

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

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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.

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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 Soberman⁷ 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 study⁷ 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 al⁸ 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 al⁹ 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

^aData 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

Carvedilol³
Metoprolol³
Nebivolol¹²⁻¹⁴

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}
Nadolol¹⁷
Sotalol¹⁷

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 study²³ 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 metoprolol³³ 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 CYP1A2³⁰ and 2C19³⁴ and less potently inhibits CYP2D6 and 3A4,^{29,30} can be expected to increase levels of propranolol³⁵ 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 al³² 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 al³³ 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 al³⁶ after bupropion was added to ongoing treatment with metoprolol.

Onalan et al³⁷ 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 al⁹ 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 juice⁴⁴ have both been reported to reduce the oral bioavailability of atenolol.

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