Journal of Clinical Toxicology
ISSN: 2161-0495

Case Report Open Access

Fatal Verapamil Intoxication: A Case Report and Literature Review

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Abstract

Background: Verapamil intoxication is a life-threatening condition manifesting as hemodynamic instability requiring vasopressor and ventilator supports and even fatal outcome in some patients.

Case report: A 37-year-old female who intentionally took sustained-release verapamil of 3,600 mg, doxazosin of 20 mg, and chlorpheniramine of 40 mg, presented with sudden cardiac arrest. Intubation with cardiopulmonary resuscitation was promptly initiated, and then intravenous calcium gluconate, sodium bicarbonate, and vasopressor were given to maintain hemodynamic condition. During hospitalization, targeted temperature management, temporary cardiac pacing, renal replacement therapy as well as all essential supportive measures were given. However, the patient eventually expired due to refractory cardiogenic shock 4 days after hospitalization. In addition, we review all reported cases of verapamil intoxication in English literature.

Conclusion: We report herein a fatal case of verapamil intoxication, and have a literature review in all reported cases. Hence, verapamil intentional or accidental overdose, can be lethal that requires the prompt initiation of comprehensive resuscitation.

Keywords: Verapamil intoxication; Verapamil overdose; Verapamil toxicity; Calcium channel blocker; Non-dihydropyridine calcium channel blocker

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Introduction

Verapamil, a non-dihydropyridine Calcium Channel Blocker (CCB), is medically used in patients with hypertension and supraventricular arrhythmias. Verapamil intoxication is a life-threatening condition manifesting as hemodynamic instability requiring ventilator and vasopressor supports and even death in some patients [1,2]. The clinical manifestations are mostly due to cardiovascular dysfunction including hypotension, bradycardia, dysrhythmias, and intraventricular conduction delay, but derangement of other systems such as non-cardiogenic pulmonary edema, unconsciousness, hyperglycemia, hypokalemia, can be present. Herein, we report a fatal case of verapamil intoxication, and review the literature of all reported cases.

Case Report

A 37 year old female presented to our hospital, King Chulalongkorn Memorial Hospital, Bangkok, Thailand, after an unknown duration of intentional ingestion of sustained-release (SR) verapamil of 3,600 mg, doxazosin of 20 mg, and chlorpheniramine of 40 mg. One hour before arriving emergency department (ED), she suddenly gasped for air and was unconscious. On arrival at ED, electrocardiogram (ECG) showed no electrical activity and then intubation with cardiopulmonary resuscitate (CPR) was promptly initiated; 3 mg of epinephrine, 30 mL of 10% calcium gluconate, and 50 mL of 7.5% sodium bicarbonate were given. After 9 minutes of CPR, a return of spontaneous circulation (ROSC) was noted, and ECG showed sustained junctional rhythm of 40/minute (Figure 1). Continuous intravenous infusion of norepinephrine, dopamine, and adrenaline were then given to maintain her blood pressure. Initial point of care capillary glucose was 296 mg %, and hence intravenous insulin was continuously dripped at the initial rate of 1 unit/kg/hour. Gut decontamination with gastric lavage and the use of activated charcoal or sorbitol were not performed in our patient because of the unstable hemodynamic condition and marked bowel ileus.

Her past medical history was unremarkable except a recent diagnosis of hypertension in the young with suspicion of primary hyperaldosteronism.

During hospitalization in an intensive care unit, the patient had received Targeted Temperature Management (TTM), temporary cardiac pacing, high-dose inotropic therapy, High-Dose Insulin (HDI) Therapy, Renal Replacement Therapy (RRT), and intravenous Lipid-Emulsion Therapy (LET). However, the patient eventually expired due to refractory cardiogenic shock 4 days after hospitalization.

Discussion

We report herein a patient with intentional ingestion of the overdose of verapamil, in accompanying with other medications. Unfortunately, there is still a fatal outcome despite all best efforts both specific treatment and supportive measures putting on our patient.

In our patient, aggressive decontamination with gastric lavage and the use of activated charcoal or sorbitol were not performed despite the recommendation by the experts [1]. Because of the risks outweighing the benefits.

The first-line treatment as recommended by the Experts Consensus Recommendations for the Management of Calcium Channel Blocker Poisoning in Adults 1 despite handful cases of verapamil intoxication includes 1) intravenous calcium and/or atropine in the presence of symptomatic bradycardia or conduction delay, 2) epinephrine,

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Received: March 05, 2019; **Accepted:** March 25, 2019; **Published:** April 01, 2019

Citation: Prasoppokakorn T, Suteparuk S (2019) Fatal Verapamil Intoxication: A Case Report and Literature Review. J Clinic Toxicol 9: 421.

norepinephrine, and/or dopamine in the presence of cardiogenic shock, 3) intravenous HDI in the presence of myocardial dysfunction with maintenance of euglycemia, and 4) LET in the setting of refractory to first-line treatment [2]. In our patient, all 4 measures were given but unfortunately without adequate response.

The mechanism of actions of CCBs is blocking the L-type voltage-gated calcium channels in the cell membrane, but each member of the CCBs varies in the chemical structure, pharmacokinetics, pharmacodynamics, and tissue selectivity. Verapamil hydrochloride (Figure 2) is a phenylalkylamine-derivate calcium-channel blocking agent. Chemically, it is a basic (log K=9.1) and highly hydrophobic compound (log $P_{o/w}$=9.1)3. The pharmacokinetics, more than 90% of verapamil is absorbed when given orally, but due to high first-pass metabolism, bioavailability is much lower (10%-35%).

It is 90% bound to plasma proteins, takes 1 to 2 hours to reach peak plasma concentration after oral administration. It is metabolized in the liver, 70% is excreted in the urine and 16% in feces [3-5]. Verapamil is one of the most widely used non-dihydropyridine CCBs, can block the rapid influx of calcium into the cardiac myocytes and conduction system as well as vascular smooth muscle cells. The final results of these blocking are as followed: 1) decreased myocardial contractility, 2) blocked atrioventricular nodal conduction time, and 3) peripheral vasodilatation, leading to congestive heart failure, conduction abnormalities, hypotension, respectively, and cardiac arrest in severe cases [6]. According to American Association of Poison Control Centers in 2009, there were 18 of 52 deaths attributable to CCBs especially to verapamil [7]. Furthermore, the blockage of L-type voltage-gated calcium channels will decrease the release of insulin from the pancreatic beta-islet cells and hence reduce the glucose uptake by peripheral tissues (insulin resistance) [8]. The reported toxic doses of verapamil both nonfatal and fatal cases range from 800 mg to 24,000 mg; however, the correlation between the ingested dosage and the clinical outcome is not demonstrated in every case. In our case, the ingestion of SR verapamil of 3,600 mg can cause the fatal toxicity, likely due to the combination of adverse effects from both verapamil (CCB) and doxazosin (alpha-adrenergic blocking agent) leading to a marked hypotension and peripheral vasodilatation [9-27].

In addition, we review all English literature published from 1977 to 2018 for 50 patients (including our patient) with verapamil intoxication (Table 1).

There are 20 males and 30 females with the mean age of 33.7+14.8 (range: 14-69) years. The amount of verapamil ingestion ranges from 480 to 19,200 mg, which ranges from 480 to 12,000 mg and from 600 to 19,200 mg in fatal and survived cases, respectively. The lowest dose in the fatal case is 480 mg, and on the other hand, the highest dose in the survived case is 19,200 mg. Clinical presentations vary from hypotension, bradycardia, conduct abnormalities, and cardiac arrest of 50 cases, hypotension is the most common presenting symptom (40 cases, 80.0%). Two patients including our patient, developed asystole upon arrival to the hospital. In addition, the ECG ranges from normal sinus rhythm (5 cases, 10.0%), sinus bradycardia (3, 6.0%), first (6, 12.0%), second (1, 2.0%), and third-degree atrioventricular block including of AV dissociation (20, 40.0%), junctional rhythm (4, 8.0%), right and left bundle branch block (4, 8.0%), and asystole (2, 4.0%). Our patient had cardiac asystole and junctional rhythm after ROSC. There are 18 (36.0%) cases with severe cardiac conduction block requiring temporary cardiac pacing. Apart from cardiovascular involvement of verapamil, the adverse effects of the other systems include the airway compromise requiring assisted ventilation (28 cases, 56.0%), non-cardiogenic pulmonary edema (7, 14.0%), altered mental status (31, 62.0%), hyperglycemia (10, 20.0%), and hypocalcemia (5, 10.0%). The complications after the treatment include severe metabolic acidosis (3, 6.0%), seizure (2, 4.0%), acute ischemic stroke (1, 2.0%), cerebral anoxia (1, 2.0%), pneumonia (1, 2.0%), ischemic colitis (1, 2.0%), and cardiogenic shock (1, 2.0%). Of 50 cases, there are 39 (78.0%) and 11 (22.0%) survived and fatal cases, respectively. The duration of respiratory support ranges from 0.5 to 13 days and the length of hospitalization ranges from 1 to 55 days [28-51].

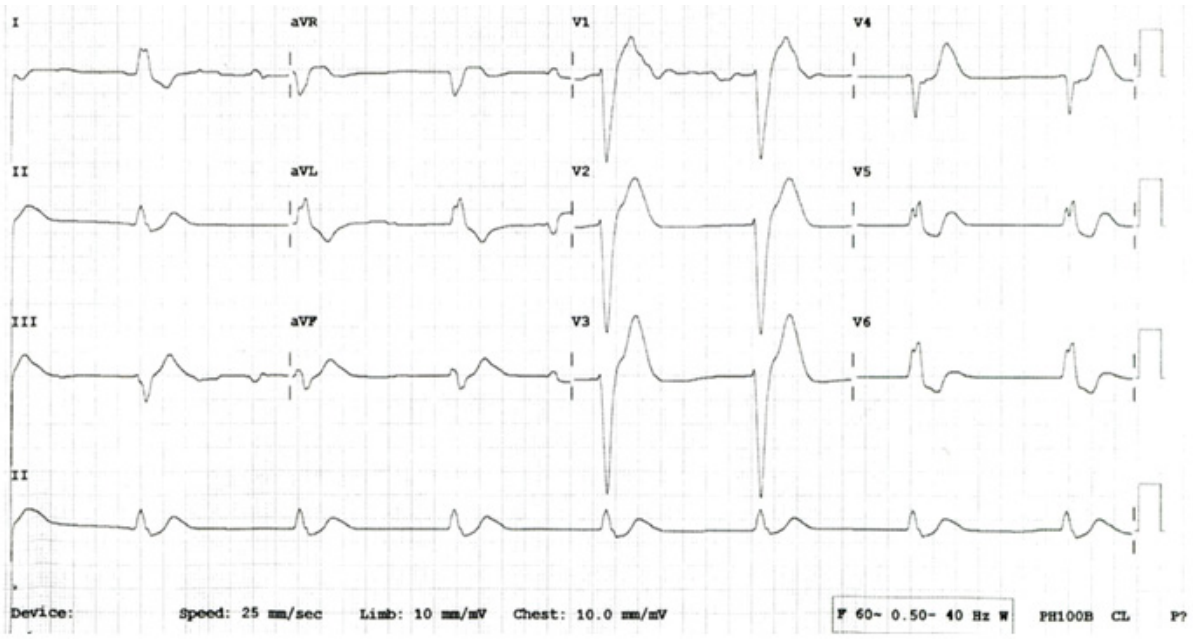

Figure 1: Electrocardiogram showing junctional rhythm with rate of 40/min, left bundle branch block, prolonged QTc interval (480 ms).

Patient	Gender/ age (year)	Ingested amount (mg)	Co-ingested drug	Other medical problems	Duration after ingestion (hour)	Hemodynamics at presentation	ECG	Decreased mental status	Hypo-calcemia	Hyper-glycemia	Treatment/ vasopressor	Complication	Duration of intubation/ hospitalization (day)	Outcome
1[9] (2015)	F/24	7,200	None	None	1-2	BP 65/30 mmHg HR 80 bpm	NA	NA	NA	NA	Fluid, Ca, glucagon, HDI, LET (via intra-osseous), ETT, NE 20 mcg/min	None	2/2	Died
2[10] (2014)	F/36	2,000	None	None	1	BP 60/40 mmHg HR 40 bpm	NA	+	NA	NA	Fluid, Ca, HDI, plasma exchange, ETT, Dopamine 30 mcg/kg/min, Dobutamine 10 mcg/kg/min	ARDS	0.5/NA	Survived
3[11] (2014)	M/40	3,600	Fluoxetine 400 mg, carbamazepine SR 1800 mg, alcohol, oxycodone SR, amlodipine, valsartan, simvastatin, trazodone metformin,	HT MDD Obesity	3	BP 110/70 mmHg HR 97 bpm	Sinus rhythm	+	NA	+	Fluid, Ca, atropine, HDI, LET, RRT (due to carbamazepine intoxication), ETT, NE 120 mcg/min, E 30 mcg/min, vasopressin 0.03 units/min	Alcohol and opioid withdrawal, non-cardiogenic pulmonary edema	7/NA	Survived
4[12] (2014)	F/51	9,600	None	MDD	8	NA HR 38 bpm	Sinus bradycardia	-	NA	NA	Fluid, Ca, LET, RRT, ECMO, ETT, NE 10 mcg/min, E 10 mcg/min	None	7/18	Survived
5[8] (2013)	F/27	2,400	Furosemide 4,000 mg	None	NA	BP 60/35 mmHg HR 40 bpm	First degree AV block	-	NA	NA	Activated charcoal, fluid, Ca, atropine, TPM, HDI, LET, E 9 mcg/min	None	NA/4	Survived
6[13] (2011)	F/41	19,200	None	None	6	SBP 115/73 mmHg HR 59 bpm	Third degree AV block	-	-	NA	Activated charcoal, fluid, Ca, TPM, HDI, LET, RRT, ETT, NE 0.75 mcg/kg/min, E 0.04 mcg/kg/min, vasopressin 0.05 units/min	Ischemic colitis	NA/55	Survived
7[14] (2011)	M/47	6,300	None	HT	3	SBP 80 mmHg HR 40 bpm	Third degree AV block	+	NA	NA	Fluid, Ca, atropine, glucagon, HDI, LET, TPM, ETT	None	7/NA	Survived
8[15] (2009)	M/32	13,400	Levothyroxine 1,125 mg, bupropion 4,800 mg, zolpidem CR 200 mg, clonazepam, benazepril	Hypo-thyroidism MDD	12	BP 69/26 mmHg HR 55 bpm	NA	+	NA	NA	Activated charcoal, fluid, Ca, glucagon, LET, ETT, NE	None	2/5	Survived
9[16] (2007)	F/15	960	Propranolol 550 mg	None	8	BP 55/30 mmHg HR 40 bpm	Broad complex bradycardia, then asystole	+	+	+	CPR (70 minutes), activated charcoal, fluid, Ca, glucagon, bicarbonate, TPM, plasma exchange, ETT, E 0.2 mcg/kg/min, dopamine 10 mcg/kg/min, ECMO (70 hours)	Ventricular fibrillation	13/32	Survived
10[17] (2004)	M/57	1,600	Atenolol 2,800 mg	IHD MDD	1	BP 80/50 mmHg HR 40 bpm	First degree AV block	+	-	NA	Activated charcoal, fluid, Ca, enoximone, ETT, E 10 mcg/kg/min, dopamine 30 mcg/kg/min	None	5/15	Survived
11[18] (2002)	F/19	6,000	None	None	5	BP 69/42 mmHg HR 56 bpm	Sinus bradycardia	-	NA	NA	Fluid, Ca, ETT, dopamine	Non-cardiogenic pulmonary edema	5/NA	Survived
12[18] (2002)	F/19	7,200	Paracetamol 6,500 mg	None	7	BP 70/40 mmHg HR 45 bpm	Third degree AV block	-	NA	-	Fluid, Ca, ETT, dopamine	Non-cardiogenic pulmonary edema	6/NA	Survived
13[19] (1996)	F/22	4,800	Alcohol	None	1	SBP 48 mmHg HR 45 bpm	Left bundle branch block pattern	+	-	+	Activated charcoal, fluid, Ca, glucagon, bicarbonate, atropine, naloxone, ETT, dopamine	Non-cardiogenic pulmonary edema, seizure	1.5/1.5	Died
14[19] (1996)	M/43	8,640	None	HT	5	SBP 50 mmHg HR 50 bpm	Junctional rhythm	+	NA	NA	Activated charcoal, fluid, Ca, glucagon, atropine, TPM, ETT, NA 5.3 mcg/min, dopamine 3.3 mcg/kg/min	Non-cardiogenic pulmonary edema	3/NA	Survived
15[20] (1994)	F/27	1,800	Ibuprofen 4,000 mg, paracetamol 5,000 mg	None	5	NA	NA	NA	NA	NA	Fluid, Ca, ETT	Non-cardiogenic pulmonary edema	3/NA	Survived
16[21] (1994)	F/65	NA	None	HT	NA	BP 83/63 mmHg HR 42 bpm	AV nodal rhythm, right bundle branch block	+	NA	NA	Gastric lavage, fluid, Ca, TPM, ETT, E	None	1/NA	Survived
17[22] (1994)	F/25	1,200-2,400	None	None	1	BP 120/70 mmHg HR 100 bpm	First degree AV block	-	-	-	Activated charcoal, fluid No Ca, no intubation, Dopamine	Delayed hypotension	None/2	Survived
18[23] (1993)	M/33	12,000	None	None	NA	SBP 70 mmHg HR 40 bpm	Third degree AV block	-	NA	NA	Activated charcoal, fluid, Ca, atropine, TPM, ETT, isoproterenol 20 mcg/kg/min, E 20 mcg/kg/min, dopamine 20 mcg/kg/min	Severe metabolic acidosis	1.5/1.5	Died

19[24] (1991)	M/33	4,160	None	None	1	BP 97/50 mmHg HR 61 bpm	First degree AV block	-	-	+	Activated charcoal, fluid, Ca, atropine, naloxone, TPM, ETT, E, dopamine 30 mcg/kg/min, dobutamine 20 mcg/kg/min	Severe metabolic acidosis, hypokalemia	2.5 hours/2.5 hours	Died
20[25] (1991)	F/38	4,800	None	HT Migraine headache	1	BP 58/30 mmHg HR 45 bpm	Sinus bradycardia	-	+	NA	Fluid, Ca, ETT, dopamine 20 mcg/kg/min	None	1/2	Survived
21[26] (1991)	M/48	480	Cimetidine 400 mg	HT	NA	Hypotension HR 38 bpm	First degree AV block, left anterior fascicular block	NA	NA	NA	Activated charcoal, fluid, Ca, TPM, RRT, hemoperfusion, ETT, dopamine	Severe metabolic acidosis	0.5/0.5	Died
22[27] (1990)	F/27	2,900	NA	NA	NA	No hypotension	AV dissociation	+	+	NA	NA	NA	NA/NA	Survived
23[28] (1990)	M/56	NA	NA	NA	NA	NA	Asystole	+	NA	NA	NA	NA	2.5/2.5	Died
24[29] (1990)	M/37	7,200	Alcohol	HT	1	BP 140/78 mmHg HR 70 bpm	Junctional rhythm; premature ventricular contractions	+	-	-	Activated charcoal, fluid, Ca No intubation	None	None/4	Survived
25[30] (1989)	M/22	16,000	None	Hyper-trophic subaortic stenosis, AF	1	SBP 65 mmHg HR 72 bpm	AV dissociation	+	NA	NA	Activated charcoal, fluid, Ca, NE 20 mcg/min, dopamine 32 mcg/kg/min, dobutamine 5 mcg/kg/min	None	NA/NA	Survived
26[30] (1989)	M/31	8,000	None	HT	1	SBP 40 mmHg HR 60 bpm	Second degree AV block with 2:1 conduction	-	NA	NA	Activated charcoal, fluid, Ca, atropine, glucagon, TPM, ETT, NE, E, dopamine, CPR	Tonic-clonic seizure	65 min/65 min	Died
27[31] (1988)	M/41	6,800	None	HT	2.5	SBP 60 mmHg HR 50 bpm	AV dissociation, trifasicular block	+	NA	+	Activated charcoal, fluid, Ca, TPM, NE 4 mcg/min, dopamine 20 mcg/kg/min	None	NA/NA	Survived
28[32] (1988)	M/23	7,200-9,600	None	None	9	SBP 40 mmHg HR 45 bpm	Junctional rhythm, AV dissociation	+	NA	NA	Fluid, Ca, atropine, TPM, isoproterenol, dopamine	None	NA/NA	Survived

29[33] (1988)		2,280		None	NA	Undetectable BP HR 55 bpm	AV dissociation	+	NA	-	Isoproterenol	Acute ischemic stroke	NA/NA	Survived
30[34] (1986)	F/16	8,000	None	None	5	SBP 45 mmHg HR 40 bpm	Third degree AV block	+	-	+	Gastric lavage, fluid, Ca, bicarbonate, TPM, ETT, isoproterenol 4 mcg/min, dopamine 10 mcg/kg/min, aminone 3.5 mcg/kg/min	None	1/NA	Survived
31[35] (1985)	M/67	600	NA	NA	NA	Hypotension	Third degree AV block	-	NA	NA	NA	NA	NA/NA	Survived
32[36] (1985)	F/21	NA	Atenolol	NA	1	SBP 70 mmHg HR 75 bpm	Sinus rhythm	+	-	NA	Activated charcoal, fluid, Ca, isoproterenol 5 mcg/min	None	None/2	Survived
33[37] (1984)	F/25	8,000	NA	NA	NA	Hypotension	Sinus rhythm	-	NA	NA	NA	NA	NA/NA	Survived
34[38] (1983)	F/22	2,400	None	MDD	3	SBP 60 mmHg HR 30 bpm	Idio-ventricular rhythm	+	-	+	Gastric lavage, fluid, Ca, ETT, isoproterenol, dopamine	None	NA/NA	Survived
35[39] (1983)	F/16	9,600	NA	NA	NA	Hypotension	Sinus rhythm	-	NA	NA	NA	NA	7 hours/7 hours	Died
36[40] (1982)	F/38	2,400	None	MDD	2.5	SBP 50 mmHg HR 45 bpm	AV dissociation	+	NA	NA	Gastric lavage, fluid, Ca, dopamine 30 mcg/kg/min, E 0.8 mcg/kg/min	None	NA/NA	Survived
37[41] (1982)	F/17	NA	None	None	1-2	Undetectable BP HR 30 bpm	Third degree AV block	+	NA	NA	Fluid, Ca, atropine, TPM, ETT, isoprenaline 270 mcg/min, dopamine 1 mg/min	Asystole	19 hours/19hours	Died
38[42] (1982)	F/39	1,200	None	None	NA	Undetectable BP HR 48 bpm	First degree AV block	+	NA	+	Fluid, Ca, glucagon, atropine, prenalterol, ETT, dopamine 2.5 mcg/kg/min, dobutamine 40 mcg/kg/min, isoprenaline 15 mcg/min	Haematemesis, pneumonia, cerebral anoxia	NA/NA	Survived
39[43] (1982)	F/20	8,000	NA	NA	NA	Hypotension	Sinoatrial arrest	+	NA	NA	NA	NA	NA/NA	Survived
40[44] (1981)	M/33	3,000	None	AF	3	SBP 60 mmHg HR 79 bpm	AV dissociation	NA	NA	NA	Fluid, Ca, no intubation	None	NA/NA	Survived
41[45] (1981)	F/68	6,400	Aspirin	MDD	7	Hypotension HR 63 bpm	Occasional idio-ventricular bradycardia	+	NA	NA	Activated charcoal, fluid, Ca, orciprenaline, TPM	None	NA/NA	Survived
42[25] (1981)	M/30	7,200	Medazepam 400 mg	MDD	2	SBP 50 mmHg	Third degree AV block, then asystole	+	NA	NA	Fluid, Ca, isoprenaline, TPM, ETT, dopamine	Asystole	NA/NA	Survived
43[46] (1981)	M/69	800	Alcohol	IHD, AF	NA	Hypotension	Third degree AV block	+	NA	NA	NA	None	NA/NA	Survived
44[46] (1981)	F/40	NA	NA	NA	NA	Hypotension	Sinus rhythm	-	NA	NA	NA	NA	NA/NA	Died
45[47] (1980)	M/31	3,200	Alcohol	None	3	BP 60/40 mmHg HR 57 bpm	AV dissociation	+	+	NA	Fluid, hypertonic sodium chloride, Ca, dexamethasone, no intubation	None	None/14	Survived
46[48] (1979)	M/18	2,000	None	None	2	BP 90/60 mmHg HR 65 bpm	AV dissociation	-	NA	NA	Atropine, TPM	None	None/1	Survived
47[49] (1979)	F/14	2,400	None	None	2	BP 70/50 mmHg HR 40 bpm	Third degree AV block	+	+	+	Gastric lavage, Ca, atropine, bicarbonate, no intubation	None	NA/NA	Survived
48[50] (1978)	F/19	3,200	None	Prolapsed mitral valve	5	BP 80/60 mmHg HR 55 bpm	Nodal bradycardia	+	NA	NA	Ca	None	NA/NA	Survived
49[51] (1977)	F/28	5,600	NA	NA	NA	Hypotension	AV dissociation	+	NA	NA	NA	NA	NA/NA	Survived

Table 1: A summary of all 50 cases (8-50) with verapamil intoxication reported from 1977 to 2018.

50 (our case, 2018)	F/37	3,600	Doxazosin 20 mg, chlorpheniramine 40 mg	HT	Within 1-24	Asystole	Junctional bradycardia	+	-	+	CPR (9min), fluid, Ca, bicarbonate, HDI, LET, TPM, RRT, ETT, NE 1 mcg/kg/min, dopamine 30 mcg/kg/min, adrenaline 1 mcg/kg/min	Cardiogenic shock	4/4	Died

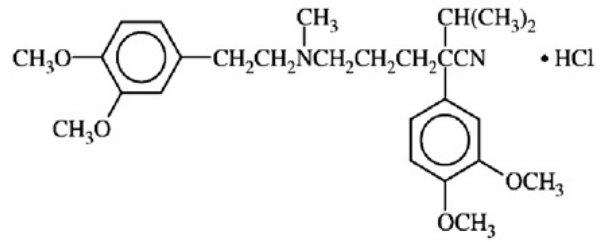

Figure 2: Structural formula of verapamil hydrochloride.

Conclusion

We report herein a fatal case of verapamil intoxication, and have a literature review in all reported cases of 50 patients, there are 11 (22.0%) patients died, including our case, regardless of amount of verapamil ingestion. Hence, verapamil intentional or accidental overdose, can be lethal that requires the prompt initiation of comprehensive resuscitation.

Funding

No.

Conflicts of Interest

None.

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