Troponine I versus Creatinine Kinase-MB as Predictor Markers of the Severity and Outcomes in Acute Theophylline Toxicity

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KEYWORDS
Theophylline;
Acute poisoning;
Troponin I;
Creatine kinase-MB;
Cardiac damage.

ABSTRACT

Theophylline is a bronchodilator drug that is used in the treatment of asthma and chronic obstructive pulmonary diseases. Cardiovascular complications contribute to morbidity and mortality that associate acute theophylline intoxication. The current study aimed to investigate troponin I and creatine kinase-MB as predictors of the severity and outcomes in cases of acute theophylline intoxication. This prospective cohort study included thirty one patients with acute theophylline toxicity admitted to Tanta Poison Control Center during the period from the first of March 2018 to the end of February 2019. Patients were subjected to personal and toxicological history taking, vital signs collection, grading of acute theophylline toxicity and measurement of serum theophylline level. Both troponin I and creatine kinase-MB were measured at admission and 12 hours post admission. Results revealed that, troponin I at time of admission and 12 hours post admission in addition to creatine kinase-MB 12 hours post admission were significantly higher in cases with severe acute theophylline intoxication and patients who required intensive care unit admission. It was concluded that, troponin I could predict the severity and the requirement of intensive care unit admission in acute theophylline toxicity either with early or delayed presentation. On the other hand, creatine kinase-MB could be considered for patients with delayed presentation.

Introduction

Theophylline is a xanthine derivative that acts primarily through stimulation of endogenous catecholamines release. Catecholamines stimulate beta-2 adreno-ceptors causing pulmonary bronchodilation, so theophylline has been effectively used in the treatment of asthma and chronic obstructive pulmonary disease (Fisher and Graudins, 2015).

Despite the effective bronchodilator effects of theophylline, its use is extremely lowered in developed countries because of its narrow therapeutic index and relatively high frequency of side effects along with production of safer and more effective bronchodilator drugs. Nevertheless, it is still widely used and considered a preferred drug in the majority of the developing countries due to its low cost (Navid et al., 2016).

Theophylline at both therapeutic and toxic doses blocks adenosine receptors. Moreover, theophylline at toxic doses inhibits phosphodiesterase causing increased cyclic adenosine monophosphate with subsequent

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increase of adrenergic activation and catecholamine release (Wilson, 2008).

Acute theophylline intoxication may occur following single ingestion of a toxic dose that is estimated by more than 10 mg/kg in adults (Henry and Minton, 2011). Chronic intoxication occurs as a result of repeated ingestion of excessive theophylline doses over 72 hours (Shannon and Perry, 2005).

Clinical manifestations of acute theophylline toxicity include nausea and vomiting as well as sinus, supraventricular and ventricular tachycardia. Neurological effects include anxiety, agitation, tremors and seizures (Hocaoğlu et al., 2014; Fisher and Graudins, 2015). The most common metabolic disturbances reported in acute theophylline toxicity are hypokalaemia, hyperglycaemia, lactic acidosis, hypomagnesaemia and hypophosphataemia (Altaie et al., 2011).

Diagnosis of acute theophylline toxicity is based mainly on history and clinical manifestations. For screening and quantitative determination of serum levels of theophylline, liquid chromatography/electrospray mass spectrometry (LC/MS) can be used (Hori et al., 2006).

Treatment of acute theophylline toxicity is based mainly on general supportive measures that include care of the airway and control of hypotension, dysrhythmias, vomiting and seizures (Nasir et al., 2009; Murray, 2015). Gastric lavage followed by activated charcoal is effective even with delayed presentation because of sustained-release preparations. As theophylline undergoes enterohepatic circulation, multiple dose activated charcoal is useful in enhancement of its elimination (Al Qadheeb, 2012).

Cardiovascular complications represent a major contribution for morbidity and mortality in cases with acute theophylline intoxication. The exact mechanism of cardiac toxicity is still not well defined. However, increased circulating catecholamines and antagonism of cardiac adenosine receptors are thought to be the predisposing factors (Shannon, 2007; Paul et al., 2010).

There were reports of cardiac muscle affection in theophylline intoxication (Starakis et al., 2003; Shamsuzzaman et al., 2016). However, cardiac enzymes are not widely investigated in acute theophylline toxicity. Thereafter, the current study was designed to investigate troponin I and creatine kinase-MB (CK-MB) as predictors of the severity and outcomes in cases of acute theophylline toxicity.

Patients and Methods:

Study design and population:

This prospective cohort study was conducted on patients with acute theophylline toxicity admitted to Tanta Poison Control Center during the period from the first of March 2018 to the end of February 2019.

Diagnosis of acute theophylline toxicity based on:

1- History of theophylline ingestion.

2-Manifestations of acute theophylline toxicity.

3-Determination of serum theophylline level.

Inclusion criteria:

Patients aged 18 years or more with acute suicidal or accidental theophylline intoxication were included in the study.

Exclusion criteria:

Patients with mixed intoxication, patients with pre-existing diseases (cardiac

diseases, hypertension, diabetes mellitus and both hepatic & renal diseases) and those with associated trauma were excluded. Patients who received any medications before hospital admission were also excluded.

Ethical consideration:

The study was carried out after approval of the Research Ethical Committee - Faculty of Medicine - Tanta University (Approval code: 31935/11/17). All participants received full information about the scope of the study. A written informed consent was obtained from each participant or from his/her guardian. Confidentiality and privacy were maintained.

Methods:

All patients were subjected to the following:

1- History taking:

Detailed history; personal, toxicological and medical history of involved patients was obtained. Personal data included name, age, sex, occupation, education, residence and marital state of the patients. Toxicological history including type and amount of theophylline ingested, manner of poisoning and pre-hospitalization period was obtained.

2- Clinical examination:

Vital signs (blood pressure, pulse rate, respiratory rate and temperature) were recorded. According to Flomenbaum et al. (2006) and Middleton (2008), normal ranges of vital signs in adults are 90-130/60-90 mmHg for blood pressure, 60-100 beats/minute for pulse rate, 16-24 cycles/minute for respiratory rate and 36.5-37.5°C for temperature.

According to Lim et al. (2005), symptoms and signs of acute theophylline intoxication were graded into mild (anorexia, nausea, vomiting, palpitations, nervousness, insomnia and tachycardia), moderate (symptoms of mild poisoning plus wide pulse pressure, initial hypertension then hypotension, tremors, agitation and hyperthermia) and severe (symptoms of moderate poisoning plus seizures, ventricular arrhythmias, extreme hyperthermia with dehydration, severe hypotension and coma).

3- Laboratory investigations:

Blood samples were collected under complete aseptic conditions. Immediately after admission and before administration of any medications, an arterial and venous blood samples were obtained. The arterial blood sample (2 ml) was used for measurement of arterial blood gases using an ion selective electrode (Rapid lab 855, Bayer Company, USA) according to Kokholm (1990) and serum electrolytes using an ion selective electrode according to Woo (1999). The venous sample (3 ml) was used for measurement random blood glucose, troponin I, CK-MB and serum theophylline levels. Random blood sugar was measured according to Trinder (1969) using kits obtained from BioSystem S.A. Costa Brava, 30. 08030 Bracelona (Spain). Serum theophylline level was measured according to Sheehan and Haythorn (1976).

Measurement of Troponine I was done based on sandwich immune detection method using kits obtained from Guangzhou Wondfo Biotech Co.,Ltd (normal troponin I level is less than 0.3 ng/ml). Creatine kinase-MB was measured based on kinetic colorimetric method using kits obtained from Egyptian company for biotechnology (normal CK-MB level is less than 25 U/L).

Both troponin I and CK-MB were measured twice. The first measurement was at admission; troponin I (1) and CK-MB (1). The second measurement was 12 hours post admission; Troponin I (2) and CK-MB (2).

Outcome measures:

The primary outcome measure was mortality. Secondary outcome measures were the need for intensive care unit (ICU) admission, need for hemodialysis and duration of hospital stay.

Statistical analysis:

Data was analyzed using SPSS software for windows, version 22. For quantitative data, the Shapiro-Wilk test for normality was performed. For normally distributed data, values were expressed as mean ± standard deviation (SD). For data that was not normally distributed median and interquartile range (IQR, expressed as 25^{th}-75^{th} percentiles) were calculated. Mann-Whitney and Kruskal-Wallis tests were used for comparison between two and three groups respectively. Wilcoxon signed ranks test was used to compare between paired samples. As regards qualitative data, they were represented as frequency (number and percentage). Receiver operation characteristics (ROC) curve analysis was carried out to test the discrimination power of the studied parameters to predict the outcome. Areas under ROC curve (AUC), sensitivity and specificity were calculated. Pairwise comparisons were conducted to assess differences between AUCs of the studied parameters. Significance was adopted at $p < 0.05$ for interpretation of results of tests.

Results

The current study was conducted on 31 patients presented by acute theophylline poisoning who have fulfilled the eligibility criteria during the study duration. Socio-demographic data and toxicological characteristics are demonstrated in table (1). The age of the participants ranged from 18 to 38 years and females represented 74.2% of the participants. The majority of cases were moderately educated (87.1%) and from urban areas (80.6%). Students represented 61.3% of all subjects. Most cases were single (67.7%) and non-smokers (77.4%). Regarding toxicological characteristics, the majority of cases (87.1%) alleged suicidal ingestion. Sustained-release preparations were registered for 83.9% of cases. The alleged ingested theophylline dose ranged from 1000 to 6000 mg and the pre-hospitalization period ranged from 0.5 to 13 hours.

Table (1): Socio-demographic data and toxicological characteristics of the studied patients with acute theophylline toxicity (n=31).

Characteristic variables		n (%)
Age (years)	Range	18.0 – 38.0
	Mean ± SD	22.9 ± 5.9
Sex	Female	23 (74.2%)
	Male	8 (25.8%)
Education	Moderate	27 (87.1%)
	High	4 (12.9%)
Residence	Rural	6 (19.4%)
	Urban	25 (80.6%)
Occupation	Housewife	9 (29.0%)
	Student	19 (61.3%)
	Worker	3 (9.7%)
Marital state	Married	10 (12.3%)
	Single	21 (67.7%)
Special habits	Non-smoker	24 (77.4%)
	Smoker	7 (22.6%)
Mode of poisoning	Alleged suicidal	27 (87.1%)
	Alleged accidental	4 (12.9%)
Type of preparation	Conventional	5 (16.1%)
	Sustained-release	26 (83.9%)
Alleged ingested theophylline dose (mg)	Range	1000-6000
	Median (IQR)	2000 (2000 – 2500)
Delay time (hours)	Range	0.5 – 13
	Median (IQR)	5.0 (4.0 – 12.0)

n: number; SD: standard deviation; IQR: interquartile range; mg: milligram.

Clinical manifestations and initial laboratory findings are summarized in table (2). For vital signs, hypotension, tachycardia, hyperthermia and tachypnea were represented in 77.4%, 93.5%, 71% and 71% of the studied patients respectively. Nausea was observed in all patients whereas, vomiting and abdominal colic were registered for 96.8% and 61.3% respectively. Tremors, agitation and disturbed level of consciousness were observed in 41.9%, 38.7% and 6.5% of the patients respectively. Regarding blood glucose level, 32.3% of the patients were hyperglycemic. Acidosis was observed in 22.6% of the cases. The majority of cases (64.5%) were presented with mild intoxication, while 12.9% and 22.6% were presented with moderate and severe intoxication respectively. For theophylline level, it ranged from 20 to 100 mg/L (median: 34 mg/L)

Table (2): Clinical manifestations, initial laboratory findings, grading of poisoning severity and serum theophylline level of the studied patients with acute theophylline toxicity (n=31).

Variables	n	%
Blood pressure		
Normal	7	22.6
Hypotension	24	77.4
Pulse		
Normal	2	6.5
Tachycardia	29	93.5
Temperature		
Normal	22	71.0
Hyperthermia	9	29.0
Respiratory rate		
Normal	9	29.0
Tachypnea	22	71.0
Gastrointestinal manifestations		
Nausea	31	100.0
Vomiting	30	96.8
Abdominal colic	19	61.3
Neurological manifestations		
Tremors	13	41.9
Agitation	12	38.7
Disturbed consciousness	2	6.5
Glycemic state		
Normal	21	67.7
Hyperglycemia	10	32.3
Potassium level		
Normal	7	22.6
Hypokalemia	24	77.4
pH		
Normal	24	77.4
Acidosis	7	22.6
Acute theophylline toxicity grading		
Mild	20	64.5
Moderate	4	12.9
Severe	7	22.6
Serum theophylline level (mg/L)	Range	20 – 100
	Median (IQR)	34.0 (33.0 – 70.0)

n: number; mg: milligram; L: liter; IQR: interquartile range.

As illustrated in table (3), the median values of troponin I and CK-MB at time of admission were 0.08 ng/ml and 24 U/L respectively. While, their median values 12 hours post admission were 0.01 ng/ml and 17 U/L for troponin I and CK-MB respectively.

Table (3): Level of troponin I and creatine kinase-MB at time of admission and 12 hours post admission in the studied patients with acute theophylline toxicity (n=31)

Variables	Range (ng/ml)	Median (IQR) (ng/ml)
Troponin I (1)	0.04 - 1.40	0.08 (0.08 – 0.10)
Troponin I (2)	0.01 – 3.00	0.01 (0.01 – 0.11)
	Range (U/L)	**Median (IQR) (U/L)**
CK-MB (1)	10.0 – 28.0	24.0 (22.0 – 25.0)
CK-MB (2)	12.0 – 77.0	17.0 (13.0 – 60.0)

Troponin I (1): troponin at time of admission; Troponin I (2): troponin 12 hours post admission; CK-MB (1): creatine kinase-MB at admission; CK-MB (2): creatine kinase-MB 12 hours post admission; ng: nanogram; ml: milliliter; U: unit; L: liter; IQR: interquartile range.

Data obtained from the current study revealed that, all cases survived. Only one case underwent hemodialysis while, three cases (9.7%) required ICU admission. The duration of hospital stay ranged from 24 to 96 hours with mean value 45.8 hours (Table 4).

Table (4): Outcome measures in the studied patients of acute theophylline intoxication (n=31)

Outcome measures		n (%)
Mortality	Died	0 (0%)
	Survived	31 (100%)
Need for hemodialysis	Yes	1 (3.2%)
	No	30 (96.8%)
Intensive care unit admission	Yes	3 (9.7%)
	No	28 (90.3%)
Duration of hospital stay (hours)	Range	24.0 – 96.0
	Mean ± SD	45.9 ± 19.5

n: number, SD: standard deviation.

Regarding troponin I level at time of admission, there was significant difference between cases with mild theophylline intoxication and cases with severe theophylline intoxication (p<0.001). On the other hand, cases with mild intoxication showed no significant difference compared to cases with moderate intoxication. Additionally, there was no significant difference between cases with moderate intoxication and severe intoxication. Similar results were obtained regarding troponin I level 12 hours post admission. Both troponin I levels at time of admission and 12 hours post admission were significantly higher in cases required ICU compared to cases not admitted to ICU (Table 5).

Table (5): Troponin I at time of admission and 12 hours post admission levels against acute theophylline toxicity grading and intensive care unit admission in studied patients of acute theophylline toxicity (n=31)

		Troponin I (1)		Tests of significance		
		Median (ng/ml)	**IQR (ng/ml)**	**Mean ranks**	**Test statistic**	***p*-value**
Acute theophylline toxicity grading	Mild	0.08	0.08 - 0.08	11.5	Z_{KW}=19.219	<0.001* Mild-moderate=0.606 Mild-severe<0.001* Moderate-severe=0.155
	Moderate	0.08	0.08 - 0.09	17.5		
	Severe	1.20	1.20 - 1.40	27.9		
Intensive care unit admission	No	0.08	0.08 - 0.09	14.7	Z_{MW}=2.593	0.010*
	Yes	1.20	1.20 - 1.40	28.2		
		Troponin I (2)		**Tests of significance**		
		Median (ng/ml)	**IQR (ng/ml)**	**Mean ranks**	**Test statistic**	***p*-value**
Acute theophylline toxicity grading	Mild	0.01	0.01 - 0.02	11.4	Z_{KW}=20.511	<0.001* Mild-moderate=0.406 Mild-severe<0.001* Moderate-severe=0.196
	Moderate	0.06	0.02 - 0.11	18.3		
	Severe	2.10	2.00 - 2.30	28.0		
Intensive care unit admission	No	0.01	0.01 - 0.09	14.6	Z_{MW}=2.807	0.005*
	Yes	2.30	2.00 - 3.00	29.0		

Troponin I (1): troponin at time of admission; Troponin I (2): troponin 12 hours post admission; ng: nanogram; ml: milliliter; IQR: interquartile range; ZKW: Kruskal-Wallis test; ZMW: Mann-Whitney test; * significant at p <0.05.

For CK-MB level at time of admission, no significant difference was observed between cases with mild, moderate and severe intoxication. Moreover, it did not show significant difference as regard ICU admission. On the other hand, CK-MB level 12 hours post admission was significantly higher in cases with severe intoxication compared to cases with mild intoxication (p<0.001). However, there was no significant difference between cases with mild and moderate intoxication or cases with moderate and severe intoxication. In addition, CK-MB level 12 hours post admission was significantly higher in patients who were indicated for ICU admission than those who did not require ICU admission (Table 6).

Table (6): Creatine kinase-MB at time of admission and 12 hours post admission against acute theophylline toxicity grading and intensive care unit admission in studied patients of acute theophylline toxicity (n=31)

		CK-MB (1)		Tests of significance		
		Median (U/L)	IQR (U/L)	Mean ranks	Test statistic	*p*-value
Acute theophylline toxicity grading	Mild	24.0	21.5 - 25.0	14.0	Z_{KW}=5.126	0.077
	Moderate	20.0	14.5 - 25.5	14.4		
	Severe	25.0	24.0 - 26.0	22.7		
Intensive care unit admission	No	24.0	21.5 - 25.0	15.3	Z_{MW}=1.430	0.153
	Yes	25.0	24.0 - 28.0	23.0		
		CK-MB (2)		**Tests of significance**		
		Median (U/L)	**IQR (U/L)**	**Mean ranks**	**Test statistic**	***p*-value**
Acute theophylline toxicity grading	Mild	13.5	13.0 - 16.0	11.0	Z_{KW}=18.649	<0.001* Mild-moderate=0.105 Mild-severe<0.001* Moderate-severe=0.885
	Moderate	25.5	21.0 - 48.5	21.4		
	Severe	70.0	69.0 - 72.0	27.3		
Intensive care unit admission	No	14.0	13.0 - 26.0	14.7	Z_{MW}=2.496	0.013*
	Yes	70.0	70.0 - 77.0	28.3		

CK-MB (1): creatine kinase-MB at admission; CK-MB (2): creatine kinase-MB 12 hours post admission; U: unit; L: liter; IQR: interquartile range; ZMW: Mann-Whitney test; ZKW: Kruskal-Wallis test; * significant at p <0.05.

According ROC curve analysis, each of troponin I (1), troponin I (2) and CK-MB (2) showed excellent performance in predicting the requirement of ICU admission in patients with acute theophylline intoxication with AUCs 0.935, 0.964 and 0.940 respectively. Whereas, CK-MB (1) had fair performance (AUC: 0.75). Optimum cut off values of troponin I (1), troponin I (2), CK-MB (1) and CK-MB (2) were >0.1 ng/ml, >0.3 ng/ml, >23 U/L and > 69U/L respectively. Pairwise comparisons revealed no significant difference among the four parameters (Table 7).

Table (7): Areas under the curve, optimum cut-off values, sensitivities and specificities of troponin I and CK-MB in predicting the requirement of intensive care unit admission in the studied patients of acute theophylline intoxication (n=31)

	Troponin I (1)	**Troponin I (2)**	**CK-MB (1)**	**CK-MB (2)**
AUC (95% CI)	0.935 (0.784-0.992)	0.964 (0.828-0.999)	0.750 (0.563-0.887)	0.940 (0.793-0.994)
***P*-value**	<0.001*	<0.001*	<0.001*	<0.001*
Cut off value	>0.1 ng/ml	>0.3 ng/ml	>23 U/L	>69 U/L
Sensitivity %	100.0	100.0	100.0	100.0
Specificity %	89.3	89.3	39.3	89.3
Pairwise comparisons				
Troponin I (1)		0.375	0.241	0.932
Troponin I (2)	0.375		0.216	0.726
CK-MB (1)	0.241	0.216		0.137
CK-MB (2)	0.932	0.726	0.137	

Troponin I (1): troponin at time of admission; Troponin I (2): troponin 12 hours post admission; CK-MB (1): creatine kinase-MB at admission; CK-MB (2): creatine kinase-MB 12 hours post admission; AUC: area under the curve; CI: confidence interval; ng: nanogram; ml: milliliter; U: unit; L: liter; * significant at p <0.05.

Discussion

Theophylline is a bronchodilator medication that is used for asthmatic patients, in addition to its use to treat bradycardia and apnea in newborns. However, it has a narrow therapeutic window and associated with potentially serious manifestations in acute overdose even with levels slightly above the therapeutic window (Schoen et al., 2014 and Greene et al., 2018).

Predicting the severity and outcomes of patients with acute poisoning is highly important to guide treatment. On the other hand, there is shortage of researches concerning the prediction of the outcomes of cases with acute theophylline intoxication (Abuelfadl et al., 2017). Cardiovascular manifestations are known to be major consequences of acute theophylline intoxication (Starakis et al., 2003 and Hocaoğlu et al., 2014). However, little is known about the role of cardiac biomarkers in such patients. Thereafter, the current study was designed to investigate troponin I and CK-MB as predictor markers of the severity and outcomes in patients with acute theophylline toxicity.

The current study was conducted on 31 patients with acute theophylline intoxication admitted to Tanta Poison Control Center. Socio-demographic data of the current study revealed that, the mean value of age was 22.9 years and students represented the major part of the studied patients. Different researches revealed that, the rate of suicide increases among young adults due to inability to face life challenges, depression and anger (Shannon, 1999 and Hooven et al., 2012). The predominance of females in the current study (74.2%) was in accordance with Hocaoğlu et al. (2014) where

females represented 72.6% of their studied population. In the current study, 87.1% were moderately educated while 12.9% were highly educated. This was partially in line with Abuelfadl et al. (2017) who found that, 39.29% of the studied cases were moderately educated while 32.14% were highly educated and the remaining were illiterate or just read and write.

Patients from urban areas represented 80.6% of the studied cases. Pattern of acute poisoning may be influenced by the area of residence; intentional poisoning with pharmaceutical agent in urban area may be more common than rural areas where pesticides and other related compounds are widely used for suicide. Regarding marital status, 67.7% of the studied patients were single; according to Azizpour et al. (2016), single people may suffer unstable life and loneliness feelings with increased risk for suicidal attempts. The majority of the studied patients were non-smoker; this could be explained by a finding that, the majority of cases in the current study were females. According to Loffredo et al. (2015), Egyptian females are rarely reported to smoke cigarettes.

Concerning mode of poisoning, patients with alleged suicides represented 87.1% of cases involved in the current study; this could be explained by wide availability of theophylline preparations. It was observed that, sustained-release preparations were incorporated in 83.9% of the studied case. Elhawary et al. (2015) reported that, 63.33% of acute theophylline intoxicated patients were due to sustained-release preparations. This is supported by the fact that, theophylline is commonly available in sustained-release formulations because of its relatively short half-life (8 hours in adults) (Rajalakshmi et al., 2011). Pre-hospitalization period in the current study ranged between 0.5 and 13 hours; appearance of symptoms, availability of transportation and distance of hospitals could influence pre-hospitalization period (Peranantham et al., 2014).

Regarding clinical manifestations, nausea, vomiting, tachycardia and hypotension were the most common manifestations. Nausea and vomiting were observed in 100% and 96.8% of the studied cases respectively; however Hafez (2018) reported vomiting in 78% of cases. Vomiting is a common symptom of acute theophylline toxicity due to inhibition of phosphodiesterase enzyme (PDE_4) in the chemoreceptor trigger zone with severe repeated vomiting that may resist antiemetic medications (Barnes, 2010). Tachycardia was observed in 93.5% in the current study. Tachycardia is considered the most common cardiovascular manifestation which is often associated with hypotension. Hypotension occurs as a result of vasodilation, volume loss and reduced cardiac output (Greene et al., 2018).

In this study, both troponin I and CK-MB were sampled at time of admission and after 12 hours post admission. Hachey et al. (2017) stated that, combined measurement of cardiac troponins and CK-MB is the most preferred investigation protocol to detect myocardial damage with recommended sampling at presentation and repeated at interval of more than 10 hours.

In the current study, troponin I showed significant difference against theophylline toxicity grading at time of admission and 12 hours post admission. This finding could explain that, troponin I at time of admission and 12 hours post admission were significantly higher in patients who required ICU admission compared to patients who were not indicated for ICU admission. According to Brandenburg et al. (2017), intoxicated patients with severe sequelae are indicated for ICU admission.

Methylxanthines including theophylline cause cardiac side effects in the form of different

types of arrhythmias, focal necrosis and subendocardial myolysis. In a study conducted by Shannon (1999), he reported that cardiac dysrhythmia of theophylline intoxication was associated with new onset of myocardiac ischaemia. Moreover, autopsy findings in asthmatic patients with methylxanthines therapy revealed multiple areas of myocardial necrosis (Schoen, 1987).

Interestingly, troponin I is not a marker of myocardial infarction only. Nevertheless, it can indicate all forms of cardiac muscle damage. A finding supported by researchers who documented elevated troponin I in the absence of acute ischemic heart disease; a condition that can occur with different pathological condition as well as with cardiotoxic drug overdose such as; theophylline (Huysa et al., 2016).

Unlike troponin I, CK-MB did not show significant difference with acute theophylline toxicity grading at time of admission, while it showed statistical significant difference with acute theophylline toxicity grading 12 hours post admission. Subsequently, CK-MB 12 hour after admission was significantly higher in patients who were admitted to the ICU. In 2000, The American College of Cardiology Committee together with The European Society of Cardiology declared that, troponin I is only expressed in cardiac muscle and it is highly sensitive to detect even small amounts of myocardial necrosis, myocardial infarction and myocytes damage than CK-MB. As a result, troponin I is more specific for myocardial damage and elevated when CK-MB is still not elevated (Korff et al., 2007). Hence, troponin is recommended to be sampled early due to its higher diagnostic accuracy (Hachey et al., 2017).

According to Collinson et al. (1992), diagnostic sensitivity of CK-MB is 100% eight hours post admission. Starakis et al. (2003) reported elevation of serum CK-MB level on the second day of hospitalization. However, Le et al. (2015) removed CK-MB from hospital ordering models without affecting patient care harmfully and saving unnecessary cost.

In the current study, troponin I (1), troponin I (2), CK-MB (1) and CK-MB (2) at cut off values >0.1 ng/ml, >0.3 ng/ml, >23 U/L and > 69U/L respectively were significantly valid ($p < 0.05$) to predict the requirement for ICU admission in acute theophylline intoxicated patients. Acute poisoning could influence the response of patients, so cut off values of different biomarkers should be unique for each poison. Setting up cut off values related to acute toxicological conditions could guide proper management and attains important clinical implications for toxicologists.

Conclusion:

In the light of data obtained from the current study, troponin I could predict the severity and the requirement of ICU admission in patients with acute theophylline toxicity either with early or delayed presentation. On the other hand, CK-MB could be considered for patients with delayed presentation. Depending on time of admission, proper choosing of the biomarker to be investigated will allow for better evaluation of patients with saving extra cost.

Limitation of the study:

In the current study, the role of troponin I and CK-MB in predicting the mortality and the need for hemodialysis in acute theophylline toxicity could not be investigated as there was no mortality and only one case required hemodialysis. Additionally, small sample size of the current study is considered another limitation. Further studies on larger samples and in different poison control centers are recommended.

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تروبونين اي مقابل كرياتين كيناز ام-بي كمؤشرات تنبؤية لشدة و نتائج التسمم الحاد بالثيوفيللين

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الثيوفيللين عقار موسع للشعب يستخدم في علاج الربو ومرض الانسداد الرئوي المزمن. وتساهم المضاعفات القلبية الوعائية للثيوفيللن في الحالات المرضية وحالات الوفيات التى تصاحب التسمم الحاد بالثيوفيللين. وتهدف هذه الدراسة إلي فحص تروبونين اي وكرياتين كيناز ام-بي كمتنبئات لشدة ونتائج حالات التسمم الحاد بالثيوفيلين. وقد تم إجراء الدراسة على واحد وثلاثين مريضاً يعانون من التسمم الحاد بالثيوفيللين وتم دخولهم مركز طنطا لعلاج التسمم خلال الفترة من أول مارس 2018 وحتى نهاية فبراير ٢٠١٩. وقد خضع جميع المرضى لأخذ التاريخ الشخصي للمريض والتاريخ السمي ، وجمع العلامات الحيوية، وتحديد درجة التسمم الحاد للثيوفيلين، وقياس مستوى الثيوفيلين في الدم. وقد تم قياس كل من تروبونين اي وكرياتين كيناز ام-بي عند دخول المريض و بعد ١٢ ساعة من الدخول. وأظهرت النتائج أن تروبونين اي وقت الدخول و ١٢ ساعة بعد الدخول وكرياتين كيناز ام-بي بعد ١٢ ساعة من الدخول أعلى بدلالة إحصائية في حالات التسمم الحاد الشديد بالثيوفيلين ومع المرضى المطلوب لهم دخول وحدة الرعاية المركزة. وقد خلصت هذه الدراسة إلي أن تروبونين اى يمكنه أن يتوقع شدة التسمم والتنبؤ بالحاجة إلي دخول وحدة الرعاية المركزة في حالات التسمم الحاد بالثيوفيلين سواء مع الوصول المبكر أو المتأخر للمريض. ومن ناحية أخرى ، فيمكن النظر بعين الاعتبار لكرياتين كيناز ام-بي للمرضى في حالة الوصول المتأخر.