Acute cholecystitis developing as a result of verapamil intoxication

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ABSTRACT

Calcium channel blockers are the drugs with the highest poisoning-related mortality. The most commonly seen finding in verapamil intoxication is hypotension, with other frequently encountered findings being bradycardia and atrioventricular block. It may also lead to potentially fatal complications such as non-cardiogenic pulmonary edema. Gastrointestinal symptoms such as nausea and vomiting are uncommon. This report describes a case brought to the emergency department with abdominal pain, in which cholecystitis was determined following tests performed when hypotension and bradycardia could not be explained, and in which it was learned that the patient had taken a high dose of verapamil with the aim of committing suicide. Cholecystitis as a result of verapamil intoxication has never previously been reported in the literature.

1. Introduction
Verapamil, a powerful calcium channel blocker (CCB), inhibits the L-type voltage gated calcium channel. This leads to vascular smooth muscle relaxation and negative inotropic and chronotropic effects in the heart (1). Verapamil is frequently used in the treatment of ischemic heart disease, arrhythmias, hypertension and hypertrophic cardiomyopathy. Potential fatal complications such as hypotension, bradycardia and non-cardiogenic pulmonary edema may develop as a result of verapamil intoxication. Other reported complications include sinus arrest, atrioventricular block, decreased cardiac output and hyperglycemia (2). This case report describes acute cholecystitis as a complication that has not previously been reported in the literature. On arrival he was lucid, with a Glasgow Coma Scale score of 15. Blood pressure was 60/40 mm/Hg, temperature of 36°C and pulse rate 40/min. Electrocardiography was compatible with sinus bradycardia. At physical examination, the skin was pale and cold. There was widespread sensitivity at abdominal examination. Laboratory findings were leukocytosis and other biochemical markers were normal. Ejection fraction at echocardiography was 65%, and no findings for coronary insufficiency were determined. Pronounced hypotension, leukocytosis and widespread abdominal sensitivity suggested the presence of a surgical pathology in the abdomen. Abdominal tomography...
revealed elevated thickness in the bile duct wall and fluid around the duct (Figure 1). The patient’s examination findings, leukocyte values and abdominal tomography findings were interpreted in favor of acute cholecystitis. But the patient had unexplained hypotension and bradycardia, he was questioned again. It was then established that he had taken some 30 verapamil tablets for the purpose of suicide. The patient was transferred to the intensive care unit. He received 20 ml/kg crystalloid over 20 min. Although appropriate volume resuscitation he had hypotension and bradycardia. Then administered dopamine 10 microgram/min. His blood pressure and heart rate resolved on the fourth day. The previous pathological appearance in the bile duct was observed to have contracted at ultrasound on the fourth day. The patient was discharged in a healthy condition following psychiatric evaluation.

3. Discussion
Verapamil is a potent CCB used in the treatment of hypertension, ischemic heart diseases and supraventricular tachycardia. It exhibits a negative inotropic and chronotropic effect by relaxing the smooth muscles. It causes dilatation in the peripheral and coronary arteries. Taken in high doses it inhibits insulin secretion in the pancreatic β cells, resulting in hyperglycemia (1,2). The most significant complications in verapamil overdose are congestive heart failure, cardiac arrest, deep hypotension and atrioventricular block. It can also cause reddening in the face edema, confusion, nausea and constipation (3).

Aggressive decontamination may be life-saving in verapamil overdose. It is recommended that patients be given 50-100 g activated charcoal by oral or nasogastric tube. In addition, digestive system irrigation should be performed with balanced saline solution. Airway management may be performed to ensure a safe respiratory tract. Decontamination performed in this way is most effective within 1 h of ingestion. Since the drug binds powerfully to protein and has a wide tissue distribution, enhanced elimination techniques such as hemodialysis and hemoperfusion are not recommended. ‘ABC’ should be evaluated as a priority in emergency treatment. A venous path should be opened and patients started on 0.9% normal saline solution infusion without delay. Patients require close monitoring. Standard support treatments such as atropine in bradycardia and vasopressor in hypotension must be administered at once. Agents that have a direct effect in hypotension and bradycardia, to play a role in the cholecystitis development mechanism. such as norepinephrine and epinephrine, should be preferred over dopamine. Calcium, and particularly calcium chloride, should be given in antidotal treatment (4). The aim in this treatment is to prevent potential bradycardia, dysrhythmia and hypotension. Calcium chloride is recommended in poisoning since it contains three times more calcium than calcium gluconate.

One gram intravenous calcium chloride may be given in 5 min or so a maximum 3-4 times every 10-20 min. If calcium does not correct the hypotension, glucagon, an agent of questionable effectiveness, may be given (5). Glucagon 0.15 mg/kg (approximately 5 mg) may be given every 5 min in IV bolus form, repeated 3 times until response is achieved. If there is no response after a 15 mg dose, other dosages will be of no clinical benefit. But if there is a significant rise in the patient’s blood pressure, IV glucagon can be commenced. Glucagon frequently leads to vomiting and hyperglycemia. In addition to these, insulin and glucose are used to achieve hyperinsulemia/euglycemia in the treatment of severe intoxication. Carbohydrate absorption to the heart is thought to be impaired as a result of hypoinsulinemia developing following CCB ingestion (6). While the exact mechanism is unclear, insulin/glucone therapy may cause a dramatic improvement in blood pressure. The initial insulin dose is 0.5-1 U/kg, and infusion at 0.5-1 U/kg/hour may be started. An additional 25 g or 50 ml 50% dextrose (0.5 g/kg 25% dextrose in children) bolus may be given. Blood glucose level should be kept at a 100-200 mg/dL level. Among the side-effects of this treatment are hypoglycemia and hypocalcemia. Series glucose and potassium follow-up must be performed together with insulin therapy. In the event of resistance to all treatments then ventricular pacing may be tried in order to regulate heart rate. In this situation it is recommended that heart rate should not exceed 60/min (7).

No cases of verapamil overdose-associated cholecystitis have been reported in the literature. The mechanism by which cholecystitis develops is unclear, but it is thought perhaps to bear a similarity to the non-cardiogenic pulmonary edema mechanism developing in association with verapamil intoxication. Cholecystitis may have developed in association with peripheral edema resulting from prostacyclin inhibition, capillary leakage syndrome and precapillary vasodilatation (3). CCBs, including verapamil, are known to affect the immune system. CCBs have been observed to suppress macrophages, mast cells and T cells in several in vitro studies (8,9). Although CCBs are thought of as immune suppressants, drugs such as amlodipine and verapamil have been found to activate BP interleukin IL-1 and IL-6-associated transcription factor and nuclear factor KB (10). The relationship between verapamil and inflammatory cytokines is to be considered.

4. Conclusions
There has been an increasing rise in drug intoxication in recent years. Drug intoxication may be confused with several life-threatening diseases. Verapamil may complicate the clinical findings of a case of intoxication resulting in acute cholecystitis. Good anamnesis and physical examination are therefore very important. This will permit early diagnosis and thus reduce mortality and morbidity.
REFERENCES
Russell RP. Side effects of calcium channel blockers. Hypertension 1988;11:42–4
Shen H, Wiederhold MD, Ou DW. The suppression of macrophage secretion by calcium blockers and adenosine. Immunopharmacol Immunotoxicol 1995;17:301–309