

Metabolic Acidosis in Multi Drug Poisoning with Antidepressants and Antipsychotics

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Received: 30-08-2020.
Accepted: 29-01-2021.
Published: 03-08-2021.

INTRODUCTION

Among the causes of mortality in the world, poisoning has particular importance. Epidemiology and characteristics of patients admitted to the emergency departments due to acute poisoning are reported in many studies.^[1-4] Antidepressants (Ad) and antipsychotics (Ap), mainly used for suicidal attempts, are often readily available for depressed patients with mental disorders. Elevated risks for mortality, including sudden cardiac death associated with the use of both Ap and Ad, have been evaluated previously.^[5-10] Significant increases in prescribing for Ad and Ap drugs in different

ABSTRACT

Objective: In this study, we evaluated the predictive factors for the occurrence of metabolic acidosis in patients with multi-drug poisoning, including antidepressants (Ad)/antipsychotics (Ap). **Methods:** This cross-sectional study was carried out in the referral poisoning center, Khorshid University Hospital, affiliated with Isfahan University of Medical Sciences. All patients with multi-drug ingestion, including Ad/Ap, were included in the study. Patients were divided into two groups with and without metabolic acidosis. Demographic factors, time from ingestion to admission, clinical manifestations, length of hospital stay, and outcome were compared in two groups. Binary logistic regression was used to identify factors associated with the risk of metabolic acidosis occurrence. **Findings:** Among the 206 evaluated patients, 45 patients (21.8%) had metabolic acidosis whom the majority were female (73.3%) with intentional purposes (77.8%). 31.1% of the patients with metabolic acidosis had tachycardia on admission ($P = 0.03$). Among all variables, time from ingestion to admission ($P = 0.02$) and lengths of hospital stay ($P = 0.002$) were significantly different between patients with and without metabolic acidosis. Tachycardia on admission (adjusted odds ratio [OR], 2.24; 95% confidence interval [CI]: 1.05–4.76; $P = 0.036$) and time from ingestion to admission (adjusted OR, 1.06; 95% CI: 1.00–1.13; $P = 0.04$) were also the predictive factors in occurrence of metabolic acidosis. Most of the patients survived without any complications (94.6%), of whom 72.3% had no previous underlying somatic diseases ($P = 0.05$). **Conclusion:** Admission tachycardia and the time elapsed from ingestion to admission may be considered important factors for predicting metabolic acidosis in multi-drug poisoning, including Ad/Ap.

KEYWORDS: Antidepressant, antipsychotic, metabolic acidosis, outcome, poisoning, tachycardia

age groups of adults during the 2011–2021 periods in the United States has been observed, and increases in the rates of mortality involving poisoning by psychotropic drugs were more significant than increases in prescribing these medications especially for persons aged 45–64 years.^[11]

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How to cite this article: Eizadi-Mood N, Dehghanzad S, Sabzghabae AM, Farajzadegan Z. Metabolic acidosis in multi drug poisoning with antidepressants and antipsychotics. J Res Pharm Pract 2021;10:65-70.

Access this article online	
Quick Response Code: 	Website: www.jrpp.net DOI: 10.4103/jrpp.JRPP_20_106

Acute poisoning with a combination of Ad and AP may have additive effects on central nervous and cardiovascular systems, changing the level of consciousness, frequency of seizure, arrhythmia, hypotension, and metabolic acidosis and the therapeutic outcome of the patients. Metabolic acidosis as one of the toxicity manifestations of Ad, particularly tricyclic Ad, may cause decreased cardiac output, hypotension, and cardiac arrhythmia, leading to patient death. Hypoxia, hypotension, and seizure also are the predisposing factors for metabolic acidosis, which increases the severity of poisoning.^[12-14]

As multi-drug poisoning, including the combination of Ad and Ap, is a common type of toxicity in our referral poisoning center in the central part of Iran. Hence, we performed a study to compare the clinical manifestations and treatment outcome of the patients with multi-drug poisoning, including Ad/Ap in patients with and without metabolic acidosis, and to find the prognostic factors for the occurrence of metabolic acidosis for clinic-epidemiological variables.

METHODS

This cross-sectional study was conducted in Khorshid University Hospital, affiliated with Isfahan University of Medical Sciences. The study protocol was reviewed and approved by the institutional board of human studies, research project number #294160. This medical center is the primary referral medical focal point for poisoning emergencies in the central part of Iran, which is facilitated, staffed, and designed to manage acute poisoning cases. Approximately 600 poisoned patients are admitted monthly there. All patients with acute poisoning who ingested Ad/Ap during the study period were included. Patients with underlying diseases causing metabolic acidosis were excluded from the study. Furthermore, patients discharged <6 h by his/her consent and those who did not have venous blood gas (VBG) analysis reports were also excluded from the study.

After the admission of patients and performing the guideline of the poisoning management department for stabilizing the patients' vital signs, they were screened for the study's inclusion criteria. Clinical data of the eligible patients' were recorded in the patients' data collection form. Patients were divided into two groups; with and without metabolic acidosis. Gender, age, type of exposure (accidental, suicide, drug of abuse), vital signs on admission (heart rate, respiratory rate, arterial blood pressure, temperature), clinical manifestations, laboratory tests including parameters of blood gas analysis [HCO_3^- , PCO_2 , pH, BE (base excess), PaO_2],

blood sugar, serum sodium (Na^+), serum potassium (K), serum creatinine (Cr), hematocrit, white blood cell count and Glasgow Coma Score, the time elapsed from ingestion to admission, length of hospital stay, and outcome (survived without complication and survived with complication or death) were recorded. Metabolic acidosis was considered in adults as pH <7.35, HCO_3^- <24 mmol/l; and in children^[15,16] as pH <7.35, and HCO_3^- <20 mmol/l in VBG analysis. Data were analyzed using SPSS16 (version 16, SPSS Inc, Chicago, IL) statistical software. A $P < 0.05$ was considered statistically significant. We used mean (\pm standard deviation [SD]) or mean (\pm standard error) and medians to summarize data regarding age, time from ingestion to admission, length of hospital stay.

Kruskal–Wallis test was used for comparisons of median in different patients groups. ANOVA or independent student *t*-test was used to compare the means; and Chi-square/Fisher's exact test to compare the frequency distribution of qualitative factors. The binary logistic regression analysis (backward conditional stepwise method) calculated odds ratio (OR) as the estimate of the relative risk of the different variables for the occurrence of metabolic acidosis. For simplicity, survived with complication and death were combined as a single ordinal variable, comprising two possible outcomes: (0) survived without complication, (1) complication/death. Discrimination was tested using the area under receiver operating characteristic (ROC) curves and classification matrices. The area under ROC curve, sensitivity, and specificity at the best cut-off point were determined to predict metabolic acidosis factors. The best cut-off point was that which maximized the sum of specificity and sensitivity in the ROC analysis. This cut-off point was also used to calculate the predicted and observed metabolic acidosis. The Chi-square or Fisher's exact test was applied to compare the metabolic acidosis rate below and above the best cut-off points for predicted variables.

RESULTS

We reviewed 268 sets of patients' records, and 31 patients were excluded considering including and excluding criteria. Therefore data of 206 patients were evaluated in this study (64 male and 142 female). Among the 206 patients, 45 patients (21.8%) had metabolic acidosis whom the majority were female (73.3%) with intentional suicidal purposes (77.8%). There were no significant differences between the two groups with respect to the level of consciousness, hypotension, seizure, hypoxia, vital signs in the initial evaluation for metabolic acidosis. However, tachycardia, time

from ingestion to admission, and length of hospital stay were different between the two groups [Table 1]. Data for the time elapsed from ingestion to the hospital admission were available for 172 cases (72.6%). The rate of abnormal ECG was 41% and 42.3% in patients with and without metabolic acidosis, respectively ($P = 0.89$). The mean \pm SD of heart rate in

patients who ingested Ad/AP was higher (99.50 ± 22.43 ; median 96) compared to those ingested Ad/AP with other drugs (89.02 ± 18.78 ; median 86) ($P = 0.04$). The time from ingestion to admission was higher in patients with tachycardia (6.01 ± 1.43 [median, 4]) compare to patients without tachycardia (3.83 ± 0.37 ; [median, 2.5]) on initial evaluation ($P = 0.036$).

Table 1: Patients' clinical characteristics in the two groups with and without metabolic acidosis

Variables	Patients with metabolic acidosis (n=45)	Patients without metabolic acidosis (n=161)	Total (206)	P
Age (year), mean \pm SD (median)	30.82 \pm 10.34 (30)	29.84 \pm 11.50 (28)	30.05 \pm 11.24 (29)	0.60
Gender, n (%)				
Female	33 (73.3)	109 (67.7)	142 (68.9)	0.47
Male	12 (26.7)	52 (32.3)	64 (31.1)	
Type of exposure, n (%)				
Intentional	35 (77.8)	113 (70.2)	148 (71.8)	0.57
Accidental	0	1 (0.6)	1 (0.5)	
Unknown	10 (22.2)	47 (29.2)	57 (27.7)	
Level of consciousness, n (%)				
Oriented	12 (26.7)	57 (35.5)	69 (33.5)	0.31
Lethargic/obtundation	24 (53.3)	87 (54)	111 (53.9)	
Stupor/coma	4 (8.9)	7 (4.3)	11 (5.3)	
Agitation	5 (11.1)	10 (6.2)	15 (7.3)	
Hypotension, n (%)				
Yes	2 (4.4)	5 (3.1)	7 (3.4)	0.64
No	43 (95.6)	156 (96.9)	199 (96.6)	
Seizure, n (%)				
Yes	2 (4.4)	4 (2.5)	6 (2.9)	0.61
No	43 (95.6)	157 (97.5)	200 (97.1)	
Hypoxia, n (%)				
Yes	34 (75.6)	131 (81.4)	165 (80.1)	0.38
No	11 (24.4)	30 (18.6)	41 (19.9)	
Tachycardia, n (%)				
Yes	14 (31.1)	27 (16.8)	41 (19.9)	0.03
No	31 (68.9)	134 (83.2)	165 (80.1)	
Vital signs, mean \pm SD (median)				
SBP (mmHg)	119 \pm 17.60 (115)	118.67 \pm 16.65 (120)	118.74 \pm 16.82	0.90
DBP (mmHg)	75.66 \pm 12.18 (75)	74.76 \pm 11.26 (75)	74.96 \pm 11.44	0.64
Heart rate (per min)	94.37 \pm 16.69 (95)	88.43 \pm 19.67 (85)	89.73 \pm 19.17	0.06
Respiratory rate (per min)	18.70 \pm 6.68 (18)	18.24 \pm 4.61 (18)	18.34 \pm 5.12	0.59
Time from ingestion to admission (h)				
Mean \pm SE (median)	6.06 \pm 0.99 (4)	3.79 \pm 0.44 (2)	4.26 \pm 0.41 (2.5)	0.025
Ingested toxin, n (%)				
Ad/AP	4 (8.9)	10 (6.2)	14 (6.8)	0.44
Ad/AP+sedative hypnotics	7 (15.6)	37 (23)	44 (21.4)	
Ad/AP+cardiovascular	1 (2.2)	13 (8.1)	14 (6.8)	
Ad/AP+anticonvulsants	3 (6.7)	12 (7.5)	15 (7.3)	
Ad/AP+other medications	30 (66.7)	89 (55.3)	119 (57.8)	
Length of hospital stay (h), mean \pm SE (median)	38.43 \pm 10.78 (19)	19.18 \pm 1.29 (15)	23.39 \pm 2.60 (15)	0.002
Outcome, n (%)				
Survived without complication	42 (93.3)	153 (95)	195 (94.7)	0.64
Survived with complication	3 (6.7)	6 (3.7)	9 (4.3)	
Death	0	2 (1.2)	2 (1.0)	

Data are presented as mean \pm SD (median) or mean \pm SE (median) or n (%) where appropriate. SBP: Systolic blood pressure, DBP: Diastolic blood pressure; Ad: Antidepressants; AP: Antipsychotics, SD: Standard deviation, SE: Standard error

Most of the patients survived without any complications (94.6%), of whom 72.3% had no previous underlying somatic diseases [$P = 0.05$]. Four patients (8.9%) with metabolic acidosis and five patients (3.1%) without metabolic acidosis were intubated ($P = 0.09$). None of the patients in both the groups had hyperkalemia on initial evaluation. The mean (SD) serum potassium level was 3.89 (0.39) and 3.94 (0.43) mEq/l in patients with and without metabolic acidosis, respectively ($P = 0.51$).

Based on logistic regression analysis, it was shown that among all variables, tachycardia on admission and time elapsed from ingestion to hospital admission were significant predictive factors for metabolic acidosis when adjusted for age and gender. Patients with tachycardia on admission had 2.24 times more chance of metabolic acidosis [Table 2].

ROC curves were constructed by varying the cut-off point for each variable and plotting the true-positive rate (sensitivity) by the false-positive rate (1-specificity) at each point. For the two predicting variables, the area under the ROC curve, sensitivity, and specificity at the best cut-off point were determined [Table 3] and compared. There was no statistically significant difference between time from ingestion to hospital admission and initial heart rate of the patients in terms of area under ROC Curve to predict the occurrence of metabolic acidosis. For prediction, the best cut-off points were 3 h for the time elapsed from ingestion to hospital admission and 92 for heart rate. The metabolic acidosis rate differed significantly below and above the best cut-off points for heart rate (60% vs. 31.9%) in patients with and without metabolic acidosis, respectively ($P = 0.001$). Furthermore, the rate of metabolic acidosis was higher in patients presented after 3 h of toxin ingestion (69.4%) compared to those presented after 3 h (44.1%), which was statistically significant ($P = 0.007$).

Table 2: Relative risk of the determinants for the occurrence of the outcomes

Parameters	β	P	Adjusted OR (95% CI)
Tachycardia	0.80	0.036	2.24 (1.05-4.76)
Time from ingestion to admission	0.06	0.049	1.06 (1.00-1.13)

β : Estimated coefficient, OR: Odds ratio; CI: Confidence interval

Table 3: Classification table for the determinants variables

Variables	Best cutoff point	Sensitivity (%)	Specificity (%)	ROC area, mean \pm SD (95% CI)
Time from ingestion to admission	3	70	56	0.65 \pm 0.05 (0.53-0.75)
Heart rate	92	60	70	0.63 \pm 0.04 (0.54-0.72)

ROC: Receiver operating characteristics, CI: Confidence interval, SD: Standard deviation

DISCUSSION

In this study, the prevalence of metabolic acidosis in multi-drug poisoning, including the combination of Ad/Ap and its prognostic factors, was investigated. Although studies have been conducted on mixed drug poisoning, there has been no study on the prevalence of metabolic acidosis. The results showed 21.8% of the patients with multi-drug poisoning, including Ad/Ap had metabolic acidosis. However, no patient died, and three patients developed medical complications. Previously, a significant relationship between metabolic acidosis and death in patients with aluminum phosphide toxicity,^[17] metformin poisoning,^[18] and salicylate poisoning^[19] is reported. Also, the effect of metabolic acidosis on the prognosis of acetaminophen poisoning has been evaluated in the study of Hegazi and colleagues.^[20]

Our results showed 68.9% of the patients were female, which is compatible with other studies. According to a published article by the National Institute for Drug Abuse, women are more likely to be at risk of anxiety disorders, depression, and sleep disorders, and therefore use more Ad and sedative-hypnotics drugs. The cases of women referring to the emergency department for over-dose of these drugs are more.^[21-23] In a study on acetaminophen poisoning cases about the association with metabolic acidosis, the female gender has been introduced as a predictive factor.^[24]

The majority of our patients were young. The average age of patients poisoned with Ad/Ap in the study performed in the University of Odense, Denmark, was 37 years.^[25] Also, in another study by Ngo and colleagues on quetiapine poisoning, the average age of the patients was 35-year-old.^[26] Emotional excitement, unemployment, family, and economic problems may be the risk factors.

Most patients ingested drugs for suicide attempts which is compatible with other studies.^[27,25] In our study, the most common drugs ingested with Ad/Ap were sedative-hypnotics, which may be due to prescribing benzodiazepines for patients with mood disorders by the main drug concurrently.^[21-23]

There was a significant difference between patients with and without metabolic acidosis with respect to time from ingestion to admission. Time from ingestion to admission was also a prognostic factor for the occurrence of metabolic acidosis. Patients who presented to the

hospital after 3 h had more chance of metabolic acidosis occurrence, which may be compatible with the peak effects of Ad/Aps for developing clinical manifestations. In a study performed by Folk and colleagues, the antidepressant overdose risk assessment system was sensitive to distinguish the high risk and low risk poisoned patients with Ad, and the time from ingestion to admission was 6 h in this criteria.^[28] In another study, the median time from ingestion to admission was 2 h.^[25] Factors such as vomiting after toxin ingestion and variability in people with respect to toxico-kinetics may be the reason for the difference in all studies.

The mean blood pressure, heart rate, and respiratory rate on admission were normal in both groups and did not differ significantly. Although changes in blood pressure and heart rate are some of the complications of antipsychotic antidepressant toxicity, these complications may have been compensated due to the concurrent use of these drugs with others, including sedative-hypnotics.^[12] As we found, there was a higher heart rate in patients' ingested Ad/Ap compare to others. Metabolic acidosis causes decreased cardiac output, hypotension, and cardiac arrhythmia, which lead to patient death. Two patients with metabolic acidosis had hypotension on admission time. Moreover, there was not a significant difference between patients with and without metabolic acidosis with respect to abnormal ECG. In patients with metabolic acidosis, 41% had abnormal ECG, and 31.1% had tachycardia. In another study, 25% of the patients had long QTc, and 49% had tachycardia.^[25]

Although hypotension, hyperkalemia, and seizure can be risk factors for metabolic acidosis, in our study small number of patients presented with hypotension ($n = 7$) and seizure ($n = 6$). Also, the serum potassium level in the initial evaluation was within the normal range in all patients. However, the severity and duration of hypotension and seizure are essential factors in producing metabolic acidosis.

The average duration of hospitalization was 38 h in the group with metabolic acidosis, higher than 17 h without metabolic acidosis. It may be due to the severity of clinical manifestations in the patients with metabolic acidosis, which require more hospitalization for the treatment. In a study conducted in Denmark, the average duration of hospitalization was 16.7 h, and 7.6% of the patients were afflicted.^[25] Also, in our study, 94.6% of the patients recovered without any complications. This is in concordance with another study in which 92.4% of patients had uncomplicated recovery.^[25] Tachycardia on admission was also a predictive factor for metabolic acidosis occurrence. We could not find any study in this regard.

Multi drug poisoning, including Ad/Ap, was seen more in women, young people, and for suicidal purposes. Time from ingestion to admission and tachycardia were predictive factors of metabolic acidosis occurrence. The outcome was not different between patients with and without metabolic acidosis.

AUTHORS' CONTRIBUTION

Nastaran Eizadi-Mood and Ali Mohammad Sabzghabae proposed the idea, Ziba Farajzadegan proposed the study design, Saba Dehghanzad evaluated and abstracted the patients' data, Ziba Farajzadegan and Nastaran Eizadi-Mood analyzed the data, and Nastaran Eizadi-Mood and Ali Mohammad Sabzghabae drafted the manuscript. All authors have revised the drafted manuscript and have the responsibility of accuracy and data integrity.

Acknowledgment

The authors would like to thank Prof. Farzad Gheshlaghi and Dr. Ghlamali Dorvashy for their kind help and support.

Financial support and sponsorship

This study was a thesis project for a medical intern (Saba Dehghanzad) and was financially supported by the vice-chancellery of research and technology of Isfahan University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

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