Doxophylline With Paroxysmal Supraventricular Tachycardia: A Case Report

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ABSTRACT

PURPOSE: We report a case of a patient experiencing paroxysmal supraventricular tachycardia after infusing doxophylline.

METHODS: Clinical evaluations and the electrocardiogram were performed by specialists.

FINDINGS: Our patient felt palpitations and chest distress after intravenous Doxophylline. The electrocardiogram showed paroxysmal supraventricular tachycardia. There was no evidence to prove that there was any problem with his heart, liver, and kidney. According to the Naranjo Adverse Drug Reaction probability scale, paroxysmal supraventricular tachycardia has a probable relationship with Doxophylline.

IMPLICATIONS: The paroxysmal supraventricular tachycardia is a rare but reasonable adverse reaction of Doxophylline, which should be paid more attention.

KEYWORDS: Doxophylline, paroxysmal supraventricular tachycardia, adverse drug reactions, theophylline

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Introduction

Doxophylline is a novel methylxanthine derivative with anti-inflammatory and bronchodilatory properties.[1] Doxophylline is commonly used to alleviate respiratory problems resulting from bronchial asthma and chronic bronchitis. Its rapid start and enduring effectsp:
j have made it an extensively utilized treatment in clinical settings.[2] Previous studies have shown that doxophylline is a more effective and tolerable methylxanthine than other types of theophylline.[3] Consequently, fewer people encounter adverse side effects, such as decreased appetite, nausea, vomiting, sleeplessness, and rapid heart rate. Nevertheless, excessive consumption might lead to the occurrence of severe arrhythmia.

Paroxysmal supraventricular tachycardia (PSVT) is a distinct clinical syndrome associated with intermittent episodes of palpitations of sudden onset and abrupt termination.[4] The electrocardiogram (ECG) pattern demonstrates regular tachycardia rhythm (150-240 bpm), narrow QRS complexes (<120 ms), and hidden or inverted P waves. Patients typically experience a sudden onset of palpitations, sometimes accompanied by symptoms such as dizziness, fainting, chest discomfort, difficulty breathing, and weakness.

Theophylline inhibits the activity of adenosine receptors (α1 and α2A), leading to an augmentation of atrial automaticity and intra-cardiac conduction. This, in turn, results in an increased likelihood of developing atrial fibrillation, supraventricular tachycardia (SVT), and multifocal atrial tachycardia.[5] Doxophylline has a significantly decreased affinity toward adenosine receptors than theophylline.[6] Moreover, unlike theophylline, doxophylline does not interfere with calcium influx into cells nor antagonizes the action of calcium channel blockers.[7] Therefore, doxophylline does not substantially impact heart rate or cause irregular heart rhythms. In the present study, we describe a case of a Chinese male who developed PSVT in association with doxophylline.

Case Present

A 68-year-old male was admitted to the hospital with cough, sputum expectoration, and wheezing for 15 years, which worsened for 1 week. A week before being admitted to the hospital, the patient experienced worsened coughing, without fever or chest pain, after he caught a cold. For 15 years, the patient's condition was diagnosed as chronic bronchitis (CB). Furthermore, he showed no signs of genetic health issues, surgery, or unhealthy personal behaviors. He additionally carried no history of drug or food allergies, and his wife and kids were in good health.

On physical examination, the patient presented with clear consciousness, a height of 1.74 m, a weight of 73 kg, a temperature of 36.6°C, a heart rate of 90 beats/minute, a respiratory rate of 21 breaths/minute, and a blood pressure of 120/75 mmHg (1 mmHg = 0.133 kPa), the blood oxygen saturation of 99%. The patient had a barrel-shaped chest, dry rales auscultated in both lungs, a positive emphysema sign, and minor lip cyanosis. The patient's abdominal examinations were normal, the rhythm was clean, and there were no murmurs. A computed tomographic (CT) scan of the chest revealed bilateral pulmonary miliary lesions. The blood test showed elevated C-reactive protein (CRP) of 103 mg/L (0-10 mg/L) and a slight leukocytosis of 11.2×10^9/L ($3.5\text{-}9.5 \times 10^9$/L). Routine urine tests

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revealed no apparent abnormalities; other markers, such as liver and kidney function, were normal. A sinus beat was visible on the ECG.

The patient was diagnosed with CB with acute exacerbation based on all exam results and clinical characteristics. He was treated for infections with cefoperazone sulbactam sodium and doxophylline bronchodilator therapy. At 8:35 am, he started an intravenous infusion of doxophylline at a dose of 0.2 g (2 ampoules) daily. The doxophylline was added to 100 mL of physiological saline and was slowly administered to the peripheral vein of the hand at a rate of 1.5 mL/minute. Six minutes later, the patient experienced palpitations and chest distress. The monitor displayed a heartbeat 196 times/minute, respiratory rate 30 times/minute, and blood pressure of 96/59 mmHg. The ECG showed paroxysmal supraventricular tachycardia (Figure 1A). Doxophylline infusion was promptly discontinued. The patient was placed in a semi-supine position and moved to a prone position, and their lower limbs were passively raised as part of the enhanced Valsalva maneuver; nevertheless, this procedure did not lower the ventricular rate.

Since our hospital could not provide adenosine, the patient was treated with 2 mL of intravenous verapamil (2 mL:5 mg), which was administered gradually and once every 20 minutes. The patient's heart rate decreased to 112 beats/minute after an hour, but the palpitations persisted. To treat the tachycardia, diltiazem 60 mg t.i.d. was recommended. The next day, the symptoms of palpitations had disappeared, and the EEG showed sinus rhythm (Figure 1B). No allergic reactions to theophylline or xanthine derivative drugs were noted. No abnormalities were found upon reexamination of the patient's liver and kidney function, 24-hour ECG Holter monitoring, cardiac markers, or echocardiography parameters. Unfortunately, it was not possible to determine the doxophylline serum concentration. After 7 days, the patient was released.

Discussion

Doxophylline is a xanthine derivative that has anti-inflammatory and bronchodilating characteristics.[8] It has comparable efficacy to theophylline in the treatment of respiratory diseases, but doxophylline possesses a distinct pharmacological profile from theophylline (no significant effect on any of the known phosphodiesterase isoforms, no significant adenosine receptor antagonism, no direct effect on histone deacetylases, interaction with β2-adrenoceptors).[9] Doxophylline can interact with β2-adrenoceptors, eliciting relaxation of blood vessels and bronchial smooth muscles.[10]

Doxophylline is mainly metabolized in the liver and partially excreted in the urine.[11] In healthy humans, intravenous injection of Doxophylline shows a biexponential serum concentration curve with a rapid elimination α-phase of, 20 minutes and total clearance.[12] Cravanzolac et al[13] discovered a correlation between the administration of theophylline and the emergence of adverse side effects, including nausea, vomiting, epigastric discomfort, sleeplessness, anxiety, restlessness, tachycardia, and extrasystoles. However, in contrast to theophylline, doxophylline has infrequent adverse effects on the digestive, cardiovascular, and nervous systems. Research demonstrated Doxophylline does not interfere with calcium influx into cells nor antagonizes the action of calcium-channel blockers. As a consequence, the effective therapeutic dose of Doxophylline has fewer cardio-stimulant effects than theophylline, such that Doxophylline does not out significantly increase the cardiac frequency nor does it have arrhythmogenic effects.[14] In a study, a significant reduction in the occurrence of ventricular premature beats per 24 hours was observed with Doxophylline when compared with patients treated with aminophylline.[15]

Ichikawa et al[5] documented a case of a patient who had congestive heart failure and supraventricular tachycardia (SVT) while using theophylline. The serum theophylline levels, in this case, were shown to be potentially harmful.[5] It has been demonstrated that theophylline enhances atrial automaticity and intra-cardiac conduction, increasing atrial fibrillation, SVT, and multifocal atrial tachycardia. Cipri et al conducted multiple studies in patients with chronic respiratory diseases. They found that intravenous doxophylline does not significantly affect heart rate and leads to a considerable reduction in the occurrence of ventricular premature beats compared to theophylline. This can be attributed to its low affinity for adenosine receptors.[16] Nevertheless, our data indicates that our patient experienced paroxysmal supraventricular tachycardia (PSVT) 6 minutes after the intravenous administration of doxophylline started.

Furthermore, the patient had no prior medical record of cardiovascular illness or hypersensitivity reactions, and the administration of doxophylline precisely adhered to the specified guidelines. In addition, doxophylline maintains serum concentrations that are more consistent than theophylline. Experimental animal studies and clinical studies in humans (adults) have shown no need for continued or repeated blood level monitoring with doxophylline, a distinct advantage of doxophylline over theophylline.[17,18] Therefore, in clinical tests, no additional measures were taken to assess the drug's serum levels and establish its maximum therapeutic range limit.[8] Hence, it is advisable to monitor the levels of doxophylline in the blood serum only when there is a significant impairment in liver function, when it is used in combination with quinolone drugs, or when patients have a previous intolerance to xanthine.[19,20] Moreover, it is essential to note that significant differences have been seen in the clearance of doxophylline, including inequalities in clearance rates between different racial groups. It is noteworthy that the study identified potential non-linear pharmacokinetics (PK) but did not thoroughly examine this aspect, probably due to the influence of the study's sponsorship.[18] It is necessary to consider these possibilities. We contacted the manufacturer, who confirmed that they have not received comparable reports. The patient's blood sample was sent to the clinical diagnostic institutions; nevertheless, they

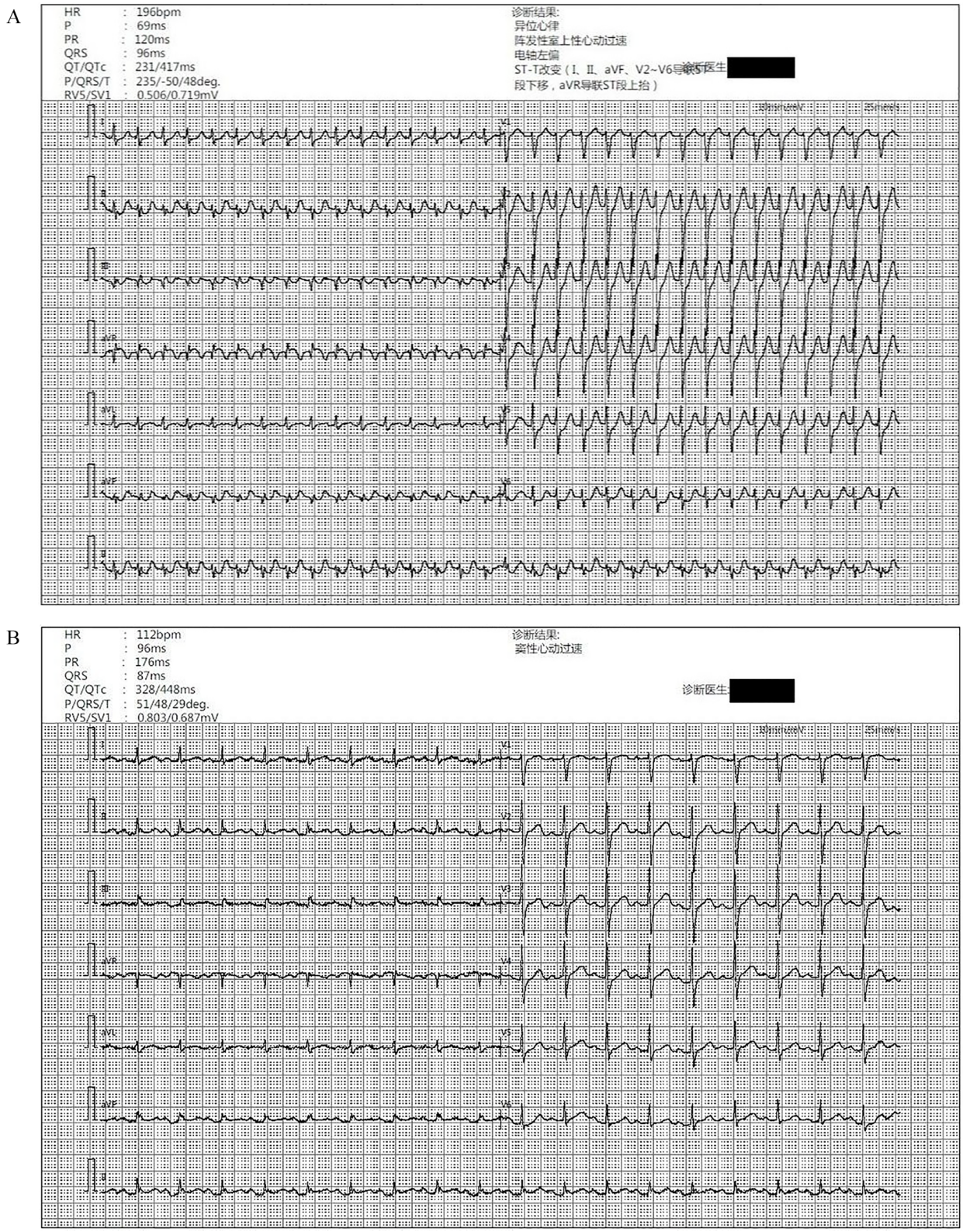

Figure 1. The electrocardiogram showed paroxysmal supraventricular tachycardia (1A) and, a day later, showed sinus rhythm (1B).

did not offer services for quantifying the blood concentration of doxophyline.

The Naranjo Adverse Drug Reaction probability scale score of 5 indicated a probable relationship between PSVT and doxophylline, with a distribution of points as follows: did the adverse event occur after the suspected drug was administered? (+2); did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? (+1); are there alternative causes (other than the drug) that could have, on their own, caused the reaction? (+2).

The potential mechanism of PSVT may be ascribed to 2 reasons. Doxophylline has the potential to enhance the permeability of the sarcoplasmic reticulum to calcium ions, facilitate calcium inflow, augment the autonomy and conduction of the atrioventricular node, and raise the occurrence of sinus tachycardia. Furthermore, doxophylline has the potential to enhance the sensitivity of abnormal pacemakers, leading to the development of different types of irregular heart rhythms.[21]

Conclusions

Doxophylline is commonly utilized for its efficacy and tolerability; however, there are variations among individuals. Our study presents a case in which a patient experienced PSVT following the administration of doxophylline via intravenous infusion. This clinical observation suggests that it is crucial for patients, particularly the elderly, to submit comprehensive medical records. In addition, clinicians should prioritize monitoring drug-drug interactions and closely observe patients during therapy. If any adverse reactions are detected, it is crucial to rapidly administer symptomatic treatment to ensure the safety of the drug.

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Author Contributions

Dandan Yu and Min Liu collected clinical data from patients together. Dandan Yu wrote the draft of the manuscript, and Min Liu revised it. During the submission process, the worked together to revise the manuscript. They contributed to the work equally and should be regarded as co-first authors.

Ethics Statement

Ethical approval of this paper was obtained from the Xinhua Hospital, Affiliated with Dalian Univerity Research Ethics Committee. And the patient had signed informed consent.

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