

Unrecognized Drug-Drug Interactions: A Cause of Intraoperative Cardiac Arrest?

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Many physicians overlook, or are unaware of, most drug-drug interactions. In our patient, the local anesthetic used for an axillary block may have been the precipitating drug in a cascade of drug-drug interactions that resulted in a cardiac arrest. The combination of multiple preoperative drug-drug interactions prevented the return of a stable native cardiac rhythm for

almost 24 h. The mechanisms of interactions of these frequently used drugs are described, and the reader is guided to sources that identify and simplify the understanding of potentially dangerous drug-drug interactions.

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We describe sinoatrial node failure resulting in asystolic cardiac arrest shortly after an uneventful brachial plexus block with mepivacaine. On *post hoc* review of the case, a panel of physicians identified a number of significant drug-drug interactions (DDIs) that likely caused or contributed to the cardiac arrest. Conclusive evidence of the significance of these DDIs is limited by the lack of serum drug levels of local anesthetic and other medications. However, supporting evidence is provided by postoperative genotyping of cytochrome P450 enzymes. This case is a cautionary example of the multiple potential DDIs in patients receiving common outpatient medications. DDI-mediated drug toxicity should be considered in cases of hemodynamic instability in the operating room, and relevant serum drug levels should be obtained.

Case Report

A 50-yr-old year man presented for carpal tunnel and cubital tunnel nerve release. His medical history included atypical

intermittent chest pain, hypertension, diabetes mellitus, gastroesophageal reflux, and depression. He had never smoked. His current medications were amitriptyline, cyclobenzaprine, metoprolol, nifedipine, omeprazole, sertraline, aspirin, and insulin. The patient drank 1–2 cups of coffee every morning, as well as 4 cups of green tea each evening. He was a habitual drinker of grapefruit juice, consuming as much as 64 ounces per week.

The preoperative electrocardiogram was unremarkable except for first-degree atrioventricular block (PR interval = 280 ms). Stress thallium testing and cardiac catheterization were negative for coronary artery disease. An echocardiogram demonstrated moderate left ventricular hypertrophy. A preoperative medical consultation recommended only increasing the dose of metoprolol.

An uneventful axillary brachial plexus block using 1.5% mepivacaine (45 mL)/1% tetracaine (5 mL) with epinephrine (3 µg/mL) was performed and surgery proceeded. There were no signs of intravascular injection. The patient was hemodynamically stable for a period of 10 min but slowly developed moderate hypotension (arterial blood pressure [BP], 85/55 mm Hg) and bradycardia (heart rate [HR], 60 bpm). He received ephedrine 50 mg and phenylephrine 400 µg in divided doses without an increase in BP or HR. At 70 min after the administration of the block, the patient had sudden asystole. He received atropine 3 mg and initial pacing by precordial thump, followed by transcutaneous cardiac pacing. An epinephrine infusion (4 µg/min) was started, which was increased incrementally to 16 µg/min during the next 30 min. Dopamine (15 µg · kg⁻¹ · min⁻¹) and norepinephrine (8 µg/min) infusions were also required to maintain the BP at approximately 80/40 mm Hg. A transvenous pacemaker was placed by the cardiology service before leaving the room. For several hours, the patient had no underlying cardiac rhythm; later that evening,

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Table 1. Preoperative DDIs

Arrhythmogenic drug	Interacting drug	DDI mechanism	Clinical effects
Amitriptyline (plus nortriptyline)	Caffeine	Inhibition of P450 1A2	1) Decreased metabolism of amitriptyline plus nortriptyline; 2) Proarrhythmic state; 3) Diminished inotropic state
	Grapefruit juice	Inhibition of P450 1A2 and intestinal 3A4	
	Omeprazole	Inhibition of P450 2C19	
	Sertraline ^a	Inhibition of P450 2C19, 2D6, 1A2, and 3A4	
Cyclobenzaprine	Caffeine	Inhibition of P450 1A2	1) Decreased metabolism of cyclobenzaprine; 2) Proarrhythmic state; 3) Diminished inotropic state
	Grapefruit juice	Inhibition of P450 1A2 and intestinal 3A4	
	Sertraline ^a	Inhibition of P450 1A2 and 3A4	
Metoprolol	Amitriptyline (plus nortriptyline)	Inhibition of P450 2D6	1) Decreased metabolism of metoprolol; 2) Diminished inotropic state
Mepivacaine	Sertraline ^a	Inhibition of P450 2D6	1) Decreased metabolism of mepivacaine; 2) Proarrhythmic state; 3) Diminished inotropic state
	Caffeine	Inhibition of P450 1A2	
	Grapefruit juice	Inhibition of P450 1A2 and intestinal 3A4	
	Sertraline ^a	Inhibition of P450 1A2 and 3A4	
Amitriptyline (plus nortriptyline), cyclobenzaprine, and metoprolol	Mepivacaine	Pharmacodynamic synergy of arrhythmogenic potential	1) Proarrhythmic state; 2) Diminished inotropic state

DDI = drug-drug interaction. ^aThe blood level of Sertraline was increased by the consumption of grapefruit juice. This further enhanced Sertraline's ability to impair the metabolism of amitriptyline (plus nortriptyline), cyclobenzaprine, metoprolol, and mepivacaine, leading to further increases in the blood levels of these drugs.

he demonstrated third-degree heart block. The decision was made not to place a permanent pacemaker. Over the next 24 h, the patient slowly regained a stable cardiac rhythm, was weaned from all infusions, and was tracheally extubated. He was ultimately discharged in stable condition.

In the months that followed, we performed several tests to better understand the preceding events. After receiving appropriate consent, a cheek swab was obtained and an analysis of the patient's Cytochrome P450 genotype was performed (Signature Genetics, Montreal, Canada). The patient's genotypes for P450 enzymes 1A2 (*1A/*1F) and 2C9 (*1/*1) corresponded to standard levels of activity for those enzymes. The patient was also found to have a polymorphism of the gene that codes for the P450 2C19 enzyme (*1/*2) that is expressed as a phenotype of mildly to moderately diminished activity of that enzyme. Also, the analysis revealed a very unusual genotype for the P450 2D6 enzyme in which there were extra allelic copies of a polymorphism associated with mildly to moderately decreased activity (*41/*41xN). The phenotype that corresponds to the genotype for that enzyme has not been well elucidated. Trough tricyclic blood levels were also obtained. The nortriptyline level was 86 ng/mL (therapeutic range, 50–140

ng/mL), and the amitriptyline level was 415 ng/mL (therapeutic range, 70–110 ng/mL) for a total tricyclic level of 501 ng/mL (therapeutic range, 120–250 ng/mL).

Discussion

Although local anesthetics, such as mepivacaine, cause decreased automaticity and slowing of cardiac conduction, this is rare after peripheral nerve blocks (1,2). However, in the case described, multiple DDIs involving the cytochrome P450 system (Table 1) and particularities of the P450 genotype resulted in a predisposition for cardiovascular toxicity. Before the administration of the anesthetic, the patient was taking metoprolol, the dose of which had been recently increased. He was taking amitriptyline and its close structural analog, cyclobenzaprine, both with potential for causing atrioventricular conduction delay and slowing of ventricular conduction. Interactions among these medications, sertraline, caffeine, and grapefruit juice likely resulted in a predisposition to bradycardia

and heart block (evidenced by baseline first-degree atrioventricular block). It is likely that the addition of mepivacaine into this milieu, combined with DDIs slowing the metabolism of mepivacaine, caused further sinoatrial node suppression and conduction slowing, resulting in asystolic arrest.

Moderate-to-potent inhibition of the 1A2 enzyme occurs with the administration of caffeine, grapefruit juice, and sertraline (3-5). This is significant because 1A2 is thought to be the enzyme primarily responsible for the metabolism of mepivacaine (6,7). Additionally, P450 1A2 is both the principal enzyme that metabolizes cyclobenzaprine and a contributor to the metabolism of amitriptyline (8-10). These structurally related compounds exert quinidine-like inhibitory effects on cardiac conduction, especially in the presence of other cardioselective drugs (11). Additive inhibition at the 1A2 enzyme would result in decreased metabolism of mepivacaine, possibly causing unexpectedly high blood levels or prolonged duration of mepivacaine. We suggest this may have accentuated the effect of the decreased metabolism and high blood levels of the other proarrhythmic drugs. Curiously, had the patient been a habitual smoker, he may have had a less pronounced alteration of his 1A2 enzymatic activity. Smoking is a potent inducer of 1A2 (12,13), which might have significantly mitigated the 1A2 inhibitory effects of caffeine, sertraline, and grapefruit juice on the metabolism of both cyclobenzaprine and mepivacaine.

DDIs at the 2D6 enzyme, whereas not as critical to this case as those at the 1A2 enzyme, impair the metabolism of metoprolol through both direct and indirect mechanisms (14). First, sertraline inhibited the metabolism of amitriptyline + nortriptyline at 2D6 and other P450 enzymes (15-17). Amitriptyline and nortriptyline also inhibited the 2D6 enzyme to decrease the metabolism of metoprolol (18). The long duration of the asystole is consistent with the extended half-life of metoprolol in the presence of impaired 2D6 functioning (19), in this case caused by the coadministration of 2D6 inhibitors.

The patient's P450 genotyping results also suggested that his enzyme phenotype for P450 2C19 contributed to his difficulties. His diminished level of activity at the 2C19 enzyme would yield a higher blood level of amitriptyline than expected for any given dose, further exacerbating the amitriptyline blood level increases described above and the DDIs that arose from this factor. Although the clinical expression of his gene variant for P450 2D6 has not been completely elucidated, it was believed that the offsetting factors of multiple copies of a less active allele yielded a normal level of P450 2D6 enzymatic activity. Given the dose of amitriptyline (100 mg of qHS) and the presence of multiple drugs that inhibited the metabolism of amitriptyline plus nortriptyline, his toxic

total tricyclic level (501 ng/mL) was not surprising and it was consistent with a normal extensive metabolizer phenotype. Thus, the polymorphism for P450 2C19 was probably the only genotypic abnormality that meaningfully contributed to the patient's cardiac complications.

Although a definitive cause could not be determined, there is much circumstantial evidence for multiple-drug toxicities leading to sinoatrial node failure and asystole. This explanation is supported by many well described DDIs involving the patient's medications, the particular P450 genotype, and the temporal association with mepivacaine administration in the absence of other apparent precipitants of cardiac arrest.

To the review panel, it was striking that neither the preoperative medical consultation team, the anesthesia team, nor the surgical team recognized any of the potential DDIs. In fact, the recommendation by the medical consulting team for increased β -blockade before surgery likely contributed toward destabilizing the patient. It is incumbent on anesthesia providers to educate themselves about the serious DDIs mediated by the P450 system and the additive effects that result from our anesthetic choices. Although mastering the P450 metabolic profiles and inhibitory and inductive capabilities of all drugs encountered in anesthetic practice is a daunting task, a straightforward and concise approach can be found in the *Concise Guide to Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, and P-Glycoproteins*, second edition (Cozza et al., American Psychiatric Publishing, Inc., 2003). Also, Dr. David Flockhart's comprehensive tables of P450 substrates, inhibitors, and inducers can be found at <http://medicine.iupui.edu/flockhart/table.htm>. This case provides an example of how a focused analysis of a patient's medications for possible DDIs may be accomplished on an enzyme-by-enzyme basis.

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