CASE REPORTS

Profound Hyperglycemia and Metabolic Acidosis After Verapamil Overdose

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Verapamil, a potent calcium antagonist, possesses varied systemic effects, including smooth muscle relaxation leading to both peripheral and coronary artery vasodilation, slowed atrioventricular nodal conduction and decreased insulin release from the pancreatic B cells. Reports concerning the effects of acute intoxication with verapamil are scarce. A case is presented of a 22 year old woman who developed profound hyperglycemia and metabolic acidosis after the inadvertent overdose of thirty 80 mg tablets (2,400 mg) of verapamil. This case illustrates the need for physicians to be aware of verapamil's inhibitory effects on insulin release and to exercise special care when prescribing verapamil in patients with preexisting diabetes mellitus.

Case Report

A 22 year old obese, nondiabetic white woman with a past history of multiple somatic complaints referable to the cardiovascular system was taken to the emergency room 3 hours after the ingestion of 30 tablets of verapamil, each containing 80 mg. She was lethargic, but responsive to painful stimuli and loud voices. The pupils were equal and reacted sluggishly to light. Respirations were spontaneous, but shallow. Deep tendon reflexes were normal. The skin was pale and cool to the touch. The systolic blood pressure was 60 mm Hg by Doppler method and the heart rate was 30 beats/min. The electrocardiogram revealed an idioventricular rhythm without evidence of atrial electrical activity.

Initial treatment. An intravenous infusion of 5% dextrose in normal saline solution was rapidly initiated and the rate was kept wide open. Atropine, 0.5 mg, was given intravenously, Subsequently, an isoproterenol infusion was started, all without apparent effect. As the patient was known to have been taking verapamil, she then received 2 g of calcium chloride intravenously with continuous electrocardiographic monitoring. There was no beneficial effect on heart rate and a temporary percutaneous transvenous pacing electrode was introduced. Ventricular pacing was achieved at a capture rate of 70/min. Simultaneously, an endotracheal tube was inserted and the patient received assisted ventilation. Gastric lavage was initiated and blood, urinary and gastric contents were sent for analysis. Hypotension persisted, necessitating the initiation of a continuous infusion of dopamine. After these measures, the patient's blood pressure increased to approximately 80 mm Hg systolic by Doppler method. Laboratory blood test results were noted (Table 1), particularly, hyperkalemia, hyperglycemia and metabolic acidosis.

Clinical course. During the next several hours, the patient's sensorium progressively improved to the point where...
she responded appropriately to simple commands. Pupillary reflexes and urinary output improved. On receipt of the blood glucose value of 832 mg/l 00 ml, intravenous solution was changed to normal saline solution and 5 units of regular insulin were given intravenously. This insulin bolus was followed by a continuous infusion of regular insulin at a rate of 0.1 mg/kg per hour. The serum electrolytes and blood glucose were measured hourly.

Three hours after hospitalization, serum chemistry determinations revealed a blood glucose of 250 mg/100 ml, serum potassium of 4.0 mEq/liter and bicarbonate of 25 mEq/liter. The temporary pacemaker was turned off, revealing a junctional rhythm at a rate of 50 beats/min. Blood pressure had stabilized at 90 mm Hg systolic.

As the patient's condition improved, the isoproterenol, dopamine and insulin infusions were gradually stopped. The serum lactic acid level had returned to normal and repeat glucose determinations were all within the normal range. The drug screen performed on blood, urinary and gastric samples obtained at the time of admission was negative. Blood samples were also obtained for determination of the serum verapamil level and the blood level was found to be 845.7 ng/ml.

Discussion

Pharmacodynamics of verapamil. Verapamil Isosptin Calan (isopropyl N-methyl-N-homoveratryl aminopropyl-3-4 dimethoxy-phenyl-acetonitril HCl), a potent calcium antagonist, has been found to be well absorbed after oral ingestion. Eighty percent of verapamil is absorbed between 45 minutes and 3 hours after ingestion (8). The peak plasma concentration is reached between the first and second hour after administration. The first pass effect through the portal circulation causes 60 to 70% of the oral dose to be biotransformed; thus, bioavailability of verapamil ranges from 20 to 35%. After repeated doses at 6 hour intervals, the half-life of verapamil increases, progressively stabilizing at a range of 4.5 to 12.0 hours; thereafter, there is a good linear correlation between plasma levels and the administered verapamil dose.

Verapamil hydrochloride is water-soluble and highly protein-bound in plasma. After an oral dose, it undergoes extensive hepatic metabolism. No fewer than 12 metabolites of verapamil have been identified in plasma. The majority of these metabolites are present only in trace amounts and possess little biologic activity. Approximately 70% of an orally administered dose of verapamil is recovered from the urine in the form of metabolites, with only about 5% of the drug being excreted unchanged. The remainder is excreted in the feces.

Physiologic effects. The action of verapamil is mediated by blocking the slow channel responsible for calcium influx in myocardial and smooth muscle cells (18,19). It has also been shown (20) to inhibit a second slow current carried by the sodium cation. Antagonism of the slow channels in smooth muscle ultimately produces smooth muscle relaxation. This relaxation in the vascular smooth muscle cells results in both peripheral and coronary artery vasodilation.

Electrophysiologic studies (8) have demonstrated that verapamil prolongs the functional and effective refractory periods of cardiac conduction tissue and has been shown to interfere with sinus node impulse generation. These alterations in the electrophysiologic properties of cardiac muscle cells manifest themselves clinically as slowed atrioventricular (AV) conduction and negative chronotropic effect. These effects are dose-dependent. It has been demonstrated that high verapamil concentrations can induce sinus arrest as well as AV block.

Toxic effect. There are relatively few reported cases of serious adverse reactions. Bradsky et al. (11) observed hepatocellular toxicity 4 weeks after initiation of oral therapy with verapamil. They concluded that the hepatotoxicity was of an idiosyncratic nature. Hypotension, advanced AV block and asystole have been reported previously (9,21,22) in cases of massive overdose, after aggressive intravenous administration and when verapamil was used in combination

<table>
<thead>
<tr>
<th>Blood Test</th>
<th>Results</th>
<th>Normal Values</th>
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<tbody>
<tr>
<td>Na⁺ (mEq/liter)</td>
<td>130</td>
<td>135 to 145</td>
</tr>
<tr>
<td>K⁺ (mEq/liter)</td>
<td>7.2</td>
<td>3.6 to 5.0</td>
</tr>
<tr>
<td>Cl⁻ (mEq/liter)</td>
<td>101</td>
<td>98 to 110</td>
</tr>
<tr>
<td>CO₂⁻ (mEq/liter)</td>
<td>16</td>
<td>22 to 30</td>
</tr>
<tr>
<td>Glucose (mg/100 ml)</td>
<td>832</td>
<td>70 to 120</td>
</tr>
<tr>
<td>Lactic acid (mmol/liter)</td>
<td>4 5</td>
<td>0 5 to 2 2</td>
</tr>
<tr>
<td>Acetone (µmol/liter)</td>
<td>500</td>
<td>0 0 to 500</td>
</tr>
<tr>
<td>BUN (mg/100 ml)</td>
<td>17</td>
<td>5 to 22</td>
</tr>
<tr>
<td>Hemoglobin (g/100 ml)</td>
<td>13 1</td>
<td>12 to 16</td>
</tr>
<tr>
<td>WBC count (× 10⁹/cmm)</td>
<td>27</td>
<td>4 5 to 10</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Differential count (%)</th>
</tr>
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<tbody>
<tr>
<td>Stabs</td>
</tr>
<tr>
<td>Segs</td>
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<tr>
<td>Lymphs</td>
</tr>
</tbody>
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Arterial blood gases

| PO₂ (mm Hg) | 54 | 83 to 108 |
| PCO₂ (mm Hg) | 39 | 35 to 45 |
| pH          | 7.21 | 7.38 to 7.42 |
| HCO₃⁻ (mmol/liter) | 16 | 21 to 28 |

BUN = blood urea nitrogen; Lymphs = lymphocytes, PCO₂ = partial pressure of carbon dioxide; PO₂ = partial pressure of oxygen; Segs = segmented neutrophils (polymorphonuclear leukocytes). Stabs = band cells (nonsegmented polymorphonuclear leukocytes). WBC = white blood cell.
with other cardiovascular drugs (beta-adrenergic blocking agents and digitalis). The toxic effects of verapamil have been successfully reversed by infusions of calcium chloride and hypertonic saline solution (12,23). The potential adverse cardiac electrophysiologic effects of verapamil have been described previously by several investigators (9,10,24) independently in patients with verapamil levels greater than 359 ng/ml. Finally, severe left ventricular dysfunction has been associated with both acute and chronic ingestion of verapamil hydrochloride. This effect is more pronounced in subjects with an ejection fraction below 34% (25).

We have found only one other reference documenting impaired carbohydrate metabolism associated with verapamil, a case report by DaSilva et al. (13) in which there was only a moderate elevation of blood glucose (344 mg/100 ml); this was the highest blood glucose level reported after ingestion of verapamil; the patient was not known to be diabetic and had experienced acute intoxication with the drug.

**Verapamil and insulin release.** Our case clearly demonstrates the spectrum of complications induced by a massive ingestion of verapamil. The hypotension, mental confusion and metabolic acidosis occurred as a result of decreased tissue perfusion, from both verapamil-mediated reduction in cardiac output and peripheral vasodilation. The AV dissociation can be explained by the depressant effect verapamil exerts on the sinoatrial and AV nodes. Finally, the massive hyperglycemia may be speculatively explained as a result of the inhibitory effect verapamil has on insulin release.

Calcium channel antagonists have been shown to affect insulin release in vivo. The concentration of extracellular calcium ions is known to play a crucial role in insulin release from the pancreatic beta cells, the secretory process being triggered by the cytosolic accumulation of calcium (26–28). Calcium antagonists, like verapamil, are known to inhibit in vitro glucose and sulfonylurea-induced insulin release by interfering with calcium entry into the beta islet cells (29–32). Several in vivo studies have also demonstrated calcium antagonists’ inhibitory effect on the beta islet cells of the pancreas and subsequent insulin production. Taniguchi et al. (33) found that the infusion of 44 mg of the calcium antagonist, diltiazem, for 2 hours in a patient with insulinnoma suppressed leucin-induced insulin release, while the basal insulin level was only transiently suppressed. In the same patient, chronic administration of diltiazem reduced the number of hypoglycemic attacks as compared with the pretreatment period. DeMarinis and Barbarino (34) also discovered that the intravenous infusion of verapamil produced a marked and significant inhibition of glucose, glucagon and sulfonylurea-induced increases in serum insulin in normal subjects. They also treated two patients with islet cell tumors with verapamil for 5 days and discovered that these patients experienced a decrease in the severity and frequency of hypoglycemic attacks while autonomous insulin release was inhibited.

**Clinical implications.** The clinical significance of our observation is obvious in view of the extensive use of calcium channel antagonists in modern medical practice. Much like the use of beta-receptor blocking agents, the use of calcium channel antagonists may continue to expand. As experience with these drugs increases, so too will the incidence of untoward effects. Just as Birnbaum et al. (35) found a positive correlation between therapeutic doses of propranolol and increased glucose intolerance, in our opinion, verapamil must also be regarded as diabetogenic. The extent of deterioration of carbohydrate tolerance in patients receiving therapeutic doses of calcium channel antagonists remains unknown. Theoretically, however, this knowledge could significantly influence prescribing practices.

**References**