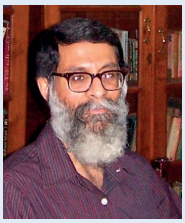
Drug Interactions in the Treatment of Depression in Patients Receiving β-Blocker Drugs

Chittaranjan Andrade, MD



Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to *JCP* readers in psychiatric and general medical settings.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

J Clin Psychiatry 2013;74(1):e75–e78 (doi:10.4088/JCP.12f08323)

Clinical Problem

Last month's column examined potential selective serotonin reuptake inhibitor (SSRI) interactions with antiplatelet drugs (aspirin, clopidogrel) in a hypothetical 67-year-old man with major depressive disorder comorbid with ischemic heart disease (IHD).[1] This month, we continue the discussion on possible concerns associated with using an antidepressant to treat depression in this patient.

Patients with IHD commonly receive β-blocker drugs. β-Blockers are also used in the treatment of hypertension, heart failure, anxiety, migraine, essential tremor, and other conditions. Commonly used β-blockers include atenolol, metoprolol, nebivolol, carvedilol, bisoprolol, and propranolol.[2–5] Many antidepressants inhibit the cytochrome P450 (CYP) enzymes that metabolize certain β-blocker drugs. If the metabolism of β-blockers is inhibited, their peak blood level and half-life will increase, resulting in an increase in dose-dependent adverse effects. Prominent among these adverse effects are bradycardia, heart block, hypotension, and loss of cardioselectivity associated with an increased risk of bronchoconstriction and altered glucose homeostasis.[6,7]

Drug Interaction: Paroxetine and Metoprolol

Several studies illustrate the interaction between paroxetine, a commonly used SSRI, and metoprolol, a commonly used β-blocker. For example, in a randomized, open-label, 3-way crossover study, Parker and Soberman[7] examined how paroxetine affects the pharmacokinetics and cardiovascular effects of metoprolol. This study was conducted in 15 healthy volunteers in whom genotyping confirmed the presence of at least 1 active *CYP2D6* allele; thus, no subject was a CYP2D6 poor metabolizer.

On the first day of each of the 3 phases of the study, these volunteers received a single dose of metoprolol extended-release (ER) 100 mg, a single dose of metoprolol ER 200 mg, or 2 doses of metoprolol immediate-release (IR) 100 mg administered 12 hours apart. The volunteers then received paroxetine 20 mg/d on days 2–8. Finally, the same metoprolol formulation was administered on day 8. In the 3 phases of the study, volunteers rotated through the 3 different formulations of metoprolol with a 14-day washout between the phases.

Important findings of the study[7] are presented in Table 1. In sum, paroxetine substantially raised the peak blood level of and the exposure to metoprolol, resulting in heightened metoprolol-induced fall in exercise-related heart rate and systolic blood pressure. Paroxetine had a greater effect on IR than on ER metoprolol.

Similar findings have been reported by other investigators. For example, in a pharmacokinetic study conducted in healthy volunteers, Stout et al[8] showed that paroxetine increased the area under the curve (AUC) of the *S* and *R* enantiomers of metoprolol by 4- and 5-fold, respectively, with the IR formulation and by 3- and 4-fold, respectively, with the ER formulation. Goryachkina et al[9] also reported the inhibition of metoprolol metabolism by paroxetine. These findings suggest that patients receiving metoprolol should receive lower doses of the drug if they are also treated

- Some antidepressants inhibit the metabolism of some β-blockers.
- Bradycardia and hypotension, heart block, or other dose-dependent adverse effects may occur in vulnerable patients as a result of these interactions.
- Strategies include prescribing an antidepressant that does not affect the metabolism of the β-blocker in use, *or* prescribing a β-blocker that is not metabolized by the antidepressant in use.
- If the interaction is unavoidable, the β-blocker dose can be down-titrated using heart rate and blood pressure as a guide.

Table 1. Important Findings of a Study of the Effects of Paroxetine on the Pharmacokinetics and Cardiovascular Effects of Metoprolol[a]

At steady state, paroxetine approximately trebled the AUC of the *S* enantiomer of metoprolol and approximately quadrupled the AUC for the *R* enantiomer with both ER and IR formulations of metoprolol
At steady state, paroxetine approximately doubled the C_{max} as well as the elimination half-life of both *S* and *R* enantiomers of both ER and IR formulations of metoprolol
The effect of paroxetine on the C_{max} of *S*-metoprolol was significantly greater for the IR formulation of metoprolol than for either of the (100- and 200-mg) ER formulations
Paroxetine significantly enhanced the metoprolol-induced fall in exercise-related heart rate and systolic blood pressure
The peak effect of the 2 doses (spaced 12 h apart) of metoprolol IR 100 mg on heart rate was significantly greater than that of the single dose of metoprolol ER 200 mg. This finding was not altered by paroxetine administration

[a]Data from Parker and Soberman.[7]
Abbreviations: AUC = area under the curve, C_{max} = maximum concentration, ER = extended-release, IR = immediate-release.

Table 2. Principal Routes of Metabolism or Elimination of Commonly Used β-Blockers

Predominantly metabolized by CYP2D6
Carvedilol[3]
Metoprolol[3]
Nebivolol[12–14]
Metabolized by multiple routes (CYP1A2, 2C19, 2D6, 3A4)
Propranolol[15,16]
Partly (50%) metabolized by CYP2D6 and 3A4 and partly (50%) eliminated by renal excretion
Bisoprolol[3,17,18]
Mainly eliminated by renal excretion
Atenolol[3,19]
Nadolol[17]
Sotalol[17]

Abbreviation: CYP = cytochrome P450.

with paroxetine; the actual dose of metoprolol can be determined by titration on the basis of its clinically measured cardiovascular effects. It may also be safer for patients to receive metoprolol ER than metoprolol IR when paroxetine and metoprolol are prescribed together.

Mechanism of the Interaction Between Paroxetine and Metoprolol

Paroxetine is a potent inhibitor of CYP2D6,[10,11] the enzyme that plays a major role in the metabolism of metoprolol.[3] This explains why paroxetine increases pharmacokinetic indices of exposure to metoprolol and, hence, the cardiovascular effects of metoprolol.

Other Antidepressants and Other β-Blockers

The interaction between antidepressants and β-blockers can be anticipated if one knows how individual β-blockers are metabolized or eliminated (Table 2) and the effects of individual antidepressants on the CYP enzyme system (Table 3). It is apparent that most of the commonly used β-blockers are either metabolized by CYP2D6 or eliminated by renal excretion[3,12–19]; thus, an awareness of which commonly used antidepressants significantly inhibit CYP2D6[10,11,20–25] will warn clinicians about the risk of a potential drug interaction. Table 3 also lists antidepressants that are mild inhibitors of CYP2D6[10,23,25,26,29–31]; these are probably associated with lower risk of CYP2D6 drug interactions at usual clinical doses.

There is evidence to show that the data in Tables 2 and 3 can reasonably be extrapolated to real-life practice. For example, in a pharmacokinetic study[23] in healthy human volunteers, duloxetine, escitalopram, and sertraline all increased exposure to metoprolol: whereas sertraline increased the metoprolol AUC by over 50%, escitalopram nearly doubled the AUC, and duloxetine nearly trebled it. Furthermore, whereas sertraline increased the maximum concentration (C_{max}) of metoprolol by 38%, the C_{max} was doubled by both escitalopram and duloxetine. Increases in C_{max} and AUC both predict an increased likelihood of physiologic and adverse effects of a drug.

In other reports and studies, paroxetine doubled the AUC of carvedilol in healthy volunteers,[32] and fluoxetine increased the exposure to metoprolol[33] and nebivolol.[14]

Propranolol is mainly metabolized by CYP1A2 and 2D6, but other CYP enzymes (including CYP2C19 and 3A4) also participate in its breakdown.[15,16] An important implication here is that if only 1 enzyme is inhibited (eg, CYP2D6, by paroxetine), the activity of the remaining enzymes will help ensure that propranolol pharmacokinetics are not excessively impacted. However, fluvoxamine, which potently inhibits CYP1A2[30] and 2C19[34] and less potently inhibits CYP2D6 and 3A4,[29,30] can be expected to increase levels of propranolol[35] and hence its biological effects.

Are the Interactions Clinically Significant?

Single-dose pharmacokinetic studies in healthy volunteers may not identify significant cardiovascular changes associated with the drug interactions described. For

Table 3. Commonly Used Antidepressants That Inhibit CYP2D6

Clinically significant inhibitors
Bupropion[20]
Clomipramine[21,22]
Duloxetine[23,24]
Fluoxetine[25]
Paroxetine[10,11]
Weak inhibitors
Citalopram[26]
Desvenlafaxine[10,27,28]
Escitalopram[23]
Fluvoxamine[29,30]
Sertraline[23,26,31]
Venlafaxine[25]

Abbreviation: CYP = cytochrome P450.

example, Stout et al[32] found that although paroxetine doubled the AUC of carvedilol in healthy volunteers, there were no clinically significant changes in heart rate, blood pressure, or PR interval. However, adverse events have indeed been reported after chronic dosing in patients.

About 2 decades ago, Walley et al[33] reported that a depressed 54-year-old man receiving metoprolol 100 mg/d for IHD developed fatigue and severe bradycardia within 2 days of starting treatment with fluoxetine: his heart rate dropped from 64 bpm to 36 bpm. His heart rate returned to normal 5 days after fluoxetine was withdrawn. Metoprolol was replaced by sotalol, and fluoxetine was reintroduced; there was no recurrence of bradycardia. Severe sinus bradycardia was also reported by McCollum et al[36] after bupropion was added to ongoing treatment with metoprolol.

Onalan et al[37] reported a 63-year-old woman who developed complete atrioventricular heart block 15 days after the addition of metoprolol (50 mg/d) to ongoing treatment with paroxetine (20 mg/d). Metoprolol was discontinued, and paroxetine treatment was also stopped several days later. After 5 further days, the heart block spontaneously resolved. No bradyarrhythmia was observed after challenge with similar doses of either metoprolol or paroxetine alone. The patient remained free of bradyarrhythmia at 2- and 3-year follow-up.

Goryachkina et al[9] studied 17 patients with acute myocardial infarction, all of whom were receiving metoprolol as a routine part of their therapy and paroxetine for depression. The authors found that paroxetine quadrupled the metoprolol AUC. In 2 (12%) of the patients, the dose of metoprolol had to be reduced because of excessive bradycardia and severe orthostatic hypotension. A quick reference to Tables 2 and 3 will explain why the interactions described in this and earlier sections occurred.

There is a theoretical risk that severe bradycardia and hypotension associated with raised levels of β-blockers may result in falls and fractures in the elderly. Although this does not appear to be a problem at the population level,[38,39] risk in individual vulnerable patients cannot be ruled out.

Patients vulnerable to adverse effects associated with raised levels of β-blockers include the elderly, those with poor left ventricular systolic function, those with asthma or other bronchospastic disease, and those with unrecognized cardiac conduction problems.[7]

Action Points

Reference to Tables 2 and 3 can help clinicians anticipate potential pharmacokinetic drug interactions between antidepressant drugs and β-blockers. Clinicians may wish to avoid prescribing an antidepressant that risks an interaction, or, if they do prescribe such an antidepressant, they would need to down-titrate the dose of the β-blocker (that the patient is receiving) using the patient's heart rate and blood pressure as a guide.

Additional Notes

The effects of CYP2D6 inhibitors (Table 3) on the β-blockers that are metabolized by this enzyme (Table 2) are most apparent in persons who are CYP2D6 extensive metabolizers; that is, the majority of the population. This is because CYP2D6 poor metabolizers already have the equivalent of an inhibited form of the enzyme. CYP2D6 poor metabolizers comprise about 0%–14% of the population, depending on geographical origin.[11]

Carvedilol and bisoprolol are P-glycoprotein substrates,[3,40] and paroxetine and sertraline both inhibit P-glycoprotein.[41] However, the impact of paroxetine or sertraline use on the transport of carvedilol and bisoprolol is presently unclear.

Interactions With Fruit Juice

Clinicians who have read up to this point may also be interested to learn that fruit juice can reduce the absorption of some β-blockers. For example, orange juice[42,43] and apple juice[44] have both been reported to reduce the oral bioavailability of atenolol.

REFERENCES

1. Andrade C. Drug interactions in the treatment of depression in patients with ischemic heart disease. *J Clin Psychiatry*. 2012;73(12):e1475–e1477.
2. Emilien G, Maloteaux JM. Current therapeutic uses and potential of beta-adrenoceptor agonists and antagonists. *Eur J Clin Pharmacol*. 1998;53(6):389–404.
3. Brodde OE, Kroemer HK. Drug-drug interactions of beta-adrenoceptor blockers. *Arzneimittelforschung*. 2003;53(12):814–822.
4. Münzel T, Gori T. Nebivolol: the somewhat-different beta-adrenergic receptor blocker. *J Am Coll Cardiol*. 2009;54(16):1491–1499.
5. DiNicolantonio JJ, Hackam DG. Carvedilol: a third-generation β-blocker should be a first-choice β-blocker. *Expert Rev Cardiovasc Ther*. 2012;10(1):13–25.
6. Erdmann E. Safety and tolerability of beta-blockers: prejudices & reality. *Indian Heart J*. 2010;62(2):132–135.
7. Parker RB, Soberman JE. Effects of paroxetine on the pharmacokinetics and pharmacodynamics of immediate-release and extended-release metoprolol. *Pharmacotherapy*. 2011;31(7):630–641.
8. Stout SM, Nielsen J, Welage LS, et al. Influence of metoprolol dosage release formulation on the pharmacokinetic drug interaction with paroxetine. *J Clin Pharmacol*. 2011;51(3):389–396.
9. Goryachkina K, Burbello A, Boldueva S, et al. Inhibition of metoprolol metabolism and potentiation of its effects by paroxetine in routinely treated patients with acute myocardial infarction (AMI). *Eur J Clin Pharmacol*. 2008;64(3):275–282.
10. Nichols AI, Fatato P, Shenouda M, et al. The effects of desvenlafaxine and paroxetine on the pharmacokinetics of the cytochrome P450 2D6 substrate desipramine in healthy adults. *J Clin Pharmacol*. 2009;49(2):219–228.

11. Zhou S-F, Liu J-P, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. *Drug Metab Rev*. 2009;41(2):89–295.
12. Lefebvre J, Poirier L, Poirier P, et al. The influence of CYP2D6 phenotype on the clinical response of nebivolol in patients with essential hypertension. *Br J Clin Pharmacol*. 2007;63(5):575–582.
13. Prisant LM. Nebivolol: pharmacologic profile of an ultraselective, vasodilatory beta1-blocker. *J Clin Pharmacol*. 2008;48(2):225–239.
14. Lindamood C, Ortiz S, Shaw A, et al. Effects of commonly administered agents and genetics on nebivolol pharmacokinetics: drug-drug interaction studies. *J Clin Pharmacol*. 2011;51(4):575–585.
15. Yoshimoto K, Echizen H, Chiba K, et al. Identification of human CYP isoforms involved in the metabolism of propranolol enantiomers—*N*-desisopropylation is mediated mainly by CYP1A2. *Br J Clin Pharmacol*. 1995;39(4):421–431.
16. Johnson JA, Herring VL, Wolfe MS, et al. CYP1A2 and CYP2D6 4-hydroxylate propranolol and both reactions exhibit racial differences. *J Pharmacol Exp Ther*. 2000;294(3):1099–1105.
17. McDevitt DG. Comparison of pharmacokinetic properties of β-adrenoceptor blocking drugs. *Eur Heart J*. 1987;8(suppl M):9–14.
18. Horikiri Y, Suzuki T, Mizobe M. Pharmacokinetics and metabolism of bisoprolol enantiomers in humans. *J Pharm Sci*. 1998;87(3):289–294.
19. Kirch W, Görg KG. Clinical pharmacokinetics of atenolol—a review. *Eur J Drug Metab Pharmacokinet*. 1982;7(2):81–91.
20. Kotlyar M, Brauer LH, Tracy TS, et al. Inhibition of CYP2D6 activity by bupropion. *J Clin Psychopharmacol*. 2005;25(3):226–229.
21. Lamard L, Pérault MC, Bouquet S, et al. Cytochrome p450 IID6, its role in psychopharmacology [in French]. *Ann Med Psychol (Paris)*. 1995;153(2): 140–143.
22. Vandel P, Haffen E, Nezelof S, et al. Clomipramine, fluoxetine and CYP2D6 metabolic capacity in depressed patients. *Hum Psychopharmacol*. 2004;19(5): 293–298.
23. Preskorn SH, Greenblatt DJ, Flockhart D, et al. Comparison of duloxetine, escitalopram, and sertraline effects on cytochrome P450 2D6 function in healthy volunteers. *J Clin Psychopharmacol*. 2007;27(1):28–34.
24. Knadler MP, Lobo E, Chappell J, et al. Duloxetine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet*. 2011;50(5):281–294.
25. Amchin J, Ereshefsky L, Zarycranski W, et al. Effect of venlafaxine versus fluoxetine on metabolism of dextromethorphan, a CYP2D6 probe. *J Clin Pharmacol*. 2001;41(4):443–451.
26. Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors. an overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet*. 1997;32(suppl 1):1–21.
27. Patroneva A, Connolly SM, Fatato P, et al. An assessment of drug-drug interactions: the effect of desvenlafaxine and duloxetine on the pharmacokinetics of the CYP2D6 probe desipramine in healthy subjects. *Drug Metab Dispos*. 2008;36(12):2484–2491.
28. Preskorn SH, Nichols AI, Paul J, et al. Effect of desvenlafaxine on the cytochrome P450 2D6 enzyme system. *J Psychiatr Pract*. 2008;14(6):368–378.
29. van Harten J. Overview of the pharmacokinetics of fluvoxamine. *Clin Pharmacokinet*. 1995;29(suppl 1):1–9.
30. Brøsen K. Differences in interactions of SSRIs. *Int Clin Psychopharmacol*. 1998;13(suppl 5):S45–S47.
31. Solai LK, Mulsant BH, Pollock BG, et al. Effect of sertraline on plasma nortriptyline levels in depressed elderly. *J Clin Psychiatry*. 1997;58(10): 440–443.
32. Stout SM, Nielsen J, Bleske BE, et al. The impact of paroxetine coadministration on stereospecific carvedilol pharmacokinetics. *J Cardiovasc Pharmacol Ther*. 2010;15(4):373–379.
33. Walley T, Pirmohamed M, Proudlove C, et al. Interaction of metoprolol and fluoxetine. *Lancet*. 1993;341(8850):967–968.
34. Yasui-Furukori N, Takahata T, Nakagami T, et al. Different inhibitory effect of fluvoxamine on omeprazole metabolism between CYP2C19 genotypes. *Br J Clin Pharmacol*. 2004;57(4):487–494.
35. Perucca E, Gatti G, Spina E. Clinical pharmacokinetics of fluvoxamine. *Clin Pharmacokinet*. 1994;27(3):175–190.
36. McCollum DL, Greene JL, McGuire DK. Severe sinus bradycardia after initiation of bupropion therapy: a probable drug-drug interaction with metoprolol. *Cardiovasc Drugs Ther*. 2004;18(4):329–330.
37. Onalan O, Cumurcu BE, Bekar L. Complete atrioventricular block associated with concomitant use of metoprolol and paroxetine. *Mayo Clin Proc*. 2008;83(5):595–599.
38. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med*. 2009; 169(21):1952–1960.
39. Gribbin J, Hubbard R, Gladman JR, et al. Risk of falls associated with antihypertensive medication: population-based case-control study. *Age Ageing*. 2010;39(5):592–597.
40. Bachmakov I, Werner U, Endress B, et al. Characterization of β-adrenoceptor antagonists as substrates and inhibitors of the drug transporter P-glycoprotein. *Fundam Clin Pharmacol*. 2006;20(3):273–282.
41. Weiss J, Dormann SM, Martin-Facklam M, et al. Inhibition of P-glycoprotein by newer antidepressants. *J Pharmacol Exp Ther*. 2003;305(1):197–204.
42. Lilja JJ, Raaska K, Neuvonen PJ. Effects of orange juice on the pharmacokinetics of atenolol. *Eur J Clin Pharmacol*. 2005;61(5-6):337–340.
43. Bailey DG. Fruit juice inhibition of uptake transport: a new type of food-drug interaction. *Br J Clin Pharmacol*. 2010;70(5):645–655.
44. Jeon H, Jang IJ, Lee S, et al. Apple juice greatly reduces systemic exposure to atenolol [published online ahead of print May 11, 2012]. *Br J Clin Pharmacol*.