

ORIGINAL PAPER

Benzodiazepines Co-ingestion in Reducing Tricyclic Antidepressant Toxicity

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Aim: Tricyclic antidepressant (TCA) overdose is generally associated with central nervous system (CNS) and cardiovascular toxicity manifested by seizure, electrocardiographic (ECG) abnormalities and arrhythmia. The objective of this study was to determine whether TCA toxicity would be reduced in patient where benzodiazepine (BDZ) was co-ingested with TCA. **Design:** Patients who were diagnosed to be poisoned by ingestion of both a tricyclic antidepressant and benzodiazepine (TCA-BDZ), and patients intoxicated solely by a TCA were assessed, provided that they had one or more clinical signs of toxicity (anticholinergic, cardiovascular or CNS findings) and no underlying cardiac disease. TCA poisoned patients who had ingested any drugs other than benzodiazepines were excluded. Patients transferred from elsewhere and those admitted after the first 24 hours were also excluded. The clinical manifestations of TCA toxicity and outcome of the patients poisoned only with TCA (N=60) were compared with those of the patients who had co-ingested TCAs and BDZs (N=60). **Main Results:** The frequency distribution of sinus tachycardia, "QRS more than 100 ms, R/S aVR equal or more than 0.7, R_{aVR} equal or more than 3 mm", arrhythmia, and generalized tonic clonic seizure was less in patients who had co-ingested BDZ with TCA. Evaluating the relationship between ingested TCA dosage and electrocardiographic findings (duration of QRS, QT and PR intervals, the amplitude of R wave in lead aVR and right axis deviation) in both study groups, demonstrated that there was a strong relationship between TCA dosage and QRS duration in the TCA group. This was significantly different from the same correlation in the TCA-BDZ group (r, 0.50 in TCA group versus r, 0.04 in TCA and BDZ group, P < 0.05). No significant differences were found in complications (aspiration pneumonia, non-cardiac pulmonary oedema and death) between the two groups. **Conclusions:** cardiovascular toxicity and seizure may be less in TCA-BDZ poisoned patients compared with patients intoxicated with TCA-alone. **Key words:** Antidepressant, Benzodiazepine, Electrophysiology, Poisoning, Overdose, Outcome.

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1. INTRODUCTION

Antidepressants are increasingly prescribed for multiple indications in children and adults. They are respon-

sible for a significant proportion of severe poisoning cases admitted to hospital (1-3). According to the American Association of Poison Control Centres'

National Poison Data System annual report antidepressants were the eighth and seventh leading cause of toxic exposures in 2007 and 2008 respectively (4, 5). Amongst the TCAs, Amitriptyline was associated with the highest number of deaths due to ingestion [4]. In an analysis of deaths due to acute poisoning 20% were antidepressant-related, of which 95% were associated with tricyclic antidepressants (TCAs) (6). Tricyclic antidepressant overdose is known to cause anticholinergic, cardiopulmonary and central nervous system (CNS) complications. The severe morbidity and mortality associated with these drugs arises largely from their well-documented cardiovascular toxicity (1, 7, 8). In addition, the worldwide expansion in the use of benzodiazepines (BDZ) 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).

Overdose with TCAs is one of the most common causes of admission to our Poisoning Emergency Department. In a pilot study, which was performed in our poisoning department, it was revealed that signs of cardiotoxicity were significantly less in patients who had ingested TCA and BDZ. However because only a small number of patients had ingested TCA together with BDZ, it was necessary to do a more reliable study. In the present study, the clinical

manifestations of TCA toxicity (anticholinergic, cardiovascular and central nervous system manifestations) and the outcome of the patients poisoned with TCA alone and the patients who had ingested TCAs with BDZs were investigated and compared.

2. METHODS

This prospective, observational clinical study was performed in the Poisoning Emergency Department of Noor and Ali Asghar (PBUH) University Hospital is the main referral centre for Isfahan Province, Iran, and is specifically staffed and designed exclusively for the management of poisoned patients. Approximately 400 patients are admitted monthly and their initial care is managed under the supervision of a clinical toxicologist with the input and involvement of anesthesiologists and forensic medicine physicians. This study involved prospective data collection, followed by retrospective analysis and was conducted by the Anesthesiology Research Department of the Noor University Hospital. The protocol was reviewed and approved by the University's Institutional Ethics Committee. Patients who were diagnosed to have been poisoned by both a tricyclic antidepressant and benzodiazepine (TCA-BDZ) and patients intoxicated by a TCA alone, were assessed, provided they had one or more clinical signs of toxicity (anticholinergic, cardiovascular or CNS findings) and had no underlying cardiac disease. TCA poisoned patients who had ingested any drugs other than benzodiazepines (based on their own/relatives report) were excluded. Patients transferred from elsewhere and those admitted after the first 24 hours were also excluded. To have an 80% chance of detecting statistical significance (at the two sided 5% level), 50 patients were required. To compensate for excluded patients a final sample size of 60 for each group was selected.

Basic information (gender, age, the type and dosage of ingested TCA, any other ingested drugs, time elapsed since ingestion to admission) were recorded. For each included patient, vital signs on admission and electrocardiographic (ECG) parameters (arrhythmia, heart rate, right axis deviation, duration

Cardiovascular manifestations	Percent of patients		P Value	Anticholinergic and CNS manifestations	Percent of patients		P Value
	TCA-only*	TCA-BDZ†			TCA-only	TCA-BDZ	
Hypotension	8.3	3.3	0.21	Seizure	15	0.0	0.001
Arrhythmia	6.6	0.0	0.05	Delirium	43.3	36.6	0.50
Sinus Bradycardia	3.3	0.0	0.24	Loss of consciousness	73.3	70	0.42
Sinus Tachycardia	43.3	18.3	0.003				
Right axis deviation	11.6	5	0.16				
QRS > 100 ms	16.6	1.6	0.004				
PR Interval ≥ 210 ms	21.6	16.6	0.32				
QT Interval ≥ 440 ms	1.6	3.3	0.50	Mydriasis	41.6	25	0.04
R aVR ≥ 3 mm	23.3	6.6	0.01	Hypertension	3.3	0.0	0.24
R/S aVR ≥ 0.7	20	6.6	0.02	Hallucination	0.0	5	0.12

TABLE 1. Comparison of cardiovascular, anticholinergic and central nervous system manifestations between two study groups * Patients ingested tricyclic antidepressant alone † Patients ingested tricyclic antidepressants and benzodiazepine TCA: tricyclic antidepressant. BDZ: benzodiazepine; CNS, Central Nervous System; sinus tachycardia (heart rate more than 120 per minutes), sinus bradycardia (heart rate less than 60 per minutes), hypotension (systolic blood pressure less than 90 mmHg), hypertension (systolic blood pressure more than 140 mmHg)

of QRS, QT and PR intervals, the amplitude of R wave and R/S ratio in lead aVR) were also recorded.

Total dosage of ingested TCA, clinical manifestations, ECG findings and the outcome (survived without complication; survived with complication including aspiration pneumonia and non-cardiac pulmonary oedema; and death) of patients who had ingested TCAs alone were compared with those of patients who had taken both a TCA and BDZ. In addition, the relationship between dosage of ingested TCA and clinical manifestations were assessed and compared between these two groups.

The data was analyzed using the Statistical Package for the Social Sciences version 13.0 (SPSS Inc, Chicago, IL, USA). Data were presented as mean ± Standard Deviation or n (%) where appropriate. An independent two-tailed sample t-test was performed to compare the means of different variables between the two groups. Statistical analysis was performed using chi square or Fisher exact test with a statistical significant level of P less than 0.05. Significant correlation coefficients were employed using Spearman analysis.

3. RESULTS

An overview of the demographic and overall features of the study population (n=120) revealed that intoxication was more common in women (59.1%) and young adults in the age group 20-40 (68.3%). Of the 120 subjects, 99 patients

(82.5%) were admitted to the hospital within two hours of ingestion. In both study groups some patients had taken more than one type of TCA or BDZ. Amitriptyline was the most commonly ingested drug (n=69) followed by nortriptyline (n=33), imipramine (n=20), clomipramine (n=3) and maprotiline (n=3). The intoxication was intentional in all cases. The mean and standard deviation of estimated ingested dosage of TCA was 795 ± 107 mg in TCA-only poisoned group and 530 ± 54 mg in TCA-BDZ group. In patients who had ingested TCA-BDZ, the most frequently ingested benzodiazepines were clonazepam (n=20), lorazepam (n=19), diazepam (n=13), alprazolam (n=7), chlorodiazepoxide (n=6), oxazepam (n=3) and flurazepam (n=2).

The results of assessments and comparisons of cardiovascular metrics including sinus tachycardia (heart rate more than 120 per minute), sinus bradycardia (heart rate less than 60 per minute), hypotension (systolic blood pressure less than 90 mmHg), ECG findings, anticholinergic and CNS manifestations in the two study groups (patients intoxicated with TCA-only versus TCA-BDZ poisoned patients) are shown in Tables 1 and 2. There were significant differences between the two groups in the frequency distribution of sinus tachycardia (heart rate more than 120 per minutes), widening QRS (QRS > 100 ms), R/S aVR ≥ 0.7, RaVR ≥ 3 mm, generalized tonic colonic seizures and mydriasis.

	Mean ± Standard Deviation		P value †
	TCA-only*	TCA-BDZ†	
QRS duration (second)	0.076 ± 0.032	0.065 ± 0.18	0.019
QT Interval (second)	0.34 ± 0.04	0.35 ± 0.036	0.109
PR Interval (second)	0.21 ± 0.026	0.20 ± 0.025	0.696
TCA dose (mg)	795 ± 107	530 ± 54	0.030

TABLE 2. Comparison of different variables between two study groups * Patients ingested tricyclic antidepressant alone **Patients ingested tricyclic antidepressants and benzodiazepine.

† Independent t-test. TCA: tricyclic antidepressant. BDZ: benzodiazepine.

Of the patients in the TCA-only group 15% had a seizure, compared with no seizures in the TCA-BDZ group.

The following patients outcome were observed: most patients survived without complications (91.8% in the TCA-only group versus 95.1% in the TCA-BDZ group). Aspiration pneumonia was observed in four patients of the TCA-only group and two patients of the TCA-BDZ group. One patient in the TCA-only group developed pulmonary oedema. Death was observed in one patient (TCA-BDZ group).

The relationship between ingested TCA dosage and electrocardiographic (ECG) findings (duration of QRS, QT and PR intervals, the amplitude of R wave in lead aVR and right axis deviation) was evaluated in both study groups. This demonstrated a strong relationship between TCA dosage and QRS duration in the TCA-only group which was significantly different from the same correlation in the TCA-BDZ group (r , 0.50 in the TCA-only group versus r , 0.04 in the TCA-BDZ group, $P < 0.05$).

4. DISCUSSION

TCA self-poisoning has remained the predominant cause of morbidity among patients with auto-intoxication by antidepressants in recent years (12, 13). In our department, TCAs and BDZs predominate as the most commonly ingested antidepressant and sedative drugs. The results demonstrated that poisoning in our study groups was more common in young adults (20-40 years old) and female patients, this is comparable to the results of some previous investigations (14, 15).

According to our data, amitriptyline and clonazepam accounted for the majority of cases intoxicated in the TCA-only and TCA-BDZ groups, respectively. A possible reason for this is

that these two categories of drugs represent the most frequently prescribed antidepressant/sedatives in the community. This finding has also been reported by other studies. These have shown a strong correlation between prescription frequency and rate of antidepressant poisoning which is more pronounced with TCAs (12, 16-18). The tricyclic antidepressant agents, particularly amitriptyline, are recognized for their potentially lethal cardiovascular and neurological effects in poisoned patients (19).

We also determined and compared the frequency of toxicity signs (cardiovascular, anticholinergic and CNS manifestations) between the TCA-only group and the TCA-BDZ group (Table 1). Data analysis of cardiovascular manifestations revealed that the frequency of sinus tachycardia, (QRS > 100 ms, R/S aVR ≥ 0.7 mm), and $R_{aVR} \geq 3$ mm was significantly higher in the TCA-only group. This would suggest that BDZs somehow have an influence on adverse cardiovascular events following TCA intoxication. It could be suggested that the differences are because the TCA-BDZ group had lower exposure to TCAs. However the results demonstrated that there was not a relationship between ingested TCA dosage and electrocardiographic findings in the TCA-BDZ group. Of course, since hypotension is a hallmark of significant TCA poisoning, finding hypotension in only 8% of patients with TCA poisoning suggests that the patients evaluated were not very ill. This is further suggested by the finding in Table 2 that the QRS duration was only 76 msec overall in the TCA-only group (even though significantly different from 65msec in the TCA-BDZ group.), with a SD that puts most below the "toxic" range.

Among anticholinergic and CNS manifestations, a significant differ-

ence between the two study groups was found in seizure (Table 1). The possible mechanism may be related to the depressive effect of BDZs on the CNS that may interact to reduce the risk of seizure in TCAs overdose patients. Tricyclic antidepressants remain one of the most common causes of drug induced seizure (20). Despite the depressive effect of BDZs on the CNS, the occurrence of some adverse outcomes including aspiration pneumonia and non-cardiogenic pulmonary oedema, did not significantly differ between the two groups. However the frequency of seizure between the two groups based on the reported dose of TCA, BDZ and past history of seizure, was not compared.

There is no study documenting the effects of benzodiazepines on TCA-induced cardiovascular toxicity, although there are several reports which demonstrate that, in the setting of cocaine use, benzodiazepines relieve chest pain and have beneficial cardiac haemodynamic effects. This suggest that cocaine users should be provided with intravenous benzodiazepines as early management of cardiac symptoms (21-24). The administration of diazepam for supportive treatment in the ICU in a case of haemodynamic instability with hydroxychloroquine has been demonstrated by Olgers et al. (25).

Our study had some limitations:

a) Because of the small sample size with respect to different TCAs and BDZs, we were not able to analyze our data based on the different TCAs and BDZs ingested by overdose patients.

b) Providing the mean estimated dose ingested may not be as helpful as this information broken down by drug since some of the doses and toxic potencies differ.

c) We did not make an adjustment in our results for the intensity of treatment.

d) The ECGs were read by a clinical toxicologist and anesthesiologists (authors) not by the computer. A recent study suggested that the ability to read subtle, uncommon abnormalities on poisoned patients' cardiograms by eye is not optimal (26).

c) Exposure to the tricyclic antidepressants or the benzodiazepines was not confirmed by laboratory analysis,

nor were the quantities ingested. In addition, the presence of other drugs was not analytically excluded.

5. CONCLUSIONS

It is concluded that some cardiovascular toxicity and the risk of seizure may be lower in TCA-BDZ poisoned patients compared with those intoxicated with TCA alone. A further well designed study considering the above mentioned limitations is suggested.

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