Trazodone-induced cardiac arrhythmias: a report of two cases

Trazodone is a phenylpiperazine antidepressant without structural similarities to other antidepressants and acts as a serotonin (5-hydroxytryptamine; 5-HT) receptor antagonist/reuptake inhibitor in the central nervous system. Its most potent pharmacological effect appears to be antagonist action at 5-HT\textsubscript{2} and 5-HT\textsubscript{1C} receptors. Trazodone has been introduced in the 1980s. Since then millions of patients have been exposed to trazodone. Because of its generally favorable tolerability and its sedative properties in addition to its antidepressant effect trazodone had been widely used as an alternative or an additional treatment to selective serotonin reuptake inhibitors (Kasper et al., 2005; Mendelson, 2005).

We would like to report on two patients, who were treated with trazodone among other drugs, and in whom we observed cardiac arrhythmia as a side effect.

CASE 1

A 55-year-old female Caucasian patient was admitted for psychiatric inpatient treatment because of bipolar depression. She had no previous cardiac history and was otherwise healthy. Electrocardiographic recordings (ECG) at admission showed a sinus rhythm with heart rates between 97 and 101 beats per minute. She was treated with valproic acid 2000 mg, lithium carbonate 900 mg, and venlafaxine ER 75 mg per day. Additionally she received treatment with trazodone 100 mg daily for depression with marked sleep disturbances. Blood pressure and heart rate were measured on a daily basis in this patient. After the first dose of trazodone heart rate decreased to 45 beats per minute with normal or only slightly reduced blood pressure values and no subjective clinical symptoms. Continuous 24-h ECG monitoring showed a heart rate as low as 41 per minute (especially during night-time). Further cardiological examinations yielded no other cardiac abnormalities and trazodone was finally suspected as the cause of this disturbance. Trough plasma levels of trazodone in a stable dose were measured to be 858 ng/ml (typical therapeutic range 650–1500 ng/ml). Treatment with trazodone was discontinued while the concomitant medication remained unchanged. Indeed, heart rate increased continuously to the normal range (between 60 and 70 beats per minute) within four days.

CASE 2

A 65-year-old male Caucasian patient was treated in a psychiatric inpatient ward for recurrent major depression with comorbid panic disorder and benzodiazepine dependence. Additionally he suffered from full metabolic syndrome. ECG at admission showed first-degree atrioventricular (AV) block (PQ = 0.28 s) with heart rate 58 beats per minute and complete right bundle branch block. Psychiatric treatment consisted of oxazepam 200 mg, which was slowly tapered down, carbamazepine 600 mg, and prothipendyl 240 mg. Treatment with trazodone was initiated to cure depressive symptoms and insomnia. Dosage was increased to 350 mg within 4 days. A week afterwards ECG controls revealed a considerable prolongation of the PQ interval (PQ = 0.40 s, heart rate = 61 beats per minute). As laboratory findings and the following cardiological examination did not explain this deterioration, trazodone was thought to be of pathogenetic relevance and daily dosage was reduced to 250 mg. Trough plasma levels at this dosage were measured to be 380 ng/ml. Cardiac pathology improved with reduced dosages of trazodone within two days and PQ interval shortened to 0.25 s. The concomitant medication except for oxazepam was administered at a stable dosage during that occurrence.

DISCUSSION

Worsening of the above-mentioned cardiac symptomatology and improvement as a consequence of discontinuation or dose reduction strongly suggest a causal relationship with trazodone treatment. However, it cannot be completely ruled out that the side effects observed in our patients were initiated or aggravated by drug interactions, since both patients received multiple psychopharmacologic compounds.
Cardiovascular side effects, such as bradycardia (Dubot et al., 1986), complete AV block (Rausch et al., 1984), prolonged QT interval (Levenson, 1999), or ventricular tachycardia (Aronson and Hafez, 1986; Vitullo et al., 1990), during treatment with trazodone and life-threatening arrhythmias at toxic plasma levels (de Meester et al., 2001) have been reported in the scientific literature. Blockage of specific cardiac potassium channels could be one of the pathogenetic factors involved (Tarantino et al., 2005). The frequency of these side effects seems to be dose-dependent, but is altogether lower than that in tricyclic antidepressants (Moises et al., 1981). Nevertheless, our observations point out that cardiac side effects might even occur in low or moderate dosages as a result of either an idiosyncratic vulnerability or a pharmacodynamic or pharmacokinetic interaction with drugs. Doctors treating elderly patients or patients at cardiac risk with trazodone are well advised to monitor the occurrence of cardiac side effects with regular electrocardiographic recordings, especially if patients are comedicated with other compounds.

STATEMENT OF INTEREST

Dr. Kasper has received grant/research support from Eli Lilly, Lundbeck, Bristol-Myers Squibb, GlaxoSmithKline, Organon, and Servier; has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Lundbeck, Pfizer, Organon, Janssen, and Novartis; and has served on speakers’ bureaus for AstraZeneca, Eli Lilly, Lundbeck, and Janssen. The other authors report no financial affiliation or other relationship relevant to the subject matter of this article.

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D. WINKLER, R. ORTNER, E. PIREK, H. ASCHAUER AND S. KASPER
Department of General Psychiatry, Medical University of Vienna, Austria

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI: 10.1002/hup.746