

The Case of the Not-So-Regional Anesthetic

Neil B. Sandson, M.D.

- Director, Division of Education and Residency Training; Sheppard Pratt Health System
- Director, Psychopharmacology Consultation Service; Sheppard Pratt Health System
- Clinical Assistant Professor, University of Maryland Medical School, Department of Psychiatry

Background Details

- 50 year-old male VA patient presenting for carpal and cubital tunnel release
- PMH
 - ◆ Atypical intermittent chest pain
 - ◆ HTN
 - ◆ Type II diabetes
 - ◆ GERD
 - ◆ Major depression (in remission)

Background Details

■ Medications

- ◆ Amitriptyline, 100 mg/day
- ◆ ASA
- ◆ Cyclobenzaprine
- ◆ Insulin
- ◆ Metoprolol
- ◆ Nifedipine
- ◆ Omeprazole
- ◆ Sertraline

Background Details

- Non-smoker (!!!)
- Prolific caffeine consumer -- 1-2 cups of coffee each morning and 4 cups of tea each evening
- Habitual grapefruit juice consumer -- as much as 64 ounces per week

Background Details

- Pre-operative ECG
 - ◆ NSR
 - ◆ 1st degree AV block (PR interval = 280 msec)
 - ◆ Non-specific ST-T wave changes
- Stress thallium negative for myocardial ischemia
- Cardiac catheterization negative for significant lesions
- Echocardiography revealed moderate LVH and normal ejection fraction

Background Details

- Given the negative cardiac workup, the Internal Medicine service recommended an increase in the standing metoprolol dose and assessed the patient to be at minimal cardiac risk for this procedure.

In The OR

- Patient received fentanyl, 50 mcg IV and midazolam, 2 mg IV.
- An uncomplicated brachial plexus block was performed using mepivacaine as a regional (local) anesthetic agent.
- At incision, the patient was awake and reported no pain.

In The OR

- About one hour later, the patient experienced extreme bradycardia, hypotension, and high-degree heart block which progressed rapidly to complete cardiovascular collapse and asystole.

Post-Operative Events

- After 36 hours (!), the patient was successfully resuscitated through ACLS protocol, external pacing followed by transvenous pacing, liberal administration of pressors, and discontinuation of all other drugs.
- Patient ultimately recovered and was discharged to home.

Analysis

■ Amitriptyline

- ◆ P-glycoprotein substrate
- ◆ Metabolism is catalyzed by:
 - ◆ P450 2D6
 - ◆ P450 2C19
 - ◆ P450 3A4
 - ◆ P450 1A2 (less important)
 - Demethylated via 2C19, 3A4, and 1A2 into nortriptyline

Analysis

- Cyclobenzaprine

- ◆ Metabolism is catalyzed by:

- ◆ P450 1A2 (primary)

- ◆ P450 3A4 (secondary)

Analysis

- Metoprolol

- ◆ Metabolism is catalyzed by:

- ◆ P450 2D6

Analysis

- Nifedipine

- ◆ Metabolism is catalyzed by:

- ◆ P450 3A4

Analysis -- Pre-Operative DDIs

- 1) Amitriptyline + Sertraline = $\uparrow\uparrow$ AMI
 - ◆ Inhibition of 2C19, 2D6, 3A4, and 1A2
 - ◆ Inhibition of P-glycoprotein
- 2) Amitriptyline + Grapefruit juice = $\uparrow\uparrow$ AMI
 - ◆ Inhibition of 3A4 and 1A2
 - ◆ Inhibition of P-glycoprotein
- 3) Amitriptyline + Omeprazole = $\uparrow\uparrow$ AMI
 - ◆ Inhibition of 2C19
 - ◆ Inhibition of P-glycoprotein

Analysis -- Pre-Operative DDIs

- 4) Cyclobenzapine + Caffeine = ↑↑ CBP
 - ◆ Inhibition of 1A2
- 5) Cyclobenzapine + Sertraline = ↑↑ CBP
 - ◆ Inhibition of 3A4 and 1A2
- 6) Cyclobenzapine + Grapefruit juice = ↑↑ CBP
 - ◆ Inhibition of 3A4 and 1A2

Analysis -- Pre-Operative DDIs

- 7) Metoprolol + Amitriptyline/Nortriptyline = $\uparrow\uparrow$ MTP
 - ◆ Inhibition of 2D6
- 8) Metoprolol + Sertraline = $\uparrow\uparrow$ MTP
 - ◆ Inhibition of 2D6

Analysis -- Pre-Operative DDIs

- 9) Nifedipine + Grapefruit juice = ↑↑ NFD
 - ◆ Inhibition of 3A4
- 10) Nifedipine + Sertraline = ↑↑ NFD
 - ◆ Inhibition of 3A4

Analysis -- Pre-Operative DDIs

- 11) Sertraline + Grapefruit juice = ↑↑ SERT
 - ◆ Inhibition of 3A4

Analysis -- Pre-Operative DDIs

- 12) AMI/NTP + CBP + MTP + NFD
 - ◆ Pharmacodynamic synergy of arrhythmogenic potential

Analysis -- Peri-Operative DDIs

- 1) Mepivacaine + Caffeine = $\uparrow\uparrow$ MPV
 - ◆ Inhibition of 1A2
- 2) Mepivacaine + Sertraline = $\uparrow\uparrow$ MPV
 - ◆ Inhibition of 1A2 and 3A4
- 3) Mepivacaine + Grapefruit juice = $\uparrow\uparrow$ MPV
 - ◆ Inhibition of 1A2 and 3A4
- 4) Mepivacaine + Fentanyl = $\uparrow\uparrow$ MPV
 - ◆ Inhibition of 3A4

Analysis -- Peri-Operative DDIs

- 5) Mepivacaine + AMI/NTP + CBP + MTP + NFD
 - ◆ Pharmacodynamic synergy of arrhythmogenic potential

Analysis -- Pharmacogenetic Factors

- To assess whether any genetic variations contributed to the patient's inability to metabolize drugs, a cheek swab was obtained after appropriate consent, and analysis of the patient's genotype for cytochrome P450 enzymes was performed (Signature Genetics; Montreal, Canada).

Analysis -- Pharmacogenetic Factors

■ Results

- ◆ P450 1A2 (*1A/*1F) -- extensive metab.
- ◆ P450 2C9 (*1/*1) -- extensive metab.
- ◆ P450 2C19 (*1/*2) -- EM with diminished activity
- ◆ P450 2D6 (*41/*41xN) -- significance uncertain

Analysis -- Pharmacogenetic Factors

- Several months later, in order to assess the approximate impact of these polymorphisms on the patient's metabolic capabilities, a trough blood level of amitriptyline + nortriptyline was obtained. The nortriptyline level was 86 ng/mL (therapeutic range = 50 – 140 ng/mL), 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).

Analysis -- Pharmacogenetic Factors

- 2 conclusions about the significance of these findings suggest themselves:
 - ◆ 1) Given the presence of multiple inhibitors of P450 2D6, 2C19, 3A4, and 1A2, at 100 mg/day of AMI, the fact that the TCA concentrations were neither astronomical nor miniscule suggests that this 2D6 genotype does NOT code for either poor or ultrarapid metabolizer phenotypes (which leaves EM, EM with diminished activity, or IM phenotypes).

Analysis -- Pharmacogenetic Factors

- 2 conclusions about the significance of these findings suggest themselves (cont.):
 - ◆ 2) The fact that the concentration of AMI is much greater than the concentration of NTP suggests that inhibition of 2C19, 3A4, and 1A2 mediated demethylation is a significantly greater influence than inhibition of 2D6 mediated hydroxylation.
 - ◆ Inhibition of these demethylating enzymes by exogenous agents, +/- the 2C19 polymorphism, are the most relevant issues in this case.

Recommendations

This was a dramatic, unusual,
and **VERY** unexpected
perioperative event!

Recommendations

- Acutely, decrease AMI dosage!
- Consider an antidepressant regimen (and for that matter, a muscle relaxant) with a higher therapeutic index.
- If patient really requires sertraline + AMI for management of depression, then monitor TCA levels and ECGs more closely.
 - ◆ 1st degree AV block coincided with the initiation of sertraline.
- Consider less GFJ and caffeine, but beware reversals of inhibition.

Recommendations

- While I would not recommend that this patient begin smoking, it is likely that his somewhat unusual non-smoking status played a large role in causing this event to occur.
 - ◆ Lack of induction of the metabolism of cyclobenzaprine, caffeine, AMI, and mepivacaine, which would have compensated for the inhibition of multiple enzymes detailed above.

Recommendations

- Although this is counterintuitive, for future regional procedures, it is probably more prudent for this patient to undergo general anesthesia with one of the flurane inhalational anesthetics (such as desflurane), whose metabolism relies on P450 2E1 (which has few inhibitors).

Recommendations

- In truth, the clinical significance of the genotypic information is unclear in this case, but that does not imply that this information was not important to obtain. In a case as complex as this, failure to obtain information on any likely contributing factors restricts us more to a reactive empiricism and impairs our ability to maximally safeguard our patients' safety.

Take-home messages

- Good luck, and may all your interactions be benign.

References

- Cozza K, Armstrong S, Oesterheld J: Concise Guide to Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, and P-Glycoproteins, 2nd Edition. Washington DC, American Psychiatric Publishing Inc, 2003
- Marcucci C, Sandson NB, Thorn EM, Bourke DL: Unrecognized drug-drug interactions: a cause of intraoperative cardiac arrest? *Anesth Analg* 102(5):1569-1572, 2006