

# Bradycardia Due to Rivastigmine Drug Interactions

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Cholinesterase inhibitors such as donepezil, galantamine, and rivastigmine are now used routinely in the treatment of mild to moderate Alzheimer's disease. Most of their side effects can be attributed to their ability to increase cholinergic activity, including gastrointestinal effects such as nausea, vomiting, and anorexia. In susceptible patients, cardiovascular effects may also occur, such as bradycardia, atrioventricular block, and hypotension.

Rivastigmine has relatively few drug interactions, largely because it does not appear to be a substrate for cytochrome P450 isozymes, nor does it appear to inhibit or induce such isozymes. The pharmacodynamic drug interactions of rivastigmine are virtually all due to its cholinergic effects.

## CASE REPORT

A recent report described a 65-year-old woman taking rivastigmine and atenolol who was admitted to the hospital with a recent history of syncope.<sup>1</sup> After admission, she developed bradycardia (heart rate in the low 40s) with sinus pauses of more than 2 seconds. The atenolol was discontinued with little improvement in the bradycardia. Subsequently, the clinical pharmacist identified rivastigmine as a possible contributing factor, and its discontinuation was followed by resolution of the bradycardia. It seems likely that the additive negative effects of rivastigmine

and atenolol on heart rate contributed to this reaction.

The above case is consistent with the results of a French report of adverse drug interactions following the use of the cholinesterase inhibitors rivastigmine, donepezil, or galantamine. The most common adverse drug interactions reported (205 cases) were cardiovascular, specifically bradycardia, atrioventricular block, and hypotension.<sup>2</sup>

## DO OTHER CHOLINESTERASE INHIBITORS CAUSE BRADYCARDIA?

Other cholinesterase inhibitors seem to have the same interaction potential with regard to additive bradycardia. Donepezil and galantamine have cholinergic effects similar to rivastigmine, and all 3 drugs tend to reduce heart rate. When they are combined with other drugs that tend to reduce heart rate (eg, beta-blockers, digoxin, some calcium channel blockers, amiodarone), cholinesterase inhibitors may exhibit additive effects. Based on current evidence, it is not possible to say that one cholinesterase inhibitor is more or less likely than the others to result in additive bradycardia.

## HOW CAN THE REACTION BE TREATED?

Stopping 1 or both drugs should result in resolution of the cardiovascular toxicity, but some clinicians have recommend-

ed insertion of a cardiac pacemaker so the patient can continue to receive the cholinesterase inhibitor. If the patient's Alzheimer's disease has improved following use of the cholinesterase inhibitor, the patient (and his or her family) may be reluctant to discontinue it.

## ARE THERE OTHER INTERACTIONS WITH RIVASTIGMINE?

Rivastigmine, donepezil, and galantamine—due to their cholinergic effects—can all interact with anticholinergic (antimuscarinic) drugs. If a patient is receiving anticholinergic drugs for Parkinson's disease or other disorders, there can be mutual inhibition of the therapeutic effects of both the cholinesterase inhibitor and the anticholinergic.

## SUMMARY

The pharmacist should be alert for evidence of cardiovascular toxicity following the use of rivastigmine, donepezil, or galantamine in combination with other drugs that can also reduce the heart rate. Fainting and intermittent bradycardia may be the presenting signs of this drug interaction. Although serious reactions appear to be rare, early detection is important, because bradycardia can sometimes lead to more serious cardiac events. **PT**

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