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Verapamil toxicity causing anterograde atrioventricular blockade with preserved retrograde conduction: An electrophysiological paradox

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A 69 year-old woman with a history of hypertension, type 2 diabetes mellitus and chronic renal insufficiency presented with generalized weakness and near syncope. In the emergency room, she was awake, alert and her physical examination was otherwise unremarkable. She was bradycardic (45 bpm) and hypotensive (85/55 mm Hg) and a 12-lead electrocardiogram (ECG) showed third degree atrioventricular (AV) block. Her medications at home included verapamil (120 mg OD), hydralazine (25 mg BID), esomeprazole (10 mg OD), and ferrous sulfate. Her serum creatinine was 3.6 mg/dL (baseline 2.5) with near normal serum electrolytes. The patient was stabilized and admitted to the telemetry unit for monitoring. However, she was later found to be confused and continued to be hypotensive (70/40 mm Hg) and bradycardic (30 bpm) requiring a transvenous temporary pacemaker (VVI mode, 70 bpm) at the bedside. All her home medications were on hold and norepinephrine was initiated and titrated to maintain her systolic blood pressure above 100 mm Hg.

Verapamil toxicity was suspected as the likely cause, after reviewing her medical records which had been obtained from another hospital where she was admitted four weeks previously for the same reason. In addition to the aforementioned initial management, the patient was started on insulin drip as per the hyperinsulinemia-euglycemia therapy (HIET) protocol [1]. The patient made a dramatic improvement in hemodynamic status, and 24 hours later she no longer required external pacing. Within 24 hours, her mental status and renal functions had also returned to baseline and the patient was transferred to the floor after discontinuing the insulin drip. Verapamil trough level which was sent out was reported later as elevated to 1,005 μg/L (normal: 100–600).

The unique nature of this case, however, lies in the ECG findings. The baseline ECG at presentation revealed complete AV block with no relation between the P wave and QRS complexes. The P wave morphology appeared to be reflecting an ectopic focus, perhaps due to the sinus suppression or perisinus tissue exit block due to drug toxicity. Nevertheless, it was noted that with a rescue transvenous right ventricular apical pacing, there was an inverted P wave with a constant VA interval indicating an intact retrograde conduction (Fig. 1A).

Furthermore, review of the patient's records from the previous hospital showed that an electrophysiologic study in the past for multiple admissions for syncope had demonstrated ventriculoatrial conduction via the AV node without the presence of a functional retrograde accessory pathway.

Verapamil, a calcium channel blocker which belongs to the sub-class of phenylalkylamines, is well absorbed after an oral administration but undergoes rapid biotransformation during its first pass through the portal circulation. This results in a bioavaila bility of 20–35% with an estimated half life of 3––7 hours. Verapamil is N-dealkylated in the liver to norverapamil, which possesses 15–20% of verapamil's pharmacologic activity and is subsequently cleared renally. Complete elimination of verapamil requires both intact hepatic and renal function [2].

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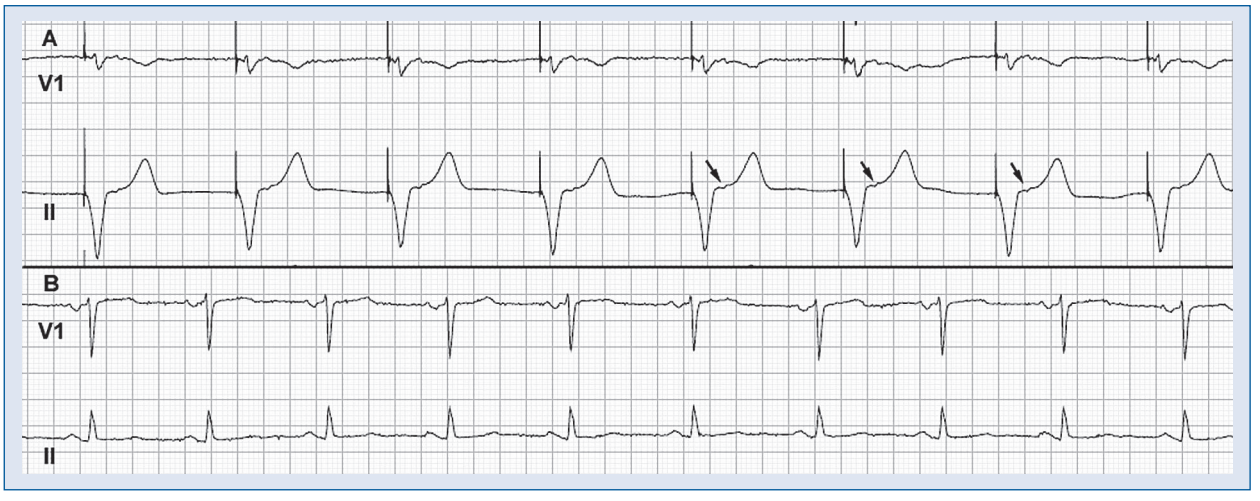

Figure 1. Electrocardiogram rhythm strips showing lead II and lead V1; **A.** Preserved retrograde ventriculoatrial conduction (note inverted p wave [arrows]) with right ventricular apical pacing; **B.** Return to normal sinus rhythm after treatment.

Verapamil antagonizes the L-type calcium channels by binding to its $\alpha 1$ subunit and it has been shown to significantly shorten open time and prolong closed time of the L-type channels, rather than change their conductance [3]. Canine experiments studying the effect of increasing plasma verapamil levels on both anterograde and retrograde AV node conduction showed that both functional and effective refractory period of the AV node is increased in a dose dependent fashion. Interestingly, the retrograde conduction was found to be blocked first with preservation of anterograde AV node conduction at plasma verapamil less than 152 ng/mL [4]. Hamer et al. [5], who studied the effect of verapamil in humans, concluded that there are intrinsic differences in the response of parts of the AV node to ventricular pacing and also to the effect of verapamil. It has also been demonstrated that in patients with intact retrograde AV node conduction at baseline, verapamil at therapeutic doses did not block the retrograde conduction in 50% of patients [6]. The differences in responsiveness of anterograde and retrograde AV node conduction to verapamil in different individuals may have an association with the patterns of distribution of the L-type calcium channels in regions of the AV node. Our patient's paradoxical retrograde AV conduction, with complete anterograde AV node conduction block at toxic levels of verapamil, may explain an unusual presentation or could be due to the existence of a hitherto silent accessory or dual pathway with less L-type channels. Elaborate animal and human studies involving molecular pharmacology and electrophysiological models are required to understand the complex electrical behavior of the AV node, thus explaining this seemingly paradoxical ECG finding.

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