Original Article

Comparison of Clinical Manifestations of Patients Poisoned with Tricyclic Antidepressants Alone or with Benzodiazepine Intoxication According to the Dose of Benzodiazepines

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Abstract

Objective: Tricyclic antidepressants poisoning (TCA) is associated with cardiovascular complications, electrocardiographic abnormalities, and central nervous system toxicity. This study aimed to compare the clinical manifestations of poisoned patients with tricyclic antidepressants alone or with benzodiazepine (BZD) intoxication according to the dose of BZDs. **Methods:** In this case–control study, 120 patients with TCA poisoning were divided into four groups: the first group of TCA poisoning alone, the second group of TCA and BZD poisoning of <7.75 mg, the third group of TCA and B poisoning of 7.75 to 80 mg, and the fourth group of more than 80 mg of TCA and BZD poisoning. Patients' demographic, clinical, and cardiac information was extracted from their records at admission and 6 h after admission. **Findings:** Cardiac complications 6 h after referral and total cardiac complications between TCA and TCA low-dose BZD groups were significantly reduced in the low-dose BZD poisoning group. Comparison of TCA and TCA groups with a moderate dose of BZD showed a significant reduction in time six and total cardiac complications. However, due to the significant difference in TCA values between the two groups, the results are not significant. Comparing the two groups of TCA and TCA with a high dose of BZD, both 6-hour cardiac complications and total cardiac complications in the high-dose BZD group, it was significantly reduced. However, the loss of consciousness was also considerably greater in the high-dose BZD group than in the TCA group. **Conclusion:** Concomitant BZDs with TCA can reduce cardiovascular complications from TCA poisoning. However, with high doses of BZDs, there is a greater loss of consciousness.

Keywords: *Benzodiazepine, cardiovascular, poisoning, tricyclic antidepressant*

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Introduction

Tricyclic antidepressants (TCAs) are used in treating depression and also a wide range of other medical conditions, e.g., chronic pain, migraine, obsessive-compulsive disorder, hyperactivity, neurological pain, anxiety, and nocturia in children.[1,2]

Due to the availability of these drugs, illegal availability without a doctor's prescription, narrow therapeutic and toxic dose gap, and the presence of underlying diseases such as depression, there is a high risk of suicide with these drugs alone or in combination with other medications, including benzodiazepines (BZDs).[3,4] The most dangerous side effects of TCA poisoning are the involvement of the cardiovascular and central nervous systems, which can be life-threatening.[5] TCA lethality is often due to persistent hypotension and

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hemodynamic changes.[6] The mechanisms of the above effects include sodium channel blockade and inhibition of alpha-adrenergic receptors. Anticholinergic effects and antihistamine and antagonistic effect on gamma-aminobutyric acid receptor.[7]

Chloroquine, like TCA, can cause heart problems in cases of poisoning, such as Q wave, an R wave, and an S wave QRS complex widening, atrioventricular block, QT segment elongation, and hypotension. From high doses of BZD (diazepam 2 mg/kg intravenously over half an hour and then 1–2 mg/kg/day for 2 to 4 days), it has been used in combination with early intubation to treat cardiac complications caused by chloroquine poisoning. Numerous human and animal studies on concomitant chloroquine and BZD poisoning indicate less cardiac toxicity and the potential benefits of high doses of diazepam.[8-12]

The main theory about the mechanism of action of diazepam in this clinical condition includes BDZs' anticonvulsant effect and their antiarrhythmic effect.[9,11-13] In recent years, studies have been conducted on the effectiveness of BZDs in reducing cardiac complications due to TCA poisoning, which indicates the potential effects of BZDs on cardiovascular symptoms of TCA poisoning.[14,15] These studies only point to the effectiveness of BZD in reducing TCA cardiac toxicity, but they did not specify the specific dose of BZDs that could produce these beneficial effects.

This study aimed to determine the effective dose of oral BZD in preventing cardiac toxicity in patients with TCA and thus its potential role in reducing the subsequent mortality in these patients.

Methods

This cross-sectional chart review study analyzed 120 patients with tricyclic antidepressant poisoning hospitalized from 2016 to 2020 in the poison management ward of Isfahan Khorshid University Hospital. The institutional board approved the study protocol for research ethics (number: IR.MUI.MED.REC.1399.500). We included patients poisoned with tricyclic antidepressants with or without concomitant poisoning with BZDs who were not referred to our center from medical centers in other cities, and lack of heart disease was the underlying cause. Patients whose medical records did not contain more than 10% of the required information or who had taken drugs other than BZDs and tricyclic antidepressants were excluded. Data collection methods included referring to patients' medical records and sampling method of a nonprobability sequential type. This means that all patients were eligible for the study. The samples were included in the study and matched based on the age and sex of the patients. After collecting data based on the average dose of BZDs used by patients and determining the first and third percentiles of BZD dose, patients were divided into four groups: the first group of TCA poisoning alone, the second group of TCA poisoning with BZDs less than 7.75 mg (low BZD), the third group of poisoning with TCA and BZDs between 7.75 and 80 mg (medium BZD), and the fourth group of TCA and BZD poisoning >80 mg (high BZD).

We abstracted the demographic data of the patients including gender, age, type, ingested TCA estimated dose, type and amount of BZDs, history of addiction and heart disease, vital signs and level of consciousness upon arrival and 6 h after hospitalization, electrocardiographic changes (including sinus tachycardia, QRS widening, arrhythmia, R wavelength in Augmented vector right (aVR), deviation of the heart axis to the right, and QT fragment size), cardiac electrophysiological complications (total electrocardiography [ECG] changes and positive clinical signs in favor of TCA poisoning) at 0 and 6 h after admission as well as total cardiac complications (total cardiac complications at 0 and 6 h), changes in arterial blood gases at 0 and 6 h, duration of hospitalization in the ward, and the outcome (uncomplicated recovery, complication recovery, and mortality). The data were analyzed using SPSS software version 26 (Version 26, IBM Corporation, Armonk. NY, USA). ANOVA and Chi-square or Fisher's exact tests were used to compare the means in groups of patients. $P < 0.05$ was considered statistically significant.

Results

We abstracted and analyzed the data of 120 eligible patients. There was no significant difference between the two groups of TCA poisoning and the low BZD group based on demographic information on age, sex, marital status, time of referral, and duration of hospitalization. The two groups of TCA alone with TCA and high-dose BZDs were compared. Demographic information showed significant changes in gender, occupation, drug addiction, and a history of psychological problems. Hence, drug addiction and psychological problems in the TCA group were less than in the TCA group and high doses of BZDs. Still, according to age, time of referral, a dose of TCA used, use of charcoal, and gastric lavage, there was no significant difference between referral time and length of hospital stay [Tables 1 and 2].

Furthermore, in terms of the level of consciousness, pupil size, blood gas analysis Table 3, QRS complex width, QT length, arrhythmia, and clinical signs, there

Table 1: Demographic and clinical information of patients in the tricyclic antidepressant poisoning group and low-dose benzodiazepine + tricyclic antidepressant group

Variable	Low BZD + TCA, *n* (%)	TCA, *n* (%)	*P*
Gender			
Male	4 (21.1)	12 (29.3)	0.754
Female	15 (78.9)	29 (70.7)	
Decontamination method			
Vomiting	0	2 (4.9)	1.000
Lavage	17 (89.5)	36 (87.8)	1.000
Charcoal	18 (94.7)	39 (95.1)	1.000
Age (mean±SD)	30.94±9.50	29.36±10.31	0.570
Hospitalization time (mean±SD)	1.78±1.10	1.95±1.51	0.679

TCA: Tricyclic antidepressant, SD: Standard deviation, BZD: Benzodiazepine

Table 2: Demographic and clinical information of patients in the tricyclic antidepressant poisoning group and high-dose benzodiazepine + tricyclic antidepressant group

Variable	High BZD + TCA, *n* (%)	TCA, *n* (%)	*P*
Gender			
Male	15 (71.4)	12 (29.3)	0.002
Female	6 (28.6)	29 (70.7)	
Decontamination method			
Vomiting	0	2 (4.9)	0.54
Lavage	20 (95.2)	36 (87.8)	0.65
Charcoal	21 (100)	39 (95.1)	0.54
Age (mean±SD)	32.71±8.04	29.36±10.31	0.19
Hospitalization time (mean±SD)	1.69±1.12	1.95±1.51	0.49

TCA: Tricyclic antidepressant, SD: Standard deviation, BZD: Benzodiazepine

was no significant difference between the two groups of TCA poisoning and the low BZD group. However, total cardiac complications at 6 h after the admission decreased significantly in the patients with low dose BZD plus TCA poisoning group compared to the TCA group alone (P = 0.04). The mean blood pH at 6 h of hospitalization also showed a significant difference ($P < 0.05$). Comparing the two groups of TCA alone with TCA and a moderate dose of BZDs, significantly different results ($P < 0.05$) were seen in patients' GCS, arterial pH, pulse rate, and cardiac complications at 6 h and total cardiac complications and PCO2 at time 0 and 6.

Finally, cardiac complications at 6 hours and total cardiac complications were significantly lower in high-dose BZDs than in the TCA group (P = 0.05 and P = 0.02). Furthermore, the mean QT and PH at 6 o' clock and PCO_2 at zero time were significant ($P < 0.05$) Tables 3 and 4.

Discussion

The present study results showed that low-dose BZDs in intoxication with tricyclic antidepressants have no negative effect on the level of consciousness. However, high doses of BZDs significantly reduce the level of consciousness and suppress the central nervous system. In the Yaraghi *et al*.'s study, with a sample size similar to the present study, the effect of concomitant use of BZDs on the toxicity of tricyclic antidepressants has been investigated. The state of consciousness was better in the group that did not take BZDs than with BZDs with antidepressants. However, the exact amount of BZD used in that study was not specified.[4] However, in a study by Eizadi-Mood *et al*., midazolam injection into patients with antidepressant poisoning did not significantly differ in central nervous system manifestations.[3]

In terms of changes in blood gases, this study showed that low-dose BZD poisoning with antidepressants has no effect on pH, PCO_2, and HCO_3 and does not cause acidosis or alkalosis. However, in the high-dose BZD intoxication group with antidepressants compared to the TCA group alone, the decrease in pH and the increase in PCO_2 were significantly greater than in the TCA group. Therefore, there is a risk of respiratory acidosis at high doses of BZDs. In Yaraghi *et al*.'s study, the pH was significantly lower in the TCA and BZD poisoning groups than in the TCA poisoning group.[5] The cause of respiratory acidosis and loss of consciousness is BZD-induced suppression of the central nervous system and respiratory center.[16,17]

ECG results, clinical signs, and hemodynamic findings in our study showed that, although BZDs in low doses as well as in high doses compared to the TCA group could not to make a significant difference in the peer-to-peer comparison of any of the parameters, low dose and high dose BZDs were able significantly reduce cardiac complications totally in TCA poisoning at 6 h after admission (P = 0.04 and P = 0.02 respectively). Eizadi-Mood *et al*.'s study showed a significant reduction in tachycardia in the TCA and BZD groups compared with the TCA group alone.[3] In another study by Eizadi-Mood *et al*., the frequency distribution of sinus tachycardia, QRS, R aVR, and arrhythmia was lower in the TCA and BZD poisoning group than in the TCA group.[15] However, there was no significant difference in hemodynamic symptoms, ECG changes, clinical symptoms, and even outcomes in patients in the TCA and BZD poisoning group compared to the TCA group.[4] In studies on chloroquine poisoning, cardiac complications were similar to those of TCA poisoning. Moreover, patients treated with high doses of BZDs had lower

Table 3: Laboratory findings in the tricyclic antidepressant poisoning group and the low-dose benzodiazepine + tricyclic antidepressant poisoning group at baseline and 6 h later

Variables	Time	Mean±SD		*P*
		Low BZD+TCA	TCA	
pH	0	7.35±0.07	7.36±0.05	0.57
	6	7.35±0.05	7.40±0.05	0.02
HCO_{3-} (mEq/L)	0	21.55±3.29	22.79±4.16	0.27
	6	25.22±6.51	24.51±3.83	0.72
pCO_2 (mmHg)	0	39.88±10.29	39.66±7.49	0.92
	6	44.22±6.51	39.95±9.07	0.21

TCA: Tricyclic antidepressant, SD: Standard deviation, BZD: Benzodiazepine

Table 4: Laboratory findings in the tricyclic antidepressant poisoning group and the high-dose benzodiazepine + tricyclic antidepressant poisoning group at baseline and 6 h later

Variables	Time	Mean±SD		*P* (*t*-test)
		High BZD + TCA	TCA	
pH	0	7.34±0.04	7.36±0.05	0.14
	6	7.36±0.04	7.40±0.05	0.02
HCO_{3-} (mEq/L)	0	24.95±4.80	22.79±4.19	0.08
	6	24.38±3.09	24.54±3.83	0.89
pCO_2 (mmHg)	0	48.40±10.89	39.66±7.49	0.01
	6	44.84±9.23	39.95±9.07	0.13

TCA: Tricyclic antidepressant, SD: Standard deviation, BZD: Benzodiazepine

cardiovascular toxicity compared to controls.[8,11] It was also shown that survival and recovery were significantly better than the control group in patients with severe chloroquine poisoning who were initially intubated and received high doses of intravenous diazepam with cardiac inotropia. However, another study showed that diazepam alone could not reduce the cardiovascular toxicity of chloroquine. However, along with an inotropic, it can reduce cardiac toxicity such as QRS flattening, QT prolongation, and hypotension.[18]

In this study, due to the separation of patients into three groups and decreasing sample size in each group, no significant change in seizure reduction was observed in the benzodiazepine and TCA groups. However, in Eizadi-Mood *et al*.'s study, the frequency of seizures was lower in the TCA and BZD poisoning group compared to the TCA group.[15]

In comparison of the TCA poisoning group and a moderate dose of BZD with the TCA group, significant differences were observed in cases such as GCS, PH, PCO2, PR, and total cardiac complications. However, the results were not significant due to the significant difference in the amount of TCA consumed between the two groups. Moreover, it cannot be said that this dose has positive effects in reducing the cardiovascular toxicity of TCA.

The strength of this study was the lack of clear differences in terms of referral time, gastric lavage, charcoal administration, age of individuals, and the amount of TCA consumed between the low-dose and high-dose BZD groups with the TCA group. One of the study's limitations was the shortcomings of the files and the impossibility of complete trust in the patients' history.

The bottom line is that low-dose BZDs can be used to reduce the cardiovascular side effects of tricyclic antidepressants without causing complications such as loss of consciousness and acidosis. High doses of BZDs, although helpful in reducing TCA-induced cardiovascular complications, can cause loss of consciousness, decreased breathing, and respiratory acidosis by suppressing the central nervous system. Therefore, as mentioned before, in the case of chloroquine poisoning, it is recommended that in cases of severe TCA poisoning, the patient should be intubated first. We also recommend that a high dose of intravenous BZD can be considered injected without worrying about the level of consciousness and acidosis in these patients.

All procedures involving the human participant were in accordance with the ethical standards of the institutional and/or national research committee, the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards. Private information, including name, surname, and burial permit, was removed from the data sheet to comply with ethical concerns.

Authors' contribution

G. Dorooshi and N. Eizadi-Mood designed the study and prepared the initial proposal. N. Eizadi-Mood and A. M. Sabzghabaee critically reviewed the proposal. R. Kermani gathered the data. M. Mansourian analyzed the data. All authors read the manuscript and agreed for the final version of the submitted manuscript.

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Conflicts of interest

There are no conflicts of interest.

References

1. Rochester MP, Kane AM, Linnebur SA, Fixen DR. Evaluating the risk of QTc prolongation associated with antidepressant use in older adults: A review of the evidence. Ther Adv Drug Saf 2018;9:297-308.
2. Odigwe CC, Tariq M, Kotecha T, Mustafa U, Senussi N, Ikwu I, *et al*. Tricyclic antidepressant overdose treated with adjunctive lipid rescue and plasmapheresis. Proc (Bayl Univ Med Cent) 2016;29:284-7.
3. Eizadi-Mood N, Aboofazeli E, Hajhashemi V, Gheshlaghi F, Badri S, Sabzghabaee AM. Effect of intravenous midazolam on cardiac parameters in acute tricyclic antidepressants poisoning. ARYA Atheroscler 2016;12:195-200.
4. Yaraghi A, Noori A, Eizadi-Mood N, Sabzghabaee AM, Mansourian M. Comparing cardiovascular complications of poisoned patients with antipsychotics and antidepressants with or without benzodiazepines. J Isfahan Med Sch 2019;36:1511-6.
5. Yaraghi A, Eizadi-Mood N, Katani M, Farsaei S, Hedaiaty M, Mirhosseini SM, *et al.* Arterial blood gas analysis and the outcome of treatment in tricyclic antidepressants poisoned patients with benzodiazepine coingestion. Anesthesiol Res Pract 2015;2015:232401.
6. Mandour RA. Antidepressants medications and the relative risk of suicide attempt. Toxicol Int 2012;19:42-6.
7. Gheshlaghi F, Eizadi-Mood N, Emamikhah-Abarghooeii S, Arzani-Shamsabadi M. Evaluation of serum sodium changes in tricyclic antidepressants toxicity and its correlation with electrocardiography, serum pH, and toxicity severity. Adv Biomed Res 2012;1:68.
8. Clemessy JL, Taboulet P, Hoffman JR, Hantson P, Barriot P, Bismuth C, *et al.* Treatment of acute chloroquine poisoning: A 5-year experience. Crit Care Med 1996;24:1189-95.
9. Marquardt K, Albertson TE. Treatment of hydroxychloroquine overdose Am J Emerg Med 2001;19:420-4.
10. Crouzette J, Vicaut E, Palombo S, Girre C, Fournier PE. Experimental assessment of the protective activity of diazepam on the acute toxicity of chloroquine. J Toxicol Clin Toxicol 1983;20:271-9.
11. Riou B, Barriot P, Rimailho A, Baud FJ. Treatment of severe chloroquine poisoning. N Engl J Med 1988;318:1-6.
12. Riou B, Rimailho A, Galliot M, Bourdon R, Huet Y. Protective cardiovascular effects of diazepam in experimental acute chloroquine poisoning. Intensive Care Med 1988;14:610-6.
13. Reddy VG, Sinna S. Chloroquine poisoning: Report of two cases. Acta Anaesthesiol Scand 2000;44:1017-20.
14. Liaw GW, Hung DZ, Chen WK, Lin CL, Lin IC, Kao CH. Relationship between acute benzodiazepine poisoning and acute pancreatitis risk: A population-based cohort study. Medicine (Baltimore) 2015;94:e2376.
15. Eizadi-Mood N, Sabzghabaee AM, Saghaei M, Gheshlaghi F, Mohammad-Ebrahimi B. Benzodiazepines co-ingestion in reducing tricyclic antidepressant toxicity. Med Arh 2012;66:49-52.
16. Kazemzadeh N, Mohammadi S, Emamhadi M, Amirfarhangi A, Sanaeizadeh H. Electrocardiographic manifestations of benzodiazepine toxicity. Iran J Toxicol 2014;7:952-5.
17. Arroyo Plasencia AM, Ballentine LM, Mowry JB, Kao LW. Benzodiazepine-associated atrioventricular block. Am J Ther 2012;19:e48-52.
18. Hughes DA. Acute chloroquine poisoning: A comprehensive experimental toxicology assessment of the role of diazepam. Br J Pharmacol 2020;177:4975-89.