

Metoprolol and Bupropion Interaction: A Case Study

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Drug interactions can result in serious adverse responses. These are the ones we most want to avoid. Responses may also be mild and not a serious health threat. Mild responses, however, may still cause consternation to the subject. Here we present a case of a mild interaction that may have gone unexplained if the subject had not taken time to read a recent review on drug interactions [1]. While the potential for bradycardia to ensue from co-administration of bupropion and metoprolol has been previously described [2], we wish to illustrate how a low dose of bupropion and metoprolol can cause an interaction that disrupts a patient's daily activity.

Case

A 61 year-old male with an approximately 43-year history of smoking almost a pack of cigarettes per day. The subject was in fair health and had a regular exercise routine, mostly moderate, but including swimming approximately 75 minutes per week. The subject was under treatment to manage hypertension, and had been using a combination of metoprolol tartrate (50 mg, 2 per day) and amlodipine besylate (10 mg one per day) for three years.

In an effort to quit smoking the subject started taking bupropion hydrochloride (150 mg one per day taper for 5 days and then 2 per day). Shortly after starting the medication the subject went to swim and found himself gasping for breath after only 2 laps (50 yards). After rest, he was able to swim a few more laps, but had to stop far short of his normal routine secondary to dyspnea. While this abrupt change in stamina was bewildering and confusing to the subject, he felt otherwise normal and did not seek immediate medical attention.

Fortuitously, the subject came across the review on drug interactions by Polasek et al. [1], and found bupropion listed as a strong inhibitor of cytochrome P450 (CYP) 2D6 based on the study by Kotlyar et al. showing bupropion inhibited the *in vivo* metabolism of dextromethorphan [3]. Metoprolol is extensively metabolized by CYP 2D6 [4-6].

The subject then discussed this case with his pharmacist. She cautioned the subject to divide his 50 mg metoprolol tartrate tablet in half and just take one-half tablet (25 mg) twice per day. The subject could still not swim his usual workout, but the length he could swim progressed and within 2-3 weeks he was back to his normal distance. Soon after this the subject had a regular appointment with his primary physician and discussed the incident with him. He concurred with the reduction in metoprolol dose. The subject subsequently had no further episodes of dyspnea with exertion, nor episodes of syncope, or cardiac symptoms.

Discussion

We have now added another example to the singular report by McCollum et al. [2] on the potential for bradycardia to arise from the interaction of bupropion and metoprolol. While such an interaction may be inferred from the metabolic route of metoprolol clearance and the effect of bupropion on CYP2D6, a clinical study demonstrating a significant effect of bupropion on the pharmacokinetics and/or pharmacodynamics of metoprolol has yet to be done. The previous case study described the incidence of severe sinus bradycardia after addition of bupropion to the medical regimen of a patient on metoprolol (75

mg twice per day). Bupropion (150 mg BID) had been administered 12 days prior to this incident [2]. In the current case, the interaction, realized in a shorter time frame, was not so severe, but illustrates how even milder drug interactions can disrupt ones daily life.

Sinus bradycardia does occur following treatment with metoprolol alone, but is not a common adverse event. In clinical trials experience with extended-release metoprolol, bradycardia was reported among the most common (greater than 2%) adverse reactions. In the MERIT-HF study (a study in heart failure patients), bradycardia was observed in 1.5% of patients taking up to 200 mg daily of metoprolol succinate extended-release (n=1990) vs. 0.4% taking placebo (n=2001) [7]. Bradycardia and shortness of breath occurred in about 3% of hypertension and angina patients receiving metoprolol tartrate immediate release. In randomized controlled studies involving patients with a history of myocardial infarction, bradycardia (heart rate less than 40 beats per minute) was seen in 15.9% of patients taking metoprolol tartrate immediate release vs. 6.7% taking placebo [8].

The probability of the interaction occurring now rests solely on clinical evidence that bupropion inhibits the *in vivo* metabolism of other CYP2D6 substrates including dextromethorphan, [3,9] venlafaxine [10] and imipramine [11]. *In vitro* studies indicate the inhibition may be due to the more potent competitive inhibition by the reductive metabolites of bupropion, erythrohydrobupropion and theohydrobupropion, rather than by the parent compound [12].

Conclusion

Bupropion is an established inhibitor of CYP2D6. We now add a second case report to illustrate the specific effect this inhibition can have on metoprolol, resulting in a mild case of bradycardia. While serious drug interactions can be life threatening, even mild interactions must be appreciated for the impact they may have on ones daily life.

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References

1. Polasek TM, Lin FPY, Miners JO, Doogue MP (2011) Perpetrators of pharmacokinetic drug-drug interactions arising from altered cytochrome P450 activity: a criteria-based assessment. *Br J Clin Pharmacol* 71: 727-736.

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2. McCollum DL, Greene JL, McGuire DK (2004) Severe sinus bradycardia after initiation of bupropion therapy: a probable drug-drug interaction with metoprolol. *Cardiovasc Drugs Ther* 18: 329-330.
3. Kotlyar M, Brauer LH, Tracy TS, Hatsukami DK, Harris J, et al. (2005) Inhibition of CYP2D6 activity by bupropion. *J Clin Psychopharmacol* 25: 226-229.
4. Lennard MS, Silas JH, Freestone S, Ramsay LE, Tucker GT, et al. (1982) Oxidation phenotype-a major determinant of metoprolol metabolism and response. *New Engl J Med* 307: 1558-1560.
5. Otton SV, Crewe HK, Lennard MS, Tucker GT, Woods HF (1988) Use of quinidine inhibition to define the role of the sparteine/debrisoquine cytochrome P450 in metoprolol oxidation by human liver microsomes. *J Pharmacol Exp Ther* 247: 242-247.
6. Mautz DS, Nelson WL, Shen DD (1995) Regioselective and stereoselective oxidation of metoprolol and bufuralol catalyzed by microsomes containing cDNA-expressed human P4502D6. *Drug Metab Dispos* 23: 513-517.
7. Astra Zeneca L (2010) Product Information: TOPROL-XL(R) oral extended release tablet, metoprolol succinate oral extended release tablet.
8. Corporation NP (2009) Product Information: Lopressor(R) oral tablets, IV injection, metoprolol tartrate oral tablets, IV injection.
9. Guzey C, Norstrom A, Spigset O (2002) Change from the CYP2D6 extensive metabolizer to the poor metabolizer phenotype during treatment with bupropion. *Ther Drug Monit* 24: 436-437.
10. Kennedy SH, McCann SM, Masellis M, McIntyre RS, Raskin J, et al. (2002) Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. *J Clin Psychiatry* 63: 181-186.
11. Shad MU, Preskorn SH. (1997) A possible bupropion and imipramine interaction. *J Clin Psychopharmacol* 17: 118-119.
12. Reese MJ, Wurm RM, Muir KT, Generaux GT, St John-Williams L, et al. (2008) An in vitro mechanistic study to elucidate the desipramine/bupropion clinical drug-drug interaction. *Drug Metab Dispos* 36: 1198-1201.