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Altered mental status in a man with metabolic syndrome

A 29-YEAR-OLD MAN WAS found by his father to be unresponsive with shallow breathing and foaming at the mouth. The man's father called emergency medical services and reported his son had a history of bipolar I disorder, posttraumatic stress disorder, hypertension, type 2 diabetes, and severe obesity (body mass index 44.5 kg/m^2). The patient had been to the emergency department in the past for depression and mania, but had no past suicidal ideation or attempts. His relevant home medications are listed in **Table 1**. The patient was intubated and transported to the emergency department.

PHYSICAL EXAMINATION

In the emergency department, the patient's vital signs were blood pressure of 76/28 mm Hg, heart rate of 113 beats per minute, and respiration rate of 8 to 10 breaths per minute. During the physical examination, he was stuporous and had limited responsiveness to verbal and physical stimuli. Computed tomography of the head revealed mild cerebral edema with concern for global anoxic injury. Chest radiography showed consolidation suggestive of aspiration. Electroencephalography was not done at the time.

Differential diagnosis included medication overdose, stroke, central nervous system injury, sepsis, cardiogenic shock, severe electrolyte imbalances, carbon monoxide poisoning, and toxin exposures such as botulism.

Pertinent results of laboratory testing include glucose 46 mg/dL (reference range 70–100 mg/dL), creatinine 2.78 mg/dL (0.7–1.3 mg/dL), potassium 5.5 mmol/L (3.5–5 mmol/L), lactate 4.5 mmol/L (0.5–2.2 mmol/L), and creatine kinase 166 U/L (24–204 U/L). His elevated creatinine was likely due to prolonged hypotension and his normal creatine kinase ruled out rhabdomyolysis.

Electrocardiogram showed sinus tachycardia. Initial arterial blood gases were notable for pH 7.20 (7.35–7.45), partial pressure of carbon dioxide 68 mm Hg (35–45 mm Hg), partial pressure of oxygen 95 mm Hg (75–100 mm Hg), bicarbonate 26 mEq/L (22–26 mEq/L), and a base excess of -4 mEq/L (−2 to +2 mEq/L). Urine toxicology was positive for tetrahydrocannabinol and lithium levels were within normal limits. No other serum concentrations of medications were obtained. The number of pills remaining in all medication bottles were consistent with the date of last refill and were not concerning for overdose.

The patient received intravenous fluids and broad-spectrum antibiotics for possible sepsis and aspiration pneumonia and was admitted to the intensive care unit (ICU) for hemodynamic support and mechanical ventilation. In the ICU, he received norepinephrine and vasopressin infusions due to persistent hypotension. Sepsis was ruled out by repeat negative blood cultures and his antibiotic regimen was deescalated to amoxicillin-clavulanic acid for aspiration.

POSSIBLE MEDICATION OVERDOSE

1 With a history of substance abuse, overdose of what drug from the patient's list of medications is most consistent with the patient's symptoms?

- ☐ Aripiprazole
- ☐ Lithium
- ☐ Metoprolol
- ☐ Metformin

The patient's clinical presentation is most consistent with metoprolol overdose. Beta-blockers such as

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TABLE 1
Relevant home medications

Medication	Dosage	Notes
Aripiprazole	400 mg intramuscularly every 4 weeks	Initiated 9 days prior to admission
Clonazepam	0.5 mg twice daily	
Fluoxetine	20 mg daily	Initiated 29 days prior to admission
Lithium extended release	600 mg in the morning, 900 mg at bedtime	
Metformin	500 mg twice daily	Initiated 2 years prior to admission
Metoprolol	50 mg twice daily	
Quetiapine	50 mg at bedtime	

metoprolol, propranolol, and labetalol are commonly used to treat a wide range of conditions including hypertension, heart failure, arrhythmias, ischemic heart disease, tremor, glaucoma, and hyperthyroidism. When ingested in excessive amounts, as competitive inhibitors of adrenergic receptors, beta-blockers disrupt the metabolic and circulatory functions of catecholamines through the decrease of intracellular cyclic adenosine monophosphate.[1] Although bradycardia and hypotension are most common, tachycardia had also been reported in some cases.[2] Severe toxicity commonly presents with altered mental status, cardiogenic shock, seizure, hypoglycemia, and bronchospasm. In most cases, symptoms develop within 2 hours of ingestion.[3]

Each type of beta-blocker has specific pharmacodynamic properties that may contribute to differential clinical manifestation of toxicity. Lipophilic agents including propranolol and nebivolol readily cross the blood-brain barrier to cause central nervous system effects such as seizure and delirium.[1,4] Beta-blockers with membrane stabilization activity, such as propranolol and carvedilol, pose higher risks of arrhythmia and QRS prolongation due to inhibition of fast sodium channels in the myocardium.[4,5] Co-ingestion of other cardioactive medications such as calcium channel blockers, cyclic antidepressants, and neuroleptics significantly elevates the risks of morbidity.[2,5] Treatment involves proactive airway management, fluid resuscitation for hypotension, atropine for bradycardia, and activated charcoal for gastrointestinal decontamination.[6,7] Hypoglycemia should be treated with intravenous dextrose, and seizure should be treated with benzodiazepines.[6,7] Glucagon, insulin with glucose, and calcium salts are also used to reverse symptoms.[8] Lipid emulsion therapy is particularly useful for lipophilic beta-blockers.[9]

Overdose of aripiprazole is limited to mild sedation in most cases.[10,11] Hemodynamic instability and cardiovascular disturbances are rare.

Although lithium poisoning can cause altered mental status and central nervous system symptoms such as delirium, tremor, and seizure, it is typically associated with gastrointestinal symptoms such as nausea, vomiting, and diarrhea.[12] Medications that cause renal impairment or dehydration such as nonsteroidal anti-inflammatory drugs and diuretics increase the risk of lithium toxicity.[13]

Metformin overdose most commonly causes gastrointestinal symptoms such as nausea and abdominal pain.[14] Tachypnea develops during increased acidosis. In severe cases, altered mental status, hypotension, and tachycardia can also occur.[15] High serum levels of metformin can also cause hypoglycemia, especially when taken concomitantly with other glucose-lowering medications. Hyperglycemia has also been reported.[15] Metformin-associated lactic acidosis, although rare, was associated with a mortality rate of 18% (2 of 11) in an analysis of 330 patients with diabetes.[16] While this patient's symptoms may resemble those of metformin toxicity, the pill counts indicate that the patient did not take more than his prescribed dosage. Metformin was a maintenance medication prescribed at a low initial dose of 500 mg twice daily. Since there were no new medications that may have contributed to metformin accumulation, metformin toxicity is not the most likely cause of the patient's symptoms.

CASE CONTINUED

After 3 days in the ICU, the patient was weaned off vasopressors and mechanical ventilation due to improved hemodynamic status and respiratory function. He was then transferred to the medical floor and appeared to be at his baseline emotional and cognitive state. There was no readily identified reason for his medical presentation; therefore, psychiatry was consulted to evaluate the patient for possible overdose. The patient denied any intentional overdose. Of note, he was recently discharged from a 10-day hospital stay at a psychiatric unit following a manic episode. There, medications were changed including initiation of aripiprazole and fluoxetine. A pharma-

cogenomics consult was ordered to ascertain the role that drug-drug and drug-gene interactions may have played in his presentation.

Pharmacogenomics overview

Pharmacogenomics is the study of how an individual's genes affect the response to drugs and possible clinically significant changes to drug metabolism. Given the complexity of translating genetic variants to clinical recommendations, pharmacogenomic test results are typically classified by metabolizer status (ie, phenotype) for each genetic variant (ie, genotype)—for example, CYP2D6 normal metabolizer or CYP2C19 poor metabolizer.[17] Zanger and Schwab[18] reported CYP2D6 is involved in the metabolism of an estimated 25% of prescribed medications as cited in Meloche et al,[17] and dosing recommendations or impacts of pharmacogenomic variants can be found in select US Food and Drug Administration-approved package inserts or in the guidelines from the Clinical Pharmacogenetics Implementation Consortium.[19–21]

Of the more than 50 cytochrome P450 enzymes, 6 are involved in the metabolism of more than 90% of medications

Drug metabolism

The pharmacokinetics of medications involves 4 stages: absorption, distribution, metabolism, and elimination. Variations in genes that code for enzymes can potentially impact the pharmacokinetics of many drugs. Of the more than 50 cytochrome P450 (CYP) enzymes, 6 are involved in the metabolism of more than 90% of medications.[22] Drugs that are activated or inactivated by CYP enzymes are known as substrates, while drugs that impact the functioning or production of CYP enzymes are known as inhibitors or inducers.

Baseline enzyme activity can also vary based on inherited genetic variants for different enzymes. For any given CYP enzyme, the majority of the population are normal metabolizers. However, for certain CYP enzymes, an individual could be a rapid metabolizer, which indicates an increase in that specific enzyme activity. Intermediate metabolizers have reduced enzyme activity, and poor metabolizers have even further reduction in enzyme activity. Other factors such as age, organ function, and other medications can affect CYP-mediated metabolism of medications, or exert their own, independent effect. All of these factors taken together ultimately inform the patient's therapeutic response and possible occurrence of adverse effects.

POTENTIAL DRUG-DRUG AND DRUG-GENE INTERACTIONS

2 Which of the patient's home medications have potential drug-drug and drug-gene interactions with metoprolol?

- ☐ Clonazepam
- ☐ Aripiprazole
- ☐ Fluoxetine

Before admission, the patient was taking standard doses of 2 CYP2D6 substrates: metoprolol 100 mg daily (usual range 100–200 mg daily)[20] and aripiprazole intramuscular (400 mg every 4 weeks).[19] The prescribing information for aripiprazole recommends a 50% dose reduction for known CYP2D6 poor metabolizers.[18] The metoprolol prescribing information reports higher plasma concentrations of metoprolol in CYP2D6 poor metabolizers.[20] A heart rate reduction of 3 beats per minute while taking metoprolol was reported in a 15-study meta-analysis (N = 1,146) in CYP2D6 poor metabolizers, though the clinical significance of these findings is unclear.[17]

When these medications had been previously prescribed, the CYP2D6 phenotype for the patient was unknown. *CYP2D6* genotyping was performed during this admission to help guide selection and dosing of future medications. The patient's pharmacogenomic testing results are shown in **Table 2**.

Pharmacogenomic testing showed the patient to be a *CYP2D6* (**4/*33*)*2N* genotype, which correlates to an intermediate metabolizer phenotype. In CYP2D6 intermediate metabolizers, drug-gene interactions associated with metoprolol and aripiprazole have not been demonstrated to have a clinically significant impact on drug response.

However, 29 days before presentation, the patient started fluoxetine 20 mg daily (usual range 20–60 mg daily), a CYP2D6 inhibitor shown to cause clinically significant inhibition of CYP2D6 enzyme activity.[23] The inhibition of CYP2D6 in a patient with baseline decreased CYP2D6 enzyme activity, such as an intermediate metabolizer, can lead to "phenoconversion" in which the CYP2D6 enzyme activity is similar to that in a CYP2D6 poor metabolizer.[24] It is hypothesized that this combination of drug-drug and drug-gene interactions resulted in an effective beta-blocker overdose, supported by the finding of hypo-

TABLE 2
Pharmacogenomic testing results

Gene	Genotype	Phenotype
CYP2C19	**1/*17*	Rapid metabolizer
CYP2D6	*(*4/*33)2N*	Intermediate metabolizer

glycemia, hypotension, and altered mental status at presentation.

Clonazepam does not have known drug-drug interactions with metoprolol. It is primarily metabolized by CYP3A enzymes.

MEDICATIONS THAT REQUIRE PHARMACOGENOMIC TESTING

3 Which of the following medications requires pharmacogenomic testing in at-risk populations?

- ☐ Aripiprazole
- ☐ Fluoxetine
- ☐ Metoprolol
- ☐ Carbamazepine

All these medications have known potential drug-gene interactions. Populations at risk include patients concurrently taking medications with potential drug-drug interactions or patients with comorbidities making them more vulnerable to adverse reactions. No requirement on dose adjustment for metoprolol or fluoxetine based on CYP2D6 phenotype currently exists. The aripiprazole package insert recommends dose adjustment in known CYP2D6 poor metabolizers, but testing is not required prior to therapy initiation.[19] Only a few medications have mandated pharmacogenomic testing prior to use in the FDA-approved prescribing information. These are typically drug-gene associations with high safety risk that provide straightforward and clinically actionable results, such as the avoidance of carbamazepine in patients who are *HLA-B*15:02*-positive.[25] Other commonly used medications that impact the CYP pathway have been previously described.[26]

Routine pharmacogenomic testing

There are several challenges to implementing routine, universal pharmacogenomic testing, as well as logistical concerns regarding cost and availability. Currently, only a limited number of third-party payers reimburse for testing. Those that cover pharmacogenomic testing may have limited coverage based on indication or previous medication history. Most laboratories do not offer point-of-care testing, which is needed in urgent care situations.

The lack of strong clinical data limits decision-making based on pharmacogenomic test results for many drug-gene pairs. A few pairings, such as carbamazepine and *HLA-B*15:02*, have clearly defined appropriate action based on results of pharmacogenomic testing. However, for other pairs, such as the heart rate reduction with metoprolol seen in CYP2D6 poor metabolizers demonstrated by Meloche et al,[17] it is not clear what, if any, clinical action should be taken.[17,25]

The utility of routine pharmacogenomic testing must also consider other patient-specific clinical factors, such as comorbid disease states and drug-drug interactions. There are reports of patients tolerating metoprolol even while taking an antidepressant that acts as a strong CYP2D6 inhibitor, making it unclear if routine, empiric dose adjustments should be made.[27] Evaluation of these common yet complex interactions necessitates the continued involvement of a pharmacotherapy specialist and disease-state expert to interpret and apply the results of pharmacogenomics testing.

FURTHER MANAGEMENT

The patient's symptoms were suspected to be a result of possible drug-drug and drug-gene interactions. Pharmacogenomic testing revealed that the patient is a CYP2D6 intermediate metabolizer, which puts him at potential risk for adverse reactions to medications metabolized by CYP2D6. The use of a strong CYP2D6 inhibitor likely further decreased his CYP2D6 enzyme activity. From the clinical team's standpoint, the use of several medications metabolized by this enzyme likely precipitated a "perfect storm" of decreased metabolism and increased serum concentrations of those agents. This combination may have ultimately led to the patient's symptoms, which were indicative of beta-blocker overdose and respiratory failure. This understanding of a potential drug-drug and drug-gene interaction identified by inpatient pharmacogenomic testing resulted in discontinuation of the strong CYP2D6 inhibitor fluoxetine.

On day 7, the patient was discharged to an acute care facility to receive intensive physical therapy due to deconditioning. He was in stable condition with good hemodynamic status and respiratory function. He was instructed to follow up with his psychiatrist regarding changes to his medications. Lab values such

as electrolytes, creatinine, glucose, and lithium levels continued to be monitored.

Medical records indicate the patient has been mentally and physically stable since his medications were adjusted according to his pharmacogenomics testing results. He has been saving money by working alongside his father and losing weight through regular exercise. Although he endorses some generalized anxiety, no acute psychiatric or medical episodes have been reported since his hospitalization.

UTILITY OF PHARMACOGENOMIC TESTING

Our patient's experience could lend credence to an argument favoring increased use of preemptive pharmacogenomic testing. Knowledge of CYP2D6 intermediate metabolizer status in the setting of fluoxetine initiation could have allowed for anticipation of the patient's "phenoconversion" to a poor metabolizer. This may have in turn led to dose reduction of aripiprazole to account for a new effective phenotype of CYP2D6 poor metabolizer. This knowledge could also have led to use of an alternative beta-blocker not metabolized by CYP2D6 or use of an alternative medication class. Similarly, these results may have led to avoidance of fluoxetine in favor of another selective serotonin reuptake inhibitor without CYP2D6 inhibition.

While pharmacogenomics may have illuminated these drug-gene interactions, the theorized inciting interaction of fluoxetine inhibition of CYP2D6 is a well-known drug-drug interaction. Fluoxetine-mediated inhibition of CYP2D6 would be expected to reduce aripiprazole metabolism, irrespective of baseline phenotype. Similarly, symptomatic bradycardia with metoprolol in the presence of the CYP2D6 inhibitor bupropion has also been described in a non-poor metabolizer.[28] Therefore, some degree of drug-drug interaction could have been anticipated, and selection of alternatives to fluoxetine and metoprolol would have been reasonable and clinically appropriate even without pharmacogenomics testing results.

Clinicians can routinely use available drug-drug interaction checkers, many of which are integrated into electronic medical record and prescribing systems. Sources also exist for evaluating drug-gene interactions, but they are rarely embedded in the prescribing process and therefore can easily be missed.

The true challenge often lies in understanding possible drug interactions and their clinical significance if they occur. Medications are routinely used in combination without clinically significant interactions or adverse reactions when managed with appropriate monitoring. A good steward of healthcare resources would conclude that preemptive pharmacogenomic testing was likely not necessary in this case. The selection of an alternative to fluoxetine such as citalopram, sertraline, or escitalopram would have been an appropriate first-line selective serotonin reuptake inhibitor. The use of any of these medications would have avoided the known drug-drug interactions between fluoxetine and both aripiprazole and metoprolol. However, a role remains for pharmacogenomics testing in specific circumstances such as if these interactions were unavoidable due to previous therapy failure with alternative agents.

TAKE-HOME POINTS

- Pharmacogenomic testing can identify patients at higher risk for adverse events related to drug-drug and drug-gene interactions.
- Potential drug-drug interactions should be checked and patients appropriately monitored for adverse reactions.
- Universal pharmacogenomic testing is currently not feasible due to cost, availability, insurance, and other limitations.
- Careful assessment of the severity of potential reactions, cost, and the opportunity to use an alternative regimen that avoids the interaction of concern entirely should be considered before performing pharmacogenomic testing.
- As more is known about pharmacogenomics and possible personalization of therapeutic regimens, continual evaluation of clinical considerations that warrant testing should occur to facilitate both resource stewardship and optimal patient care.

DISCLOSURES

Dr. Hockings has disclosed consulting for MCG Health. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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