay drug screens (UDS).

Patients with advanced heart failure commonly have ventricular arrhythmias treated with antiarrhythmics, such as mexiletine. We report the first evidence of mexiletine being associated with false-positive UDS for amphetamines in 3 patients with advanced heart failure being considered for transplantation (cases are summarized in Table 1 and Figure 1). All cases had negative confirmatory testing, correlated with the initiation of mexiletine, and involved patients who were not taking any other medications known to cause false-positive results. Given the high prevalence of drug and alcohol abuse, it is not surprising that on detailed social history all 3 patients described a previous history of substance abuse, further complicating assessment of current use and risks after transplantation.

Although the results of immunoassay testing are binary, interpretation is often not straightforward. Immunoassays, commonly used in UDS, employ antibodies designed to recognize either the drug of interest or its metabolites. Immunoassay false-positive results depend primarily on the cross-reactivity profile of immunoassays used and the specific substance in question. The various forms of immunoassays include cloned enzyme donor immunoassay, enzyme-multiplied immunoassay technique, fluorescence polarization immunoassay, and radioimmunoassay.² Our center uses the Beckman Coulter Emit II Plus

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Amphetamines Assay, which is run on Beckman AU5800 Platform (Beckman Coulter, Inc., Brea, CA). False-positive immunoassay results for amphetamines and methamphetamines are the most common among UDS with common culprits being over-the-counter medications (i.e., antihistamines, decongestants, histamine-2 antagonists, energy supplements), antipsychotics, and antidepressants (Table 2).^{3,4} Mexiletine is structurally similar to amphetamine and methamphetamine, containing a benzene ring with a hydrocarbon tail that terminates with a functional amine group (Figure 2). This structural similarity likely explains the false-positive amphetamine immunoassay result. In addition, amphetamine and methamphetamine are simple molecules, which makes it difficult to design specific antibodies and increases the potential for cross-reactivity.⁴

It is important for providers to understand the various causes of false-positive UDS to avoid straining the provider-patient relationship, to select individuals who would benefit most from advanced therapies for heart failure, and to guide drug rehabilitation services. Confirmatory testing with a secondary specific laboratory technique, such as high-performance liquid chromatography with mass spectrometry, should be considered before making high-consequence clinical decisions based on immunoassay screen results.²

In summary, mexiletine can cause false-positive results for amphetamines on urine immunoassay. Providers should confirm results of UDS with a second laboratory method.

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Figure 1.
Timing of mexiletine initiation of positive urine drug screens.

Figure 2.
Structures of amphetamine, methamphetamine, and mexiletine.

Table 1**Patient Demographics**

	Patient 1	Patient 2	Patient 3
Age (y)	44	53	66
Etiology	Ischemic cardiomyopathy	Ischemic cardiomyopathy	Non-ischemic cardiomyopathy
Initial indication for left ventricular assist device	Bridge to transplant	Destination therapy	Destination therapy
Substance abuse history	Tobacco	Tobacco	Tobacco
	Alcohol	Alcohol	Alcohol
	Opiates		
Confirmatory testing	Negative	Negative	Negative
Type of arrhythmia	Ventricular tachycardia	Ventricular tachycardia	Ventricular tachycardia
Antiarrhythmics	Mexiletine 150 mg 3 times daily	Mexiletine 150 mg 3 times daily	Mexiletine 150 mg 3 times daily
Other medications (including over-the-counter)	Acetaminophen	Acetaminophen	Alendronate
	Aspirin	Ascorbic acid	Allopurinol
	Cholecalciferol	Aspirin	Ascorbic acid
	Citalopram	Bumetanide	Aspirin
	Docusate sodium	Cholecalciferol	Calcium carbonate–vitamin D ₃
	Furosemide	Ferrous sulfate	Ergocalciferol
	Gabapentin	Levothyroxine	Esomeprazole
	Levetiracetam	Losartan	Ferrous sulfate
	Magnesium oxide	Melatonin	Insulin
	Nitroglycerin	Mexiletine	Levothyroxine
	Oxycodone	Oxycodone	Magnesium oxide
	Pantoprazole	Pantoprazole	Mycophenolate
	Polyethylene glycol	Spironolactone	Nystatin
	Potassium chloride		Potassium chloride
	Senna		Pravastatin
	Spironolactone		Prednisone
	Warfarin		Tacrolimus
			Valganciclovir

Table 2

Agents Causing False-Positive Urine Immunoassay Results for Amphetamines

Amantadine
Benzphetamine
Bupropion
Chlorpromazine
Clobenzorex
Deprenyl
Desipramine
Dextroamphetamine
Ephedrine
Fenproporex
Isometheptene
Isoxsuprine
Labetalol
Levmetamfetamine (Vicks Vapor inhaler)
Methamphetamine
Methylenedioxymethamphetamine (MDMA)
Methylphenidate
Phentermine
Phenylephrine
Phenylpropanolamine
Promethazine
Pseudoephedrine
Ranitidine
Ritodrine
Selegiline
Thioridazine
Trazodone
Trimethobenzamide
Trimipramine