

# Irreversible profound symptomatic bradycardia requiring pacemaker after tizanidine/loxoprofen combination therapy: a case report

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## Abstract

A 37-year-old man suffered irreversible profound symptomatic bradycardia requiring a pacemaker 3 days after beginning tizanidine/loxoprofen combination therapy for neck pain. This combination therapy is prescribed frequently for joint pain; however, combining loxoprofen with tizanidine could increase the risk of symptomatic bradycardia that is both permanent and severe. Similar cases have not been reported. This case suggests that tizanidine should be used cautiously when combined with loxoprofen, and drug interaction screening should be performed.

## Keywords

Case report, tizanidine, loxoprofen, bradycardia, side effect, pacemaker

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## Introduction

Tizanidine, an  $\alpha_2$ -adrenergic receptor agonist, is a widely used medication for the treatment of muscle spasticity and pain.<sup>1</sup> However, adverse events have been reported with its use, including somnolence, dry mouth, asthenia, and dizziness.<sup>2–4</sup> Bradycardia is among the reported events following tizanidine overdose.<sup>5</sup>

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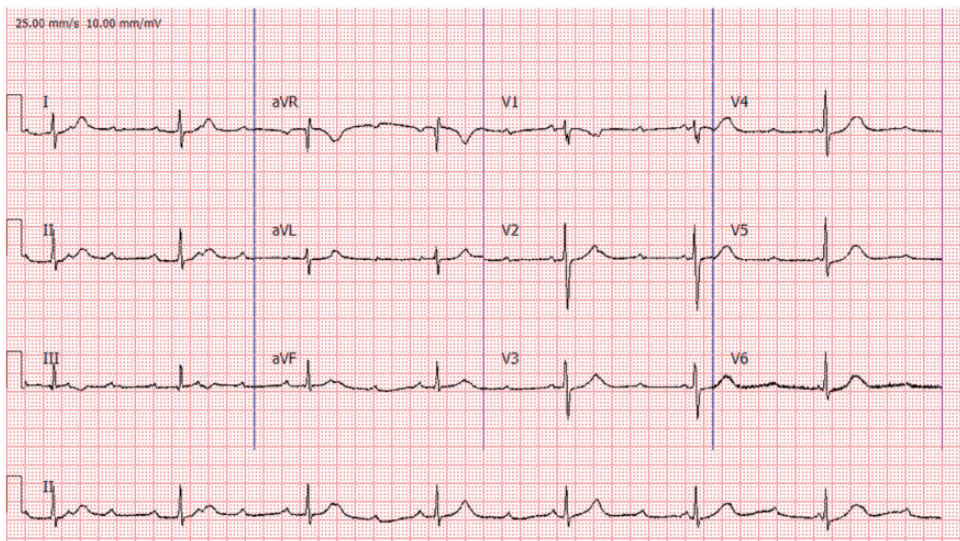
There are only rare reports of bradycardia as a side effect of tizanidine at conventional doses.<sup>6,7</sup> In those cases, the heart rate improved after tizanidine was stopped. Another report describes a 93-year-old woman with irreversible profound symptomatic bradycardia from tizanidine.<sup>8</sup> Here we report the case of a man who experienced irreversible profound symptomatic bradycardia requiring pacemaker placement after tizanidine/loxoprofen combination therapy.

### Case report

A 37-year-old man with the chief complaints of profound dyspnea and dizziness for 3 days was admitted to the hospital with blood pressure 130/66 mmHg and heart rate 42 beats per minute. He was previously healthy and had been taking no other medications. His personal history and family history were unremarkable; specifically, he had no family history of heart disease. Three days before hospital admission, he had been seen at a pain clinic and was started on tizanidine and loxoprofen for

neck pain. After taking an 18-mg total dose of tizanidine and 300 mg of loxoprofen, the patient developed severe symptomatic bradycardia. At admission, his oxygen saturation was normal, and an electrocardiogram revealed third-degree atrioventricular block with a heart rate of 42 beats per minute (Figure 1). His echocardiogram was normal. Laboratory testing revealed elevated triglycerides at 2.72 mmol/L. Troponin T and CK-MB were negative both at admission and 6 hours later. Tizanidine and loxoprofen were withheld, and IV fluids were administered upon admission. Cardiac catheterization was performed with no abnormal finding, and a transvenous pacer was placed immediately. During the next few days, his heart rate improved only slightly. Before discharge, the patient received a dual-chamber pacemaker for continued severe symptomatic bradycardia. After receiving the pacemaker, an electrocardiogram (Figure 2) and Holter electrocardiogram (Figure 3) revealed continuous paced rhythm.

The study protocol was approved by the Ethics Committee of The Fourth Affiliated



**Figure 1.** Electrocardiogram before pacemaker.

Hospital of Zhejiang University School of Medicine. The patient provided written informed consent for this case report.

### Discussion

The usual causes of bradycardia such as electrolyte disorders, intracranial pressure elevation, hypothyroidism, infection, hypothermia, hyperactive carotid sinus reflex,

organic heart disease, and pharmacotherapy with digitalis, beta-blockers and antiarrhythmics were excluded in this case.

Bradycardia as a side effect of tizanidine has been reported.<sup>5-7</sup> In such cases, the heart rate improved after tizanidine was stopped. The heart rate of this adult patient barely improved despite cessation of tizanidine. It is possible that the severe permanent bradycardia experienced by this

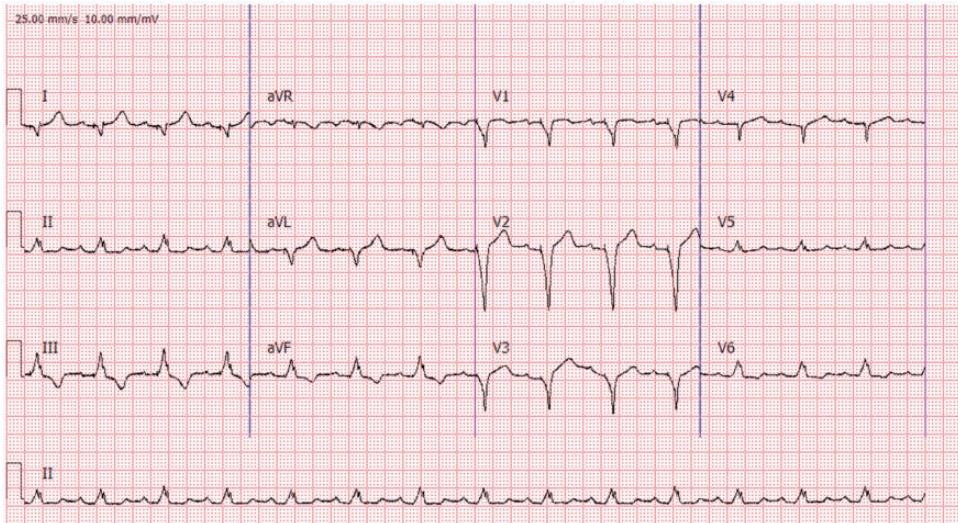


Figure 2. Electrocardiogram after pacemaker.

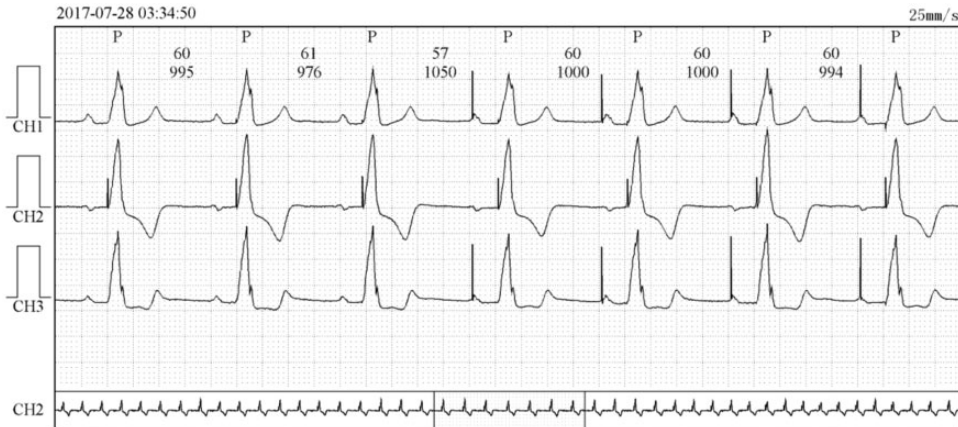


Figure 3. Holter electrocardiogram after pacemaker.

patient resulted solely from tizanidine; however, tizanidine/loxoprofen combination therapy could be the cause. A case involving the interaction of tizanidine combined with rofecoxib has been reported.<sup>7</sup> Tizanidine is mainly metabolized by cytochrome P450;<sup>9</sup> loxoprofen inhibits this enzyme,<sup>10</sup> so an interaction between these drugs is possible.

Irreversible profound symptomatic bradycardia has never been reported as a side effect of loxoprofen; however, palpitations may occur with oral loxoprofen.<sup>11</sup> The cardiac electrophysiological properties of tizanidine and loxoprofen have yet to be clarified. Thus, it should be considered that the combined use of tizanidine and loxoprofen increases the risk of tizanidine-associated irreversible profound symptomatic bradycardia.

Irreversible profound symptomatic bradycardia requiring pacemaker placement after using tizanidine/loxoprofen combination therapy has not been reported. Through this case, we believe that tizanidine should be used cautiously when combined with loxoprofen and drug interaction screening should be performed.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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