Original Article

What are the Predictive Factors for the Treatment Outcomes in Multi Drug Poisoning Including Antidepressants/Antipsychotic Drugs?

Abstract

Background: There have been studies on the outcome of acute intoxication with antidepressants or antipsychotics. We performed outcome prediction analysis in acute poisoning patients with antidepressants/antipsychotics with or without combination with other drugs. **Materials and Methods:** A cross-sectional study was performed in Khorshid (PBUH) University Hospital affiliated with Isfahan University of Medical Sciences from March 2016 to May 2017. Patients with acute poisoning ingested antidepressants and antipsychotics with or without other drugs were included in the study. The outcome was categorized as survived without complications and complications/death. Binary regression analysis was performed for outcome prediction. **Results:** The data from 239 patients were analyzed. Most of the patients were female (68.2%), 5.9% of patients admitted to the Intensive Care Unit. About 94.99% of patients survived without complications. There was a significant difference between patients with and without complications with respect to the level of consciousness, hypotension, seizure, electrocardiography findings, pulse rate after 24 hours (h) of admission, and need to endotracheal intubation ($P < 0.0001$). Binary logistic regression analysis showed admission level of consciousness (stupor/coma) (odds ratio [OR] =8.07; $P = 0,005$), hypotension (OR = 12.16; $P = 0.001$), seizure (OR = 11.15; $P = 0.009$), tachycardia after 24 h of admission (OR = 22.50; $P = 0.003$), and need for endotracheal intubation (OR = 10.47; $P = 0.002$) were determinant factors in outcome prediction. **Conclusions:** Stupor/coma and hypotension were the predictive factors for outcome. Patients with seizure and tachycardia after 24 h of admission; and those intubated and received mechanical ventilation had a higher chance of complications.

Keywords: *Antidepressant, antipsychotic, complication, outcome, poisoning*

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Introduction

Acute poisoning is among the most common causes of mortality. A number of presentations with multidrug intoxication have been reported in some studies.[1,2] Because of drug toxicokinetics and metabolism, coingestion of drugs may have different effects on severity and complications.[3] Demographic factors, ingested agents, length of hospital stay, and outcome of poisoning in multidrug intoxication may not be the same in different societies due to drug availability, the level of diagnostic tests as well as treatment facilities. Mortality rates may be low in countries with legislative restrictions on drug availability, good quality of supportive care, and adequate antidote supplies.

Combination of antidepressants and antipsychotics with and without other drugs may have additive effects on a variety of clinical manifestations of their toxicity including seizure, decreased level of consciousness, arrhythmia, hypotension, serotonin syndrome, as well as the outcome of the patients. There have been studies on the effects of intoxication with antidepressants or antipsychotics alone in the outcome of the patients.[4-10] In this study, we evaluated the predicting factors for the outcome of the patients intoxicated with antidepressants, antipsychotics, and their combination with and without other drugs as no study reported yet.

Materials and Methods

A cross-sectional study was performed in Khorshid (PBUH) University Hospital affiliated with Isfahan University of Medical Sciences from March 2016 to May 2017.

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Our department is the major referral center for poisoning cases in the central part of the country and is designed for the management of acute poisoning cases. Approximately 500 poisoned patients are monthly admitted to this center. The poisoning cases ingested antidepressants, antipsychotics, and their combination with and without other drugs were included in the study by searching the electronic patient database. Patients with internal or neurological disease were excluded from the study. Patients who discharged with his own decision and those transferred from elsewhere were also excluded. The research committee of Isfahan University of Medical Sciences approved the study (Research Project Number 395003).

Age, gender, type of exposure (accidental and intentional), clinical manifestations including generalized tonic–clonic seizure, level of consciousness, vital signs on arrival and 24 hour (h) later, venous blood gas parameters including bicarbonate (HCO_3), partial carbon dioxide pressure (PCO_2), pH, base excess, coingested drugs, time from ingestion to admission, length of hospital stay, and outcome (survived without complications, complication/ death) were recorded in a data gathering form.

Data were collected from ambulance charts, medical history, and toxicity screening urine test if needed to identify coingestion drugs. Hypotension was defined as a systolic blood pressure <90 mmHg and tachycardia as a heart rate above 100 beats/min. Prolongation of QTc interval above 440 ms, R/avR equal or >3 mm, QRS interval above 100 ms, and arrhythmias were categorized as abnormal electrocardiography (ECG).[11] Ingested drugs categorized into five groups: Antidepressant (Ad)/antipsychotic (Ap), Ad/Ap with sedative hypnotic (Sh), Ad/Ap with cardiovascular drugs (Cv), Ad/Ap with anticonvulsants (Ac), and Ad/Ap with other drugs.

Data were analyzed using SPSS 16 software (version 16, SPSS Inc., Chicago, IL, USA) and a $P < 0.05$ was considered statistically significant. We used one-way analysis of variance (ANOVA) to compare the means and Chi-square or Fisher exact test to compare the frequency distribution of qualitative factors. Results were presented as mean ± standard deviation and number (percent). The backward stepwise binary logistic regression test was used to assess the determinants factors for outcome prediction.

Results

Two hundred and sixty-eight patients had inclusion criteria during the study period. Twenty-nine patients were excluded from the study. Therefore, the data from 239 patients were analyzed. One hundred and sixty-three patients (68.2%) were female and 76 (31.8%) were male ($P = 0.52$). Most patients (68.2%) had been ingested drugs for suicidal purposes, 4.2% of

patients intubated and 5.9% admitted to the Intensive Care Unit. The most common substance ingested by the patients was as following: selective serotonin reuptake inhibitor ($n = 71$), tricyclic antidepressants (TCA) ($n = 70$), first-generation antipsychotics ($n = 8$), second-generation antipsychotics ($n = 35$), antidepressant and antipsychotic ($n = 10$), and combination of drug groups ($n = 45$). There was not a significant difference among patients in different ingested drugs groups with respect to clinical manifestations, ECG findings, and need for intubation. With respect to coingested drugs, we categorized them into five groups of medications [Table 1]. 94.99% of patients survived without complications, 3.76% developed complications and 1.25% died. For simplicity, the outcome was divided into two categories; without complications and complications/death. There was a significant difference in the level of consciousness on admission, hypotension, seizure, abnormal ECG, need to endotracheal intubation, and tachycardia after 24 h between patients with and without complications/ death ($P < 0.0001$) [Table 1].

The comparison of the mean age, vital signs on admission and 24 h later, time from ingestion to admission, and length of hospital stay in patients are shown in Table 2.

All variables analyzed based on different drugs groups. Abnormal ECG ($P = 0.004$) and hypotension ($P = 0.04$) were different among groups [Table 3].

Binary logistic regression analysis showed admission level of consciousness (stupor/coma), hypotension, seizure, tachycardia after 24 h of admission, and need for endotracheal intubation were determinant factors in outcome prediction [Table 4].

Discussion

We evaluated the predicting factors for the outcome of patients intoxicated with antidepressants, antipsychotics, and their combination with and without other drugs. 94.99% of patients survived without complication. We did not find significant differences in the outcome with respect to different types of ingested drug. In Borg study in 2016 on the identification of the patients at risk with antidepressant or antipsychotic overdose, 92.4% of the patients did not develop complications during their stay in the Intensive Care Unit.[11] The overdose of duloxetine in combination with other antidepressants and benzodiazepines resulted in benign outcome in the study of Menchetti *et al*.[12] Although sudden cardiac death related to antipsychotics; and high morbidity and mortality with tricyclic medications has been reported previously,[13,14] combinations of these medications because of possible ingestion of a lower dose of each group may have a better outcome.

Table 1: Comparison of the demographic variables and coingested drugs of the patients with respect to their treatments' outcomes

Variables	Total (*n*=239)	Outcome		*P*
		Without complication (*n*=227)	Complication/death (*n*=12)	
Gender				
Female	163 (68.2)	156 (68.7)	7 (58.3)	0.52
Male	76 (31.8)	71 (31.3)	5 (41.7)	
Type of exposure				
Accidental	2 (0.8)	2 (0.9)	0	0.33
Intentional	163 (68.2)	155 (68.3)	8 (66.6)	
Unknown	74 (33)	70 (30.8)	4 (33.3)	
Endotracheal intubation				
No	229 (95.8)	220 (96.9)	9 (75)	0.01
Yes	10 (4.2)	7 (3.1)	3 (25)	
ECG report				
Normal	163 (68.21)	163 (63.4)	0	0.00
Abnormal	76 (31.79)	64 (36.6)	12 (100)	
Tachycardia after 24 h of admission				
No	235 (98.3)	225 (99.1)	10 (83.3)	0.01
Yes	4 (1.7)	2 (0.9)	2 (16.7)	
Hypotension				
No	228 (95.4)	219 (97.3)	9 (75)	0.007
Yes	11 (4.6)	8 (2.7)	3 (25)	
Seizure				
No	233 (97.5)	223 (98.2)	10 (83.3)	0.03
Yes	6 (2.5)	4 (1.8)	2 (16.7)	
Admission level of consciousness				
Alert or lethargic	227 (95)	218 (96)	9 (75)	0.01
Stupor/coma	12 (5)	9 (4)	3 (25)	
Ingested drugs				
Ad and Ap	15 (6.3)	14 (6.2)	1 (8.3)	0.21
Ad/Ap with sedative hypnotics	50 (20.9)	50 (22.0)	0 (0.0)	
Ad/Ap with anticonvulsants	18 (7.5)	18 (7.9)	0 (0.0)	
Ad/Ap with cardiovascular drugs	18 (7.5)	17 (7.5)	1 (8.3)	
Ad/Ap with other drugs	138 (57.7)	128 (56.4)	10 (83.3)	

Data are presented as *n* (%). ECG: Electrocardiography, Ad: Antidepressants, Ap: Antipsychotics, *n*: Number of patients, h: hour

In our study, poisoning was more common in women may be due to more vulnerability to psychopathology and to psychosocial stressors.[15] Rijcken *et al*. reported the sex differences in concomitant medication with benzodiazepines or antidepressants.[16] Psychotherapeutic activities should consider psychological and personality traits associated with gender identity.[17] However, drug-related deaths have been reported to be more in men.[18] In our study, complication and death was also occurred more in men. The majority of patients were young in both groups of patients. In the study on multidrug with antipsychotics, antidepressants, or benzodiazepines, the mean age of the mortality in the study population was 37.8 years.[19] The average age of the patients poisoned with antipsychotic agents was 35.6 years in the study of Toft *et al*.[20] The average age of patients poisoned with antidepressants or antipsychotics in the study of the University of Odense, Denmark, was 37 years old.[11] Moreover, in the reported study of quetiapine poisoning,

the average age was 35 years old.[21] Emotional excitement, unemployment, family problems, and economic problems may prevalent in young people. Most patients ingested drugs for suicide purposes, similar to studies conducted in Denmark and Australia.[11,22] The suicidal intention is correlated with an absence of family support, with the severity of the psychosocial problem, and with multidrug abuse, and also with requests for treatment.[23]

Binary logistic regression analysis showed among the different evaluated variables, lower level of consciousness (stupor/coma); hypotension; seizure; need to endotracheal intubation; and tachycardia after 24 h of admission were determinant factors in outcome prediction. Until now, there is no reported study on the outcome prediction factors in mixed drug intoxication with an antidepressant, antipsychotics, and their combination with and without other drugs. In our study, 4.2% of patients were intubated. In the study on antidepressant or antipsychotic overdose, 1.9% patients

Table 2: Comparison of age, vital signs on admission and 24 h later, time from ingestion to admission, and the length of hospital stay with respect to their outcomes

Variables	Outcome		P
	Without complication	Complication/death	
Age (year)	29.40±11.13	33.75±12.24	0.19
Vital signs on admission			
Systolic blood pressure (mmHg)	118.89±16.20	110.42±30.70	0.09
Diastolic blood pressure (mmHg)	75.23±11.33	71.81±16.77	0.34
Pulse rate (per min)	90.00±19.51	88.91±20.07	0.85
Respiratory rate (per min)	18.25±4.90	18.75±3.54	0.72
Temperature (°C)	36.92±0.27	36.92±0.13	0.97
Vital signs after 24 h			
Systolic blood pressure (mmHg)	118.33±16.69	114.17±21.77	0.58
Diastolic blood pressure (mmHg)	71.52±9.13	68.33±17.22	0.48
Pulse rate (per min)	85.53±11.43	101.17±14.63	0.004
Respiratory rate (per min)	17.97±1.44	16.80±2.77	0.14
Temperature (°C)	37.12±0.42	36.90±0.10	0.37
Venous blood gas parameters on admission			
pH	7.36±0.06	7.39±0.08	0.16
PCO_2 (mmHg)	47.77±22.10	46.45±15.60	0.84
HCO_3 (mEq/l)	22.81±4.03	23.70±3.03	0.47
Base excess	−2.25±3.70	−0.77±4.03	0.20
Time from ingestion to admission (h) (Mean±SE)	4.34±0.39	3.77±1.15	0.75
Length of hospital stay (h) (Mean±SE)	21.20±2.33	33.22±9.59	0.26

Data are presented as mean±SD. SD: Standard deviation. Bicarbonate (HCO_3), partial carbon dioxide pressure (PCO_2); h: Hour

Table 3: Comparison of patients' variables with respect to the different coingested drugs

Variables	Ingested drugs					P
	Ad and Ap	Ad/Ap with sedative hypnotics	Ad/Ap with anticonvulsant	Ad/Ap with cardiovascular drugs	Ad/Ap with other drugs	
Endotracheal intubation						
No	15 (6.6)	48 (21.0)	18 (7.9)	18 (7.9)	130 (56.8)	0.92
Yes	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	8 (80.0)	
Total	15 (6.3)	50 (20.9)	18 (7.5)	18 (7.5)	138 (57.7)	
Admission mental status						
Alert or lethargic	15 (6.6)	48 (21.1)	17 (7.5)	18 (7.9)	129 (56.8)	0.84
Stupor/coma	0 (0.0)	2 (16.7)	1 (8.3)	0 (0.0)	9 (75.0)	
Total	15 (6.3)	50 (20.9)	18 (7.5)	18 (7.5)	138 (57.7)	
Hypotension						
No	14 (6.1)	48 (21.1)	18 (7.9)	15 (6.6)	133 (58.3)	0.04
Yes	1 (11.1)	0 (0.0)	0 (0.0)	3 (33.3)	5 (55.6)	
Total	15 (6.3)	48 (20.3)	18 (7.6)	18 (7.6)	138 (58.2)	
Tachycardia after 24 h						
No	15 (6.4)	49 (20.9)	18 (7.7)	18 (7.7)	135 (57.4)	1.00
Yes	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	3 (75.0)	
Total	15 (6.3)	50 (20.9)	18 (7.5)	18 (7.5)	138 (57.7)	
Seizure						
No	14 (6.0)	49 (21.0)	17 (7.3)	18 (7.7)	135 (57.9)	0.40
Yes	1 (16.7)	1 (16.7)	1 (16.7)	0 (0.0)	3 (50.0)	
Total	15 (6.3)	50 (20.9)	18 (7.5)	18 (7.5)	138 (57.7)	
ECG						
Abnormal	5 (6.8)	8 (11.0)	3 (4.1)	2 (2.7)	55 (75.3)	0.004
Normal	6 (5.4)	26 (23.4)	12 (10.8)	12 (10.8)	55 (49.5)	
Total	11 (6.0)	34 (18.5)	15 (8.2)	14 (7.6)	110 (59.8)	
Time from ingestion to admission (h)	2.88±0.78	5.04±0.82	4.14±0.61	2.21±0.38	4.55±0.57	0.37

The results are presented as mean (SE) or *n* (%). Ad: Antidepressants, Ap: Antipsychotics, ECG: Electrocardiography, SE: Standard error; h: hour

Table 4: Determinant factors for the outcome prediction of the studied patients (survived without complication versus complication/death)

Parameter	*P*	OR	95% CI for OR	
			Lower	Upper
Endotracheal intubation	0.002	10.47	2.31	47.32
Admission mental status (stupor, coma)	0.005	8.07	1.86	35.00
Hypotension	0.001	12.16	2.61	56.63
Tachycardia after 24 hour	0.003	22.50	2.86	176.49
Seizure	0.009	11.15	1.82	68.25

OR: Odds ratio, CI: Confidence interval

had been intubated.[11] The difference may be due to toxicity severity.

The frequency of abnormal ECG was 31.79% in our study. In the Borg study, 25% of patients had long QTC.[11] The association of QTc interval prolongation with antipsychotic and antidepressant drugs has been reported in the study of Zemrak and Kenna.[24] Hypotension and tachycardia after 24 h of admission was also an outcome predictive factor. The frequency of hypotension was higher in patients' ingested cardiovascular drugs as coingestion. In another study, heart rate was significantly higher in patients who intubated and received mechanical ventilation.[13] Tachycardia was also the most frequent abnormality noted in Borg study.[11]

A seizure episode happened in 2.5% of our patients. Patients with seizure had 11.5 times more the chance of complication. Both antidepressants and antipsychotics overdose pose a risk for seizure.[25] The low frequency of seizure may be partly due to sedative–hypnotic coingestion which was noted in 20.9% of our patients. Patients with coingestion of sedative hypnotic had also lower abnormality in the ECG. Coingestion with benzodiazepines has reduced the risk of seizure and cardiac toxicity in TCA poisoning.[9,26]

Conclusions

There was a significant difference between patients with and without complications with respect to the level of consciousness, hypotension, seizure, ECG findings, pulse rate 24 hour later and need to endotracheal intubation ($P < 0.0001$). Stupor/coma and hypotension were the predictive factors for outcome. Patients with a seizure during hospitalization, tachycardia after 24 h of admission, and those intubated and received mechanical ventilation have a higher chance of complications.

We did not confirm ingested substances by measuring serum drug level although we performed toxicology urine screen test. Substances ingested were confirmed by information from history, along with information from relatives, ambulance technicians, and empty drug containers. This can be a limitation of our study.

Conflicts of interest

There are no conflicts of interest.

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