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CASE REPORT

Intravenous lipid emulsion in the treatment of verapamil intoxication

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Abstract

Calcium channel blockers are commonly used in a variety of cardiovascular diseases. Their extensive clinical use concurs with an increase in the incidence of deliberate and accidental poisonings. Intoxication with non-dihydropyridine calcium channel blockers is currently treated with supportive therapies, since no antidote is available. When conventional therapies fail to achieve haemodynamic stability, alternative approaches should be considered.

In this case report we describe the effect of continuous renal replacement therapy and intravenous lipid emulsion in the treatment of severe verapamil intoxication. High-volume continuous venovenous haemofiltration did not have a substantial effect on verapamil clearance. However, after intravenous administration of lipid emulsion the haemodynamics stabilised, which suggests that this intervention is beneficial after life-threatening verapamil intoxication, although the exact underlying mechanism remains to be elucidated.

Introduction

The incidence of cardiovascular disease, especially hypertension and congestive heart failure, is increasing. Calcium channel blockers are commonly used in a variety of cardiovascular diseases, including angina pectoris, supraventricular tachycardias and hypertension, and in noncardiac conditions such as migraine and Raynaud's phenomenon. Their extensive clinical use concurs with an increase in the incidence of deliberate and accidental poisonings.[1] Overdosage of the non-dihydropyridine calcium channel blocker verapamil causes a variety of symptoms including cardiogenic shock, arrhythmias, conductance disturbances, vasodilatation, central nervous system depression, pulmonary oedema and paralytic ileus (*table 1*).[2] Treatment of intoxication with calcium channel blockers is controversial.[3-5] Generally, accepted treatment options are prevention of absorption by giving active charcoal, and supportive care including calcium suppletion, glucagon and insulin infusion.[6] Recently, high-dose lipid solutions have been advocated in these intoxications. In this case report we describe the use of intravenous lipid emulsion in a severe verapamil intoxication and discuss the potential benefit of this intervention to improve outcome.

Case description

A 68-year-old man was brought to the emergency room one hour after a suicide attempt by ingestion of 6700 mg of verapamil, of which 6300 mg (94%) in extended-release capsules. Four weeks previously he was diagnosed with AV-nodal re-entry tachycardia for which verapamil was prescribed. On evaluation we saw a drowsy man. His blood pressure was 80/50 mmHg, pulse rate 70 beats/min in sinus rhythm, and respiratory rate 19 breaths/min with oxygen saturation 98% while breathing 5 litres O_2. Examination of heart, lungs, abdomen and extremities was unremarkable. Laboratory tests on arrival showed normal serum potassium and glucose levels, and an increased level of lactate.

Gastric lavage did not show traces of the consumed medication. Supportive treatment was started, including volume resuscitation and administration of low-dose norepinephrine. Absorption prevention was attempted by colon lavage. Despite this treatment, the patient deteriorated and developed deep vasoplegic shock within a few hours after admission to the ICU. High doses of inotropes and vasopressors, and respiratory support were necessary (*figure 1*). Transthoracic echocardiography, while substantial amounts of inotropes were administered, showed relatively normal contractility of the right and left ventricle without valve pathology. Eight hours later, an external pacemaker was introduced because of severe bradycardia, followed by ventricular fibrillation requiring resuscitation by defibrillation and basic life support for one hour.

High-volume continuous venovenous haemofiltration (HVCVVH; substitution fluid rate 9.4 litre/h) was started because of severe metabolic acidosis due to vasoplegic shock (lactate 11 mmol/l). Twelve hours after intake of verapamil, intravenous lipid emulsion 20% (Intralipid®) was administered, starting with a bolus of 1.5 ml/kg, followed by 0.25 ml/kg/min for one hour. A few hours after starting HVCVVH and administration of the lipid emulsion, less vasopressors were required to stabilise the patient (*figure 1*). Verapamil and norverapamil concentrations were measured in the serum and by ultrafiltration (*figure 2, table 2*). There was not a substantial amount of verapamil or norverapamil ultrafiltrated, resulting in a low sieving coefficient.

Three days after ingestion, the vasoplegic shock had resolved. Due to the development of acute kidney failure, intermittent haemodialysis was necessary. Six months later, the patient had fully recovered without renal replacement therapy.

Table 1. Symptoms caused by verapamil intoxication

Clinical features
Altered mental status, dizziness, seizures
Respiratory depression
Nausea, vomiting, abdominal pain
Physical examination
Hypotension, bradycardia, cardiogenic shock
Paralytic ileus
Jugular venous distension
Pulmonary crackles
Diagnostic clues
Electrocardiogram: conduction abnormalities of the SA/AV nodes, idioventricular arrhythmias
Laboratory results: hyperglycaemia, metabolic acidosis, elevated transaminase values
Chest X-ray: pulmonary oedema

Figure 1. Vasocative medication and blood pressure during treatment

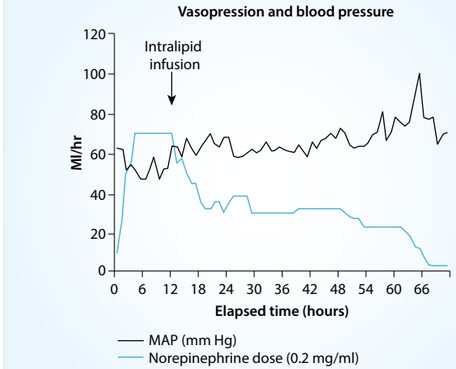

Figure 2. Total verapamil and norverapamil concentration in serum over time. High-volume continuous venovenous haemofiltration started at a rate of 9.4 l/h; after 12 hours the filtration rate changed to 3 l/h

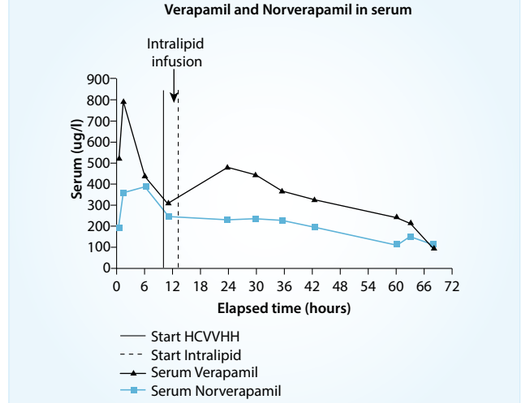

Table 2. Concentrations of verapamil (V) and norverapamil (NV) in serum and ultrafiltrate (UF) and the resulting sieving coefficients (Si) during continuous venovenous haemofiltration

Time (h)	Serum V (µg/l)	Serum NV (µg/l)	UF V (µg/l)	UF NV (µg/l)	Si V	Si NV
0	525	190				
1	793	360				
6	437	390				
11	308	246				
24	483	231	54	35	0.10	0.14
30	446	236				
37	370	228	40	29	0.11	0.13
43	325	191				
61	245	113				
64	217	148	13	8	0.06	0.05
69	101	113	12	9	0.12	0.08
75	101	114	6	10	0.06	0.09
78	98	94	7	9	0.07	0.10
79	90	50				

Discussion

Verapamil is a non-dihydropyridine L-type calcium-channel blocker, acting on myocardial muscle, the conduction system and vascular smooth muscle. Verapamil antagonises calcium channels and inhibits calcium influx into myocardial and vascular tissue. The negative inotropic and chronotropic effects of verapamil result in bradycardia, decreased cardiac output, vasodilatation of smooth muscle and cardiovascular collapse (*table 1*).[6] Only 13-65% of a normal verapamil dose reaches the systemic circulation after absorption in the gastrointestinal tract due to an extensive first-pass effect in the liver, via multiple cytochrome P450 (CYP) isoenzymes. These enzymes,

responsible for hepatic metabolism, may become saturated in cases of overdose. This will decrease the effect of first-pass metabolism, allowing increased quantities of active drug to reach the systemic circulation, thus prolonging the half-life of the calcium-channel blocker.[2] The plasma half-life of verapamil is 2-8 hours but can increase to 4.5-12 hours after ingestion of large amounts of verapamil or slow-release preparations. The primary metabolite of verapamil is norverapamil, which has 20% of the pharmacological activity of verapamil.[5,7] In plasma, both verapamil and norverapamil are highly protein bound and have large volumes of distribution. Metabolites of verapamil are mainly (70%) excreted in the urine, while faecal elimination accounts for 9-16% of the excreted dose.[8] Treatment of verapamil intoxication consists of several supportive interventions, since no antidote is available for calcium channel blockers. Gastric and bowel lavage may be considered in any patient with potentially life-threatening ingestion to prevent absorption. This can be futile since an overdose of verapamil can cause paralytic ileus.[9] Intravenous calcium is given to treat cardiac symptoms from mild to moderate intoxications, in order to raise the extracellular calcium concentration gradient, although it does not significantly affect peripheral vascular resistance or heart rate.[2,5] Glucagon and phosphodiesterase inhibitors may also be considered because they have a potent inotropic effect by increasing formation of intracellular cyclic adenosine monophosphate (cAMP) in myocardial cells.[5,10] Because hyperglycaemia is reported with verapamil intoxication, insulin should be given to reach normoglycaemia and promote more efficient cardiac metabolism.[11,12]

Besides the aforementioned treatment modalities, other strategies may be considered, such as levosimendan, which acts as a calcium sensitiser.[13]

In cats, 4-aminopyridine effectively reversed the toxic effects of verapamil,[14] but no human case reports are available.

The application of plasmapheresis, as a method of detoxification in several intoxications, is rapidly increasing.[15] In patients who have ingested substances that are highly lipid bound, plasmapheresis is more effective than haemodialysis because in plasmapheresis clearance is achieved through the longer total blood-filter time compared with intermittent haemodialysis.[16] Plasmapheresis resulted in cardiovascular stability in three cases with severe verapamil intoxication; unfortunately verapamil and norverapamil levels were not measured in the ultrafiltrate, only in serum.[17,18] In our case, we started HVCVVH in an attempt to correct metabolic disturbance due to severe metabolic acidosis. The low sieving coefficient of verapamil and norverapamil, calculated using verapamil and norverapamil concentrations in serum and ultrafiltrate, supported the hypothesis that HVCCVH is not effective in removing verapamil and the active metabolite norverapamil (*table 2*). Serum verapamil concentration shows a bimodal course: after ingestion first an increase, a few hours later a decrease followed by an increase of serum concentration (*figure 2*). Hypothetically the extended-release modality and clustering of verapamil capsules due to paralysis of the gastrointestinal tract could explain this bimodal course.

More recently, lipid emulsion, described in several animal and human case reports, seems to be beneficial in the treatment of verapamil intoxication.[4] The product we used (Intralipid®) is an intravenous emulsion composed of triglycerides and a phospholipid emulsifier. The currently favoured mechanism for lipid emulsion in verapamil intoxication is the formation of a 'lipid sink'.[19-21] An expanded intravascular lipid phase will sequester lipophilic toxins, thereby reducing the active free serum verapamil concentration and its toxic effect. Alternative mechanisms are based on the assumption that lipid emulsion improves adenosine triphosphate (ATP) synthesis in the cardiomyocyte, thereby improving contractility of the intoxicated heart.[19] Lipid emulsion infusion might also directly increase intra-cardiomyocyte calcium levels and lead to a direct positive inotropic effect.[19,20,22,23] Infusion of lipid emulsion in rats intoxicated with verapamil resulted in prolonged survival after administration of double doses of verapamil, as compared with the control group.[3] In another animal model, in which dogs were intoxicated with verapamil, lipid emulsion increased blood pressure and survival rate.[23] The use of lipid emulsion in humans intoxicated with verapamil remains doubtful. A recent review mentioned five cases of verapamil intoxication and use of lipid emulsion.[24] In these cases, administration of lipids seemed to be beneficial. After infusion of lipid emulsion, inotropes could be tapered,[25,26] and haemodynamic parameters stabilised.[26] Intravenous lipid emulsion could be beneficial in intoxications with other lipid-soluble agents as well as verapamil. An Australian review article describes data of human case reports suggesting a possible benefit of intralipid in potentially life-threatening cardiotoxicity from bupivacaine, mepivacaine, ropivacaine, haloperidol, tricyclic antidepressants, lipophilic beta blockers and calcium channel blockers.[19] Other human and animal studies subscribe this.[4,24]

The section on cardiac arrest associated with toxic ingestions of the American Heart Association guidelines mentions the use of lipid emulsion as possibly beneficial in the treatment of beta-blocker overdose, when other standard therapies are not effective. Lipid emulsion is not mentioned in the treatment of intoxication with calcium-channel blockers.[27]

In our case, it was administered 12 hours after arrival on the ICU. A few hours after administration of lipid emulsion, the norepinephrine dose could be tapered (*figure 1*). A positive response to lipid emulsion seems likely. Although circulating levels of verapamil and norverapamil were already decreasing prior to the start of the intralipids, there was an obvious direct correlation between stabilising haemodynamic parameters and the infusion of lipid emulsion (*figure 1*). The lipid sink theory only applies to the 10% of unbound verapamil, so beneficial effects could also be caused due to unmeasurable effects, e.g. the intracellular or receptor-mediated effects.

In theory, the use of lipid emulsion after intoxication with calcium channel blockers should be properly evaluated against standard therapy to evaluate the effect, side effects and potential interactions. However, since this intoxication is rare, additional case reports are necessary to support the inclusion of intravenous lipid emulsion in treatment guidelines. Nevertheless, publication bias should be taken into account.

In conclusion, intoxication with calcium channel blockers such as verapamil should be managed with conventional therapies. When these therapies are insufficient to reach haemodynamic stability, alternative therapies are indicated. High-volume continuous venovenous haemofiltration did not show a substantial effect on verapamil and norverapamil clearance, resulting in a low sieving coefficient. Administration of intravenous lipid emulsion may be beneficial and it may be considered as treatment for life-threatening intoxication with verapamil.

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