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CASE REPORT
ΕΝΔΙΑΦΕΡΟΥΣΑ ΠΕΡΙΠΤΩΣΗ

Metoprolol and sertraline combined treatment may increase the risk of bradycardia

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(5):692–695

A. Protopapas,
E. Lambrinou

Department of Nursing, Faculty of Health Sciences, Cyprus University of Technology, Limassol, Cyprus

Αυξημένος κίνδυνος εμφάνισης βραδυκαρδίας μετά από συνδυασμό μετοπρολόλης και σερτραλίνης

Περίληψη στο τέλος του άρθρου

Patients with cardiovascular disease (CVD) commonly have anxiety and depressive disorders. They may need to take selective serotonin reuptake inhibitors (SSRIs) along with metoprolol, one of the most common drugs prescribed to patients with CVD. This is a case study of a 64-year-old woman who developed severe sinus bradycardia after taking metoprolol for the management of paroxysmal atrial fibrillation (AF) and sertraline treatment of depression symptoms. Despite the fact that sertraline is a weaker inhibitor of CYP2D6, it may increase the risk of severe bradycardia. Health professionals need to be aware of this possible interaction and conduct clinical monitoring of heart rate and electrocardiogram during combined treatment, and to encourage the patients to self-monitor for bradycardia.

Key words

Bradycardia
CYP2D6
Metoprolol
Sertraline

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Depression and cardiovascular diseases (CVD) are both common diseases in the developed world today. Both diseases significantly affect the quality of life (QoL) and can lead to disability.[1] Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, sertraline and citalopram are commonly used for the treatment of depression,[2] and in many countries are the most frequently prescribed antidepressants.[3] Metoprolol is one of the most common drugs prescribed to patients with CVD.[4] Patients with CVD commonly present anxiety and depressive disorders and may need to take both of these drugs.[5]

Pharmacological treatment for depression has been reported to be associated with an increased risk of drug interactions. The pharmacokinetic interactions usually involve the cytochrome P450, which is included in numerous antidepressants, and which interacts with many cardiovascular medications at the metabolic level.[6] To date, numerous articles have been published referring to the risk of bradycardia due to an interaction of SSRIs with metoprolol,[2,7] but we found no reference to symptoms of bradycardia with the combination of sertraline and metoprolol.

This report describes the case of a woman who developed severe sinus bradycardia after taking metoprolol and sertraline for the management of paroxysmal atrial fibrillation (AF) and treatment of depression symptoms, respectively.

CASE PRESENTATION

A 64-year-old woman with a history of paroxysmal AF and hypothyroidism presented at the emergency department with symptoms of severe fatigue of a few hours' duration. She had been taking metoprolol succinate extended-release in a dose of 12.5 mg daily for 6 months, and the dose had been increased to 25 mg daily one month earlier, because she had an episode of paroxysmal AF every month for four months. In the past, sotalol 20 mg daily had been prescribed to reduce the paroxysmal episodes, but was discontinued 3 days later because of a prolonged QT interval. Despite the low dose of metoprolol, a recent 24h ambulatory Holter monitor showed sinus rhythm with heart rate (HR) 54–91 beats per minute (bpm) during waking state and 48–58 bpm during rest, with a mean sinus HR of 63 bpm. The initial HR before starting metoprolol was 65–68 bpm. Three days before admission

to the emergency department, sertraline 25 mg daily had been prescribed as the initial dose to treat her symptoms of depression and anxiety.

Physical examination revealed a low regular rhythm HR 38 bpm, blood pressure (BP) 140/80 mmHg, temperature (T) 36.7 °C, respiratory rate (RR) 19/min and SpO_2 97% in room air. Laboratory tests (cardiac biomarkers, electrolytes, renal and liver function) were within normal limits. Recent evaluation of the thyroid gland function showed no abnormalities. Her electrocardiogram (ECG) demonstrated severe sinus bradycardia with HR 38 bpm and normal PR, QRS and QTc (fig. 1). A prior ECG, 15 days earlier, had shown normal sinus rhythm with HR 60 bpm (fig. 2).

She stayed in the emergency department for clinical observation and monitoring. After 12 hours, her HR had increased to 58–61 bpm, and she was discharged from the hospital with normal HR. The metoprolol therapy was replaced with bisoprolol 2.5 mg daily.

COMMENTS

The case is reported here of a patient experiencing severe symptomatic bradycardia after taking sertraline in combination with metoprolol. This case report, we believe, is the first concerning sertraline. To date, several studies have reported the interaction of other SSRIs (most commonly paroxetine or fluoxetine) with metoprolol, leading to bradycardia due to increased serum metoprolol levels,[2,7–9] but there has been no report of sertraline increasing the risk of bradycardia when combined with metoprolol.

The interaction between SSRIs and metoprolol can be explained by the biotransformation of the cytochrome P450. The family of cytochrome P450 contains more than 50 isoenzymes, including CYP2D6, which are essential for the metabolism of many medications. The biotransformation of metoprolol is mediated by CYP2D6, and this enzyme has been found to absent in about 8% of Caucasian and 2% of most other populations. This may cause asymptomatic bradycardia due to decreased metabolism of metoprolol.[4] It is also known that SSRIs inhibit CYP2D6. The concentration of metoprolol in plasma may be increased by all the SSRIs, which inhibit their biotransformation, leading to an increased risk of toxic effects.[10] Sertraline, citalopram and escitalopram are considered to be weaker inhibitors of CYP2D6 compared to paroxetine and fluoxetine,[2,11] which may be why the probability of sertraline interaction is considered to be low.[11,12] It is also reported that the danger of interaction is increased with the combination of SSRIs and lipophilic beta-blockers such as metoprolol.[12] In contrast,

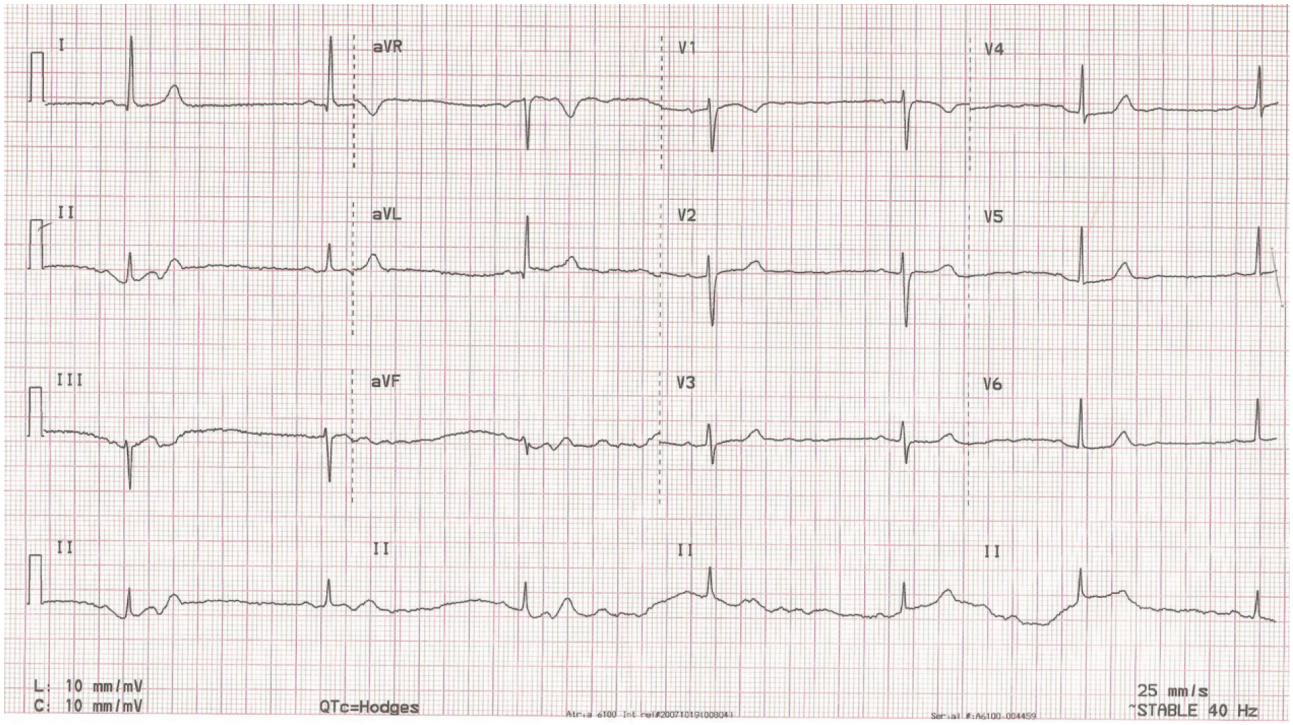

Figure 1. Interaction of metoprolol and sertraline in a 64-year-old woman: Electrocardiogram (ECG) in the emergency department showing sinus bradycardia at 38 bpm.

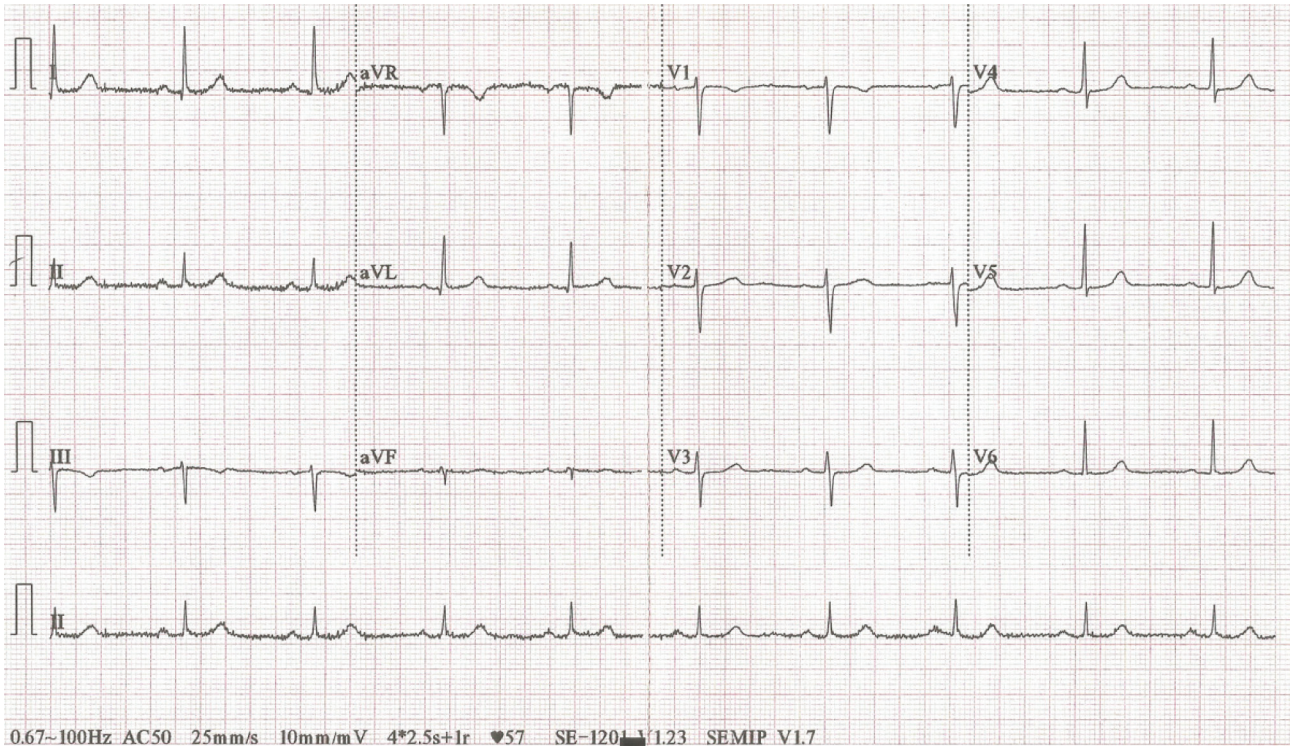

Figure 2. Treatment of paroxysmal tachycardia by metoprolol in a 64-year-old woman: Electrocardiogram (ECG) 15 days before the visit in the emergency department showing sinus rhythm (60 bpm).

atenolol and nadolol, as water-soluble beta-blockers, are not metabolized by the liver.[13]

Several case studies illustrate the interaction between SSRIs and metoprolol. For instance, Onalan and colleagues (2013) reported the case of a 63-year-old woman who had complete atrioventricular block for 15 days, after one year's treatment with paroxetine (20 mg daily) and metoprolol (50 mg daily). After paroxetine discontinuation, the atrioventricular block resolved in 5 days.[8] Walley and colleagues (1993) reported a similar case of a 54-year-old man who took metoprolol 100 mg daily, after a coronary artery bypass grafting, for 4 years and his HR was 64 bpm at rest. Two days after he started receiving fluoxetine 20 mg, he showed fatigue and bradycardia, with a HR of 36 bmp. When the fluoxetine was discontinued, the HR recovered within 5 days, and metoprolol was replaced by water soluble beta-blockers.[14] Ozdilek (2016) reported three cases of elderly patients who were receiving escitalopram without beta-blockers who showed bradycardia and noted that elderly patients who have low HR (50–60 bpm) before the administration of SSRIs may develop bradycardia.[15]

A large study evaluated the ECG recording in patients who were treated by citalopram. Enemark (1993) reported that citalopram managed to reduce the HR in the first week of treatment without further reduction later, and that bradycardia was caused only in a very small percentage (3–4%). The reduction of heart rate was observed particularly in patients who had low heart rate at baseline.[16] On the other hand, according to Yanagisawa and colleagues (2010), sometimes the beta-blockers are not tolerated in elderly patients, and this should be taken into consideration when prescribing other drugs which may interact with beta-blockers.[17]

Despite the fact sertraline is a weaker inhibitor of CYP2D6, patients who have poor tolerance to beta-blockers and whose HR is low at baseline of treatment, sertraline may increase the risk of severe bradycardia. Health professionals need to be aware of this possible interaction and conduct clinical monitoring of HR and ECG during initiation of antidepressive treatment, especially in patients who are taking lipophilic beta-blockers. Additionally, the patients themselves should be made aware of the possibility of interaction between SSRIs and beta-blockers (particularly metoprolol) in order to check their HR regularly in the first week.

ΠΕΡΙΛΗΨΗ

Αυξημένος κίνδυνος εμφάνισης βραδυκαρδίας μετά από συνδυασμό μετοπρολόλης και σερτραλίνης

Α. ΠΡΩΤΟΠΑΠΑΣ, Α. ΛΑΜΠΡΙΝΟΥ

Τμήμα Νοσηλευτικής, Σχολή Επιστημών Υγείας, Τεχνολογικό Πανεπιστήμιο Κύπρου, Λεμεσός, Κύπρος

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Ασθενείς με καρδιακές παθήσεις εμφανίζουν συχνά άγχος και καταθλιπτική συμπτωματολογία και ως εκ τούτου πιθανόν να απαιτείται η λήψη αναστολέων επαναπρόσληψης σεροτονίνης (SSRIs) μαζί με μετοπρολόλη, ένα από τα πλέον συνήθη φάρμακα που συνταγογραφούνται σε ασθενείς με καρδιαγγειακά νοσήματα. Η παρούσα μελέτη περιγράφει την περίπτωση μιας γυναίκας με σοβαρή φλεβοκομβική βραδυκαρδία μετά τη λήψη μετοπρολόλης και σερτραλίνης για τη διαχείριση της παροξυσμικής κολπικής μαρμαρυγής (AF) και τη θεραπεία των συμπτωμάτων κατάθλιψης, αντίστοιχα. Παρά το γεγονός ότι η σερτραλίνη είναι ασθενέστερος αναστολέας του CYP2D6, μπορεί να αυξήσει τον κίνδυνο εμφάνισης σοβαρής βραδυκαρδίας. Οι επαγγελματίες υγείας πρέπει να γνωρίζουν αυτή την πιθανή αλληλεπίδραση, αξιολογώντας κλινικά τον καρδιακό ρυθμό και το ηλεκτροκαρδιογράφημα κατά τη διάρκεια της θεραπείας, καθώς και να ενθαρρύνουν τον ασθενή για αυτοπαρακολούθηση της καρδιακής συχνότητας.

Λέξεις ευρετηρίου: Βραδυκαρδία, CYP2D6, Μετοπρολόλη, Σερτραλίνη

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Corresponding author:

A. Protopapas, Department of Nursing, Faculty of Health Sciences, Cyprus University of Technology, Vragadinou 15 street, 3041 Limassol, Cyprus
e-mail: aprotopap@gmail.com