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Prolonged half-life of verapamil in a case of overdose: implications for therapy

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After an overdose of verapamil (2.4 g) in a 59-year-old man the apparent half-life of verapamil was prolonged (15 h). The most likely mechanism is rate-limiting absorption, although changes in clearance and volume of distribution may contribute. As the elimination half-life of verapamil is increased in overdose, therapy may have to be continued for longer than expected. Moreover since the half-life of absorption of verapamil in overdose may be prolonged, activated charcoal should be given in repeated doses, even if an ordinary-release formulation has been taken.

Keywords verapamil overdose pharmacokinetics

Introduction

There is little information on the pharmacokinetics of verapamil in overdose. We report a case of poisoning with verapamil in which the elimination half-life of verapamil was prolonged. This has implications for treatment of verapamil overdose.

Case report

A 59-year-old 80 kg man took an overdose of verapamil (60 ordinary-release 40 mg tablets), with about 9 units of alcohol, at 16.00 h. He normally took Tenoretic® (atenolol 100 mg plus chlorthalidone 25 mg) once daily for hypertension. On arrival at hospital (18.30 h), his heart rate was 30 beats min^{-1} (complete heart block), systolic blood pressure 90 mm Hg, and laboratory results as shown in Table 1.

Immediate treatment included gastric lavage, oral activated charcoal 50 g, intravenous fluids (6 units of polygeline and 2 l of isotonic saline), and intravenous atropine 1 mg and calcium gluconate 2 g. Hypokalaemia responded to intravenous potassium and hyperglycaemia to intravenous insulin. A temporary transvenous pacing wire was inserted (rate set at 100) but he remained hypotensive. At 21.00 h he had a cardiac arrest (EMD). He was successfully resuscitated, intubated, and given noradrenaline (0.4 mg h^{-1} i.v.). His arterial pH was 6.9 and he was given intravenous sodium bicarbonate (8.4%, 100 ml). At 22.00 h he had another cardiac arrest (VF), treated with defibrillation. He was given adrenaline (2 mg h^{-1} i.v.) but remained hypotensive and developed oliguria with a metabolic acidosis (blood gases pH 6.9, PaO_2 11 kPa, $PaCO_2$ 8.1 kPa, base excess −20). Glucagon 10 mg was given intravenously. He was ventilated, and haemofiltered because of acidosis and a rising serum creatinine (maximum 424 μM). His cardiac output was 8.6 l min^{-1} (reference range 4–8), pulmonary capillary wedge pressure 21 mm Hg (6–12), and systemic vascular resistance 456 dyn s^{-1} m^{-2} (800–1200). He required dopamine, noradrenaline, and adrenaline to maintain systolic pressure. Over the next 3 days these inotropic drugs were slowly withdrawn. Haemofiltration was stopped on day 3. He was extubated on day 5 and discharged on day 11 with no neurological or cardiological deficits.

Methods

Serum concentrations of verapamil, norverapamil, and the *N*-dealkylated derivative D617 were measured at 6, 7.5, 17 and 30.5 h after the overdose (see Figure 1) by h.p.l.c. (limit of detection 5 μg l^{-1}). Samples and serum standards (100 μl) containing the analytes (0.5, 1.0 and 2.0 mg l^{-1}), sodium hydroxide (4 mol l^{-1}, 50 μl), and aqueous benzoquinoline as internal standard (0.5 mg l^{-1}, 50 μl) were extracted

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Table 1 Laboratory data on admission (abnormal results in bold)

Measurement	*Value*	*Reference range*
Sodium (mM)	**132**	135–145
Potassium (mM)	**2.1**	3.5–5.0
Urea (mM)	4.2	2.5–6.7
Creatinine (μM)	137	70–150
Calcium (corrected) (mM)	2.6	2.12–2.65
Glucose (mM)	**21.1**	3.9–5.5
Albumin (g l^{-1})	**34**	35–50
Bilirubin (μM)	7	3–17
Aspartate transaminase (iu l^{-1})	39	15–42
Alkaline phosphatase (iu l^{-1})	126	100–300
Paracetamol	Not detected	
Salicylate	Not detected	
Haemoglobin (g dl^{-1})	13.8	12–18
Mean cell volume (fl)	86.7	80–95
White cell count ($\times 10^9$ l^{-1})	**17.9**	4–11
Platelets ($\times 10^9$ l^{-1})	295	150–400
INR	1.2	
Arterial blood gases on a rebreathing mask (i.e. almost 100% oxygen)		
pH	**7.30**	7.36–7.44
PaO_2 (kPa)	**27.8**	11–15
$PaCO_2$ (kPa)	**4.3**	4.5–6.0
Saturation	99%	

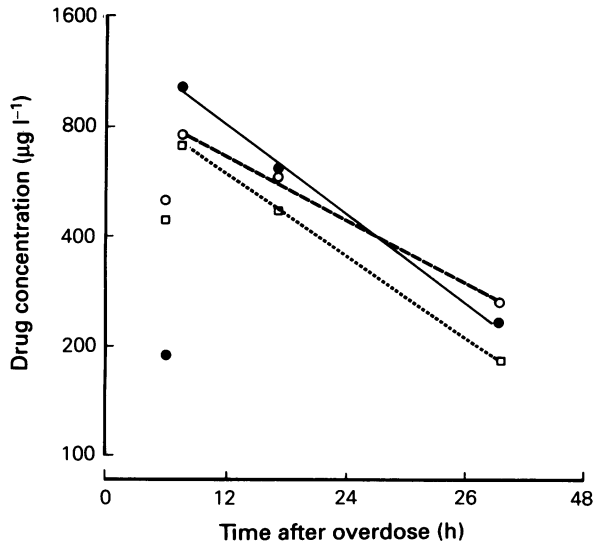

Figure 1 Plasma concentrations of verapamil (●), norverapamil (○) and D617 (□) after an overdose of 2.4 g verapamil.

into methyl *tert* butyl ether. An aliquot was injected on to the h.p.l.c. column (Spherisorb S5 SCX Phase Separations), eluted (flow rate 2 ml min^{-1}) with methanol:acetonitrile:water (40:40:20) containing perchloric acid (0.2% v/v; pH 1.7), and detected fluorometrically (excitation wavelength 200 nm).

Results and discussion

The verapamil and metabolite serum concentrations are shown in Figure 1. The half-lives were: verapamil 15 h, norverapamil 21 h, and D617 16 h. The oral clearance (CL/*F*) of verapamil was 21 ml min^{-1} kg^{-1}; the apparent volume of distribution (V_z/F) was 27 l kg^{-1}.

In the second, third and fourth samples the serum atenolol concentrations were 0.92, 0.80 and 0.55 mg l^{-1} (target range 0.1–1.0), giving a half-life of 43 h.

Pharmacokinetics of verapamil in overdose

Verapamil is well absorbed after oral administration, with peak plasma concentrations within 2 h. However its systemic availability is low because of high first-pass metabolism in the liver [1, 2]. Its elimination half-life is 2.7–4.8 h after single oral and intravenous doses, and is prolonged to 4.5–9.6 h during long-term oral administration, perhaps because verapamil reduces liver blood flow [3–5]; this is accompanied by increased systemic availability [3].

Verapamil is widely distributed to body tissues and is highly bound to albumin and α_1-acid glycoprotein.

The major active metabolite of verapamil is norverapamil (the *N*-demethylated product), which has about 20% of its activity [2]. Other active metabolites are rapidly conjugated.

There is little information on the pharmacokinetics of verapamil in overdose. In two patients the half-life was reportedly 8 and 13 h, but plasma concentrations were not shown in one case [6], and calculation of the half-life is not possible from the data given in another case [7].

The elimination half-life in our patient was 15 h. There was little change in the apparent volume of distribution (V_z/F) compared with single oral-dose data from healthy subjects [1]. The oral clearance (CL/*F*) was within the range of reported values [1].

There are three possible mechanisms which could account for the prolongation of half-life that we observed:

- *Rate-limiting absorption* Slow absorption of verapamil at high doses may rate-limit the apparent half-life. The fact that the peak plasma concentration occurred at 6–7 h supports this.
- *Impaired liver clearance, secondary to reduced liver blood flow* Our patient's low systemic vascular resistance suggests reduced liver blood flow, which would have increased the systemic availability of verapamil and reduced total clearance. However, that would have reduced oral clearance (CL/*F*), which did not happen. Furthermore, the increase in half-life was too large to be explained simply by this.
- *Increased apparent volume of distribution* An increased apparent volume of distribution, perhaps due to saturable protein binding in overdose, would have prolonged the half-life. Since V_z/F was not changed, if the systemic availability increased because of a fall in liver blood flow, the volume of

distribution would also have been increased. Chronic liver disease alters the volume of distribution (and clearance) of verapamil [8], but our patient had no evidence of chronic liver disease.

Therefore the most likely mechanism accounting for the prolonged half-life in overdose seems to be rate-limiting absorption. The importance of rate-limiting absorption is that repeated doses of activated charcoal should be given, with a cathartic, even when an ordinary-release formulation has been taken; this is not a current therapeutic recommendation.

The half-life of norverapamil was 21 h, which is longer than the steady-state value in patients (10.5 h) [3]. This is attributable to renal impairment, and the prolonged half-life of atenolol supports this.

Treatment of verapamil overdose

Treatment regimens and outcomes in verapamil overdose have been inconsistent [6, 7, 9–17]. There is no concentration-survival relation and serum concentrations do not predict outcome [11]. Deaths have occurred with plasma concentrations as low as 600 $\mu g\ l^{-1}$ (therapeutic target range 100–500 $\mu g\ l^{-1}$) and survival with concentrations as high as 4000 $\mu g\ l^{-1}$ [9]. The largest dose associated with survival is 16 g [12].

Several variables worsen the prognosis after verapamil overdose: advanced age, delay in treatment, other (e.g. cardiac) disease, and other drugs. For example, the adverse cardiovascular effects in our patient were probably exacerbated by atenolol.

Early treatment should include gastric lavage plus activated charcoal, given repeatedly after a modified-release formulation. Whole-bowel lavage with polyethylene glycol has been used in poisoning with modified-release verapamil [13] and should be considered for a large overdose. Ipecac is contra-indicated, because of rapid changes in neurological status and vagal stimulation induced by emesis [10].

Continuous ECG monitoring is important, because sudden deterioration with cardiovascular collapse and abrupt asystole may occur [10].

Hypotension and myocardial depression after verapamil poisoning are often refractory to standard measures. Adequate fluid replacement is important, and intravenous calcium may improve myocardial contractility and even atrioventricular conduction. Glucagon, by stimulating cyclic AMP production, may be beneficial [14]. High doses of positive inotropic drugs are often required even when the pulse rate is restored to normal for example by pacing. An intra-aortic balloon pump may help in unresponsive hypotension, and cardiopulmonary bypass has been used [15]. Mechanical ventilation may be used for severe acid/base disorders, pulmonary oedema, neuromuscular blockade, and loss of airway control. We used haemofiltration for severe acidosis and renal impairment; however haemofiltration will not remove verapamil from the body, because of its high volume of distribution.

In atrioventricular dissociation a temporary transvenous pacemaker is required, as atropine and isoprenaline are rarely effective [10].

The mechanism of severe hypokalaemia [16] is unknown, but diuretic therapy may have contributed here. It is important to correct hypokalaemia, as it will exacerbate the cardiotoxic effects of verapamil.

Conclusions

Poisoning with verapamil may be lethal primarily through its cardiovascular effects [9,10]. However, aggressive, pre-emptive treatment often results in recovery, even in very severe cases [11]. Because the half-life of verapamil is prolonged in overdose, therapy may have to be continued for longer than expected. Repeated doses of activated charcoal should be given, no matter what type of formulation has been taken.

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References

1 Hamann SR, Blouin RA, McAllister RG. Clinical pharmacokinetics of verapamil. *Clin Pharmacokin* 1984; **9**: 26–41.

2 McAllister RG, Hamann SR, Blouin RA. Pharmacokinetics of calcium-entry blockers. *Am J Cardiol* 1985; **55**: 30B–40B.

3 Kates RE, Keefe DLD, Schwartz J, Harapat S, Kirsten EB, Harrison DC. Verapamil disposition kinetics in chronic atrial fibrillation. *Clin Pharmac Ther* 1981; **30**: 44–51.

4 Freedman SB, Richmond DR, Ashley JJ, Kelly DT. Verapamil kinetics in normal subjects and patients with coronary artery spasm. *Clin Pharmac Ther* 1981; **30**: 644–652.

5 Shand DG, Hammill SC, Aanonsen BS, Pritchett ELC. Reduced verapamil clearance during long-term oral administration. *Clin Pharmac Ther* 1981; **30**: 701–703.

6 Sauder PH, Kopferschmitt J, Dahlet M, *et al.* Acute verapamil poisoning (six cases). *J Toxicol clin Exp* 1990; **10**: 261–270.

7 Crump BJ, Holt DW, Vale JA. Lack of response to intravenous calcium in severe verapamil poisoning. *Lancet* 1982; **ii**: 939–940.

8 Somogyi A, Albrecht M, Kliems G, Schäfer K, Eichelbaum M. Pharmacokinetics, bioavailability and ECG response of verapamil in patients with liver cirrhosis. *Br J clin Pharmac* 1981; **12**: 51–60.

9 Watling SM, Crain JL, Edwards TD, Stiller RA.

Verapamil overdose: case report and review of the literature. *Ann Pharmacother* 1992; **26**: 1373–1377.
10 Kenny J. Treating overdose with calcium channel blockers. *Br med J* 1994; **308**: 992–993.
11 Hofer CA, Smith JK, Tenholder MF. Verapamil intoxication: a literature review of overdoses and discussion of therapeutic options. *Am J Med* 1993; **95**: 431–438.
12 Horowitz BZ, Rhee KJ. Massive verapamil ingestion: a report of two cases and review of the literature. *Am J Emerg Med* 1989; **7**: 624–631.
13 Buckley N, Dawson AH, Howarth D, Whyte IM. Slow release verapamil poisoning. Use of polyethylene glycol whole bowel lavage and high dose calcium. *Med J Aust* 1993; **158**: 202–204.
14 Doyon S, Roberts JR. The use of glucagon in a case of calcium channel blocker overdose. *Ann Emerg Med* 1993; **22**: 1229–1233.
15 Hendren WG, Schieber RS, Garretson LK. Extracorporeal bypass for the treatment of verapamil poisoning. *Ann Emerg Med* 1989; **18**: 984–987.
16 Minella RA, Schulman DS. Fatal verapamil toxicity and hypokalaemia. *Am Heart J* 1991; **6**: 1810–1812.
17 Krick SE, Gums JG, Grauer K, Cooper GR. Severe verapamil (sustained-release) overdose. *Ann Pharmacother* 1990; **24**: 705–706.

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