ORIGINAL ARTICLE

Arterial Blood Lactate Level as a Biomarker of Risk among Antipsychotics Poisoned patients

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ABSTRACT

Aim: Antipsychotics (APs) are commonly used in suicidal attempts among their users or their relatives. This study had investigated early arterial blood lactate levels as a biomarker for severity and outcome in APs poisoned patients.
Methods: Male patients attended to Toxicology unit of Mansoura Emergency Hospital was involved in this study during the period from September, 2013 to January 2015. The Clinical data were collected in addition to the serum levels of the ingested APs. Arterial radial blood lactate levels were assessed on admission and later on after 48 hrs.
Results: Thirty cases were studied. Cases were intoxicated with chlorpromazine (CPZ), Risperidone (RIS), haloperidol (HAL) or olanzapine (OLZ). Most cases were manifested by tachycardia and disturbed conscious level. Lactate levels were found to be correlated with the ingested APs drugs serum levels (*P*= 0.0028, <0.0001, <0.0001 and 0.0073 for CPZ, HAL, OLZ and RIS respectively; Spearman rank correlation). Furthermore, Lactate levels were inversely correlated with systolic blood pressure, Diastolic blood pressure and Glasgow coma scale (*P*<0.0001 for each clinical parameter; Spearman rank correlation). However, lactate levels were directly correlated with the pulse of the studied cases (P=0.0007; Spearman rank correlation). In addition, there was statistically significant difference in arterial lactate levels between discharged, wards and intensive care unit admitted cases (P<0.0001; ANOVA).
Conclusion: Arterial lactate levels can be used as a biomarker with important prognostic value in APs poisoned patients' risk assessment.
MeSH words: Lactate, antipsychotics, Biomarkers, overdose.

INTRODUCTION

Antipsychotics (APs) are widely used medications, which are mainly prescribed to manage psychosis in schizophrenia and bipolar disorders. They are classified by different ways. They are mostly classified as typical and atypical preparations. Both generations of medication tend to block the brain's dopamine pathways receptors. The newer atypical preparations are targeting also serotonin receptors[1].

The degree of potency of the typical preparations is directly proportional to their dopamine receptors antagonism, which varies from the high potency as haloperidol to the lower potencies as chlorpromazine (CPZ) and loxapine[2]. Mostly the new preparations are serotonin (5HT2A) antagonists with mild D2 antagonists except risperidone (RIS), which has a moderate- or high-potency traditional neuroleptics[3].

In 2003, poison information centers in the United States reported about 37,126 APs exposures. Of these reports, 32,422 were related to atypical APs, while 4704 cases were phenothiazines toxicities [4]. Other APs were not reported. By comparison, in 1993, phenothiazines were the only cause of APs overdoses and were the subject of 10,975 calls, despite 27% fewer total calls to poison centers[5]. The changing pattern of AP overdose reflects the recent evolution of new APs drugs prescription pattern[6].

The vast majority of poison center calls related to intentional overdoses in patients aged 19 years or older with the majority showing a good outcome. Some observational data suggest that the low-potency, typical APs, such as thioridazine, chlorpromazine (CPZ) and mesoridazine, are associated with more fatal toxicities than other APs[7]. A retrospective cohort study supports this observation that thioridazine is associated with greater adverse cardiovascular toxicity than other APs[8].

Toxicity from the APs mostly occur following intentional suicidal overdose. Dose-related toxicity varies according to the ingested APs agents, patients ages, habituation, and comorbid conditions. Toxic effects are often an overextension of an agent's pharmacologic effects. Because of a large toxic-to therapeutic ratio, fatalities are rare. Antipsychotics overdose can produce a spectrum of toxic manifestations affecting multiple organ systems, but most serious toxicity involves the CNS and cardiovascular system. Some of these manifestations are present to a minor degree during therapeutic use. They tend to be most pronounced during the early period of therapy but disappear with continued use[9,10].

Increased lactate levels were previously observed as a laboratory finding in patient on APs therapy and higher levels of lactate were observed with occurrence of APs induced side effects including extrapyramidal symptoms (EPSs)[11,12]. Generally, increased lactate is associated with increased morbidity and mortality in patients with chronic illnesses or critically ill patients[13]. In this study the manifestations of APs' overdose, in patients attended to Mansoura emergency hospital toxicology unit, were studied in relation to their arterial blood lactate level to evaluate lactate as a biomarker for the fatality of APs-induced toxicities and their outcomes.

MATERIALS AND METHODS

Male patients attended to Toxicology unit of Mansoura Emergency Hospital was involved in this study after a

signed informed consents from participants or their caregivers. The study lasted from September, 2013 to January 2015. Exclusion criteria included patients with co-ingestion of multiple drugs, patients on treatment for other chronic illness and tobacco smokers. Women were excluded due to significant changes in lactate levels during menstrual cycle[14].

As a part of their management, patients were assessed by conscious level by Glasgow coma scale (GCS), pulse, blood pressure, temperature, pupil diameter and ECG. Serum levels of the ingested APs were measured. Serum levels for other drugs were assayed to exclude common co-ingestion as paracetamol, phenytoin and valproic. Also urine samples were collected and screened for substances of abuse (cannabis, benzodiazepine, barbiturates and tramadol). Cases were managed according to their clinical conditions. Blood lactate were assessed using arterial blood samples (femoral or radial). Blood lactate level was assessed on admission with arterial blood gases sample and later on after 48 hrs. The normal basal lactate levels in a healthy adult are <1.5 mmol/L [15].

Statistical analysis: All statistical procedures were performed using PRISM 5 (GraphPad Software Inc., San Diego, CA). As data showed non parametric distributions, Kruskall Wallis and multiple comparisons Dunn's post-tests were used. Spearman rank correlation test was used for the correlation studies. The statistical significance is defined as P<0.05.

RESULTS

The study was conducted to evaluate the arterial lactate level as a prognostic factor for APs poisoned patients among male patients attended to Mansoura Toxicology unit. After consenting, thirty patients were enrolled in the study. The demographic and clinical data of patients involved in the study are shown in table 1. Cases had attended to the toxicology unit within 1-3 hours after ingestion of the tablets. According to the history, only 16 patients involved in the current study were on APs therapy, while the other 14 patients have no history of psychic illness.

In the toxicology unit emergency room, patients were evaluated. Most of cases were presented by disturbed conscious level with Glasgow coma scale (GCS) <15 in 80% of cases. Only eight cases were represented by GCS conscious level ≤12. Also majority of cases showed cardiovascular manifestations in the forms of tachycardia (Heart rate >90 in 80 % of cases) and hypotension (systolic blood pressure <90 mmHg in 20% of cases).

Intravenous line was established in all patients and isotonic saline (0.9 NaCl) was given in a dose 10-20 ml/kg. Continuous monitoring of pulse and blood pressure and oxygen saturation was conducted. Regarding treatment, only 10 cases were conscious and cooperative and managed by 60 gm activated charcoal. Serum levels for the ingested APs were evaluated in venous blood samples, while lactate level were studied using radial arterial blood samples. Results for the APs and lactate levels are shown in table 2. There were significant correlations between arterial blood lactate and the studied clinical parameters and serum levels of the APs as shown in figure 1.

According to the discharge or admission decision of the studied cases, only nine cases were admitted to intensive care unit. Another nine cases were admitted to the ward, while 12 cases were discharged after 6 hours monitoring in the emergency room without appearance of any symptoms. There was a significant difference between the fore-mentioned three groups regarding their lactate level (P<0.0001; Kruskall Wallis test) (Fig. 2).

Table 1: Demographic and clinical data of the studied cases (n=30)

Number	Total (30)
Age	
Mean (SD)	35.3±11.5
Range	12-43 years
Taken antipsychotic	
CPZ	7 (23%.3)
HAL	12 (40%)
OLZ	4 (13.4%)
RIS	7 (23.3%)
GCS	
15	6 (20%)
12-14	16 (53.3%)
12-9	8 (26.7%)
Pulse :	
60-90 B/min	6 (20%)
91-120 B/min	18 (60%)
>120 B/min	6 (20%)
Systolic blood pressure:	
<90	6 (20%)
90-140	24 (80%)
Diastolic blood pressure	
<60	6 (20%)
60-80	24 (80%)
Respiratory rate: Mean (SD)	16±2.2 cycle/min
Temperature:	
Mean(SD)	38±0.64˚C
Fate:	
Observation and discharges	12 (40%)
Ward admission	9 (30%)
ICU	9 (30%)

Table 2: serum level of ingested APs and arterial blood lactate studied cases:

Ingested APs	Patients Serum level Mean ± SD (µg/ml)	Therapeutic level (µg/ml) [16]	Serum lactate (mmol/l)
CPZ	1.47±0.17	0.01-0.5	2.8±0.04
HAL	0.16 ±0.09	0.006-0.245	2.88±0.47
OLZ	0.052±0.09	0.009-0.023	2.9±o.5
RIS	0.04± 0.017	0.003-0.012	2.9±0.43

Figure 1: Correlation of Arterial blood lactate (ABL) levels with and antipsychotics serum levels, systolic blood pressure (SBP mmHg), Diastolic blood pressure (DBP mm Hg), Pulse rate (beat/minute) and conscious level (GCS).

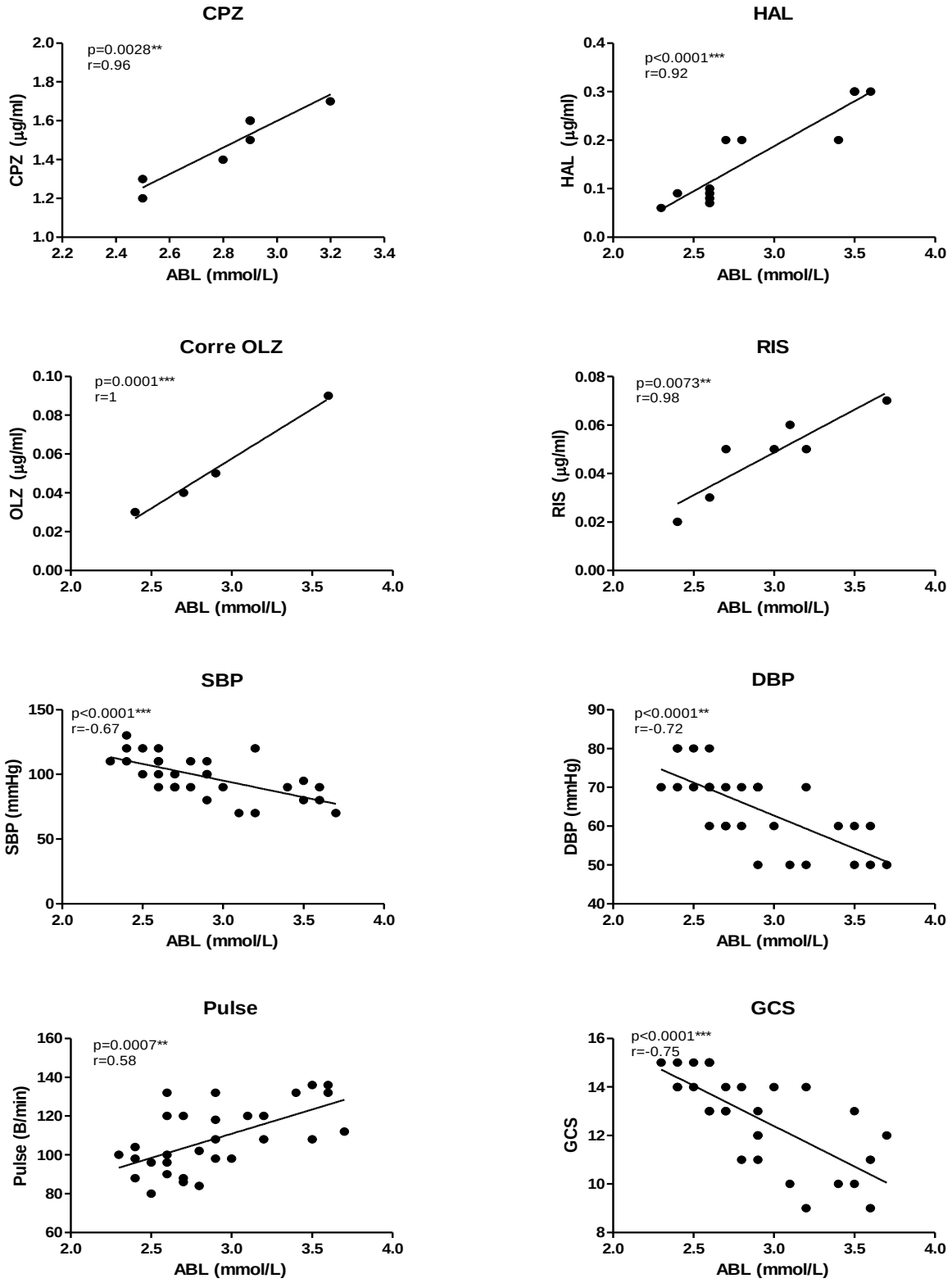
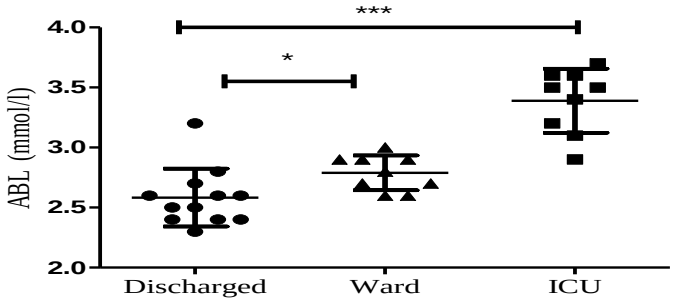


Fig. 2. Arterial blood lactate (ABL) level of the studied cases in relation to the clinical decision regarding admission or discharge. There was statistically significant difference in lactate level among the three groups (P<0.0001; Kruskall Wallis). Dunn's multiple comparisons post-test showed highly significant difference between the ICU admitted patients are each other group separately. Data were shown as means± standard deviation. * means *P*-value <0.05 and *** means *P*-value<0.0001.



DISCUSSION

The present study had evaluated that arterial blood lactate levels as a biomarker of fatality in APs intoxicated patients among the male patients attended to Mansoura emergency hospital (toxicology unit) within the period of the study. Majority of the enrolled cases were caused by typical preparations overdose (63% of cases), which is different from previously reported toxicology patterns in USA[4]. This is mainly due to more popularity of typical preparations prescriptions among the cases due to economic reasons as most of patients were not covered by insurance system and they could not afford the prices of the newer preparations all over the length of therapy courses.

All symptomatizing cases in the present study showed symptoms within 90 minutes after ingestion. Disturbed conscious level was the most common presentation in this study. This is in accordance with the previous reports about APs overdose[17-20]. Anticholinergic manifestations in the forms of hyperthermia and dilated pupil were seen in cases with CPZ and OLZ. Miosis is more likely to occur in seriously poisoned patients with both atypical and typical agents; it has been described in 75% of adults after phenothiazine overdose [18]. Hypotension and tachycardia were the most common manifestations in the studied cases. These findings are in agreement with the previously published data about APs overdose manifestations[9,10,21].

Serum lactate level was highly correlated with the clinical data which was found in the enrolled cases (hypotension, tachycardia and disturbed conscious level). Interestingly it was also highly correlated with the APs' serum level. It was reported before that APs caused elevated lactate level on patient on their therapeutic doses which was associated with the appearance of the commonly reported APs-induced side effects including EPSs [11,12]. This increase in arterial blood lactate levels in the therapeutic and toxic levels can be explained by the reported inhbitory effect of APs on mitochondrial respiratory chain[22-26]. This effect will alter the mitochondrial membrane potential and will negatively affect adenosine triphosphate (ATP) production via the oxidative phosphorylation of glucose. This will shift the metabolism toward the anaerobic side with increased lactate production. The current results found that the manifestations of overdose were significantly correlated to the lactate level. This means that APs effect on mitochondria and glucose metabolism plays a major role in APs overdose-induced toxic manifestations, hence serum lactate level can be considered as a biomarker of fatality in such cases. Interestingly, data revealed that early arterial blood lactate level was relevant to the clinical decision regarding admission or discharge. Furthermore, case with higher lactate levels were admitted to ICU, according to their clinical data. This means that arterial blood lactate level may have a highly important clinical prognostic value in APs overdosed patients.

CONCLUSION

From the present study data, it can be concluded that arterial blood lactate level have great potential to be used a s a biomarker in APs overdosed males as it was found to be well correlated with the important clinical manifestations seen in the studied cases. Furthermore, early arterial lactate levels were highly prognostic regarding the clinical decision regarding admission or discharge. These data are in need for further larger studies for more data robustness.

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