Research Article

การดูแลรักษาผู้ป่วยได้รับพิษจากการกินยาลดความดันโลหิตในกลุ่มยาปิดกั้นแคลเซียมเกินขนาดที่รายงานมายังศูนย์พิษวิทยารามาธิบดี

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บทคัดย่อ

การดูแลรักษาผู้ป่วยได้รับพิษจากการกินยาลดความดันโลหิตในกลุ่มยาปิดกั้นแคลเซียมเกินขนาดที่รายงานมายังศูนย์พิษวิทยารามาธิบดี

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การรักษาที่จำเพาะของการรักษาผู้ป่วยที่มีอาการแสดงที่รุนแรงเนื่องมาจากการได้รับพิษจากการใช้ยาลดความดันโลหิตในกลุ่มยาปิดกั้นแคลเซียมเกินขนาด ได้แก่ แคลเซียม ยาอินซูลินขนาดสูง และยากระตุ้นความดันโลหิตขนาดสูง วัตถุประสงค์งานวิจัยเพื่อที่บรรยายการดูแลรักษาและผลลัพธ์เนื่องจากการรับสารพิษจากใช้ยาลดความดันโลหิตในกลุ่มยาปิดกั้นแคลเซียมเกินขนาดในบริบทของประเทศไทย **วิธีดำเนินการวิจัย:** การศึกษานี้เป็นการศึกษาทบทวนย้อนหลังจากข้อมูลศูนย์พิษวิทยาโรงพยาบาลรามาธิบดี ของผู้ป่วยที่รับสารพิษจากใช้ยาลดความดันโลหิตในกลุ่มยาปิดกั้นแคลเซียมเกินขนาดตั้งแต่ปี พ.ศ. 2555 ถึง 2559 **ผลการวิจัย:** จากการรายงานพบว่าผู้ป่วย 145 รายที่ได้รับสารพิษจากการใช้ยาลดความดันโลหิตในกลุ่มยาปิดกั้นแคลเซียม สาเหตุส่วนใหญ่เนื่องมาจากเจตนารับประทานยาแอมโลดิปีน อาการแสดงที่ปรากฏบ่อยได้แก่ ภาวะความดันโลหิตต่ำและภาวะหัวใจเต้นเร็ว จากการศึกษาพบว่าผู้ป่วยที่มีผลลัพธ์รุนแรงจำนวน 30 ราย ได้รับการรักษาจำเพาะได้แก่ แคลเซียม (76.7%), ยากระตุ้นความดันโลหิตขนาดสูง (33.3%), ยาอินซูลินขนาดสูง (16.7%), กลูคากอน (10.0%), และไขมัน (6.7%) จากการศึกษานี้พบผู้เสียชีวิต 6 ราย 4 ราย เสียชีวิตเนื่องจากได้รับยากระตุ้นความดันโลหิตในขนาดที่ไม่เหมาะสม 1 ราย มีภาวะหัวใจหยุดเต้นเนื่องจากภาวะโพแทสเซียมในเลือดสูงอย่างรวดเร็วเนื่องจากการปรับลดยาอินซูลินขนาดสูง รายสุดท้ายเสียชีวิตเนื่องจากโรคปอดอักเสบ **สรุปผลการวิจัย:** โดยทั่วไปการรักษาจำเพาะ ได้แก่ การให้แคลเซียมทางหลอดเลือดดำ ยากระตุ้นความดันโลหิตขนาดสูงและยาอินซูลินขนาดสูง แต่อย่างไรก็ตามยังพบกรณีเสียชีวิตเนื่องจากการบริหารยากระตุ้นความดันโลหิตและยาอินซูลินขนาดสูงที่ไม่เหมาะสม

คำสำคัญ: การดูแลรักษา, ยาลดความดันโลหิตในกลุ่มยาปิดกั้นแคลเซียม, เกินขนาด

Management in Calcium Channel Blocker Overdose Patients Reported to Ramathibodi Poison Center

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Abstract

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Besides supportive care, specific managements of severe calcium channel blocker (CCB) overdose are varied, including calcium, high-dose insulin euglycemic therapy (HIE), and high-dose vasopressor. The objective of this study is to describe management and outcome of CCB poisoning in Thailand. **Methods.** This is a retrospective study of CCB poisoning cases consulted to Ramathibodi Poison Center, during 2012 to 2016. **Results.** One-hundred and forty-five CCB poisoning cases were retrieved. Most common scenario was intentional amlodipine ingestion. Common manifestations were hypotension and tachyarrhythmia. In 30 cases with severe poisoning, the prescribed specific treatment included, IV calcium (76.7%), high-dose vasopressor (33.3%), HIE (16.7%), glucagon (10.0%), and lipid emulsion (6.7%). There were 6 deaths. Four deaths resulted from inappropriate dose of vasopressor. One had cardiac arrest from rebound hyperkalemia during the decrease of HIE. One was recovered from poisoning, but later died from pneumonia. **Conclusion.** Common prescribed specific treatments were IV calcium, high-dose vasopressor, and HIE; however, fatal cases have been found, resulting from inappropriate administration of vasopressor and HIE.

Keywords: management, calcium channel blocker, overdose

Introduction

Calcium channel blockers (CCBs) are commonly prescribed antihypertensive medications due to their minimal side-effects. However, severe and fatal CCB poisonings have been reported (Hofer *et al*., 1993). Mechanism of CCB is blocking L-type calcium channels which have a key major role in contractility of vascular smooth muscle and myocardium (St-Onge *et al*., 2014). CCBs are categorized into two types as dihydropyridines (amlodipine, nicardipine, felodipine, and nifedipine) and nondihydropyridine (verapamil and diltiazem).

Dihydropyridines, which have high affinity to vessel smooth muscle, result in hypotension and reflex tachycardia while non-dihydropyridines, which have high affinity to cardiac muscle and pacemaker cells, are related to bradydysrhythmia and conduction block (Holstege *et al*., 1998; Tanen *et al*., 2000; Spiller *et al*., 1991). Moreover, presentation of severe CCBs overdose may be pulmonary edema, conduction block, metabolic acidosis, seizure, coma, cardiac arrest and death (Rizvi *et al*., 2012).

Besides supportive treatment, specific interventions for CCB poisoning treatments are including intravenous (IV) calcium, high-dose insulin euglycemic therapy (HIE), high-dose vasopressor, glucagon, and lipid emulsion. CCB poisoning is not common in Thailand, thus, physicians' experience management of CCB poisoning is limited. The objective of this study is to describe the incidence, clinical manifestations, treatment, and medical outcome of CCB poisoning in Thailand.

Materials and Methods

Study design and data collection

This is a retrospective study. The CCB poisoning cases consulted to Ramathibodi Poison Center from January 1st, 2012 to December 31st, 2016 were included. This study was approved by Committee on Human Rights Related to Research Involving Human Subjects Faculty of Medicine Ramathibodi Hospital, Mahidol University.

Ramathibodi Poison Center is the first poison control center in Thailand. It has served the entire Thai population of all regions for more than 22 years. Consultation calls are more than 20,000 calls per year. Follow-up calls are made to provide ongoing recommendations and determine medical outcomes. All data of poisoning are recorded in poison center database. For CCB poisoning cases, the poison center has a treatment protocol and would send to the attending physician by e-mail, or personal message application. The specific treatment including calcium, high-dose insulin euglycemic therapy (HIE), high-dose vasopressor, and glucagon.

The CCB poisoning cases were retrieved by senior poison center information scientists who had experienced in managing the poison center database. Demographic data, exposed product, dose, time duration from exposure to medical attention, intent of exposure, clinical effects, initial vital signs, treatment, initial severity, and medical outcome were included. Details of specific treatment included maximum rate of vasopressor and insulin, total dose of lipid emulsion, and intravenous calcium.

Definition

The severity of the case was determined using IPCS/INTOX Poison Severity Score (Persson *et al*., 1998). A patient was considered to received "high-dose vasopressor" when at least one of the following vasopressors' dose was prescribed; 1) more than or equal to 1.0 mcg/kg/min of norepinephrine, 2) more than or equal to 10 mcg/min of epinephrine, or 3) more than 50 mcg/kg/min of dopamine (Auchet *et al*., 2017; Bassi *et al*., 2013; Gleason and Fitzgerald, 2013). A patient was considered to received HIE when receiving insulin IV infusion rate more than or equal to 0.5 units/kg/hr after an insulin IV bolus (Levine *et al*., 2013).

Statistical analysis

All of the statistical analyses were performed with the SPSS for Windows Software Package, Version17 (SPSS Inc., Chicago, Ill., USA). The data were analyzed and presented by descriptive statistic and Pearson's chi-square test or Fisher's exact test**.** Clinical effects of calcium channel blockers overdose were compared between the group of patients exposed to co-ingested drugs and patients ingested CCBs alone by Pearson's chi-square test or Fisher's exact test.

Results and Discussion

Results

There were 145 CCB poisoning cases during the study period, There were 80 (55.1%) female and 65 (44.8%) male (Table 1). The median age was 46.5 years (interquartile range (IQR): 28.3 to 59.0 years). Most common

comorbidity was hypertension (17 cases, 11.7%). Most of the exposures were intentional (144 cases, 99.3%). Nearly all of them were oral ingestion (99.3%) except one patient got IV nicardipine injection for suicidal attempt. One hundred and thirty cases (89.7%) were overdose with dihydropyridine, the other 15 cases (10.3%) ingested non-dihydropyridine. The most common drug was amlodipine (115 cases, 79.3%). The median duration from exposure to initial medical assessment were 3 hours (IQR 1 to 8 hours). Ninety-one (62.8%) exposed to more than one substance. The common co-ingested drugs were ACE inhibitors (12 cases, 8.3%), beta-blockers (10 cases, 6.9%), and aspirin (9 cases, 6.2%). The median dose exposure of amlodipine was 100 mg (interquartile range (IQR): 35 to 200 mg) while the median dose exposure of verapamil and diltiazem were 1320 mg (interquartile range (IQR): 70 to 7200 mg) and 750 mg (interquartile range (IQR): 300 to 1200 mg) respectively (Table 2).

Common clinical effects were hypotension (40, 27.6%) and tachyarrhythmia (27, 18.6%), acute kidney injury (25, 17.2%), and bradyarrhythmia (22, 15.2%) (Table 3). The tachyarrhythmia were sinus tachycardia (25, 17.2%), atrial fibrillation (1, 0.7%), and ventricular tachycardia (1, 0.7%). The bradyarrhythmia were sinus bradycardia (16, 11.0%), sinus bradycardia with first degree AV block (1, 0.7%), junctional bradycardia (4, 2.8%), and third degree AV block (1, 0.7%). There were 20 cases (13.8%) developed respiratory failure. Patients exposed to co-ingested drugs developed acute kidney injury more than patients ingested CCBs alone (p=0.004). These data were appeared in Table 3.

The common treatments were IV fluid (104, 71.7%), vasopressors (59, 40.7%), gastric lavage (62, 42.8%), activated charcoal (54, 37.2%), oxygen supplementation (39, 26.9%), and IV calcium (30, 20.7%) (Table 4). The prescribed vasopressors were dopamine (32, 22.1%), norepinephrine (21, 14.5%), and epinephrine (6, 4.1%).

There were 6 deaths (4.1%), and 24 cases (16.6%) with severe outcome (Table 5). All deaths were amlodipine poisoning, who presented with initial severe symptoms. The median time from exposure to medical attention were 11.5 hours (IQR 6 to 25 hours) in death group, and 6 hours (IQR 1.25 to 10.5 hours) in severe group.

Among the 30 severe and fatal cases, specific treatments were IV calcium bolus (23, 76.7%), high-dose vasopressor (10, 33.3%), HIE (5 cases, 16.7%), glucagon (3, 10%), and lipid emulsion (2, 6.7%). One cases (3.3%) received calcium IV continuous infusion. The administered high-dose vasopressors were dopamine (4, 13.3%; median maximum dose = 69.9 mcg/kg/min, the highest maximum dose = 111.1 mcg/kg/min), norepinephrine (5, 16.7%; median maximum dose = 1.33 mcg/kg/min, the highest dose = 1.75 mcg/kg/min), and adrenaline (4, 13.3%; median maximum dose 28.3 = mcg/min, the highest maximum dose = 41.7mcg/min). In 5 cases with HIE, the median maximum insulin infusion rate 1 u/kg/h (range 0.5 to 1 u/kg/h). There was no difference in specific treatment between deaths and severe cases.

Regarding the six deaths, 2 cases received usual maximum dose of vasopressor without further titration. One was treated with HIE at dose rate 1 u/kg/h and usual dose of vasopressor without further titration of insulin and vasopressor. One got delayed increasing dose of vasopressor more than 12 hours. One had cardiac arrest from rebound hyperkalemia with during rapid tapering off HIE. One was recovered from CCB poisoning, but further died from pneumonia after 15 days of admission. Summary of fatal cases were in Table 6.

Table 1. Characteristics of calcium channel blockers (CCBs) overdose cases consulted to the Ramathibodi Poison Center.

Characteristics	Number of cases; n (%)
	145 Cases
Age (median, IQR)	46.5 (28.3, 59.0)
Sex	
Male	65 (44.8)
Female	80 (55.1)
Comorbidities	
Hypertension	17 (11.7)
Chronic kidney disease	2 (1.4)
Diabetes mellitus	2 (1.4)
Dyslipidemia	4 (2.8)
Types of CCB	
Dihydropyridines	130 (89.7)
Amlodipine	115 (79.3)
Manidipine	6 (4.1)
Nifedipine	6 (4.1)
Nicardipine	2 (1.4)
Felodipine	1 (0.7)
Nondihydropyridines	15 (10.3)
Verapamil	9 (6.2)
Diltiazem	6 (4.1)
Intent of exposure	
Intentional self-harm	144 (99.3)
Unintentional	1 (0.7)
Only CCBs	54 (37.2)
Co-ingestion	91 (62.8)
ACE inhibitors	12 (8.3)
Beta-blockers	10 (6.9)
Aspirin	9 (6.2)
Losartan	6 (4.1)
Hydralazine	4 (2.8)
Alpha-blockers	1 (0.7)
Others	49 (33.8)
Initial Severity of CCBs overdose	
No effect	32 (22.1)
Minor	68 (46.9)
Moderate	30 (20.7)
Severe	15 (10.3)
Known time duration after exposure CCBs	136 (93.8)
Unknown time duration after exposure CCBs	9 (6.2)
Time duration after expose CCBs (hours); median (IQR)	3 (1, 8)

CCBs: calcium channel blockers, IQR: Interquartile range, ACE inhibitors: Angiotensin converting enzyme

Table 2. Types of CCBs and dose exposure consulted to the Ramathibodi Poison Center.

Type of CCBs	Number of cases; n (%)	Dose exposure (mg) Median (IQR)
Unknown dose of CCBs	54 (37.2)	
Known dose of CCBs	91 (62.8)	
Dihydropyridine	83 (57.2)	
Amlodipine	75 (51.7)	100 (35, 200)
Manidipine	4 (2.8)	100 (35, 135)
Nifedipine	3 (2.1)	50 (20, 200)
Felodipine	1 (0.7)	5 (5, 5)
Nondihydropyridine	8 (5.5)	
Verapamil	6 (4.1)	1320 (70, 7200)
Diltiazem	2 (1.4)	750 (300, 1200)

CCBs: calcium channel blockers, mg: milligram, IQR: Interquartile range

Table 3. Clinical effects of calcium channel blockers overdose cases consulted to the Ramathibodi Poison Center.

Clinical effects	Number of cases; n (%)	CCB alone n=54	Co-ingested CCB n=91	p-value
Hypotension	40 (27.6)	11 (20.4)	29 (31.9)	0.134
Tachyarrhythmia	27 (18.6)	12 (22.2)	15 (16.5)	0.455
Sinus tachycardia	25 (17.2)	12 (22.2)	13 (14.3)	0.221
Atrial fibrillation	1 (0.7)	0 (0.0)	1 (1.1)	1.000
Ventricular tachycardia	1 (0.7)	0 (0.0)	1 (1.1)	1.000
Acute kidney injury	25 (17.2)	3 (5.6)	22 (24.2)	0.004[a]
Bradyarrhythmia	22 (15.2)	9 (16.7)	13 (14.3)	0.930
Sinus bradycardia	17 (11.7)	7 (13.0)	10 (11.0)	0.721
Junctional bradycardia	4 (2.8)	1 (1.9)	3 (3.3)	1.000
First degree AV block	1 (0.7)	0 (0.0)	1 (1.1)	1.000
Third degree AV block	1 (0.7)	1 (1.9)	0 (0.0)	0.372
Respiratory failure	20 (13.8)	3 (5.6)	17 (18.7)	0.270
Hypokalemia	21 (14.5)	8 (14.8)	13 (14.3)	0.930
Acidosis	13 (8.9)	2 (3.7)	11 (12.1)	0.072
Hypoglycemia	11 (7.6)	1 (1.9)	10 (11.0)	0.054
Pulmonary edema	10 (6.9)	2 (3.7)	8 (8.8)	0.567
Anuria	8 (5.5)	1 (1.9)	7 (7.7)	0.068
Cardiac arrest	6 (4.1)	0 (0.0)	6 (6.6)	0.084
Hyperglycemia	6 (4.1)	3 (5.6)	3 (3.3)	0.671
Hyperkalemia	3 (2.1)	0 (0.0)	3 (3.3)	0.294
Seizure	1 (0.7)	0 (0.0)	1 (1.1)	1.000

AV: Atrioventricular node, [a]: p-value <0.05

Table 4. Treatment of calcium channel blockers overdose (CCB) consulted to the Ramathibodi Poison Center.

Treatment	Number of cases; n (%)
Specific treatment	
Calcium	30 (20.7)
High-dose vasopressor	10 (6.9)
High-dose insulin euglycemic therapy (HIE)	5 (3.4)
Glucagon	3 (2.1)
Lipid emulsion	2 (1.4)
Supportive treatment	
Intravenous fluid	104 (71.7)
Vasopressors	49 (33.8)
Dopamine	32 (22.1)
Norepinephrine	21 (14.5)
Epinephrine	6 (4.1)
Gastric lavage	62 (42.8)
Activated charcoal	54 (37.2)
Oxygen supplementation	39 (26.9)
Potassium supplementation	20 (13.8)
Intubation and ventilator support	20 (13.8)
Intravenous glucose	14 (9.7)
Antibiotics	13 (8.9)
Proton pump inhibitors	12 (8.3)
Sodium bicarbonate	11 (7.6)
Insulin	10 (6.9)
Diuretics	9 (6.2)
Atropine	6 (4.1)
Benzodiazepines	4 (2.8)
Whole bowel irrigation	3 (2.1)
Hemodialysis	2 (1.4)
CVVH	1 (0.7)
Peritoneal dialysis	1 (0.7)
Muscle relaxant	1 (0.7)

CVVH: Continuous Veno-Venous Hemofiltration

Table 5. Characteristics of deaths and surviving cases associated with severe CCBs overdose consulted to the Ramathibodi Poison Center.

	Number of cases; n (%)		
Characteristics or treatment	**Death (6 cases)**	**Survive (24 cases)**	**Total (30 cases)**
Age; years (mean, SD)	66.8 (12.1)	50.8 (19.9)	54 (19.6)
Sex			
Male	2 (33.3)	8 (33.3)	10 (33.3)
Female	4 (66.7)	16 (66.7)	20 (66.7)
Comorbidities			
Hypertension	5 (83.3)	7 (29.2)	12 (40.0)
Chronic kidney disease	2 (33.3)	-	2 (6.7)
Time duration after exposure CCBs hours (median, IQR)	11.5 (6, 25)	6 (1.25, 10.5)	6 (1.5, 12)
CCBs related to severe CCBs overdose			
Amlodipine	6 (100.0)	17 (70.8)	23 (76.7)
Verapamil	-	3 (12.5)	3 (10.0)
Others	-	4 (16.7)	4 (13.3)
Initial severity			
Minor	-	1 (4.2)	1 (3.3)
Moderate	-	14 (58.3)	14 (46.7)
Severe	6 (100.0)	9 (37.5)	15 (50.0)
Treatment of severe CCBs overdose			
High-dose vasopressor	3 (50.0)	7 (29.2)	10 (33.3)
High-dose insulin euglycemic therapy (HIE)	2 (33.3)	3 (12.5)	5 (16.7)
Calcium	5 (83.3)	18 (75.0)	23 (76.7)
Glucagon	1 (16.7)	2 (8.3)	3 (10.0)
Lipid emulsion	1 (16.7)	1 (4.2)	2 (6.7)
Complication			
Pneumonia	1 (16.7)	1 (4.2)	2 (6.7)
GI bleeding	-	2 (8.3)	2 (6.7)

SD: standard deviation, CCBs: calcium channel blockers, IQR: Interquartile range, GI: Gastrointestinal, HIE: High-dose insulin euglycemic therapy

Table 6. Fatal calcium channel blocker overdose cases consulted to Ramathibodi Poison Center during 2012 to 2016

Case no	Age/ sx	Time from exposure to HCF (hours)	Exposed drug(s)	Total dose of IV calcium bolus (g)	Highest epinephrine dose (mcg/min)	Highest dopamine dose (mcg/kg/min)	Highest norepinephrine dose (mcg/kg/min)	Highest insulin rate (u/kg/h)	Lipid emulsion	Glucagon	Remarks
1	79 y female with HT, CKD	6	Unknown dose of amlodipine, enalapril, and hydralazine	-	-	20	-	-	-	-	
2	78 y male with HT	24	Unknown dose of amlodipine, atenolol, and hydrochlorothiazide	2	-	20	-	-	√	-	
3	59y female	11	Unknown dose of amlodipine, and hydralazine	20	23.33	5	1.07	-	-	-	Delay increase vasopressor
4	52y female with HT, hyperlipidemia	12	Amlodipine (450mg), and enalapril (400mg)	9	-	0.43	0.25	1.0	-	-	No titration of vasopressor or HIE
5	57y male with HT	28	Unknown dose of amlodipine	7	-	33.33	1.333	1.0	-	√	Hyperkalemia 8.1 mEq/L and arrhythmia while decreasing HIE
6	76y female with HT, CKD	6	Amlodipine (350mg)	3	16.67	20	0.5334	-	-	-	Death from hospital acquired pneumonia after 15 days of admission

All presented with initial severe symptoms. All were intubated and admitted to ICU.

mcg/min: microgram/minute, mcg/kg/min: : microgram/kilogram/minute, mg: milligram, ml: milliliter

√: The treatment was administered, -: The treatment was not administered

Discussion

This study describes CCB poisoning cases consulted to a poison center. Majority of the cases were intentional amlodipine ingestion. In cases with severe and fatal outcome, the common specific interventions are IV calcium, high-dose vasopressors, and HIE.

Hypotension was found only 27.6% as clinical effect as a result of intravenous fluid was firstly administered for both patients with hypotension and normotension. Furthermore, CCB's decontamination by gastric lavage and activated charcoal were firstly demonstrated as well.

The boluses of IV 10% calcium gluconate were used for 23 cases with severe and fatal outcome whereas only one got continuous infusion of IV calcium gluconate. The common bolus doses were 10% calcium glucose as more than or equal to 30 ml. Intravenous calcium is preferable agent as antidote for CCBs-induced hypotension to overcome blockage of L-type calcium channels, allowing calcium influx (Engebretsen *et al*., 2011). Calcium infusion can increase blood pressure by increased stroke volume, heart rate, and peripheral vascular resistance (Ellison *et al*., 2011; Hung and Olson, 2007). According to Hoffman's literature (Hoffman *et al*., 2015), the positive effects of calcium are short duration; therefore, many bolus doses at least 0.6 ml/kg and/or continuous infusion of calcium and added other medical treatments should be administered in the severe cases, corresponding with Horowitz's study (Horowitz and Rhee, 1989) and Hung's study (Hung and Olson, 2007). In the case of efficacy of continuous infusion,

the evidence is limited in few case reports (Hung and Olson, 2007; Hariman *et al*., 1979; Zhou *et al*., 2013; Luscher *et al*., 1994; Lam *et al*., 2001). The bolus doses of 10% calcium gluconate are recommended as more than or equal to 30 ml whereas information of recommended dose of continuous 10% calcium gluconate infusion is still limited.

High-dose vasopressors were administered for three fatal and seven severe cases. Of six deaths, four deaths resulted from inadequate titration and delayed increasing of vasopressors due to inexperience in taking care of severe CCB poisoning case. There was no report of limb ischemia or gangrene in our study. In Levine's study (Levine *et al*., 2013), 33 patients with verapamil and diltiazem overdose survived as a result of receiving adequate vasopressors; however, five patients suffered from ischemic complication such as ischemic bowel. Therefore, physicians should be trained for accurate and appropriate titration of vasopressor as well as should be encouraged to use high-dose vasopressors for severe cases. However, ischemic complication should be concerned during further titration of vasopressors (Levine *et al*., 2013). In terms of the recommended dose for treatment, it is difficult to predict for each patient. However, maximum dose of vasopressors in practice were reported in Levine's study (Levine *et al*., 2013) as the following; 100 mcg/min of norepinephrine, 100 mcg/kg per min of dopamine and 150 mcg/min of epinephrine. The appropriate dose of vasopressor should be determined based on patients' response and frequently adjusted.

HIE was simultaneously used with other medical treatments including calcium and vasopressors. Only five patients with severe and fatal outcome got HIE. Of two deaths, one received HIE while usual dose of vasopressor without further titration of insulin and vasopressors. Another death resulted from rebound hyperkalemia during rapid tapering off HIE. Positive mechanism of HIE is the increase of insulin level, resulting in enhancement of myocardial glucose uptake and inotropic function (Engebretsen *et al*., 2011; Kerns, 2007; Kline *et al*., 1995). HIE causes vascular dilation, which also increases cardiac output (Engebretsen *et al*., 2011). In cases with dihydropyridine CCB poisoning that also have distributive shock, vasopressors should be co-administered to maintain adequate vascular tone. Rana *et al*. (Rana *et al*., 2016) reported that HIE improved hemodynamic and reduced mortality from CCB overdose. High-dose insulin therapy has significant effects to glucose and potassium homeostasis; therefore, close monitoring of glucose and potassium level should be done (Page *et al*., 2017). In Thailand, HIE were not administered for other indication except CCB overdose; therefore, many physicians may be not familiar with HIE administration. Importantly, close monitoring of serum potassium level during insulin titration could reduce mortality.

Lipid emulsion or IV 20% intralipid was used for patients with severe and fatal outcome. In this study, one severe case simultaneously received 20% intralipid with vasopressors, calcium and insulin. Another one died due to inadequate dose of calcium and vasopressors although he received lipid emulsion. Intravenous lipid emulsion (ILE) is mostly used to trap lipophilic CCBs in the plasma (lipid sink phenomenon) (Young *et al*., 2009); however, Cole *et al*. reported lipid emulsion may increase risk of mortality due to increased gastric absorption and retarded redistribution of drug, resulting in elevated serum drug's concentration (Perichon *et al*., 2013). Furthermore, JoviĆ-StošiĆ et al. showed that lipid emulsion may be ineffective for dihydropyridines toxicity (JoviĆ-StošiĆ *et al*., 2016). According to Rietjen et al. (Rietjens *et al*., 2016), lipid emulsion should be recommended after physicians fully managed with conventional and specific treatment such as HIE, and high-dose vasopressors. Therefore, adequate doses of calcium, vasopressors, and HIE are still essential treatment, while lipid emulsion can be considered in refractory cases.

In this study, only three severe and fatal cases were treated with glucagon in 2013. One death resulted from rebound hyperkalemia during rapid tapering off HIE. Glucagon increases intracellular cyclic adenosine

monophosphate (cAMP), leading to influx of calcium ion and stimulation of cardiac and smooth muscle contraction (Shah *et al*., 2012); however, glucagon effect has short duration, hardly longer than 15 minutes (Kerns, 2007). In clinical practice, glucagon might not be useful for treatment of CCB poisoning (St-Onge *et al*., 2014; Kerns, 2007). Due to lack of efficacy, glucagon was removed from Thai National Antidote Project after 2015.

Levosimendan, a calcium sensitizer, has been studied for treatment of severe CCBs overdose. The clinical experiences with levosimendan in CCB overdose are still inconsistent (Graudins and Wong, 2010; Osthoff *et al*., 2010; Graudins *et al*., 2008). Levosimendan is not available in Thailand. Methylene blue, with guanylate cyclase inhibition effect, is another studied intervention in CCBs overdose (Jang *et al*., 2015; Jang *et al*., 2011). Currently in Thailand, methylene blue is only indicated for treatment of methemoglobinemia.

Limitation

Population of this study is originated from a single poison center database, which is voluntarily reported data. With the nature of retrospective study and voluntary reported data, this study may have problems with missing, underreporting, and/or incomplete data. Finally, the population was limited by consulted cases from one country, other countries may have different type of CCB exposures, treatment experiences, and outcome.

Conclusions

In Thailand, most CCBs overdose cases resulted from amlodipine. In severe cases, the common specific medical interventions were IV calcium, high-dose vasopressors and HIE. Provision of knowledge in terms of appropriate titration of vasopressors and close monitoring of both clinical effects and laboratory investigations could reduce risk of morbidity and mortality.

Conflicts of Interest

The authors declare no conflict of interests. The authors alone are responsible for the content and writing of this article.

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