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Overdose of sustained-release verapamil

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SUMMARY

Verapamil toxicity results in hypotension, myocardial depression and disturbances in cardiac conduction. There is no specific therapy available for treatment of verapamil poisoning and management is therefore largely supportive. Overdose of sustained-release verapamil may result in prolonged toxicity which is often delayed in onset. This report describes two patients who ingested large doses of sustained-release verapamil. One patient developed severe toxicity resulting in hypotension and third-degree heart block which persisted for 48 h. In a second patient, significant toxicity was prevented by achieving adequate gastrointestinal decontamination. The mechanisms, presentation and management of verapamil poisoning are discussed. (Br. J. Anaesth. 1994; **72**: 361–365)

KEY WORDS

Pharmacology verapamil.

Verapamil hydrochloride is a calcium channel blocker used in the treatment of a variety of cardiovascular diseases, including angina, supraventricular tachyarrhythmia, hypertension and non-cardiac conditions such as migraine. Widespread use has led to an increasing number of reports of verapamil overdose in the past 15 years [1–11]. Verapamil toxicity results in disturbances of cardiac conduction, depressed myocardial contractility and hypotension. During the 1980s, sustained release preparations of calcium channel blockers were marketed to allow more convenient dosing schedules, and since 1988 case reports of overdose with sustained-release verapamil have appeared in the literature [12–17]. The sustained-release preparation has a different pattern of toxicity compared with the immediate-release formulation because of the slower rate of drug absorption.

The mainstay of treatment in verapamil toxicity is supportive, although a variety of therapies, including calcium [1, 3–17], inotropic agents [4–6, 8–13, 15, 17], glucagon [5, 15] and cardiac pacing [6, 8, 12, 13, 15, 17] have been used. Although most patients recover fully, several deaths have been reported [5, 6, 10, 13, 17].

This report describes two patients who ingested massive doses of sustained-release verapamil. The mechanisms and treatment of verapamil toxicity are reviewed, including problems encountered with the sustained-release preparation.

CASE REPORTS

Patient No. 1

A 42-year-old woman ingested 30 tablets of sustained-release verapamil 240 mg (total 7.2 g) after a domestic dispute. She was previously healthy and this medication was prescribed for her husband. The precise time of ingestion was unknown. On admission to the emergency department she was alert, orientated and not in acute distress. Arterial pressure was 115/60 mm Hg and heart rate 95 beat min^{-1} and regular. The initial electrocardiogram (ECG) showed first-degree heart block and right bundle branch block. She was given activated charcoal 50 g and Go-Lytely 6 litre (a polyethylene glycol and electrolyte solution for gastrointestinal lavage). However, satisfactory catharsis was not produced. Continuous cardiac monitoring was started and 40% oxygen administered by face mask.

Six hours after admission, her arterial pressure decreased to 70/48 mm Hg with heart rate 42 beat min^{-1} and her level of consciousness deteriorated. The trachea was intubated and positive pressure ventilation started. Repeat ECG revealed third-degree heart block with a ventricular rate of 50 b.p.m. An external cardiac pacing device was applied, captured easily and a ventricular rate of 80 b.p.m. set. However, arterial pressure remained low at 60/32 mm Hg. Normal saline 2 litre was infused rapidly and 10 ml of 10% calcium gluconate (1 g) administered i.v. without effect on arterial pressure. Over the next hour, i.v. glucagon 9 mg, calcium chloride 3 g, atropine 1 mg and bolus doses of adrenaline 1 mg were given. Arterial pressure remained at 65/30 mm Hg with persistent complete heart block. A transvenous pacing wire was inserted and a paced rate of 70 b.p.m. was set. Arterial pressure increased slightly to 70/52 mm Hg. Inotropic support was begun and a combination of adrenaline 0.38 $\mu g\ kg^{-1}\ min^{-1}$, noradrenaline 0.38 $\mu g\ kg^{-1}\ min^{-1}$ and dopamine 13 $\mu g\ kg^{-1}\ min^{-1}$ failed to increase arterial pressure. Serum concentrations of electrolytes from the time of deterioration were as follows (mmol $litre^{-1}$): sodium 141, potassium 3.5, chloride 103 and bicarbonate 19. The

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calculated anion gap was 19 mmol with a blood concentration of lactate of 6.8 mmol litre^{-1}. Blood glucose was 7.9 mmol litre^{-1} and total serum calcium was 2.0 mmol litre^{-1} with a serum albumin concentration of 36 g litre^{-1}. Arterial blood tensions ($F_{I_{O_2}}$ 0.7) were: pH 7.12, P_{O_2} 13.9 kPa and P_{CO_2} 5 kPa. A toxicology screen revealed no evidence of ingestion of any other drug or toxin.

The patient was transferred to the intensive care unit (ICU) where a pulmonary artery catheter was inserted. Pulmonary artery wedge pressure (PAWP) was 30 mm Hg, cardiac index 3.6 litre min^{-1} m^{-2} and calculated systemic vascular resistance 500 dyn s cm^{-5}. Echocardiography showed a diffusely hypokinetic left ventricle with an ejection fraction of 35%. An infusion of calcium chloride 1 g h^{-1} was commenced but resulted in no haemodynamic improvement. Blood glucose concentration increased to 28 mmol litre^{-1} and an insulin infusion was required for the next 7 h as the glucose concentration returned to normal. The patient remained hypotensive with arterial pressure of 84/52 mm Hg. Because of persisting oliguria and a high PAWP, attempts were made to induce diuresis with frusemide, but were unsuccessful.

During the next day (day 2), arterial pressure increased to 105/65 mm Hg and inotropic support was decreased. Metabolic acidosis resolved gradually. However, serial blood gas measurements showed a widening alveolar–arterial P_{O_2} difference. PAWP was 21 mm Hg and cardiac index 2.7 litre min^{-1} m^{-2}. The chest radiograph was consistent with pulmonary oedema. The patient failed to respond to further doses of frusemide and required ultrafiltration. Removal of 3.5 litre of fluid led to a marked improvement in gas exchange but did not alter the haemodynamic state. Thirty-six hours after admission the patient remained in complete heart block requiring continuous pacing.

By the following day (day 3), inotropic support was discontinued. Arterial pressure was 115/62 mm Hg, cardiac index 4.2 litre min^{-1} m^{-2} and a satisfactory urine output was re-established. Spontaneous sinus rhythm returned, allowing discontinuation of the pacemaker. The total duration of cardiac pacing was 52 h. The patient was weaned successfully from mechanical ventilation and made an uneventful recovery.

Patient No. 2

A 44-year-old woman was admitted to hospital 2 h after ingesting 75 tablets of sustained-release verapamil 240 mg (total 18 g). She gained access to the tablets while her sister (patient No. 1) was in hospital recovering from verapamil overdose. Her past medical history included alcohol abuse and epilepsy, for which she was taking phenobarbitone and phenytoin.

On admission to the emergency department she was alert, orientated and not in acute distress. Arterial pressure was 100/70 mm Hg and heart rate 84 beats min^{-1}. The ECG showed first-degree heart block with a P-R interval of 0.28 s. Serum concentrations of electrolytes, calcium, magnesium and blood glucose concentrations were normal. A toxicology screen showed no evidence of ingestion of any other drug or toxin. Activated charcoal 100 mg was given and continuous cardiac monitoring started.

A repeat ECG 6 h later showed that the P-R interval had increased to 0.32 s. She remained stable in all other respects. The ICU team was consulted and they decided immediately to administer a further dose of activated charcoal 50 g and induce vigorous gastrointestinal lavage. This was achieved by administering Go-Lytely 10 litres, which was extremely effective. An i.v. infusion of normal saline was commenced to ensure the patient was well hydrated throughout the lavage. Calcium gluconate 1 g was given i.v. with no resulting change in the ECG. She was admitted to the ICU for further monitoring and remained stable with an arterial pressure of 105/60 mm Hg. Calcium chloride 1 g was administered but had no effect on heart rate, P-R interval or arterial pressure.

Fourteen hours after admission to hospital the P-R interval decreased to 0.16 s and arterial pressure increased to 120/78 mm Hg. She was discharged from the ICU and made an uneventful recovery.

DISCUSSION

Mechanism of action

The clinical effects of verapamil are caused by block of slow calcium channels in the cell membrane. In cardiac and smooth muscle cells the influx of extracellular calcium through these channels results in release of stored calcium from the sarcoplasmic reticulum, producing an increase in intracellular calcium. This increase in intracellular calcium is important in the production of excitation–contraction coupling and muscle contraction. Cardiac and smooth muscle cells have little sarcoplasmic reticulum and are therefore highly dependent on transmembrane calcium influx for the initiation of intracellular events. This makes cardiac and smooth muscle cells particularly susceptible to calcium channel block which results in reduced myocardial contractility and vasodilatation [18].

Calcium channels are also important in the cells of the cardiac conduction system. In pacemaker cells, depolarization is dependent on an initial rapid influx of sodium ions followed by a slower influx of calcium ions. The influx of calcium ions contributes to the plateau (phase two) of the cardiac action potential. Calcium channel block results in decreased impulse generation at the sino–atrial (SA) node and decreased conduction at the atrio–ventricular (AV) node [18].

Pharmacokinetics

Between 80 and 90% of verapamil is absorbed from the upper gastrointestinal tract. It undergoes extensive first-pass metabolism by the liver and only 20–30% of the drug reaches the systemic circulation [19]. Peak serum concentrations are reached 1–2 h after ingestion of the conventional release preparation. Peak concentrations of sustained release verapamil are reached 6–8 h after ingestion, although great variability has been described [20]. The drug is about 90% protein-bound and the serum half-life varies between 2 and 8 h. The liver metabolizes

verapamil to norverapamil, a compound with about 20% of the activity of the parent drug. Both verapamil and norverapamil are excreted by the kidney. Because of the high degree of protein binding and a large volume of distribution, neither verapamil nor its active metabolite are removed by dialysis [17, 21].

Clinical features of verapamil toxicity

The clinical features of verapamil toxicity result from its effects on the cardiac conduction system, cardiac muscle and vascular smooth muscle. The reported clinical features of overdose vary, although some features occur consistently. The most common early feature is hypotension, which is thought to arise from relaxation of vascular smooth muscle [1–11]. Cardiac conduction abnormalities are present in nearly all patients. Sinus bradycardia may be present initially [11] but AV block is more common, with consequent AV dissociation and junctional and idioventricular rhythms [2–6, 8–10, 12, 13, 15–17]. Asystole is present in the most severe cases of toxicity [6, 15, 17]. Various other features of toxicity have been described, including central nervous system depression [4–8, 10, 12, 13, 17], seizures [10, 11, 13], metabolic acidosis [5, 8, 10, 13, 15, 17] and oliguric renal failure [15, 17]. However, these features were associated with severe hypotension and may simply reflect systemic hypoperfusion. Hyperglycaemia has also been described [5, 8–10, 13, 15, 17]. Release of insulin from pancreatic islet β-cells is dependent on release of calcium and insulin and may be inhibited therefore by calcium channel block. In some patients, hyperglycaemia may result from treatment with glucagon.

The clinical features of overdose with conventional release verapamil are often present on admission to hospital or develop over the following 2 h. In these patients, signs of verapamil toxicity usually resolve within 8–12 h [1–5, 7–11]. In overdose of sustained-release verapamil, most patients are asymptomatic on admission and do not develop signs of toxicity until 6–8 h after ingestion. In these patients, the duration of verapamil toxicity varies widely between 24 and 72 h [13–17]. This is probably because of continued release of verapamil from drug fragments remaining within the gastrointestinal tract. Deaths from verapamil overdose occur either early from profound cardiovascular depression [6, 10, 13], or late from ongoing toxicity and complications secondary to prolonged hypotension [5, 17]. Nevertheless, most patients survive and make a full recovery.

Treatment of Verapamil Toxicity

General measures

The initial treatment of verapamil overdose is dictated by the presence and degree of toxicity at presentation. Even if asymptomatic on admission to hospital, the patient should be observed in a high dependency area because of the large variability in the severity and rate of presentation of toxicity. This is particularly important in overdoses of the sustained-release preparation as most patients are asymptomatic on presentation. This may lead to a false sense of security as severe toxicity may present up to 6–8 h later [13, 16]. As verapamil is absorbed extensively from the upper gastrointestinal tract, early gastric decontamination is vital and may prevent significant toxicity. This should be accomplished with activated charcoal. With sustained-release verapamil, the importance of vigorous gastrointestinal lavage has been demonstrated [14]. This may prevent delayed toxicity arising from absorption of tablets remaining within the gastrointestinal tract [22]. Without vigorous gastrointestinal lavage, activated charcoal may not prevent the onset of severe toxicity after ingestion of sustained-release verapamil [16, 17]. The induction of emesis with syrup of ipecacuanha is not recommended as increased vagal tone may worsen bradycardia [10].

In patients where there is evidence of significant toxicity on admission to hospital, initial treatment should comprise resuscitation. However, it is still important to achieve gastric decontamination in these patients as there may be ongoing absorption of verapamil from the gastrointestinal tract.

Pharmacological measures

Calcium. Calcium has been used in most patients with verapamil overdose. However, the response has been extremely variable. Calcium was reported initially to correct hypotension in patients receiving i.v. verapamil for treatment of supraventricular arrhythmia [23]. In early reports of verapamil overdose, i.v. calcium was the only drug therapy used, resulting in partial or complete reversal of hypotension [1–3, 7]. In some patients, calcium has resulted also in reversal of AV conduction abnormalities [1, 16]. However, other patients have shown marked resistance to calcium and lack of response would seem to be a feature of more severe toxicity [5, 8–10, 17]. The mechanism whereby increased extracellular calcium might antagonize the effects of verapamil toxicity is not clear. However, no adverse effects of calcium administration in overdose with calcium channel blockers have been described and the response to treatment should always be assessed.

Atropine. Atropine has been used to treat bradycardia and AV block in verapamil toxicity, but it has been ineffective [2, 5, 6, 10, 17]. Atropine antagonizes vagal inhibition of the SA node, so is unlikely to be of any benefit in antagonizing conduction delay at the AV node. Therefore, it has a limited role in treatment of verapamil overdose.

Inotropes and vasopressors. Stimulation of $beta_1$ and $alpha_1$ adrenergic receptors increases the availability of intracellular calcium for cardiac and smooth muscle contraction. The use of inotropes has been beneficial in some cases of verapamil overdose, although there have been many reports describing little or no benefit in the treatment of severe toxicity.

Dopamine has been used most frequently and it may be effective when used in the range 10–30 μg kg^{-1} min^{-1} [11, 15]. This may be a result of the increased $alpha_1$ agonist effect at these doses, resulting in increased peripheral vascular tone. There are also several reports of verapamil toxicity

where dopamine has been ineffective with no detectable haemodynamic effect [4, 8, 9, 13, 17]. Dobutamine has also been used in the treatment of verapamil toxicity. It was reported to be effective in one patient [15], but was ineffective at doses of up to 40 $\mu g\ kg^{-1}\ min^{-1}$ in other patients [5, 10, 17]. Dobutamine may increase cardiac contractility by $beta_1$ stimulation, but does not improve peripheral vascular resistance as it lacks significant alpha agonist activity. Indeed, systemic vascular resistance may even decrease at large doses because of increasing $beta_2$ stimulation, making dobutamine unsuitable in this situation.

Because they cause both $alpha_1$ and $beta_2$ stimulation, adrenaline and noradrenaline are the most logical choices of inotrope for the treatment of verapamil toxicity. In one patient, verapamil overdose was treated successfully with calcium and an infusion of adrenaline [4]. However, more severe cases of toxicity have exhibited marked resistance to the effects of adrenaline [4, 13, 17]. Noradrenaline has been used in the treatment of verapamil toxicity and it reversed hypotension in two patients [9, 10].

Isoprenaline has been used to treat cardiac conduction abnormalities of verapamil overdose, with an improvement in heart rate and arterial pressure in some patients [5, 6, 8, 15, 17, 21] but it was of no benefit in others [4, 13]. At larger doses, $beta_2$ stimulation may lead to a reduction in systemic vascular resistance and increased hypotension.

Phosphodiesterase inhibitors may also increase the availability of intracellular calcium by increasing the concentration of cyclic AMP. There are two case reports describing the use of a phosphodiesterase inhibitor in the treatment of verapamil overdose. In one report, a combination of amrinone and isoprenaline led to improvement in the patient's arterial pressure [8]. However, the improvement occurred 12 h after ingestion by which time spontaneous recovery may already have started. In another report, a combination of amrinone, dopamine and adrenaline was ineffective in reversing severe hypotension [13].

Glucagon. Glucagon is a positive inotrope and causes increased formation of cyclic AMP in myocardial cells. It also exhibits a mildly positive chronotropic effect on the SA node and enhances conduction at the AV node. It has been used for several years for treatment of hypotension and myocardial depression in patients with beta blocker toxicity [24]. In animal studies of verapamil toxicity, glucagon was found to be effective in increasing heart rate and reversing myocardial depression and hypotension [25, 26]. In patients with verapamil overdose, the efficiency of glucagon has been variable. There was reversal of hypotension in two patients with verapamil toxicity after glucagon 1 and 17 mg [10, 15]. However, in other reports of severe verapamil toxicity there was no response to glucagon [5, 10, 13].

Specific therapy. The most specific antidote for calcium channel blocker toxicity may be 4-aminopyridine (4-AP), a competitive antagonist of non-depolarizing neuromuscular blocking agents. It enhances transmembrane influx of calcium [27] and may act as a competitive antagonist of verapamil at slow calcium channels [28]. In a cat model of verapamil toxicity, 4-AP was effective in rapidly reversing third-degree heart block and hypotension [28]. In a similar canine model, 4-AP resulted in increased heart rate and cardiac output [29]. There is only one report of treatment of verapamil toxicity with 4-AP in humans. A patient in renal failure presented with third-degree heart block caused by chronic verapamil toxicity. This failed to respond to a combination of atropine, calcium and isoprenaline. Sinus rhythm returned after the patient was given 4-AP 10 mg i.v. [21].

Two experimental compounds that promote intracellular calcium flux, Bay K 8644 and CGP 28932, were compared with 4-AP in a study of verapamil intoxication in rabbits [30]. Bay K 8644 was most effective in improving hypotension, ECG and cardiac conduction abnormalities of verapamil toxicity. No human trials of Bay K 8644 have been reported.

Cardiac pacing

The heart should be paced in patients with heart block when there is no initial response to pharmacological measures [6, 8, 12, 13, 15, 17]. However, pacing may not reverse hypotension, as depression of myocardial contractility and relaxation of vascular smooth muscle may persist. Prophylactic insertion of a pacing wire in any patient with evidence of AV conduction delay is recommended as asystole may develop. Nevertheless, ventricular capture may be unsuccessful in patients developing asystole due to severe toxicity [10].

In conclusion, there is no specific therapy available for the treatment of verapamil toxicity and management is mainly supportive. Whereas mild toxicity may respond to calcium, glucagon or inotropes, more severe toxicity is resistant to intensive pharmacological support. Cardiac pacing may be necessary to treat conduction abnormalities but will often fail to reverse hypotension. Despite the lack of specific therapy, most patients with verapamil poisoning survive without significant sequelae.

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