B-Type Natriuretic Peptide and Troponin I as Possible Predictive Biomarkers for Cardiotoxicity Induced By Tricyclic Antidepressants and Antipsychotics Overdose

Aya Sabry Mohamed, Hoda M Salah Eldin and Manal Elsayed Abdel Salam

Abstract

Overdose by tricyclic antidepressants and antipsychotic drugs can lead to potentially life-threatening cardiotoxicity. In clinical medicine, B-type natriuretic peptide (BNP) and cardiac troponin I (cTnI) are used as serum biomarkers in the diagnosis of cardiac affection.

Aim: The study aimed to investigate the utility of BNP and troponin I as early predictors for TCA and antipsychotic drug-induced cardiotoxicity and correlation with severity of poisoning.

Method: The study enrolled 45 patients admitted in ICU of Poison Control Center of Ain Shams University Hospitals (PCC-ASUH) with history of tricyclic antidepressants (TCA) and/or antipsychotics overdose. Collected data included sociodemographic data, manner of exposure, clinical variables, ECG changes, Poison Severity Score (PSS), serum levels of BNP and cTnI. Duration of ICU and hospital stay, and outcome were also noted.

Results: In contrast to cTnI level, BNP level was significantly higher in cardiotoxicity group. Mean BNP level correlated with ECG and blood pressure changes. Biomarkers levels were non-significantly correlated with PSS, total hospital stay & ICU stay. PSS had low sensitivity and accuracy for prediction of cardiotoxicity. Both BNP and cTnI showed at specific cut off point showed 100% specificity with sensitivity of 53.13% & 25.0% respectively

Conclusion: Although unsuitable for screening purposes, BNP surpassed cTnI as a useful tool for the diagnosis of cardiotoxicity due to overdose by tricyclic antidepressants and antipsychotic drugs

Key words: B-type natriuretic peptide - Troponin I - biomarkers - cardiotoxicity - tricyclic antidepressants - antipsychotics - overdose

Introduction

Accidental and intentional drug overdoses constitute a significant cause of morbidity, mortality, and increased health care cost worldwide. Although trends vary according to geographical region, psychiatric agents are among the most commonly encountered drugs in poisoning cases. Clinical effects of tricyclic antidepressants and antipsychotic drugs overdose can lead to potentially life-threatening neurological and cardiac complications (Borg et al., 2016).

Both tricyclic antidepressants and antipsychotic drugs can significantly induce distinct cardiotoxicity through multiple and sometimes divergent effects on the cardiovascular system; both are known to increase the risk of potentially life-threatening arrhythmias and sudden cardiac death (SCD). These proarrhythmic effects have been linked to prolongation of QT interval of the electrocardiogram (ECG). Studies have also shown that TCAs directly decrease myocardial contractility in a dose dependent manner and cause peripheral vasodilatation by antagonism of peripheral alpha-1 adrenergic receptors resulting in refractory hypotension (Pierog et al., 2009; Tarek et al., 2016; Sabah et al., 2017). Antipsychotics were additionally implicated in other cardiac complications including myocarditis, cardiomyopathy and left ventricular dysfunction with sometimes fatal effect (Curto et al., 2015).

In clinical practice, numerous serum biomarkers are proposed for diagnosis of drug-induced cardiotoxicity. Previous studies point that troponin I can be used as a potent biomarker of toxic cardiac injury when irreversible myocyte injuries with loss of sarcolemmal integrity are present regardless of the cardiotoxic agents involved (Sorodoc et al., 2013). B-type natriuretic peptide (BNP) and N-terminal fragment of its prohormone (NT-proBNP) are cardiac-derived polypeptides predominately secreted from ventricular myocardium in response to volume and pressure overload. Both can be viewed as quantitative markers of ventricular dysfunction and well-established predictors of disease state in symptomatic and asymptomatic patients with suspected heart failure (Mueller et al., 2007; Khalaf et al., 2011; Sorodoc et al., 2013; Zoltani, 2014).
As cardiotoxicity was suggested as a significant determinant of morbidity and mortality in both therapeutic and overdose cases, assays for clinical detection of cardiotoxicity can be employed in risk stratification, management and clinical prediction of morbidity/mortality.

**Aim of work**

The study aimed to investigate the role of BNP and troponin I as early predictors for TCA and antipsychotic drug-induced cardiotoxicity and correlation with severity of poisoning.

**Patients and method**

**Design and setting**

A cross-sectional hospital-based observational study was carried out on 45 patients of both genders admitted in ICU of Poison Control Center of Ain Shams University Hospitals (PCC-ASUH) with history of tricyclic antidepressants (TCA) and/or antipsychotics overdose.

**Ethical Considerations**

The study was approved by the Research Ethics Committee of Faculty of Medicine Ain Shams University. All collected data were stored anonymously with consideration of confidentiality issues and used only for the purpose of the study and were considered.

**Participant selection and grouping**

Patients exposed to tricyclic antidepressants and/or antipsychotics ingestion within 6 h and admitted in ICU were selected. The diagnosis of intoxication was based on history and clinical examination. Diagnosis of cardiotoxicity was determined by the presence of one or more of the clinical manifestations that include hemodynamic instability, heart failure, cardiac conduction abnormalities and dysrhythmias; and/or ECG manifestations. Patients were divided into two major groups:

- **First group (Exposure without cardiotoxicity):** patients exposed to one of the selected cardiotoxic agents, but without detectable cardiotoxicity.
- **Second group (Exposure with overt cardiotoxicity):**

Based on the possibility of alteration in measured parameters and/or biomarkers exclusion criteria included ages above 60 years and history of cardiovascular or medical disease.

**Parameters**

Sociodemographic data (age, gender, residence) and manner of exposure were recorded at enrollment. This is in addition to recording duration of admission in the ICU, total period of hospitalization and outcome (including complete recovery, or fatality).

Examination of the patients was carried out at the time of presentation to the PCC and periodically for follow up. Clinical data included pulse, mean blood pressure, respiratory rate and temperature. Normal values were stated according to McGrath & Bachmann (2018). CNS manifestations included evaluation of conscious level according to Reed’s classification (Karmakar, 2015) seizures and agitation. Electrocardiography was performed at the time of admission in addition to continuous cardiac monitoring.

Investigations and treatment were performed according to specific requirements of each patient following the guidelines of the PCC protocols. General laboratory investigations (done routinely in the ICU) included random blood sugar, serum sodium and potassium, serum urea and creatinine, serum ALT and AST and arterial blood gases. Serum biomarkers namely BNP and cTnI were measured on admission.

- **BNP measurement:** was done using the Human Brain Natriuretic Peptide Enzyme Linked Immunosorbent Assay (ELISA) Kit of Bioassay Technology Laboratory., Shanghai, China.
- **Cardiac TnI:** measurement was done by using Enzyme Immunoassay test kit for the Quantitative determination of cardiac troponin-I in human serum.

All clinical and laboratory variables were recorded and employed in the calculation of poison severity score (PSS) which is a classification scheme for cases of acute poisoning in adults and children. Based on the overall clinical course, PSS was applied according to the most severe symptomatology (including both subjective symptoms and objective signs). The severity was graded from 0 to 4, ranging from absent toxicity to death (Persson et al., 1998).

**Results**

By the end of the study, antipsychotics overdosed cases outnumbered those overdosed by TCA: constituting 75.56% of total number of cases. In relation to the occurrence of overt cardiotoxicity, group II included 32 cases (71.11%) with statistically non-significant difference in relation to the type of drug (Table 1).

Mean age among overall patients in the study was 24.51±9.715 years with a statistically significant higher mean in cases with overt cardiotoxicity (26.500±10.100 yrs.) versus (19.615±7.343 yrs.) in those without detectable cardiotoxicity (Table 2).

As regard gender and residence, patients enrolled in this study were mostly females (68.89 %) and from urban areas (84.44%). The manner of exposure was mostly suicidal (93.33% of cases). No statistically significant difference was found between group I and group II as regard gender, residence and manner of exposure (Table 3).

Although, tachycardia was observed in 73.33% of cases mostly among overt cardiotoxicity group, there was no significant difference between the two groups as regard pulse. Regarding ECG findings, all patients had regular rhythm, with normal PR interval. Prolonged QTc interval was observed in 35.56% of cases, and in association with wide QRS complex in 13.33% all among group II. Hypertension was observed in 33.33% of cases, while hypotension was only observed in a minority (8.89%) all among cardiotoxicity group. Prolonged QTC and/or wide QRS and blood pressure changes showed significant differences between the two groups. While hyperthermia was observed in 13.33%, tachypnea was observed in 53.33% of cases mostly among group II, however with no statistical significance in relation to cardiotoxicity (Table 4).

Coma grade II was recorded in nearly half of the cases (51.11%) followed by coma grade I in 42.22%, while coma grade III and IV were only
recorded in a minority of cases. Seizures and agitation were recorded in 12.50% and 26.67% of patients respectively. The majority of cases recovered completely on discharge (93.33%). Fatality was only recorded in 3 cases. Neither neurological manifestations nor outcome had significant difference between group I and II as (Table 4).

Calculated PSS for cases ranged from 2-4 with no significant difference between the two groups. The mean length of stay in ICU and total hospital stay were longer in group II compared to that of group I, however it was not statistically significant (Table 5).

Mean serum levels of cTnI levels ranged from 0.01-1 ng/ml while those of BNP ranged from 250-600 pg/ml. Both biomarkers had higher mean values among overt cardiotoxicity group compared to group I, however this difference had statistical significance only for BNP (Table6).

Test characteristics of cTnI for diagnosis of cardiotoxicity were 25 % sensitivity, 100 % specificity, 35.1 % negative predictive value and 62.5% accuracy. The mean values of cTnI showed no statistically significant difference in relation to pulse, blood pressure and ECG finding in addition to PSS, length of ICU and total hospital stay. In contrast to TnI, BNP levels showed statistically significant difference in group II as regards blood pressure changes and QTc interval (Table 7, Figure1).

Calculated PSS for cases ranged from 2-4 with no significant difference between the two groups. The mean length of stay in ICU and total hospital stay were longer in group II compared to that of group I, however it was not statistically significant (Table 5).

Mean serum levels of cTnI levels ranged from 0.01-1 ng/ml while those of BNP ranged from 250-600 pg/ml. Both biomarkers had higher mean values among overt cardiotoxicity group compared to group I, however this difference had statistical significance only for BNP (Table6).

Table (1): Chi-Square statistical analysis showing comparison between group I and II as regards distribution of the type of drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Groups</th>
<th>Group I</th>
<th>Group II</th>
<th>Overall cases</th>
<th>Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>X²</td>
</tr>
<tr>
<td>TCA</td>
<td></td>
<td>4</td>
<td>30.77</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td>9</td>
<td>69.23</td>
<td>25</td>
<td>34</td>
</tr>
<tr>
<td>Overall cases</td>
<td></td>
<td>13</td>
<td>100.00</td>
<td>32</td>
<td>45</td>
</tr>
</tbody>
</table>

N: number of cases  p>0.05 = statistically non-significant, p<0.05 = statistically significant

Table (2): Student's t-test statistical analysis showing comparison between group I and II as regards age

<table>
<thead>
<tr>
<th>Age</th>
<th>Groups</th>
<th>T-Test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
<td>t</td>
</tr>
<tr>
<td>Range</td>
<td>8</td>
<td>15</td>
<td>-2.224</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>19.615 ± 7.343</td>
<td>26.500 ± 10.100</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation, p>0.05 = statistically non-significant, *p<0.05 = statistically significant

Table (3): Chi-Square statistical analysis showing comparison between group I and II as regards gender, residence & manner of exposure

<table>
<thead>
<tr>
<th>Groups</th>
<th>Groups</th>
<th>Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10</td>
</tr>
<tr>
<td>Residence</td>
<td>Rural</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Urban</td>
<td>10</td>
</tr>
<tr>
<td>Manner of exposure</td>
<td>Suicidal</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Accidental</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic</td>
<td>0</td>
</tr>
</tbody>
</table>

N: number of cases, p>0.05 = statistically non-significant, p<0.05 = statistically significant
### Table (4): Chi-Square statistical analysis showing comparison between group I and II as regards clinical variables and outcome

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Group I (N=13)</th>
<th>Group II (N=32)</th>
<th>Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cases</td>
<td></td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>N</td>
<td>45</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>Pulse Normal</td>
<td>12</td>
<td>26.67</td>
<td>5</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>33</td>
<td>73.33</td>
<td>8</td>
</tr>
<tr>
<td>ECG No abnormality</td>
<td>23</td>
<td>51.11</td>
<td>13</td>
</tr>
<tr>
<td>Prolonged QTC</td>
<td>16</td>
<td>35.56</td>
<td>0</td>
</tr>
<tr>
<td>Prolonged QTC &amp; Wide QRS</td>
<td>6</td>
<td>13.33</td>
<td>0</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>26</td>
<td>57.77</td>
<td>13</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
<td>33.33</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4</td>
<td>8.89</td>
<td>0</td>
</tr>
<tr>
<td>Temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>39</td>
<td>86.67</td>
<td>10</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>6</td>
<td>13.33</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>18</td>
<td>40.00</td>
<td>7</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>24</td>
<td>53.33</td>
<td>5</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3</td>
<td>6.67</td>
<td>1</td>
</tr>
<tr>
<td>Neurological manifestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coma Grade I</td>
<td>19</td>
<td>42.22</td>
<td>7</td>
</tr>
<tr>
<td>Grade II</td>
<td>23</td>
<td>51.11</td>
<td>5</td>
</tr>
<tr>
<td>Grade III</td>
<td>2</td>
<td>4.44</td>
<td>0</td>
</tr>
<tr>
<td>Grade IV</td>
<td>1</td>
<td>2.22</td>
<td>1</td>
</tr>
<tr>
<td>Seizures</td>
<td>4</td>
<td>8.89</td>
<td>0</td>
</tr>
<tr>
<td>Agitation</td>
<td>12</td>
<td>26.67</td>
<td>4</td>
</tr>
<tr>
<td>Fatality</td>
<td>3</td>
<td>6.67</td>
<td>1</td>
</tr>
</tbody>
</table>

| Outcome Recovery | 42 | 93.33 | 12 | 92.31 | 30 | 93.75 | 0.031 | 0.860 |
| Fatality         | 3  | 6.67  | 1  | 7.69  | 2  | 6.25  | |

N: number of cases, p>0.05 = statistically non-significant, *p<0.05 = statistically significant

### Table (5): Student’s t-test statistical analysis showing comparison between group I and II as regards PSS, duration of hospital stay, and ICU stay

<table>
<thead>
<tr>
<th>Groups</th>
<th>PSS</th>
<th>Hospital stay (Days)</th>
<th>ICU stay (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean ±SD</td>
<td>Range</td>
</tr>
<tr>
<td>Group I (N=13)</td>
<td>t</td>
<td>P-value</td>
<td>Group II (N=32)</td>
</tr>
<tr>
<td></td>
<td>2 - 4</td>
<td>2.308 ± 0.630</td>
<td>1 - 7</td>
</tr>
<tr>
<td></td>
<td>-0.634</td>
<td>0.529</td>
<td>-1.210</td>
</tr>
<tr>
<td>SD: standard deviation, p&gt;0.05 = statistically non-significant, *p&lt;0.05 = statistically significant</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table (6): Student’s t-test statistical analysis showing comparison between group I and II as regards investigated cardiac biomarkers.

<table>
<thead>
<tr>
<th>Groups</th>
<th>cTnI (ng/ml)</th>
<th>BNP (pg/mL)</th>
<th>T-Test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I (N=13)</td>
<td>Group II (N=32)</td>
<td>t</td>
<td>P-value</td>
</tr>
<tr>
<td>Range</td>
<td>0.01 - 0.2</td>
<td>0.01 - 1</td>
<td>-1.567</td>
<td>0.124</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>0.046 ± 0.073</td>
<td>0.162 ± 0.260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>180 - 320</td>
<td>250 - 600</td>
<td>-3.651</td>
<td>0.001*</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>261.538 ± 50.801</td>
<td>355.313 ± 86.360</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation, p>0.05 = statistically non-significant, *p<0.05 = statistically significant
Table (7): Correlations between investigated cardiac biomarkers and selected parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>BNP (pg/mL)</th>
<th>Troponin I (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P-value</td>
</tr>
<tr>
<td>PSS</td>
<td>0.163</td>
<td>0.284</td>
</tr>
<tr>
<td>Hospital stay (Days)</td>
<td>0.030</td>
<td>0.842</td>
</tr>
<tr>
<td>ICU stay (Days)</td>
<td>0.068</td>
<td>0.656</td>
</tr>
<tr>
<td>PR</td>
<td>0.105</td>
<td>0.494</td>
</tr>
<tr>
<td>QRS</td>
<td>0.182</td>
<td>0.231</td>
</tr>
<tr>
<td>QTc</td>
<td>0.339</td>
<td>0.023*</td>
</tr>
</tbody>
</table>

*p<0.05 = statistically significant, r=Pearson correlation coefficient.

Table (8): Sensitivity and specificity of investigated cardiac biomarkers and PSS in diagnosis of cardiotoxicity

<table>
<thead>
<tr>
<th>ROC curve between Group I and Group II</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP (pg/mL)</td>
<td>&gt;320</td>
<td>53.13</td>
<td>100.0</td>
<td>100.0</td>
<td>46.4</td>
<td>80.4%</td>
</tr>
<tr>
<td>cTnI (ng/ml)</td>
<td>&gt;0.2</td>
<td>25.0</td>
<td>100.0</td>
<td>100.0</td>
<td>35.1</td>
<td>62.5%</td>
</tr>
<tr>
<td>PSS</td>
<td>&gt;2</td>
<td>37.50</td>
<td>76.92</td>
<td>80.0</td>
<td>33.3</td>
<td>56.5%</td>
</tr>
</tbody>
</table>

PPV: positive predictive value, NPV: negative predictive value.

Figure (1): Correlation between BNP and QTc

Figure (2): Receiver Operating Characteristic (ROC) curves of cTnI and BNP for the diagnosis of cardiotoxicity.
Numerous physiological processes, leading to an
other hand, hypotension occurs
chotics, Levine & Ruha, detailed
ence of
n the contrary to studies
women to drug
ing the occurrence of overt cardiotoxicity
among women was also linked to urban
tation
oven cardiotoxicity

Mean age among overall patients in the study was
4.511±9.715 years with a statistically significant
higher mean in cases with overt cardiotoxicity although
patients over 60 years old were excluded. Several
studies have identified increased age as an important
cardioxic risk factor (Naumann et al., 2013; Perez et
al., 2008; Tan-Chiu et al., 2005).

On the contrary, a study performed by Jones
et al.(2013) to assess risk of cardiac events and
mortality among users of some antipsychotics relative
to nonusers, increased risk of both cardiac mortality
and all-cause mortality was observed in younger versus
older patients.

Aging is associated with a progressive decline
in numerous physiological processes, leading to an
increased risk of health complications and disease.
Both the heart and vasculature undergo numerous
alterations during aging including hypertrophy, altered
left ventricular (LV) diastolic function, increased
arterial stiffness, and impaired endothelial function. At
the molecular level, as endothelial cells age, they
exhibit a reduction in endothelial nitric oxide
synthetase activity. At the cell level, cardiomyocytes
become more susceptible to stress, including oxidative
stress leading to decrease in absolute number of
cardiomyocytes as a result of increased apoptosis and
necrosis and a decrease in repopulation of
cardiomyocytes from cardiac stem cell reserves (North

The female predominance among patients in
the present study can be viewed in relation to the
prevalence of deliberate self-poisoning as the main
manner of intoxication and urban living as the main
residence. Studies demonstrated that females tend to
prefer auto-aggressive behaviors as intentional
poisoning compared to violent methods in suicide
attempts. In the same way, increased suicide risk
among women was also linked to urban residence
(Qin, 2005; Kaess et al., 2011; Foto-Ozdemir et al.,
2016).

No statistically significant gender difference
in the occurrence of overt cardiotoxicity was observed
in the current study. This is on the contrary to studies
suggesting a biological difference in sensitivity of
women to drug- induced cardiac arrhythmias owing to
longer QT interval from the age of puberty to old age.
However, detailed actions of gender hormones and
their role in the gender differences in QTc is not clearly
defined and requires further research (Kannankeril et
al., 2010; Rabkin, 2016).

In the current study sinus tachycardia was
observed in 73.33% of cases. This was not unexpected
as sinus tachycardia was reported as the most common
arrhythmia with TCA overdose and was attributed to
anticholinergic activity and/or inhibition of
norepinephrine uptake by TCAs. Similarly
antipsychotics cause tachycardia as a vasomotor reflex
to hypotension or due to anticholinergic effects.
(Thanacoody & Thomas, 2005; Juurlink 2015).

As regard blood pressure, normal blood
pressure was observed in a more than half of cases,
hower blood pressure changes either as hypertension
or hypotension showed statistical difference in
cardioxicity group.

TCAs and antipsychotic drugs have multiple
effects on the cardiovascular system. Early
hypertension is common with overdose as a result of
their anticholinergic effect and excess norepinephrine
in the synapse from blockade of norepinephrine
uptake. On the other hand, hypotension occurs
mainly as a result of alpha-receptor antagonism,
norepinephrine depletion. Hypotension may also reflect
decreased myocardial contractility due to sodium
channel antagonism by TCAs especially in overdose
cases (Khasawneh & Shankar, 2014; Levine & Ruha,
2012).

In the present study, tachypnea was observed in
53.33% of patients, while hyperthermia was
observed in 13.33%. The present study showed no
significant difference regarding temperature and
respiratory rate in relation to occurrence of
cardioxicity. Hyperventilation may be attributed to
arterial hypoxemia or tissue hypoxia which stimulates
peripheral chemoreflex. Also, it may be a response to
hyperthermia or anxiety. On the other hand,
anticholinergic effects of TCA and antipsychotics,
especially in the presence of seizures or agitation may
account for the associated hyperthermia ((Juurlink,
2015; Greenbaum, 2016).

Figure (3): ROC curves of PSS for the diagnosis of cardiotoxicity.
In the present study, regarding ECG findings, statistically significant difference between the two groups was found as prolonged QTc and/or wide QRS were observed in almost half of the cases (48.89%) all among overt cardiotoxicity group.

Liebelt (2008) pointed to the occurrence of ECG changes both in the setting of therapeutic and toxic doses of Antipsychotics and TCAs. Several studies reported QTc prolongation and wide QRS complex were common findings in patients with TCAs or antipsychotics overdose (Aşıkalan et al., 2010; Khalaf et al., 2011; Saleh et al., 2013; Karakılıç et al., 2016; Misra & Kumar, 2018).

The potential mechanism underlying QT prolongation by antipsychotic drugs is based on their ability to block the rapidly activating delayed rectifier potassium current (I_{Kr}), which leads to lengthening of cardiac repolarization. Regarding TCAs, they inhibit sodium channel conductance, so that phase 0 cardiac depolarization is delayed. This may cause slower conduction within the His-Purkinje fibers and ventricular myocardium, causing prolongation of the QRS complex on the ECG (Leung et al., 2012; Waring, 2012).

In the current study, neurological manifestations (either in the form of coma, seizures or agitation) showed no significant difference between group I and II. TCAs and antipsychotics induced altered mental status, agitation and seizures could be attributed to their antimuscarinic and antihistaminic action, diminished cerebral perfusion secondary to hypotension and γ-amino butyric acid antagonism (Levine et al., 2012; Ruha & Levine, 2014).

In the present study, calculated PSS for cases showed no significant difference between the two groups. Moreover, PSS at cut off point >2 was 37.50% sensitive, 76.92% specific with accuracy of 56.5% for prediction of cardiotoxicity.

These results can be interpreted in view of studies stating that PSS may not be the ideal score to be used for all global toxicological exposures. PSS has several subjective criteria, is time consuming to score, and is likely to be of little use with some types of poisonings, limiting its clinical utility. Also, being frequently modified or misapplied, makes it difficult to assess its accuracy or utility so (Schwarz et al., 2017).

On the contrary, Zaaqoq et al. (2012) found that a PSS of 2 has a sensitivity of 88% and a specificity of 64.7% for prediction and early diagnosis of cardiotoxicity. Also, Churi et al. (2012) mentioned that PSS score demonstrated excellent sensitivity with clinical outcome, thereby indicating its usefulness to predict severity in emergency centers.

In the current study, although troponin I levels ranged from 0.01-1 ng/ml with higher mean among overt cardiotoxicity group compared to group I, however this difference had no statistical significance. Similarly, this study found no association between troponin I elevation as diagnostic marker of cardiotoxicity and clinical predictors of severity of acute drug overdose due to TCA and antipsychotics: the mean values of troponin I showed no statistically significant difference in relation to pulse, blood pressure and ECG finding in addition to PSS, length of ICU and total hospital stay.

However, the current study highlighted the diagnostic ability of troponin in detection of induced cardiotoxicity with 100% specificity, 35.1% negative predictive value and 62.5% accuracy at cut-off points at values >0.02 ng/mL.

Low sensitivity of troponin I in this setting may be interpreted on the grounds of the potential for false negatives: Cardiac troponin is controversial as a marker for cell injury which does not involve cell membrane disruption such as sublethal and cytotoxic injuries and hence not associated with measurable increases in the serum. Sub-lethal injury may be present in rhythm changes, altered electrical activity, contractile dysfunction or reversible ischemic injury. Similarly, depending upon the extent of secondary necrosis, apoptotic myocardial injury in the setting of some types of cardiotoxicity may not lead to release of troponin into the serum within the diagnostic window (Wallace et al., 2004; Jaffe & Wu, 2012).

On the contrary to the present work, a large body of research demonstrated the utility of cardiac troponins monitoring potential drug-induced myocardial injury following the administration of antineoplastic drugs in both clinical and preclinical studies (Adamcova et al., 2005; Gaz & Collinson, 2005; Manini et al., 2016).

Despite the advantages of cardiac troponins of high specificity and sensitivity however a number of questions are still unanswered including the assessment of suitable cutoff for drug-induced cardiotoxicity and determination of critical diagnostic window related to the optimal timing of sample collection, which may be drug-dependent. Additionally, presence of troponin elevation implies that myocardial cell death has already occurred, hence raising questions about its role as an effective early marker of cardiotoxicity (Adamcova et al., 2005; Tan & Lyon, 2018; Pointon A & Edmunds, 2019).

As regards BNP in the present study, mean serum levels ranged from 250-600 pg/ml with significantly higher mean among overt cardiotoxicity group compared to group I. It is worth noting that BNP levels in both group I and II were both above the threshold value of elevated BNP for cardiac dysfunction has been accepted to be 100 pg/mL in the literature.

In comparison with recorded troponin I mean values, the mean values of BNP showed no statistically significant difference in relation to some clinical parameters including pulse, PSS, length of ICU and total hospital stay but correlated significantly with blood pressure changes and ECG findings namely QTc interval.

Taken together, these results may reflect the potential of BNP to serve as a biomarker to indicate sub-clinical cardiac dysfunction in the context of acute cardiotoxicity due to acute overdose by TCA and antipsychotics.

The correlation between increased BNP levels and hypotension is in accordance with Dillinger et al. (2011) who noted that serial BNP measurements...
following cardiotoxic drug poisoning are useful to identify patients at the highest risk of cardiogenic shock and in hospital mortality. Karakiliç et al. (2016) similarly detected a significant correlation between measurement of blood BNP level and degree of cardiac involvement indicated by hypotension and ECG findings in patients with poisoning by drugs having cardiotoxic potential.

BNP is a clinical indicator of cardiac hemodynamic responses and dysfunction widely accepted for diagnosis of congestive heart failure, septic shock and myocardial infarction. Clinically relevant levels of BNP have been linked to severity of left ventricular failure and predicted cardiovascular events in asymptomatic cases. Studies have shown the potential to serve as a biomarker for sub-clinical cardiac dysfunction in the context of cardiotoxicity prior to any measurable changes in traditional echocardiography (Wang et al., 2016; Pointon A & Edmunds, 2019).

In the present study, at cut-off levels >320 pg/mL BNP was superior in sensitivity (53.13 %) and higher diagnostic accuracy (80.4%) over troponin I with equal specificity (100%) in detection of induced cardiotoxicity. These data suggest that the use of BNP can increase the accuracy of clinical evaluation of cardiotoxicity.

Conclusion
TCA and antipsychotic drug overdose are related to occurrence of cardiac toxicity. Although PSS is an “at-hand” tool for evaluation of poisoning cases but it has a limited significance in this work owing to its low sensitivity and accuracy for diagnosis of cardiotoxicity and being uncorrelated to biomarkers levels. BNP level correlated with QTc interval and blood pressure changes and surpassed cTnI as a useful tool for the diagnosis of cardiotoxicity. However, both tested biomarkers are unsuitable for screening purposes.

Recommendation
Studies are needed to better characterize time-course of BNP changes in acute drug-induced cardiovascular disturbances by serial measurements of plasma levels. Moreover, combination of a cardiac biomarker approach with an ECG approach is strongly suggested and should be furtherly investigated for risk stratification of drug overdose patients and clinical prediction of acute drug-induced cardiotoxicity. As the field of prediction, detection, and management of cardiotoxicity is receiving much interest, future studies are needed to incorporate new biomarkers and their role in drug-induced cardiotoxicity.

References


Tanchiu E, Yothers G, Romond E et al., (2005): Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. Journal of Clinical Oncology. 23(31), pp.7811-7819.


Wallace KB, Hausner E, Herman E, et al., (2004): Serum troponins as biomarkers of drug-


الملخص العربي

البيبتيد المدور للصوديوم من النوع ب وتروبونين -آي كعلامات بيولوجية محتملة للتنبؤ بالسمية القلبية الناجمة عن الجرعة المفرطة من مضادات الاكتئاب ثلاثية الحلقات ومضادات الذهان

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الجرعة المفرطة من مضادات الاكتئاب ثلاثية الحلقات والأدوية المضادة للذهان يمكن أن تؤدي إلى مضاعفات قلبية حادة يمكن أن تهدد الحياة. في الطب السريري يتم استخدام البيبتيد المدور للصوديوم من النوع ب وتروبونين -آي كعلامات بيولوجية في تشخيص مرض القلب.

هدفت الدراسة إلى دراسة فائدة البيبتيد المدور للصوديوم من النوع ب وتروبونين -آي كأداة تنبؤية مبكرة للسمية القلبية الناجمة عن مضادات الاكتئاب ثلاثية الحلقات والأدوية المضادة للذهان والعلامة المترافقة مع هذه السمية.

الطريقة: سجلت الدراسة 45 مريض تم حجزهم في وحدة العناية المركزة في مركز علاج التسمم ب المستشفى بسموحة عن حادثة سماع المسمى بسبب جرعة مفرطة من مضادات الاكتئاب ثلاثية الحلقات و/أو من مضادات الذهان. جمعت البيانات التي تم جمعها البيانات الاجتماعية، الديموغرافية، وطريقة العلاج، والمفاهيم السريرية، وظروف رسم القلب، نقاط شدة السمية، وخصوصيات السمية، وكيفية التشخيص بمساعدة السمية، والوقت في المستشفى، والنتائج.

النتائج: على عكس مستوى تروبونين -آي، كان مستوى البيبتيد المدور للصوديوم من النوع ب أعلى بكثير في مجموعة السمية القلبية. ارتبط كل من مستوى البيبتيد المدور للصوديوم من النوع ب وتروبونين -آي مع تغيرات رسم القلب واضطرابات المناعة. وكانت مستويات المؤثرات الحيوية غير مرتبطة بشكل كبير مع أي من نقاط شدة السمية، وإجمالي الإقامة، وجرعة العناية المئوية. كان نقاط شدة السمية ذات حساسية ودقة متفاوتة لتقييم السمية القلبية. أظهر كل من البيبتيد المدور للصوديوم من النوع ب وتروبونين -آي عند مستوى محددة خصوصية 100 % مع حساسية 53,123 % و 0.5% و 43,125 % على التوالي.

النتائج: تجاوز البيبتيد المدور للصوديوم من النوع ب وتروبونين -آي كأداة مفيدة لتشخيص السمية القلبية بسبب الجرعة المفرطة من مضادات الاكتئاب ثلاثية الحلقات والعقاقير المضادة للذهان على الرغم من أنه غير مناسب لأغراض الاستطلاع.

الوصول: هناك حاجة إلى دراسات تلقيح أدق للتحليل الدقيق للتغيرات البيولوجية لبيبيتيد المدور للصوديوم من النوع ب في الاستجابات القلبية الناجمة عن الأدوية وذلك عن طريق الفيامات المتعاثلة لمستويات البلازما. علاوة على ذلك، يقترح بناء الجيل بين هذين يتضمن معتمد على الفيامات البيولوجية الفيما وأخر يوم على تخزين القلب، مع وجب إجراء مزيد من البحث على ذلك من أجل تقييم الجرعة المفرطة للاستجابة القلبية وتروبونين السريرية لسمية القلب الناجمة عن الأدوية، نظرًا لأن حالات التنبؤ بالسمية القلبية والكشف عنها وإدارتها يعتمد بشكل كبير، يتم إجراء دراسات مستقبلية لإجراء مؤشرات جديدة ودورية في نسب القلب الناجم عن الأدوية.

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