

High-Dose Cholinergic Therapy With Rivastigmine Patch Does Not Prolong QTc Time in Patients With Alzheimer's Disease

To the Editor: Cholinesterase inhibitors are widely accepted as established therapeutic intervention across the entire severity spectrum of Alzheimer's disease. However, fear of increased corrected QT interval (QTc) time is one of the main reasons for nonprescription of cholinergic drugs.¹ While it is generally accepted that therapeutic efficacy of cholinergic therapy is dose dependent, a large number of patients are treated with a low dose for fear of dose-dependent increase of QTc time.

Previous studies in small numbers of patients reported that treatment with a low and medium dose of donepezil² and rivastigmine³ did not prolong QTc time, while treatment with galantamine was shown to be associated with some risk of QTc time prolongation.⁴ Since these data were obtained, higher doses of donepezil and rivastigmine have been licensed to be used in routine clinical practice. Appraisal of risk of QTc time prolongation with a high dose of any cholinergic drug is thus of great clinical importance to reduce potential undertreatment of patients with Alzheimer's disease. The objective of the current analysis was to determine whether high-dose rivastigmine patch induces prolongation of QTc time in patients with Alzheimer's disease.

Method. The study sample and design are described in detail elsewhere⁵; additional data for this analysis were requested from and provided by Novartis Pharma GmbH. In brief, 1,584 patients were included in an open-label treatment phase with rivastigmine patch 9.5 mg/24 h. A total of 22.1% of these patients were diagnosed with cardiac disease, among whom were 5.4% with coronary artery disease, 5.1% with atrial fibrillation, 3.9% with myocardial infarction, 1.5% with bradycardia, and 1.5% with arrhythmia. The only cardiac exclusion criteria were current diagnosis of severe or unstable cardiovascular disease (eg, unstable coronary artery disease, uncontrolled cardiac arrhythmia) and a current diagnosis of bradycardia (< 50 bpm), sick sinus syndrome, or conduction deficits (sinoatrial block or second- or third-degree atrioventricular block). After 24 weeks of treatment, 567 patients, ie, those who experienced functional or cognitive decline during open-label treatment with rivastigmine patch, entered a double-blind phase in which they either continued treatment with 9.5 mg/24 h (n = 287) or increased the dose to 13.3 mg/24 h rivastigmine patch (n = 280). QTc time was assessed with standard 12-lead electrocardiography; both the Fridericia (QTcF) and the Bazett (QTcB) method were used to calculate frequency-adapted QT time.

Results. At baseline, groups treated with either rivastigmine patch 9.5 mg/24 h or rivastigmine patch 13.3 mg/24 h were

comparable regarding heart frequency (RR time), time to travel of the electrical signal from the sinus node to the atrioventricular node (PR time), and time for the electrical depolarization and repolarization of the heart muscle (QT time). Frequency-adapted QT time intervals according to both the Fridericia and the Bazett method were also similar between groups (Table 1). After 48 weeks of treatment in the double-blind phase, the heart frequency was slowed slightly in the group receiving rivastigmine patch 13.3 mg/24 h, while the sinoatrial conduction time was similar in both groups. Likewise, change from baseline for QT time and QTcF time was comparable between groups, and QTcB time even showed a small decrease in the group treated with the higher-dose rivastigmine patch (Table 1).

Fear of cardiac adverse events, namely QTc time prolongation, is a frequent cause of undertreatment with cholinergic drugs in patients with Alzheimer's disease.¹ The present analysis does not provide evidence for QTc prolongation even with high-dose treatment with rivastigmine patch (13.3 mg/24 h). As nearly one-fourth of patients were diagnosed with cardiac disease, these data are also relevant for routine clinical practice and demonstrate that rivastigmine patch is well tolerated and does not increase risk of potentially lethal torsades de pointes.

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Potential conflicts of interest: Dr Riepe has served on the speakers/advisory board for Novartis.

Funding/support: Data reported were supplied by Novartis Pharma GmbH as requested by the author.

J Clin Psychiatry 2014;75(3):288 (doi:10.4088/JCP.13108730).

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Table 1. Electrocardiographic Data for the Safety Population in Patients Receiving Transdermal Rivastigmine 9.5 or 13.3 mg/24 h From the OPTIMA Study^{a,b}

Interval	Double-Blind Baseline			Double-Blind Endpoint		Change From Baseline		
	Rivastigmine 9.5 mg/24 h	Rivastigmine 13.3 mg/24 h	P Value ^c	Rivastigmine 9.5 mg/24 h	Rivastigmine 13.3 mg/24 h	Rivastigmine 9.5 mg/24 h	Rivastigmine 13.3 mg/24 h	P Value ^c
RR, ms	955.1 ± 147.33	937.1 ± 153.01	.1556	929.6 ± 155.01	943.1 ± 164.26	-25.6 ± 140.64	6.0 ± 134.77	.01603
PR, ms	166.2 ± 25.98	166.1 ± 28.37	.9652	167.4 ± 27.68	166.5 ± 27.48	1.2 ± 16.30	0.4 ± 16.50	.6157
QT, ms	404.9 ± 28.81	404.1 ± 31.47	.7531	402.8 ± 32.68	404.2 ± 33.82	-2.1 ± 27.37	0.1 ± 27.49	.3988
QTcF, ms	412.4 ± 21.79	414.4 ± 23.00	.2899	414.1 ± 23.67	413.7 ± 22.09	1.7 ± 19.85	-0.7 ± 19.47	.1991
QTcB, ms	416.6 ± 25.24	419.9 ± 25.56	.1238	420.4 ± 26.72	419.2 ± 24.68	3.8 ± 23.81	-0.8 ± 22.13	.0354

^aData on file, Novartis Pharma GmbH. Values shown as mean ± SD unless otherwise noted.

^bThis population consists of all patients who received at least 1 dose of study drug during the double-blind phase and had at least 1 postbaseline safety assessment during the same phase. The study sample and design are described in Cummings et al.⁵

^cP values represent 2-sided Student *t* test for independent samples.

Abbreviations: OPTIMA = OPTimizing Transdermal Exelon in Mild-to-moderate Alzheimer's disease, QTcB = QT interval corrected using Bazett formula, QTcF = QT interval corrected using Fridericia formula.