A Case of Severe Verapamil Overdose

Hiroshi Oe, MD; Takehito Taniura, MD; Nobuhisa Ohgitani, MD

We report here on a 73-year-old woman who ingested 3.6 g (40 mg × 90 tablets) of verapamil in a suicide attempt. On arrival, the patient was awake and well oriented. Two and a half hours after ingestion, she lost consciousness, as her heart rate and blood pressure began to decrease. Cardiac monitoring showed atrioventricular dissociation. Although she suffered from extreme hypotension, an echocardiogram revealed that the wall motion of the heart was almost normal, and cardiac output measured with a Swan-Ganz catheter was well preserved. The plasma verapamil concentration in this patient was 1499 ng/ml 4 h after ingestion. Hyperglycemia and hypokalemia, laboratory data revealed, continued for 18 h after admission. The patient was successfully resuscitated with intravenous saline, dopamine, and norepinephrine. Besides reporting on this case, we also report on a treatment for severe verapamil overdose.

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Key Words: Verapamil; Overdose; Hypotension; Treatment

Verapamil is a calcium channel blocker commonly used to manage angina, cardiac arrhythmia, and hypertension. It inhibits the slow, inward cell membrane current of calcium ions! This blockade of slow calcium channels is considered to lead to a decrease in myocardial contractile force, suppression of the activities of both the spontaneous sinoatrial node and the atrioventricular system, and smooth muscle relaxation. Although many patients are at risk from accidental or deliberate verapamil poisoning, few cases of verapamil overdose have been reported in Japan? We report here on a case of massive verapamil ingestion because it has implications for the treatment of verapamil overdose.

Case Report

A 73-year-old woman was brought to the emergency department of our hospital 1.5 h after ingesting 90 tablets (40 mg each) of verapamil (3.6 g) in a suicide attempt. She had a history of mental depression, paroxysmal supraventricular tachycardia, and 2 previous suicide attempts. On arrival, she was awake and well oriented but had slightly slurred speech. She was in sinus rhythm with a pulse rate of 70/min and a blood pressure of 95/41 mmHg. Physical examination revealed no evidence of head trauma, pupils were 3 mm, round, and reactive to light, and there was no papilledema. There were no carotid bruits or jugular venous distensions. Auscultation of the chest revealed no rales or cardiac murmurs. Her extremities were slightly mottled and cool but had equal pulses. We carried out gastric lavage followed by the administration of 100 g of activated charcoal. A small tablet fragment was evacuated. She was treated with 100% oxygen via a face mask. Atrial blood gases revealed normal oxygenation with metabolic acidosis (pH 7.389, pO₂ 77.6 mmHg, pCO₂ 35.9 mmHg, Base Excess −2.3 mmol/L). Fluid administration with normal saline was begun. However, as her blood pressure did not respond to the first liter of fluid, an additional 3 L of normal saline was infused. Dopamine infusion was initiated (10 mg/kg per min) and increased to 20 mg/kg per min.

Within 1 h of admission, the patient's heart rate and blood pressure began to decrease (60/min, 75/32 mmHg, respectively), and she developed first-degree atrioventricular (AV) block. Fig 1 shows the time course of hemodynamics, treatment, and changes in the electrocardiogram. While preparations for airway control were being made, the patient lost consciousness. She was therefore orally intubated and ventilated immediately. Cardiac monitoring revealed atrioventricular dissociation (54/min, 54/32 mmHg).
Fig 1. Time course of hemodynamics, treatment, and electrocardiogram changes. On arrival, the patient was in sinus rhythm with a heart rate (HR) of 70/min, and blood pressure (BP) of 95/41 mmHg. Within 1 h of admission, her HR and BP began to decrease and she developed atrioventricular dissociation. Also illustrated are samples of the electrocardiogram after development of atrioventricular (AV) dissociation: dopamine 20 mg/kg per min (A) and first-degree AV block (B).

An echocardiogram showed mild left atrial dilation and symmetrical hypertrophy, but the wall motion of the heart was almost normal (AoD 29 mm, LAD 35 mm, IVS 12 mm, PW 11 mm, EDD 42 mm, ESD 25 mm, EF 78%, FS 40%) (Fig 2). Her blood pressure increased transiently from 54/32 mmHg to 82/40...
Table 1  Laboratoty Values Obtained After Admission

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>3</th>
<th>12</th>
<th>18</th>
<th>36</th>
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<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>137</td>
<td>132</td>
<td>134</td>
<td>136</td>
<td>138</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.6</td>
<td>3.3</td>
<td>3.6</td>
<td>3.9</td>
<td>4.0</td>
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<tr>
<td>Chloride (mmol/L)</td>
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<td>104</td>
<td>105</td>
<td>104</td>
<td>104</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>138</td>
<td>258</td>
<td>220</td>
<td>128</td>
<td>111</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.3</td>
<td>1.6</td>
<td>2.0</td>
<td>1.8</td>
<td>1.1</td>
</tr>
<tr>
<td>$pO_2$ (mmHg)</td>
<td>77.6</td>
<td>73.2</td>
<td>88.4</td>
<td>92.4</td>
<td>153</td>
</tr>
<tr>
<td>$pCO_2$ (mmHg)</td>
<td>35.9</td>
<td>30.7</td>
<td>41.5</td>
<td>40.8</td>
<td>47.9</td>
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<tr>
<td>pH</td>
<td>7.389</td>
<td>7.414</td>
<td>7.404</td>
<td>7.414</td>
<td>7.395</td>
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<tr>
<td>$HCO_3^-$ (mmol/L)</td>
<td>21.6</td>
<td>19.6</td>
<td>25.9</td>
<td>26.3</td>
<td>29.3</td>
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<tr>
<td>Sat. $O_2$ (%)</td>
<td>95.4</td>
<td>95.1</td>
<td>96.7</td>
<td>97.1</td>
<td>98.9</td>
</tr>
<tr>
<td>BE</td>
<td>-2.3</td>
<td>-3.5</td>
<td>1.7</td>
<td>1.2</td>
<td>4.5</td>
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</table>

On arrival, arterial blood gases revealed normal oxygenation with metabolic acidosis. Three hours after admission, the patient was hypokalemic and hyperglycemic.

![Plasma Concentration Graph](image)

Fig.3  Plasma concentrations of verapamil (○) and norverapamil (●) after an overdose of 3.6 g of verapamil.

mmHg. A Swan-Ganz catheter was placed and revealed mean right atrial pressure of 18 mmHg and pulmonary artery pressure of 50/28 mmHg with an occlusion pressure (wedge) of 28 mmHg. Cardiac output was 6.84 L/min (cardiac index was 4.72 L/min per m$^2$) and systemic vascular resistance was 385 dyne·sec·cm$^{-5}$·m$^2$.

Because of persistent hypotension, a norepinephrine drip was added 3 h after verapamil ingestion (0.4 mg/kg per min). Laboratory values revealed a potassium level of 3.3 mg/dl, a glucose level of 258 mg/dl, a verapamil level of 1499 ng/ml (therapeutic range 50–200 ng/ml), and a norverapamil level of 618 ng/ml (therapeutic range 50–200 ng/ml). The results of the laboratory investigations are shown in Table 1 and Fig.3. We did not measure serum calcium levels, so calcium gluconate was not administered.

Twelve hours after admission, there was a progressive improvement in cardiac rhythm and hemodynamic status (116/50 mmHg, 70/min, first-degree AV block) with improved urine output. During this period of time, the patient’s sensorium improved markedly. The hyperglycemia and hypokalemia initially noted were gradually reversed 18 h after admission. The first-degree AV block continued for 3 days after verapamil ingestion. On hospital day 5, because the patient’s cardiovascular status was assessed as stable, she was discharged and she has done well since leaving hospital.

Discussion

Verapamil, first introduced in 1962 in Europe as an antianginal agent, is a calcium channel blocker that selectively inhibits the slow current movement of calcium ions. It has gradually been found to have a profound effect on the cardiovascular system. Nowadays, it is used to manage angina, cardiac arrhythmias, and hypertension. Despite the increase in the use of calcium channel blockers for the past few decades, there have been few reports of verapamil poisoning in Japan.

Verapamil is well absorbed after oral administration, with peak plasma concentrations attained within 2 h. However, its systemic availability is low because of its high first-pass metabolism in the liver. Its elimination half-life time is 2.7–5.0 h following a single oral dose, which increases to 4.5–10 h in cases of long-term oral administration, perhaps because verapamil reduces
liver blood flow. Verapamil is widely distributed throughout body tissues and is highly bound to albumin and α1-acid glycoprotein. The major active metabolite of verapamil is norverapamil, which accounts for about 20% of its activity. Other active metabolites are rapidly conjugated.

It has been reported that in cases of overdose the elimination half-time is prolonged (8–15 h). One possible mechanism that could account for this prolongation is the slow absorption of verapamil at high doses and the peak plasma concentration occurring at 6–7 h. Because verapamil cannot be removed by hemodialysis owing to its high distribution in body tissues, immediate treatment to prevent absorption is important. This can be accomplished by using activated charcoal and a cathartic such as sorbitol. The usual dose of activated charcoal in a mildly intoxicated adult is 30–100 g.

There is no concentration-survival relation. Deaths have occurred with plasma concentrations as low as 600 ng/ml and individuals have survived with concentrations as high as 4000 ng/ml. In the former case, the verapamil level measured approximately 40 min after ingestion may not represent a peak plasma level. Additional blood levels were not available. The highest plasma verapamil concentration reported in the literature is 5340 ng/ml, which occurred in an individual who did not survive.

Our case clearly demonstrates the complications induced by a massive ingestion of verapamil. The marked hypotension noted in this patient is secondary to the verapamil-mediated peripheral vasodilation and reduction in cardiac output. The reduction in cerebral perfusion caused an altered sensorium in the patient. The first-degree atrioventricular (AV) block and AV dissociation can be explained by the depressant effect that verapamil exerts on the sinoatrial node, AV node, and the specialized conducting tissues. This case also typifies the metabolic effects of verapamil overdose. These include lactic acidosis secondary to hypoperfusion and hyperglycemia secondary to the inhibition of insulin release. Our patient also had a profound hypokalemia, which has been reported in other patients. Its mechanism is unknown. It may be related to the blockage of late outward potassium conductance secondary to the potential of verapamil to lower intracellular calcium levels. Serum potassium levels should be measured on an emergency basis in patients with verapamil toxicity, as hypokalemia can exacerbate electromechanical disturbances in this setting.

An echocardiogram revealed that the wall motion of the heart was almost normal, and cardiac output measured with a Swan-Ganz catheter was well preserved despite marked hypotension. This suggests that the hypotension is mainly due to verapamil-mediated peripheral vasodilation rather than to a reduction in cardiac output. The reason is considered below. In the myocardial cells, transmembrane calcium influx is not sufficient to initiate contraction, because the increase in cytoplasmic calcium triggers calcium release from the sarcoplasmic reticulum (SR), which can initiate contraction of actin and myosin. In vascular smooth muscle, the transmembrane influx of calcium binds directly to a regulatory protein, calmodulin, without requiring a release from the SR. As the pharmacologic action of verapamil specifically blocks calcium influx through the calcium channel, there is no reason to believe that vascular smooth muscle is most susceptible to calcium channel blockade.

The management of verapamil ingestion begins with attention to airway protection and the maintenance of adequate oxygenation. Gastric lavage plus activated charcoal, which has a delayed action, is preferred. Ipecacuanha-induced emesis may enhance vagal stimulation, causing or worsening bradycardia or AV block. Continuous electrocardiogram monitoring is important, as a sudden deterioration with cardiovascular collapse and abrupt asystole may occur. Adequate fluid replacement is also important, and intravenous calcium may improve myocardial contractility and AV conduction. Mechanical ventilation may be used for severe acid-base disorders, pulmonary edema, neuro-muscular blockade, and loss of airway control. In AV dissociation, a temporary transvenous pacemaker is required, as atropine and isoproterenol are rarely effective. The predominant action of atropine is through vagally mediated inhibition at the SA node. It is therefore unlikely that it would be effective in reversing AV nodal conduction delay and block. At high doses isoproterenol worsens hypotension, decreases perfusion, and increases myocardial oxygen consumption through β2 stimulation.

Constant infusion of short-acting inotropic agents may improve the cardiovascular status. Dopamine is the most frequently used inotropic agent in cases of verapamil overdose. In addition to its positive inotropic effect, dopamine also has a mild positive chronotropic effect. Dopamine increases systemic vascular resistance at high doses, when its predominant α-adrenergic effect occurs. However, in 5 cases of verapamil overdose, dopamine had no detectable hemodynamic effects. There are no cases in the literature in which an isolated dopamine infusion was able to support blood pressure in any case of verapamil overdose. In 3 cases, it was able only to slightly
improve blood pressure when used in conjunction with a $\beta_1$-agonist. Dobutamine is known to increase cardiac contractility without significantly changing the heart rate; however, the use of dobutamine in the treatment of verapamil overdose (up to 40 mg/kg per min) has been reported only once, and it proved to be ineffective.

Alpha-1-agonists are capable of stimulating smooth muscle contraction by a receptor-mediated pathway independent of calcium channels. Recent studies suggest that $\alpha_1$ stimulation may increase the calcium sensitivity of the contractile apparatus in vascular smooth muscle. An epinephrine infusion of 0.8 mg/kg per min was used with maximal improvement in 1 case of verapamil overdose. An epinephrine infusion up to 100 mg/min with a low dose of dopamine was claimed as the best combination to support blood pressure in case of mild diltiazem and metoprolol overdose. Thus, the use of epinephrine or norepinephrine should be considered early in the course of severe verapamil overdose associated with severe hypotension.

The use of verapamil and other calcium channel blockers has increased dramatically over the last several decades. Verapamil poisoning could prove lethal primarily because of its cardiovascular effects. However, aggressive treatment often leads to recovery, as it did in this severe case.

References
