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【 CASE REPORT 】

Bradycardia Shock Caused by the Combined Use of Carteolol Eye Drops and Verapamil in an Elderly Patient with Atrial Fibrillation and Chronic Kidney Disease

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Abstract:
Ophthalmic carteolol is often used to treat glaucoma. Elderly patients with atrial fibrillation (AF) and chronic kidney disease (CKD) are common among the super-elderly in Japan. Because these patients are exposed to polypharmacy, they are at a high-risk of adverse drug interactions. We herein report an elderly patient with CKD who suffered bradycardia shock after the combined use of carteolol eye drops and verapamil for glaucoma and paroxysmal AF. This case highlights the fact that eye drops have a similar systemic effect to oral drugs, and especially in elderly patients with polypharmacy, drug interactions can unwittingly lead to serious events.

Key words: eye drops, carteolol, verapamil, chronic kidney disease, hyperkalemia

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Introduction

Ophthalmic beta blockers, represented by timolol and carteolol, are often used to treat glaucoma in the elderly (1). As the elderly population is dramatically increasing in Japan, we often encounter elderly patients with atrial fibrillation (AF) and chronic kidney disease (CKD) (2). Because such patients tend to have multiple comorbidities, they often visit several medical institutions, and accordingly, they are prescribed multiple medications (i.e. polypharmacy). One clinical issue in those patients is that they may unwittingly experience drug interactions due to their polypharmacy, leading to a potential risk of adverse clinical events (3).

There have been two case reports of bradycardia with the combined use of timolol eye drops and verapamil, with their combined use first reported in the 20th century (4, 5). However, the interaction between carteolol eye drops and verapamil has not been reported. We herein report a case of bradycardia shock caused by the combined use of carteolol eye drops and verapamil in an elderly patient with a history of CKD and glaucoma, who suffered from paroxysmal AF (PAF).

Case Report

An 84-year-old woman presented with a 3-day history of shortness of breath and chest discomfort. She was determined to be frail as evaluated by a Canadian Study of Health and Aging Clinical Frailty Scale of 6 on admission. She had a history of glaucoma, hypertension, and CKD (estimated glomerular filtration rate 32.6 mL/min/1.73 m^2) from over 10 years earlier and was being treated separately at ophthalmology and internal medicine outpatient clinics. She had blindness in her right eye due to glaucoma, and her left eye had been treated with ophthalmic carteolol and travoprost for the last few years. She had been taking azilsartan and doxazosin in addition to diet therapy for hypertension and CKD. As a result, she had been taking five kinds of internal medications, two kinds of external medications, and four kinds of eye drops a day, resulting in polypharmacy.

Five days before admission, she had been diagnosed with

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symptomatic PAF, so verapamil [40 mg twice a day (b.i.d.)] had been newly initiated by her internal medicine physician.

Table. Laboratory Data at the Time of Admission.

WBC	5,900 /mm^3	Na	139 mEq/L
Hb	11.4 g/dL	K	6.5 mEq/L
Plt	14.2×10^4 /μL	Cl	110 mEq/L
BUN	35.6 mg/dL	Ca	8.5 mg/dL
Cre	1.21 mg/dL	T-Chol	160 mg/dL
eGFR	32.6	HDL-Chol	67 mg/dL
CCR	21.25	LDL-Chol	66 mg/dL
CRP	0.11 mg/dL	TG	64 mg/dL
TP	5.2 g/dL	UA	6.3 mg/dL
Alb	3.0 g/dL	CK	66 U/L
T-Bil	1.20 mg/dL	CK-MB	4 U/L
AST	234 U/L	Troponin I	0.01 ng/mL
ALT	119 U/L	NT-proBNP	3,722 pg/mL
LDH	421 U/L	TSH	7.79 μlU/mL
ALP	248 mEq/L	Free T3	2.36 pg/mL
BS	157 mg/dL	Free T4	1.20 ng/mL
HbA1c	5.3 %	Lactate	2.9 mmol/L

Alb: albumin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BS: blood sugar, BUN: blood urea nitrogen, Ca: serum calcium, CCR: creatinine clearance, CK: creatine kinase, Cl: serum chloride, Cre: serum creatinine, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, Free T3: free triiodothyronine, Free T4: free thyroxine, Hb: hemoglobin, HbA1c: hemoglobin A1c, HDL-Chol: high density lipoprotein cholesterol, K: serum potassium, LDH: lactate dehydrogenase, LDL-Chol: low density lipoprotein cholesterol, Na: serum sodium, NT-proBNP: N-terminal pro-Brain Natriuretic Peptide, Plt: platelets, T-Bil: total bilirubin, T-Chol: total cholesterol, TG: triglyceride, TP: total protein, TSH: thyroid-stimulating hormone, UA: serum uric acid, WBC: white blood cells

According to the information from the previous doctor, her heart rate had been about 60-80 beats/minute (bpm) before the start of verapamil. At admission, her heart rate was 29 bpm, and her blood pressure could not be obtained, although her radial artery pulse was palpable. Her respiratory rate and body temperature were 15/min and 36.0 °C, respectively.

Her laboratory data on admission are shown in Table, revealing high serum potassium, high liver enzyme, and high lactate levels. A 12-lead electrocardiogram (ECG) during the initial examination showed a heart rate of 24 bpm and narrow QRS rhythm followed by retrograde P-waves with a Wenckebach phenomenon without significant ST-segment changes (Fig. 1). Transthoracic echocardiography revealed a normal left ventricular function without any asynergy, D-shape, echo-free space, or valvular disease with a normal size of the left atrial diameter (32.0 mm). Chest X-ray revealed pulmonary edema and enlargement of the cardiothoracic ratio.

Her clinical course is shown in Fig. 2. Because she had bradycardia shock, represented by high serum lactate and liver enzyme levels, with hyperkalemia, a temporary pacing catheter was placed through the right internal jugular vein, and right ventricular pacing was performed at 90 bpm while administrating an intravenous injection of calcium gluconate hydrate and glucose-insulin therapy for hyperkalemia. Anticholinergics could not be used due to glaucoma. With this treatment, the shock immediately resolved, and the symptoms disappeared. The carteolol eye drops, verapamil, and azilsartan were discontinued, and the patient was treated with a pacing rhythm until the next day (Fig. 3). The morning after she was hospitalized, her heart rhythm returned to

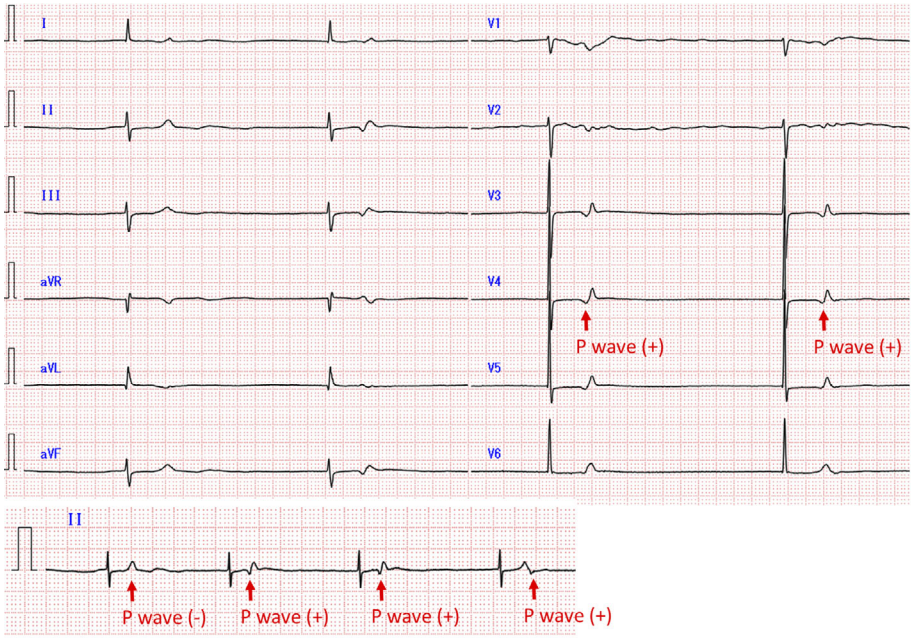

Figure 1. A 12-lead electrocardiogram during the initial examination. A heart rate of 24 bpm and a narrow QRS rhythm followed by retrograde P-waves with a Wenckebach phenomenon without significant ST-segment changes were noted.

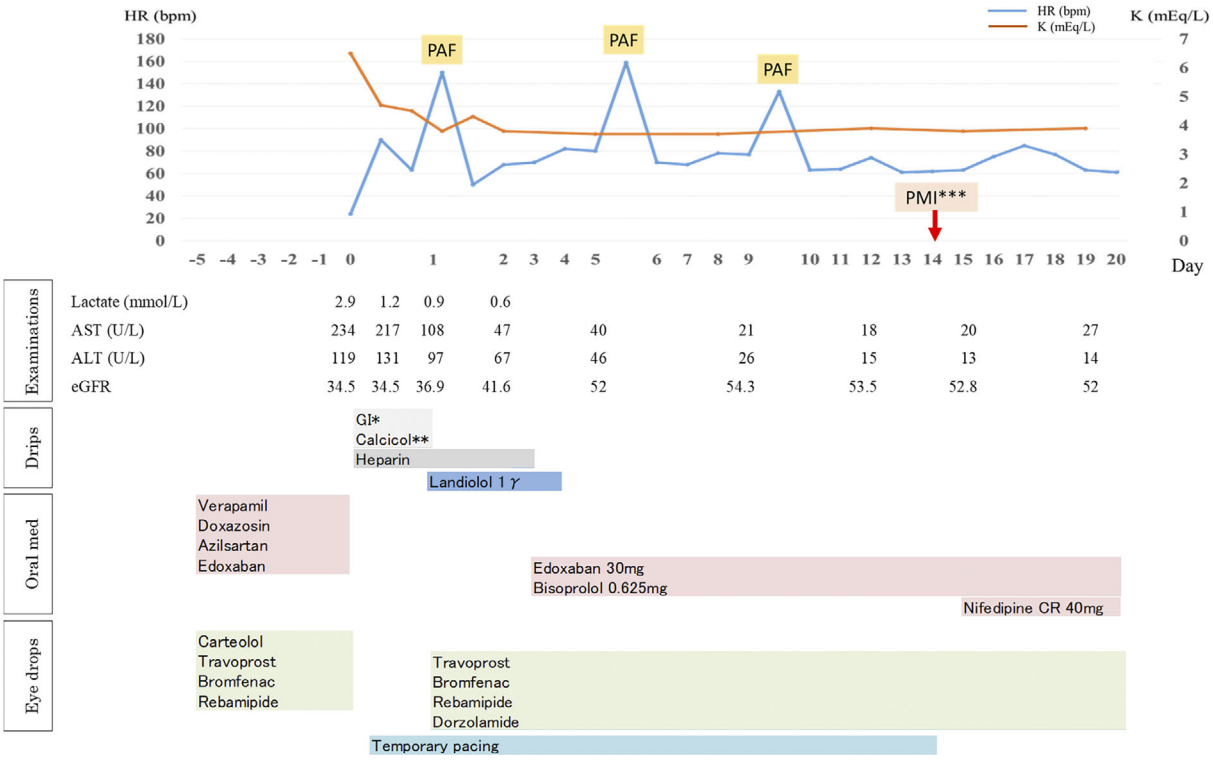

Figure 2. **Clinical course of this case. ALT: alanine aminotransferase, AST: aspartate aminotransferase, Calcicol: calcium gluconate hydrate, GI: glucose-insulin therapy, HR: heart rate, PAF: paroxysmal atrial fibrillation, PMI: pacemaker intubation**

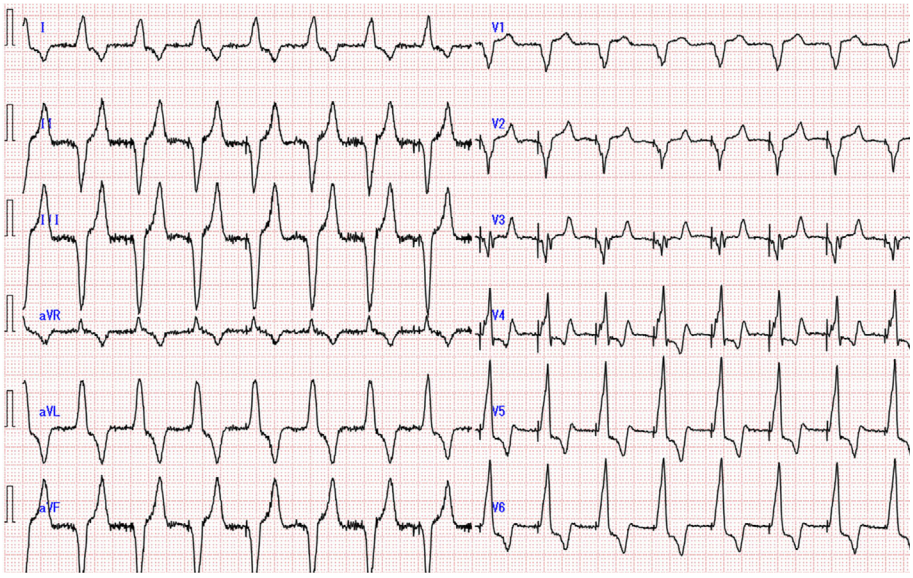

Figure 3. **A 12-lead electrocardiogram after initiating temporary pacing. A heart rate of 93 bpm, wide QRS rhythm with a left bundle branch block and upper axis pattern, and right ventricular apex origin were noted.**

a normal sinus rhythm with a heart rate of 63 bpm (Fig. 4). The carteolol eye drops were discontinued after consultation with the ophthalmologist, and a different non-beta blocker for glaucoma (dorzolamide hydrochloride) was prescribed to protect her non-blind left eye. The bradycardia no longer appeared after normalization of the potassium level and discontinuing verapamil and the carteolol eye drops.

However, she had symptomatic PAF with a rapid ventricular response on the first hospital day. When the PAF stopped, she temporarily had a backup pacing with VVI 50 bpm due to sick sinus syndrome. Based on her clinical course, it was judged that the use of antiarrhythmic drugs alone for PAF carried a risk of bradycardia shock, so it was decided to administer antiarrhythmic drugs after pacemaker

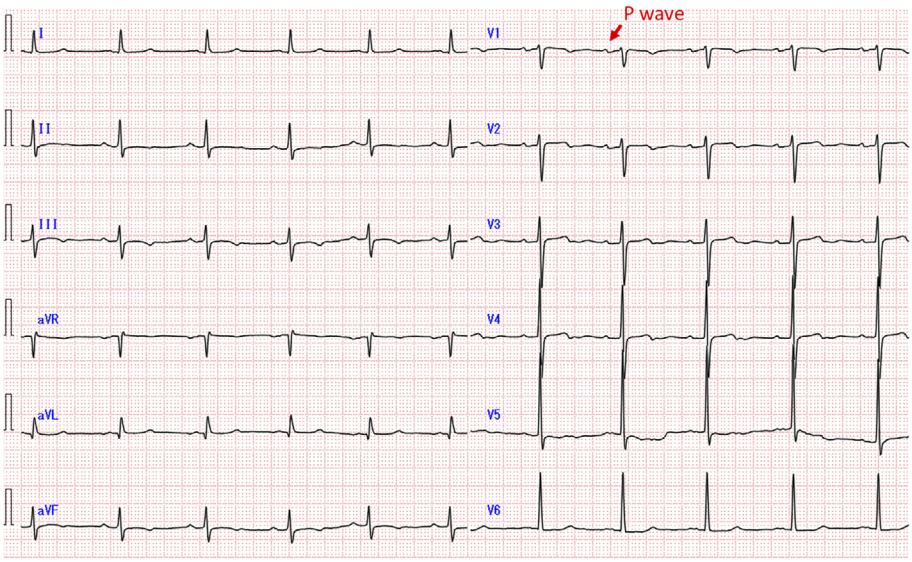

Figure 4. **A 12-lead electrocardiogram the day after the hospitalization. A heart rate of 63 bpm with normal sinus rhythm and T-wave flattening in leads III and aVF were observed.**

implantation. However, pulmonary vein isolation was not selected due to her age and activity of daily living. Pacemaker implantation was performed on the 14th hospital day. Finally, her arrhythmia, blood pressure, and glaucoma were controlled with the pacemaker implantation and adjustment of her medications, as shown in Fig. 2, and she was discharged in good health on the 20th hospital day.

Discussion

Ophthalmic carteolol, as well as timolol, is used as an eye drop beta blocker for glaucoma. Carteolol has been considered to have a lower risk of cardiovascular events than timolol because carteolol generally has a weaker effect on slowing the heart rate than timolol, depending on the characterization of the intrinsic sympathomimetic activity (ISA) (6, 7). Although warning clues of cardiovascular events, such as bradycardia, heart block, and hypotension, have been reported due to the use of timolol eye drops (8), there have been no reports of severe cardiovascular events with the use of carteolol eye drops. Because timolol eye drops are absorbed via the nasal mucosa through the nasolacrimal duct, their bioavailability is approximately 50% of that after oral administration, and they have a systemic effect similar to oral administration; however, they are topically administered (9). Furthermore, because both carteolol and timolol are metabolized by cytochrome P450 2D6 (CYP2D6), their effect can be enhanced in elderly people with a weakened CYP2D6 when combined with a drug with a CYP2D6 inhibitory effect and/or verapamil (10).

Verapamil is a commonly used class IV antiarrhythmic medication that blocks calcium-dependent slow channels, depresses the cardiac contractility, slows the myocardial conduction, and relaxes vascular smooth muscle. It serves to decrease sino-atrial (SA) node discharges and slow atrioventricular (AV) conduction, and the concomitant use with beta blockers can potentially cause severe bradycardia (11).

Elderly patients sometimes have both AF and CKD (2). Because carteolol is mainly excreted by the kidneys, it may have a strong cardiac depressant effect in elderly patients with CKD (12). Elderly people tend to have polypharmacy (3, 13), and if prescriptions are obtained from multiple medical institutions, it is possible that the same drugs may be prescribed. In addition, as in the present case, when the serum potassium level is increased due to a side effect of an angiotensin II receptor blocker (ARB) (14), a cardiac depressant effect due to hyperkalemia may exacerbate the cardiac function. In the present case, both the SA node and AV node were likely suppressed by the combination of the ophthalmic carteolol, verapamil, and hyperkalemia, resulting in serious bradycardia due to sick sinus syndrome.

Of note, eye drops have a systemic effect similar to oral drugs. Drug interactions are more likely to occur in the elderly, especially when ophthalmic beta blockers are used in glaucoma patients, and careful follow-up in terms of cardiovascular events is needed; furthermore, verapamil should not be used for rate control in patients with AF. Although the mechanism may have involved the interaction between the carteolol eye drops and either verapamil or azilsaltan-related hyperkalemia, it is equally likely that the interaction was between all three drugs under the existence of CKD in this elderly patient.

In conclusion, physicians should always consider the potential risk of adverse drug interactions when prescribing a new medication to a patient, especially in elderly patients with polypharmacy. Even topical medications, such as carteolol eye drops, might have significant systemic absorption, leading to serious side effects through drug interactions in elderly patients.

Author's disclosure of potential Conflicts of Interest (COI).
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