ORIGINAL ARTICLE

Pattern and management of antihypertensive drug toxicity among admitted patients to Alexandria poison center, Egypt

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Abstract

Background: Despite different antidotes, antihypertensive toxicity, especially beta-blockers (BB) and calcium channel blockers (CCB), have a significant morbidity and mortality. This study aimed to determine the prevalence and characteristics of antihypertensive toxicity among the admitted patients to Alexandria Poison Center (APC).
Method: A-cross-sectional study was carried out on all patients with antihypertensive toxicity, admitted to APC throughout year 2022. The management plan with adding methylene blue (MB) as a single bolus dose of 1mg/kg over 10 min to shocked cases was assessed.
Results: This work included 105 patients; with a mean age of (23.3 ± 13.3 years), (22.9%) were males and (77.1%) were females. The majority ingested BB and CCB. ECG showed bradycardia (8.6%), prolonged QTC (11.4%), prolonged PR interval (9.5%) and wide QRS complex (1.9%). Of all patients, (8.6%) received atropine, (4.8%) received vasopressors, (7.6%) received intravenous (IV) calcium and (4.8%) received high insulin glucose. In the current work, two cases presented with shock (1.9%) received IV MB early and survived. Refractory shock was the cause of death in (1.9%) of the cases who died before starting MB. The mean length of hospital stay was 34.06 ± 21.42 hours. Ingestion of antihypertensive agents from different classes and prolonged PR interval were the main predictors of the length of hospital stay where P = 0.012, 0.021 at 95% CI respectively.
Conclusion: Beta-blockers were the commonest ingested antihypertensive agent. Simultaneous ingestion of antihypertensive agents from different classes and prolonged PR interval have a significant prediction of the hospital stay length.

Key words: Antihypertensive toxicity, BB, CCB, Methylene blue

How to cite this article: Ghanem MAH, Abdelaziz MH, Mohamed Megahed M, Ghoneim EE-S, Ghitani SA. Pattern and management of antihypertensive drug toxicity among admitted patients to Alexandria poison center, Egypt. *Asia Pac J Med Toxicol* 2024; 13(3): 104- 111.

INTRODUCTION

Nowadays, several drugs are used for treating hypertension as beta-blockers (BB), calcium channel blockers (CCB), diuretics, angiotensin converting enzyme (ACE) inhibitors, selective angiotensin II receptor blockers (ARBs) and vasodilators. Also, there are new mixtures of multiple antihypertensive drugs as the combination between CCBs and diuretics which are commonly prescribed for unresponsive patients to decrease the incidence of complications (1).

The presentation and clinical spectrum of antihypertensive overdosage range broadly from nonspecific complaints to hemodynamic instability with rapid progression to circulatory collapse and shock (2). These necessitate the admission of all patients with antihypertensive overdosage, close monitoring, and modulating the management according to the presentation. So, therapeutic measures would vary from fluids and electrolyte correction to vasopressors and antidotes as glucagon, hyperinsulinemia-euglycemia and intravenous calcium (3).

Despite these multiple treatment options, management of BB and CCB overdose in Alexandria Poison Center (APC) presents clinical challenges in stabilization, support, and treatment of multiple cardiovascular and metabolic derangements (4). In addition, absence of a specific guideline if the patients are refractory to all mentioned antidotes endangers patient's life and necessitates a need for additional treatment modalities.

The current work was aimed to determine the prevalence and characteristics of antihypertensive drug toxicity among the admitted patients to APC, to establish guiding indicators for dealing with BB and CCB toxic patients in APC.

METHODS

This study was carried out on all patients with antihypertensive toxicity, admitted to APC throughout one year from the first of January to thirty-one of December 2022. Patients with hypersensitivity to MB, severe renal insufficiency and glucose 6 phosphate dehydrogenase deficient patients were excluded from MB administration.

Informed consent:

Informed consent was obtained from all participants or

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their legal guardians after clear detailed information. Confidentiality of all data was considered. The ethical approval before starting the study was obtained from the ethical committee of Alexandria University (Serial NO: 0106944, IRB NO: 00012098, FWA NO: 00018699).

All patients were subjected to the following:

- History taking: personal history, medical history for previous diseases, toxicological history of the type, amount of antihypertensive agent and the co-ingestatnces, circumstances of poisoning and the time before seeking medical advice.
- Complete physical examination, and assessment of level of consciousness according to the Glasgow coma scale (GCS) (5).
- Complete laboratory investigations including cardiac enzymes (CKMB and troponin).
- Electrocardiogram (ECG).
- Assessment of the severity of poisoning using the Poisoning Severity Score (PSS) (6).
- The management plan with adding methylene blue to shocked cases and the outcome were assessed.

Statistical analysis:

Statistical analysis was done using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percentages. Quantitative data were described using range, mean and standard deviation and median. The significance of the results was judged at the 5% level. Chi-square test was used for categorical variables to compare between different groups and Fisher's Exact or Monte Carlo correction when more than 20% of the cells have count less than 5. Kruskal-Wallis test to compare between abnormally distributed quantitative variables. Regression analysis was done to detect the most independent affecting factor for length of hospital stay. Significance of the obtained results was judged at the 5% level.

RESULTS

This work included 105 patients; (22.9%) were males and (77.1%) were females, and the highest admission percentages (18.1%) and (14.3%) occurred during June and March, respectively.

1. Age:

About (66.7%) of the patients were in the age group (18-65 years), followed by the age group of >1-12 years (16.2%), then the age group of 13-17 years (15.2%). The mean age was (23.3 ± 13.3 years).

2. Past medical history

Cardiovascular disorders, psychiatric disorders, and diabetes mellitus were among 20%, 6.7% and 1.9% of the studied patients respectively.

3. Circumstances of poisoning

Most of the patients (83.8%) ingested the drugs to commit suicide. Only (16.21%) ingested the drugs accidentally. A significant relation was detected between the age and the circumstances of poisoning and the sex and the circumstances of poisoning where $^{MC}p < 0.001$.

4. The ingested antihypertensive:

The majority (74.3%) ingested single antihypertensive drug while (25.7%) ingested mixed antihypertensive drugs (Table 1).

5. Presence of co-ingestion:

Only 26 cases (24.8%) had co-ingestion of other drugs. The commonest were CNS drugs and analgesics antipyretics among 12.4% and 11.4% of the patients, respectively.

6. Time passed before seeking medical advice:

Fifty-eight patients (55.2%) presented within 2-6 hours after ingestion and (22.9%) presented within less than 2 hours of ingestion. The mean delay of seeking toxicological advice is 6.21 ± 8.99 hours.

7. Clinical assessment:

- Eighty-one patients (77.1%) were normotensive, only (16.2%) were hypotensive (BP<90/60). The mean systolic BP and diastolic BP were 108.86 ± 22.78 and 68.70 ± 16.0 respectively.
- The Glasgow coma scale (GCS) score was mild among (96.2%) and moderate in only (3.8%).
- Only nine patients (8.6%) were presented with bradycardia. Moreover, (11.4%) had prolonged QTC interval. The PR interval and QRS complex were prolonged among (9.5%) and (1.9%) of the patients, respectively.
- The PSS showed minor and moderate grades among (22.9%) and (8.6%). Severe and fatal poisoning among 1% and 1.9%, respectively. A significant relation between the class of the ingested drug and the PSS where $^{MC}p = 0.020$.
- Only (5.7%) of the patients were oliguric.

8. Laboratory investigations:

- Metabolic disturbance was detected in the form of

Table 1. Distribution of the studied cases according to the type of ingested antihypertensive (n=105)

Class of antihypertensive agent	No. (n=105)	%
Single class ingestion		
ACE inhibitor	8	7.6
ARBs	1	1.0
Diuretics	3	2.9
Vasodilators (NG)	4	3.8
Sympatholytic drugs		
• BB	46	43.8
• CCB	16	15.2
Total	78	74.3
Multiple classes ingestion		
At least two classes of ACEI, ARBs, Diuretics and VD	4	3.8
BB + others	20	19.0
BB + diuretic	16	15.2
BB +ACE inhibitor	4	3.8
CCB + others	2	1.9
CCB + ARBs	1	1.0
CCB+ diuretics	1	1.0
BB+CCB	1	1.0
Total	27	25.7

Table 2. Distribution of the studied cases according to their laboratory results

	Number (n=105)	%
Laboratory results		
Normal	86	81.9
Abnormal	19	18.1
Cardiac enzymes		
Normal	99	94.3
High	6	5.78
Troponin	Min.- Max 0.0-8.77 Mean ± SD 0.10 ± 0.86 Median 0.0	
CKMP	Min.- Max 0.0-22.0 Mean ± SD 1.20 ± 2.36 Median 0.60	
Potassium (mmol/L)		
Low (<3mmol/K)	5	4.8
Normal (3.5-5.2 mmol/L)	98	93.3
High (>5.5 mmol/L)	2	1.9
K+	Min. – Max Mean ± SD Median	2.90– 5.70 4.13 ± 0.51 4.0
Sodium (mmol/L)		
Low (<135 mmol/L)	5	4.8
Normal (135-145 mmol/L)	100	95.2
Na+	Min. – Max Mean ± SD Median	131.0– 145.0 139.08 ± 2.73 139.0
Liver function tests		
Normal	101	96.2
High (> normal range)	4	3.8
ALT (normal: 7-56 U/L)	Min. – Max Mean ± SD Median	14.0– 275.0 30.06 ± 26.55 25.0
AST (normal:8-33 U/L)	Min. – Max Mean ± SD Median	13.0– 257.0 27.23 ± 24.60 23.0
Creatinine(mg/dl)		
Low (female < 0.6 mg/dl, male <0.7 mg/dl)	5	4.8
Normal (female 0.6-1.1, male 0.7-1.3 mg/dl)	97	92.4
High (female >1.1, male >1.3 mg/dl)	3	2.9
Creatinine	Min. – Max Mean ± SD Median	0.20– 3.2 0.84 ± 0.45 0.70
Total	105	100.0

metabolic acidosis (3.8%) and compensated metabolic acidosis in (27.6%). Meanwhile respiratory disturbance in the form of respiratory alkalosis in 4.8% and respiratory acidosis in 2.9% of the patients.

- Only (6.7%) were hyperglycemic and (2.9%) were hypoglycemic.
- The commonest laboratory disturbance was the elevated cardiac enzymes, followed by electrolytes disturbance and elevated liver enzymes (Table 2).
- Also, (35.2%) had abnormal elevated Neutrophil to Lymphocyte ratio (NLR).

9. Clinical intervention implemented in APC:

Activated charcoal was administered to (42.9%) and (6.7%) of the patients received both gastric lavage and activated charcoal.

All patients received IV fluids, (8.6%) received atropine and (4.8%) received vasopressors, (7.6%) received IV calcium and (4.8%) received high insulin glucose. An equal percentage (1.9%) received glucagon and IV methylene blue.

10. Intensive care unit (ICU) admission:

Only (5.7%) of the patients required ICU admission. A significant relation was found between the type of the ingested drug and the need for ICU admission where ^{MC}p <0.017.

11. Length of hospital stay and outcome:

The highest percentage (67.6%) stayed in the hospital up to 2 days, (30.5%) stayed 2-4 days. The length of hospital stay was > 4 days among (1.9%) of the participants.

In the current work, only (1.9%) died. A significant relation was found between QRS complex duration and the outcome where FE p <0.038 (Table 3).

Multivariate linear regression was done and showed that simultaneous ingestion of antihypertensive agents from different classes (β= -0.198, p= 0.012) and prolonged PR interval (β= 0.279, p=0.021) have a significant prediction of the hospital stay length (Table 4).

DISCUSSION

In APC, antihypertensive drug toxicity accounts for 1.7% to 3.4% in a five-year duration from 2017-2021 (7) Throughout 2022, APC received 105 patients with antihypertensive poisoning, representing about 1.5% of all admitted patients (7020) from the first of January 2022 to thirty-one of December 2022. This percentages are like the national report released by Ain shams poison center (8) that was 2.66 % in 2011 (1.4% with betablockers, 0.27 % with CCBs and 0.2% with diuretics). It is also similar to Hurtado D et al (2024), who reported the rate of toxicity by antihypertensive drugs as 2.2% in Colombia (9).

In the current work, about two thirds (66.7%) of the patients were in the age group (18 -65 years) and 31.4% were children or adolescents (1-17 years). Female to male ratio was more than 3:1 with a significant difference between both regarding circumstances of poisoning where 86.4% and 13.6% represented suicidal ingestion in females and males, respectively. A similar result was mentioned by Eizadi-Mood et al (2023) (10) and Cai et al (2021) (11) who linked the elevated suicide rates with the heightened levels of discrimination against women.

On the other hand, accidental ingestion was the commonest (94.1%) among children less than 12 years, all of them had a PSS (0 or 1). It is in accordance with Hetterich N et al (2014) (12) who reported no severe nor fatal PSS among children accidentally ingested antihypertensive agents. This could be explained by ingestion of a single drug

Table 3. Relation between ECG findings and the outcome

ECG findings	Outcome				χ^2	^{FE}p
	Improved (n = 103)		Death (n = 2)			
	No.	%	No.	%		
HR						
Bradycardia	8	7.8%	1	50.0%	4.145	$^{MC}p= 0.282$
Normo-sinus	88	85.4%	1	50.0%		
Tachycardia	7	6.8%	0	0.0%		
QTC						
Normal (350-450 ms)	92	89.3%	1	50.0%	2.997	0.083
prolonged (>450 ms in males & >470 ms in females)	11	10.7%	1	50.0%		
PR interval						
Normal (120-200 ms)	94	91.3%	1	50.0%	3.876	0.182
Prolonged >200 ms	9	8.7%	1	50.0%		
QRS com plex						
Normal (80-100 ms)	102	99.0%	1	50.0%	25.240*	0.038*
Abnormal >120 ms	1	1.0%	1	50.0%		

χ^2: Chi square test
FE: Fisher Exact
MC: Monte Carlo
*: Statistically significant at $p \leq 0.05$

Table 4. Multivariate linear regression analysis for factors affecting the length of hospital stay

	B	Beta	t	p	95% CI	
					LL	UL
Class of antihypertensive agent (Multiple classes ingestion)	-0.222	-0.198	-2.572*	0.012*	-0.394	-0.050
BP at admission	-0.140	-0.074	-0.728	0.469	-0.524	0.243
HR on admission	-0.006	-0.137	-1.563	0.122	-0.013	0.002
QTC (msec)	1.558	0.069	0.785	0.434	-2.385	5.502
PR	0.238	0.279	2.342*	0.021*	0.036	0.440
Severity PSS	0.139	0.132	0.946	0.347	-0.153	0.432
U.O.P	0.000	-0.108	-0.975	0.332	-0.001	0.000
ABG Interpretation (abnormal)	0.105	0.143	1.606	0.112	-0.025	0.235
HCO_3	-0.017	-0.050	-0.554	0.581	-0.078	0.044
Troponin	0.076	0.073	0.303	0.763	-0.424	0.576
CKMP	-0.107	-0.284	-1.414	0.161	-0.258	0.044
ALT	0.001	0.016	0.072	0.943	-0.015	0.016
AST	0.016	0.433	1.513	0.134	-0.005	0.036
Neutrophil to lymphocyte ratio (NLR)	-0.001	-0.002	-0.023	0.982	-0.058	0.057
Hospital (ICU)	-0.217	-0.057	-0.363	0.717	-1.405	0.971
R^2 =0.562 , adjusted R^2 =0.471 , F =6.135* p <0.001*						

F, p: f and p values for the model
R^2: Coefficient of determination
B: Unstandardized Coefficients
Beta: Standardized Coefficients
t: t-test of significance
CI: Confidence interval
LL: Lower limit
UL: Upper Limit
*: Statistically significant at $p \leq 0.05$

or small dose for exploration. In addition, most classes of antihypertensive agents such as ACI, ARBs, and diuretics are not expected to produce significant toxicity (13).

In the current work, (74.3%) ingested single antihypertensive drug class; beta-blocker (BB) (43.8%), followed by calcium channel blocker (CCB) (15.2 %). BB and CCB toxicity have the potential for significant systemic toxicity and high rates of mortality. A significant relation was detected between types of antihypertensive agent and PSS.

Both BB and CCB affect calcium influx into myocardial muscles. BBs achieves that through competitive antagonist effect on beta-1 receptors, decreasing cyclic AMP production that affects the opening of L-type calcium channels and reducing the calcium entry into cardiac cells. Regarding CCB, it makes a direct inhibition of voltage-gated L-type calcium channels in myocardium and peripheral vasculature. It ends with negative chronotropic, dromotropic and inotropic effect with hypodynamic state and tissue hypoperfusion (14).

We found the mean delay of seeking toxicological advice is 6.21 ± 8.99. This may be related to the time of releasing the preparation (6–8 hours) and the starts of the symptoms (15). The high prevalence of suicidal ingestion should be considered as a factor in delay to seek medical service.

Only 16.2% presented with hypotension and 6.7% with hypertension. Hypertension may be explained by stress that stimulates the nervous system to produce large amounts of vasoconstricting hormones that increase blood pressure (16). It may be also attributed to the underlying cardiovascular diseases which was reported by 20% of the studied patients.

Regarding heart rate on admission, (8.6%) and (6.7%) of the patients presented with bradycardia and tachycardia, respectively. Tachycardia may occur as a reflex from hypotension due to antihypertensive poisoning or in dihydropyridine toxicity due to the initial vasodilation (17). Any BB or CCB may cause bradycardia and various heart blocks. Prolonged PR interval was detected in (9.5%) in our study. One case presented with complete heart block, two patients had 2nd degree heart block (Mobitz type) 1, one case (Mobitz 2). Prolonged PR interval is an early sign of BB or CCB toxicity that can be evident even in the absence of bradycardia. Love JN et al (2002) also reported first-degree heart block as the most common ECG change in BB poisoning (18). Furthermore, multivariate linear regression analysis showed the value of prolonged PR interval in predicting the length of hospital stay in the current work.

In the current work, prolonged QTc and wide QRS complex were detected among 11.4% and 1.9% of the participants, respectively. Various BB may have a membrane stabilizing activity causing Na or K channel blockade effect and prolongation in QRS and QTc interval. Lodhi FAK et al (2020) (19) reported wide QRS complex in CCB poisoning and Khalid MM et al (2024) (20), reported that membrane stabilizing activity potentiates toxicity in overdose.

Regarding the level of consciousness, assessment using GCS revealed only 3.8% of the patients with moderate affection of the level of consciousness. Mental status changes are more commonly seen with BB ingestion, especially lipophilic agents. On the other hand, the occurrence of altered mental status in CCB toxicity is usually linked with hypotension. In addition, coingestants would explain the scores of GCS as 11.4% and 7.6%, in the current work, co-ingested CNS drugs and antidiabetic agents. Lashari BH (2018) (21) reported severe GCS in a case ingested a mix of both BB and CCB.

Metabolic acidosis was detected in nearly a third of the cases, hyperglycemia, and hypoglycemia among 6.7% and 2.9% of the patients, respectively. Hypoglycemia may be observed with BB toxicity secondary to inhibition of glycogenolysis and gluconeogenesis (20). On the other hand, hyperglycemia is frequently noted with CCB due to blockade of the calcium channels in the pancreas. In addition, the RBG disturbance may be explained by antidiabetic co-ingestants or diabetic patients (22).

Regarding the metabolic acidosis, both BB and CCB manifested in a similar fashion of hypotension and bradycardia. The poor cardiac perfusion may be manifested as acidosis. DeWitt CR et al (2004) (23) and Chakraborty RK et al (2024) (24), explained the higher acidosis risk in CCB because of complex metabolic derangements of glucose catabolism and its interference with the Ca-stimulated mitochondrial action ending with increase in lactate production.

The commonest laboratory disturbance was the elevated cardiac enzymes in (5.7%) of the patients. Serial measurements of cardiac enzymes showed gradual improvement in all affected patients except one who died. This could be explained by bradyarrythmias or heart block (25) Manini AF et al (2016) (26) concluded that initial cardiac troponin among acutely toxic patients had excellent prediction of the mortality.

On the other hand, hyperkalemia occurred in two patients (1.9%) - both ingested only CCB. Despite being understood in BB toxicity due to the lower aldosterone levels and suppression of the catecholamine-induced renin release plus the decreased cellular uptake of potassium by the cells, CCB ability to induce hyperkalemia is controversial (27). It is not a direct action of CCB, instead it occurs with hyperglycemia due to glucose related K shift or with severe metabolic acidosis (28).

In addition, abnormally elevated liver enzymes and high creatinine level were detected among (3.8%) and (2.9%) respectively. Varghese et al (2020) (29). denoted a probable amlodipine-induced liver injury. Choi et al (2022) (30) also reported that (ARBs) can induce liver damage with elevated liver enzymes. Another explanation mentioned by Sakboonyarat et al (2023) (31) who stated that raised BP was positively correlated with elevated AST and ALT in both males and females. As regard the patients with high creatinine level, Schmidt et al (2017) (32) mentioned that creatinine level increased by 30% on use of some of the antihypertensive drugs especially renin-angiotensin system blockade.

In the current work (35.2%) of the studied cases had an abnormally high NLR. This is in accordance with Price D et al (2014) (33) who also reported an elevated neutrophilic count in a female after ingestion of toxic dose of CCB.

NLR is a well-known indicator of systemic inflammation,

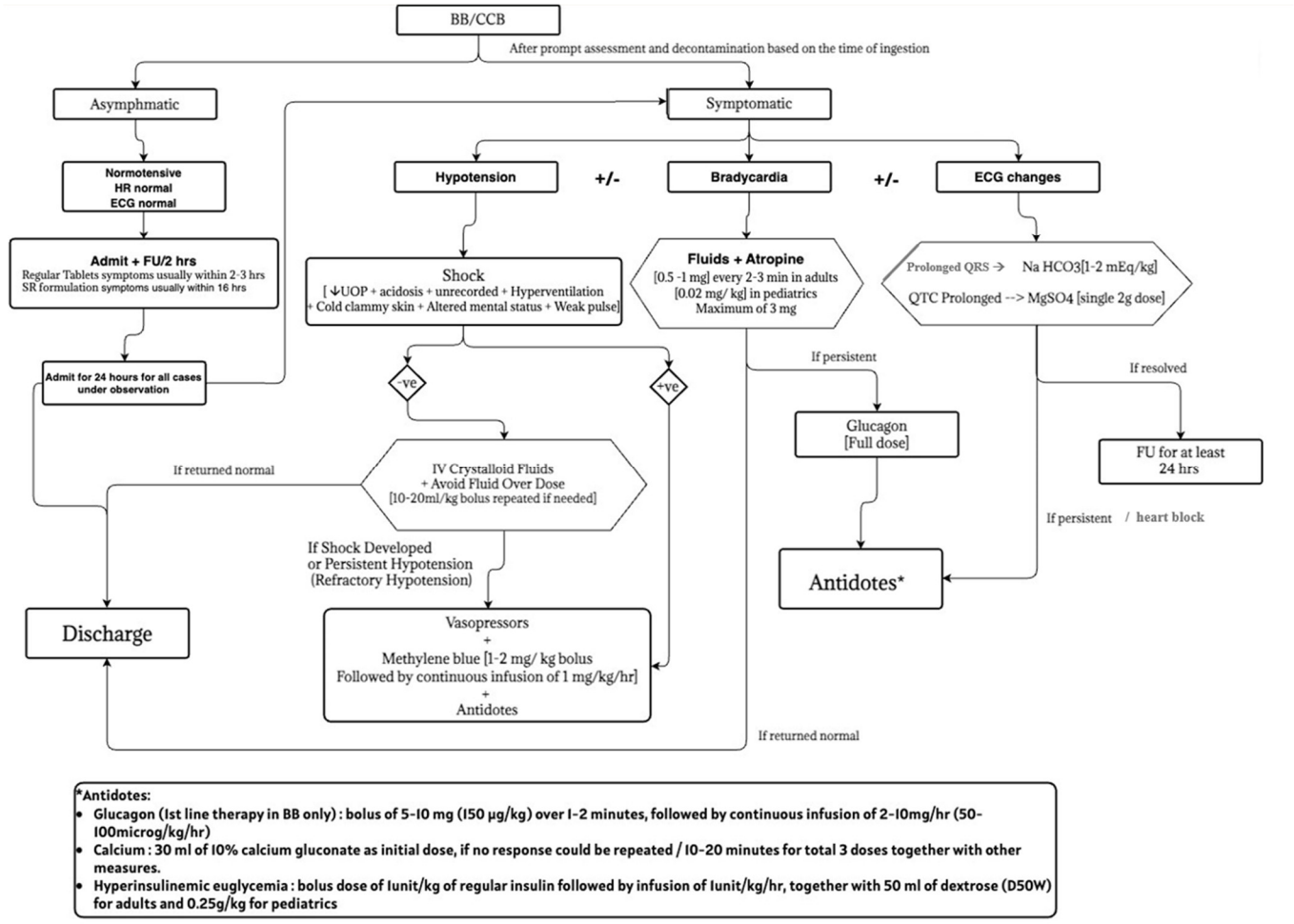
so its elevation here could be attributed to the inflammation associated with chronic diseases such as diabetes mellitus, atherosclerosis, and hypertension. Furthermore, any trigger of physiologic stress and hypovolemic shock may also increase the NLR (34). In addition, the two cases who ended with death in the current work had a markedly elevated NLR. This is similar to Josse JM et al (2016) (35), they reported that NLR could predict the mortality in the general population.

Clinical intervention in APC was done according to common lines of treatment by care of respiration. Circulation and decontamination. The initial treatment used for bradycardia and hypotension was atropine and IV fluids. These measures were insufficient in patients with severe or fatal PSS, where inotropes were started early. Despite being recognized as the most effective and useful treatment for BB toxicity, the supply of glucagon in APC is usually limited. It was used for two cases in subtherapeutic doses without any effect. So, calcium, High-dose insulin, euglycemia to augment cardiac contractility, and vasopressors were the main antidotal therapy in the current work. In addition, sodium bicarbonate for QRS widening was also used (20, 36).

Furthermore, methylene blue was also added to shocked patients. It is used in the treatment of shock through inhibiting the nitric oxide–cyclic guanosine monophosphate pathway (14). Several case reports discussed the role of methylene blue in refractory shock after BB and CCB toxicity (37-40). In the current work, four patients presented with shock, two of them (1.9%) had died. Both were not responsive to vasopressors, IV calcium and high dose insulin euglycemic regimen. They died before starting methylene blue. The other two patients who were also shocked received methylene blue early in combination with the other antidotes. The guideline indicators for BB and CCB management in APC are summarized in figure 1.

LIMITATION

The number of shocked cases in the current work is small so, further case control studies are needed to assess the effectiveness of adding methylene blue early to shocked cases after BB and CCB toxicity.



BB: beta blocker CCB: calcium channel blocker HR: heart rate
SR: sustained release IV: intravenous
FU: follow up UOP:urine output ECG: electrocardiogram

Figure 1. Flowchart for management of BB and CCB toxicity in Alexandria Poison Center, Egypt (41)

CONCLUSION

Despite representing a small percentage (1.5%) of the annual admitted cases to APC, antihypertensive toxicity has substantial morbidity and mortality. BB represented the most common single ingested agent (43.8%), followed by CCB (15.2 %). The differential toxicity of antihypertensive agents appeared as patients presented normotensive, hypotensive and even hypertensive. Bradycardia and even tachycardia appeared with varied ECG changes; PR, QTC, QRS prolongation and 1st, 2nd and complete heart block. Despite multiple treatment options, refractory shock was the cause of death among (1.9%). Starting methylene blue early in shocked cases may improve the outcome and reduce the mortality.

Conflict of Interest: None to be declared.
Funding and Support: None.

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