Effect of intravenous midazolam on cardiac parameters in acute tricyclic antidepressants poisoning

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Short Communication

Abstract

BACKGROUND: Midazolam is commonly and safely used in poisoning management and intensive care for the control of agitated poisoned patients. Despite the introduction of newer and safer antidepressants, tricyclic antidepressants (TCAs) are still prescribed and used in many countries due to their cost-effectiveness. Severe morbidity and mortality associated with these drugs arises largely from their well-documented cardiovascular toxicity. In this study we aimed to investigate the probable effect of midazolam on some hemodynamic indices in TCAs-poisoned patients.

METHODS: In this clinical trial, we have evaluated some cardiovascular and hemodynamic indices of 100 TCAs-poisoned patients whom were randomly allocated for receiving midazolam with a first loading dose of 0.1 mg/kg (2 mg/minute) followed by a 6-hour maintenance infusion of 0.1 mg/kg/h of the drug in dextrose-saline (3.33% of dextrose and 0.33% of NaCl) or placebo (dextrose-saline infusion without midazolam). Pulse rate, systolic/diastolic blood pressure, respiratory rate, neurologic status and the outcome of therapy for all patients were recorded at the time of admission and hourly for the next 6 hours.

RESULTS: There was a statistically significant reduction in the heart rate of the midazolam treated group after the first hour of hospital admission. There were no significant differences in the respiratory rate, central nervous system manifestations and other indices between the two groups.

CONCLUSION: Midazolam may reduce tachycardia (and its fatal consequences) in the first hour of admission in TCAs-poisoned patients.

Keywords: Midazolam, Tricyclic antidepressants (TCAs) Poisoning, Tachycardia

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Introduction

Tricyclic antidepressants (TCAs) are still prescribed worldwide for some psychiatric conditions especially depressive disorders in spite of their serious side effects.[1] Despite the introduction of newer and safer antidepressants (e.g. selective serotonin reuptake inhibitors), TCAs are now used in many countries due to their cost-effectiveness.[2] Even though of this obvious benefit of lower price for TCAs treatments, they are still considered as an important cause of death in poisoning emergency wards and nearly most of TCAs-poisoned cases need intensive care support and intensive care unit (ICU) admission.[3,4] According to the National Poison Data System annual report of the American Association of Poison Control Centers, antidepressants were the eighth and seventh leading cause of toxic exposures in 2007 and 2008, respectively.[5]

In an analysis of deaths due to acute poisoning 20% were antidepressant-related, of which 95% were associated with TCAs.[6,7] TCA overdose is known to cause anticholinergic, cardiopulmonary and central nervous system (CNS) complications. Severe morbidity and mortality associated with these drugs arises largely from their well-documented cardiovascular toxicity.[7,8] In addition, the worldwide expansion in the use of benzodiazepines (BDZs) has led to their frequent and often inappropriate use, including an increase in their involvement in self-induced poisoning. Previous studies have also demonstrated the effect of benzodiazepines in the management of seizure.[9-11]

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In Iran more than one third of all emergency room admissions for drug intoxication are reported to be due to TCAs (especially amitriptyline and nortriptyline) which makes this type of poisoning as the second leading cause of death due to drug overdose in many Iranian hospitals.[12-14] Overdose with TCAs is also one of the most common causes of admission to our Poisoning Emergency Department in Isfahan, Iran.[15,16] In a study, which was performed in our poisoning department, it was revealed that signs of cardio toxicity were significantly less in patients who had ingested TCA and benzodiazepine.[11]

Fatality due to TCA poisoning is highly related to the refractory hypotension and hemodynamic changes.[17-20] High accessibility (in some cases even without providing a valid prescription to the pharmacies), the nature of disease in patients with major depression whom are not reluctant to suicide, the narrow therapeutic window of these drugs, seriousness and severity of the cardiovascular and neurologic consequences after TCA overdoses and finally the limitations for specific supportive therapies (e.g. in cases of refractory hypotension and seizures) are all considered to contribute for the occurrence and poor management of this type of intoxication.[21]

Midazolam is a relatively safe benzodiazepine which is widely used for anesthesia, sedation in mechanically ventilated patients, agitated critically ill patients and refractory status epilepticus patients.[22] Hemodynamic effects of this drug in human is discussed elsewhere.[23] In our referral poisoning and drug overdose emergency ward, we have noted that TCA overdosed patients who received midazolam for other reasons seem to have lower mortality rate and their hemodynamic indices were more near stable. To clarify the answer to this research question, and with taking to consideration that cardio toxicity is one of the common causes of death in TCA poisoning, we aimed to evaluate the effects of intravenous midazolam on the electrophysiological and hemodynamic indices in acute TCA-poisoned patients.

Materials and Methods

This clinical trial was done in 2011-2012 in Isfahan. Isfahan is the second largest city in Iran and is located in the center of Iranian plateau. This industrial city has a population of near two million. Poisoning emergency department of Noor and Ali Asghar (PBUH) University hospital is the main referral center for the central part of Iran and poisoned patients from at least 5 Iranian central provinces (including Isfahan) are referred there for poison management and supportive therapy.

The study protocol was approved by the Research Council and the Institutional Board of Ethics for Human Research of the Isfahan University of Medical Sciences. Informed consent was obtained from all study subjects (if conscious and oriented) or legally eligible companion after explaining the purpose of the study, the potential use of the collected information, and procedures. If the consent was signed by the legally eligible companion, the patient was also informed completely as soon as medically possible. For individuals who were unable to read, the informed consent was read aloud and then written consent was requested.

The study population was all poisoned patients with an evident and reliable history of TCA poisoning, whom were randomly selected by simple random sampling method from patients referred to the Noor and Ali Asghar University hospital. Eligible patients for the studies were symptomatic patients with TCA poisoning during the first 6 hours after oral drug intake whom were admitted with a documented tachycardia. TCA-poisoned patients who had received sodium bicarbonate before hospitalization, or patients who had ingested any drugs that affected entry criteria and patients who were transferred to other hospitals before completing and patients who were discharged with their own consent were excluded.

To detect at least 10% reduction in the heart rate of patients between the current standard therapy and midazolam treated group, assuming presence of tachycardia in 70% of the TCA-poisoned patients at the time of admission with an 80% power and a 5% type I error, 45 subjects were needed in each group (90 for both arms). To compensate for anticipated losses to follow-up, we inflated the sample size by 10%. Hence, the final sample size, rounded to the nearest 10 was 100 individuals with 50 individuals in each arm. Power analysis and sample size software (PASS 12, Jerry Hintze, Kayeville Utah) was used to calculate the required sample size.

Using random numbers table and patient's file number, all eligible patients were allocated randomly to two groups: cases whom received midazolam as an add-on to their normal routine medical care, and controls whom received normal supportive care without midazolam administration. Patients were matched in both groups in terms of age, gender, type of poisoning (accidental, intentional) and the route of access to TCA.

Routine supportive care according to the institutional protocol [including initial steps of basic life support e.g. airway, breathing, circulation

(ABC), administration of sodium bicarbonate] were done for all patients in both groups. Cases received a first loading dose of 0.1 mg/kg (2 mg/minute) of intravenous midazolam followed by a 6-hours maintenance infusion of 0.1 mg/kg/h of the drug in dextrose-saline (3.33% of dextrose and 0.33% of NaCl). Patients in control group received all routine supportive and specific therapies for TCA poisoning and also a 6-hours infusion of dextrose-saline (3.33% of dextrose and 0.33% of NaCl) without midazolam.

After obtaining informed consent and the questionnaires, basic demographic information and vital signs were recorded. All routine laboratory tests (complete blood count, serum creatinine, blood urea nitrogen, arterial blood gas, liver function tests, blood glucose and serum electrolytes) were performed for both groups as per our institutional protocol for supportive therapy of TCA-poisoned patients.

All data were collected by certified health care professionals and a medical toxicologist attending physician (NEM) supervised all clinical and medical processes of the study. Nurses were trained for clear and precise reporting of possible side effects of midazolam and its probable adverse drug reactions before the start of the study.

Descriptive data analysis was done on baseline characteristics of the study patients. For continuous variables mean and standard deviation (SD) were calculated and histograms were plotted to assess the distribution of the variables. Kolmogorov-Smirnov test was performed for evaluating the normal distribution of the continuous variables. Descriptive statistics were computed for midazolam and placebo infusion therapy groups separately. Mean values of continuous variables were compared between the two groups (cases and controls) by independent Student's t-test. Pearson's chi-square test was used for comparing the proportions. Categorical variables that had a cell count less than five, were analyzed using Fisher's exact test. All P values were based on two-sided tests and the significance was set at a P-value of less than 0.05. Statistical analyses were done using the SPSS software for Windows (version 13.0, SPSS Inc., Chicago, IL, USA).

Results

During the 20 months of the study period, 124 patients were recruited to the both arms of the study (50 cases, 50 controls) and 24 of them left the study either by their personal consent or incomplete data as per study protocol. A full set of 100 patients finished the study completely. An overview of the demographic and overall features of the study population (n = 100) revealed that in age, gender, mode of poisoning, marital status, and job career categories there was not any statistically significant difference between cases and controls (Table 1).

Table 1. Demographic characteristics of the study patients in midazolam treated (cases) and placebo (controls) groups

Characteristic	Cases [Midazolam, (n = 50)]	Controls [Placebo, (n = 50)]	P
Age (Year) [Mean ± SD]	29.1 ± 5.1	27.3 ± 6.2	0.120*
Gender			
Male	26 (52)	24 (48)	0.670**
Female	24 (48)	26 (52)	
Type of poisoning			
Suicide	6 (12)	2 (4)	0.430***
Accidental	44 (88)	48 (96)	
Route of access to TCAs			
Personal	34 (68)	37 (74)	0.003***
Family	9 (18)	0 (0)	
Accidental	7 (14)	13 (26)	
History of depression			
Positive	28 (56)	38 (76)	0.040**
Negative	22 (44)	12 (24)	

* Independent Student's t-test; ** Chi-squared test; *** Fisher exact test
SD: Standard deviation; TCAs: Tricyclic antidepressants

Table 2. Comparison of the mean difference (**Δ**) of the hourly vital signs of patients in the first hour until the sixth in midazolam treated (cases) and placebo (controls) groups (mean ± SD)

Variable		Time interval of statistical comparison (from n1 to n2 hours after admission)				
		$n_1 = 1^{st}$, $n_2 = 2^{nd}$ hour	$n_1 = 1^{st}$, $n_2 = 3^{rd}$ hour	$n_1 = 1^{st}$, $n_2 = 4^{th}$ hour	$n_1 = 1^{st}$, $n_2 = 5^{th}$ hour	$n_1 = 1^{st}$, $n_2 = 6^{th}$ hour
Δ Pulse rate	Controls	12.0 ± 1.9	17.0 ± 2.1	19.7 ± 2.1	17.7 ± 2.7	19.3 ± 2.7
	Cases	15.3 ± 2.6	16.7 ± 2.0	18.0 ± 2.0	20.6 ± 2.6	19.1 ± 2.8
	P†	0.03	0.08	0.79	0.33	0.31
Δ Systolic blood pressure	Controls	-3.7 ± 2.2	-2.9 ± 2.8	-1.5 ± 3.2	-3.7 ± 3.6	-1.9 ± 3.7
	Cases	2.1 ± 2.7	2.4 ± 2.4	1.7 ± 2.7	0.8 ± 2.6	3.6 ± 2.5
	P†	0.79	0.28	0.33	0.30	0.17
Δ Diastolic blood pressure	Controls	-4.1 ± 2.1	-6.7 ± 3.5	-2.1 ± 4.7	-0.2 ± 5.0	-0.4 ± 3.9
	Cases	0.1 ± 3.1	3.8 ± 3.0	2.5 ± 2.9	2.5 ± 3.0	2.2 ± 3.4
	P†	0.17	0.37	0.44	0.60	0.64
Δ Respiratory rate	Controls	-0.3 ± 0.5	-0.8 ± 0.5	-0.9 ± 0.3	-0.9 ± 0.8	-0.6 ± 0.8
	Cases	-0.1 ± 0.4	-0.1 ± 0.5	-0.7 ± 0.6	-0.5 ± 0.6	-0.6 ± 0.7
	P†	0.63	0.22	0.80	0.66	0.96

† Independent student's t-test
SD: Standard deviation

Comparison of the results of the frequency distribution of the main cardiovascular symptoms caused by tricyclic antidepressants poisoning demonstrated that no significant difference was observed between cases and controls in terms of blood pressure on admission (P = 0.11) and 6 hours later (P = 0.69), R/avR more than or equal to 3 mm in the beginning (P = 0.08) and 6 hours later (P = 0.98), prolonged QTc (greater than 0.44) on admission (P = 0.11) and 6 hours later (P = 0.75) (Table 2).

On the other hand, we found a statistically significant difference of the admission time QRS complex width between the two groups (P = 0.003) but after 6 hours this variable was not statistically significant between the cases and controls (P = 0.78).

Hourly evaluation of the results of vital signs in two groups from the time of admission for the next 6 hours revealed no statistical significance between cases and controls groups for the mean heart rate (P = 0.19), systolic blood pressure (P = 0.82), diastolic blood pressure (P = 0.42) in the first hour and every hour until the sixth hours. The mean respiratory rate at the time of arrival in control group was significantly different from the cases (P = 0.003) but both were in the normal range.

Comparison of mean vital signs of patients in the first hour until the sixth hour in two groups showed significant difference in pulse rate in first hours of admission (Table 2).

The comparison of the frequency distribution of the central nervous system symptoms showed that at the time of admission, no significant difference was observed in terms of the level of consciousness (P = 0.21), occurrence of seizure (P = 0.49) and agitation (P = 0.09) between the two groups.

Discussion

The purpose of this study was to evaluate the effects of intravenous midazolam on electrophysiological and hemodynamic indices in acute TCAs-poisoned patients.

We found a statistically significant reduced heart rate in the midazolam treated group (cases) compared with the control group within the first hours of admission. Fortunately, there were no significant differences in the respiratory rate and central nervous system manifestations between two groups, thus we think that benzodiazepines, such as midazolam may reduce the tachycardia and its fatal consequences in the first hour of admission in TCAs-poisoned cases.

Mechanism of the benzodiazepine such as midazolam on TCA-induced tachycardia is not clear yet. Some possible explanations might be central suppression of the release of cathecholamines or a direct effect on the benzodiazepine receptors on heart.[24]

We also have not found any statistically significant difference in the heart rate of the two groups at other times which could be related to the extent of drug metabolism in both groups, reduction in plasma levels and effects of midazolam,

and most importantly maybe due to our drug administration protocol for the patients. For example in cocaine poisoning, midazolam was infused 1 to 2 mg every 3 to 5 minutes (to control hypertension and tachycardia) until the patient became asymptomatic,[25] while in our study we used midazolam with a bolus dose of 0.1 mg/kg and also the infusion rate was very low.

As a limitation for our results and discussion, we think that our findings should be considered with caution because the results of measurements in different times after admission were analyzed pair-wise and due to some limitations for meeting the assumptions, we did not perform repeated measure test.[26]

Conclusion

Midazolam may have a positive role in preventing tachycardia in TCA-poisoned patients which can prevent the consequences of tachyarrhythmia and its complications in the poisoned patients.

We recommend further study with higher and more frequent doses of midazolam for these patients in future.

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Conflict of Interests

Authors have no conflict of interests.

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