Prevalence and Complications of Drug-induced Seizures in Baharloo Hospital, Tehran, Iran

*Behnam Behnoush[1], Fakhredin Taghadosinejad [1], Mohammad Arefi [1], Mohsen Shahabi[*1], Mohammad Jamalian [2], Amir Mohammad Kazemifar [3]*

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ABSTRACT

Background: Seizure is a frequent and important finding in the field of clinical toxicology. Almost all poisons and drugs can produce seizure. We have evaluated frequency and complications of drug-induced seizure in present study.

Methods: The present descriptive cross-sectional study was done on patients who were referred to Baharloo Hospital, Tehran, Iran, that had developed seizure before or after hospitalization following intoxication between 20 March 2010 and 20 March 2011. The exclusion criteria were a positive history of epilepsy, head trauma, or abnormal findings in EEG or brain CT scan.

Results: Tramadol and tricyclic antidepressants were the most common causes of drug-induced seizure (31.5% and 14.7% of the cases, respectively). Overall, 6 patients (4.2%) had developed persistent vegetative state in consequence of brain hypoxia, 16 patients (11.2%) had died due to complications of seizure or the poisoning itself. Tramadol was the leading cause of drug-induced seizure and its morbidity and mortality. Tonic-colonic seizure was the most common type of drug-induced seizure. Seizure had occurred once in 58% of the patients, twice in 37.1% of the patients, and had been revolutionized to status epilepticus in 4.9% of them. Among the 7 patients who had developed status epilepticus, 3 cases had died.

Conclusion: Appropriate measures for treatment of seizure and prevention of its complications should be taken when patients with drug poisoning are admitted into hospital, especially when the offending drug(s) has a higher likelihood to induce seizure.

Keywords: Drug, Iran, poisoning, seizure.

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INTRODUCTION

Acute intoxication is an important issue in the present world. Various chemicals, drugs, and industrial products are made, and intoxication following accidental or intentional exposures is increasing among different age groups (1).

Almost every drug and toxin can produce seizure. Some drugs such as tramadol and TCA cause seizure more commonly. Withdrawal from opioids, ethanol, and some benzodiazepines and phenobarbitals may cause late seizure. Standard treatment in seizure due to unknown toxin is done with a benzodiazepine firstly and then phenobarbital or phenytoin. There are also special treatments, for example, pyridoxine in isoniazid-induced seizure, naloxone in propoxyphene-induced seizure, and glucose in seizure due to hypoglycemia (2).

In some high risk conditions, for instance, history of epilepsy, head trauma, CNS infection or malignancy, metabolic disorders, and history of use of drugs that

1- Department of Forensic Medicine, Tehran University of Medical Sciences, Tehran, Iran
2- Department of Forensic Medicine and Toxicology, Arak University of Medical Sciences, Tehran, Iran
3- Department of Forensic Medicine, Qazvin University of Medical Sciences, Qazvin, Iran
*Corresponding author E-mail: Mohshahabi@gmail.com

decrease the threshold for seizure, such as MAO inhibitors, SSRIs, TCAs, antipsychotics, alcohol, and opioid analgesics, possibility of seizure after drug intoxication increases (3). Control of seizure and its complications has a strong relationship with the final prognosis of drug poisonings; therefore, in the present study, its prevalence, causative factors and complications in a referral center for treatment of poisoning were evaluated to help in management of similar patients and reduce its mortality.

MATERIALS AND METHODS

All patients with diagnosis of drug poisoning who had developed seizure before or during hospitalization from 20 March 2010 till 20 March 2011 were included in the study. If the patients had a positive history of epilepsy, head trauma, or abnormal findings in EEG or brain CT scan, they were excluded from the study. Overall, 143 patients were studied in the present study and evaluation was made using SPSS software version 16.

RESULTS

Seizure was more frequently seen in patients 20-30 years old (40% female and 53.3% male). Mean (± standard deviation) age of the patients was 27.5 (± 10.7) years in females and 28.5(± 10.9) years in males (Figure 1).

Overall, 92 males (64.3%) and 51 females (35.7%) were included in the current study and drug-induced seizures were more commonly seen in males.

Most patients (84.6%) had improved completely and had discharged from hospital without sequels. However, 3.9% of the female and 4.3% of the male patients had developed persistent vegetative state attributable to brain hypoxia after seizure. Also, 9.8% of the females and 12% of the male patients had died as a result of poisoning itself or seizure and 68.2% of the deceased patients were 20-40 years old.

Tonic-colonic seizure was the most common type of seizure that was seen in 133 patients (93%). Myoclonic, colonic, and focal seizure were seen in 3 (2.1%), 6 (4.2%), and 1 (0.7%) patients, respectively.

Seizure had occurred once in 62.7% of the female and 55.4% of male patients and twice or more in 33.3% of the female and 39.1% of the male patients. The seizure had revolutionized to status epilepticus in 4% of the females and 5.5% of the male patients. Status epilepticus had occurred after poisoning with tramadol, organochlorate pesticides,

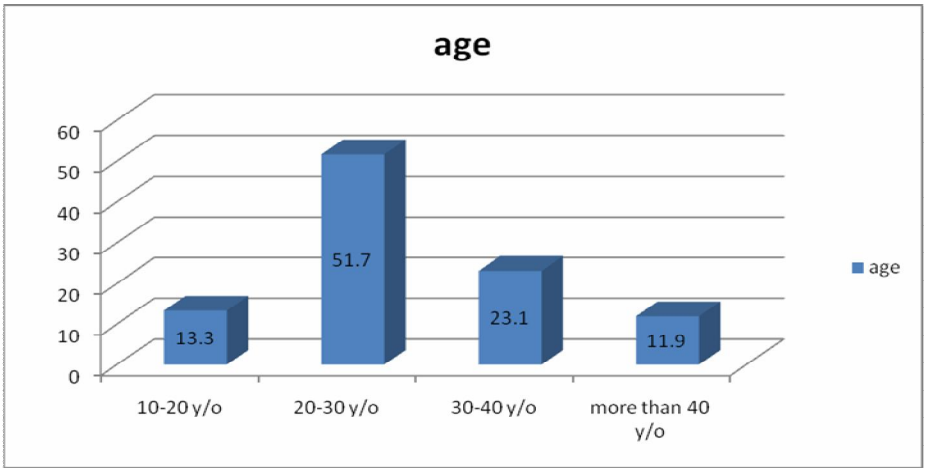

Figure1. Age distribution in patients with drug-induced seizure

methamphetamines (known as *Shisheh* in Iran), and TCAs.

The most common offending drugs causing seizure were tramadol (39.5%), TCAs (14.7%), propranolol (9.1%), and carbamazepine (6.3%) (Table 1). Among drugs of abuse, methamphetamines were the most common cause of seizure.

Multi-drug poisoning was seen in 15 patients with drug-induced seizure, among them there were 3 cases of poisoning with carbamazepine and propranolol, 2 cases of poisoning with TCAs and tramadol, and 2 cases of poisoning with TCAs and SSRIs (Table 2).

Table 1. Causative factors in drug-induced seizure in the patients

Drug or toxin	Numbers of intoxications with seizure
Tramadol	45
TCAs	21
Methamphetamines	15
Propranolol	13
Carbamazepine	9
SSRIs	7
Bupropion	7
Methanol	5
Antipsychotics	4
Theophyline	4
Isoniazid	4
Mefenamic acid	3
Aluminum Phosphide	3
Glibenclamide	3
Organophosphate pesticides	3
Organochlorate pesticides	3
Opioid with street name Norjizak	2
Others *	6
Total	143

*Others include methylphenidate, phenytoin, tranylcipromin, insulin, lindane, and carbon monoxide.

Table 2. Causes of seizure after multi-drug poisoning in the patients

Drug or toxin	Number of intoxications with seizure
Carbamazepine+ Propranolol	3
Tramadol+ TCAs	2
TCAs+ SSRIs	2
Antipsychotics+ SSRIs	1
TCAs+ Tranylcipromin	1
TCAs+ Propranolol	1
Antipsychotics+ Theophyline	1
Glibenclamide + Propranolol	1
Bupropion+Methylphenidate	1
Bupropion+Organophosphate pesticides	1
TCAs+ Propranolol+ Antipsychotics	1
Total	15

Overall, 6 patients had developed persistent vegetative state and 16 patients had died. Intoxication with tramadol had been more frequently associated with complications or death than other drugs and 5 patients (22.7%) with tramadol poisoning had developed complication or death. Next, methamphetamines and methanol abuse were the main forms of poisoning associated with complication or death, each 3 cases (13.6%) of mortality (Table 3).

Theophyline was the most common drug that had produced persistent vegetative state. Its poisoning had caused PVS in 2 patients (33.3%); one as the sole drug and in combination with antipsychotics (Table 4).

Table 3. Drugs causing death after seizure in the patients

Drug or toxin	Numbers of death	Relative percentile
Tramadol	3	18.75
Methanol	3	18.75
Methamphetamines	3	18.75
Aluminum Phosphide	2	12.5
Multi-drug Poisoning*	2	12.5
Insulin	1	6.25
Propranolol	1	6.25
TCAs	1	6.25
Total	16	100

*One case of bupropion+organophosphate pesticides and one case of tramadol+ TCAs

Table 4. Drugs causing PVS after seizure in the patients

Drug or toxin	Numbers of patients with PVS	Relative percentile
Carbon monoxide	1	16.7
Tramadol	1	16.7
Theophyline	1	16.7
Glibenclamide	1	16.7
TCAs	1	16.7
multi-drug poisoning*	1	16.7
Total	6	100

* Antipsychotics+theophyline

DISCUSSION

Patients who had developed seizure were in adolescent age in the present study. Their mean age was 28.5±10.9 years. Most of the patients were 20-40 years old. In Jovanovic's study which was done on 57 patients with tramadol poisoning, the mean age of the cases was 22.3 years (4). Izadi-Mood conducted a study on patients with drug-induced seizure. She showed that most patients were 15-40 years old (5). Poisoning is more prevalent in adolescent age and most of them are due to intentional suicidal poisoning. This may explain the more frequent occurrence of drug-induced seizure in this interlude of life.

In terms of gender, 35.7% of the patients in the present study were female. Talaie reported that 26.5% of the patients who developed seizure after tramadol poisoning were female (6). In Izadi-Mood's study, 47.6% of the patients were female (5). Jovanovic reported that 16.1% of the patients with tramadol-induced seizure were female. It seems that we cannot draw definite conclusions about gender distribution in drug-induced seizure because of the small number of cases in most of these studies. However, more predominance of drug abuse in males and their tendency to use more perilous drugs for suicidal acts may explain the higher frequency of drug-induced seizure among males.

The majority of the patients (84.6%) had developed no complications after drug-induced seizure and had been discharged from the hospital after appropriate treatment of the poisoning. Nevertheless, 4.2% of the cases had developed persistent vegetative state attributable to brain hypoxia after seizure and 11.2 % had died. Intoxication with tramadol, methamphetamines and methanol were more frequently seen in complicated patients, whereas theophyline poisoning was more commonly associated with occurrence of PVS among the patients. Boehnert's study on patients with TCAs poisoning reported no mortality (7) while 1.8% of the patients in Thundiyil's study had died (8). Olson showed that seizure in elderly is more commonly associated with complications and mortality (9). In the present study, it seems that the offending drug and severity of poisoning contribute to the outcome of the seizures.

Tonic-colonic seizure was the most common type of seizure and it was seen in 93% of the patients. After colonic seizure,

myoclonic seizure and focal seizure were found in 4.2%, 2.1%, and 0.7% of the patients, respectively. Talaie reported all of the patients with tramadol induced seizure had tonic-colonic seizure, though tonic-colonic seizure was seen only in 54.4% of patients with tramadol poisoning in Jocanovic's study (6, 4). It seems that tonic-colonic seizure is the most common type of seizure in drug-induced seizure.

Seizure had occurred once in 58% of the cases and twice in 37.1% of them. It revolutionized to status epilepticus in 4.9% of the patients, especially in poisonings with tramadol, organochlorate pesticides, methamphetamines, and TCAs. Thundiyil reported the singular incidence of seizure in 68.6% of the patients. Status epilepticus had occurred in 3.6% of the cases (8). Most cases of status epilepticus in Izadi-Mood's study were due to poisoning with organochlorate pesticides (25%), organophosphate pesticides (18.75%), TCA (18.75%), and carbamazepine (12.5%). It appears that the drug responsible for poisoning has a crucial role in recurrence of seizures.

The most common drugs associated with seizure were tramadol (31.5%), TCAs (14.7%), propranolol (9.1%), and carbamazepine (6.3%) in the present study. Methamphetamines was the most common one among drugs of abuse. Multi- drug poisoning was seen in 15 cases of drug-induced seizure, more commonly as carbamazepine plus propranolol, TCAs plus tramadol, and TCAs plus SSRIs. Thundiyil reported that bupropion (23%), diphenhydramine (8.3%), TCAs (7.7%), tramadol (7.5%), amphetamines (6.9%), isoniazid (5.9%) and venlafaxin (5.9%) as the most common causes of drug-induced seizure (8). In Izadi-Mood' study, the most common causes of drug-induced seizure were TCAs (39.7%), organophosphate pesticides (17.5%), carbamazepine (7.9%), and organochlorate pesticides (6.3%) (5). In fact, statuary regulations about delivery and sell of drugs and toxins, accessibility to drugs and toxins, and geographic variation may contribute to frequency distribution of drugs in drug-induced seizure.

CONCLUSION

Tramadol poisoning was the most common cause of drug-induced-seizure in the present study. It was also associated with mortality and complications more frequently. It is recommended that its access be limited for laypeople and not be sold as an OTC drug in pharmacies.

Physicians working in emergency wards should be familiar with drug-induced seizure and its importance and management, such as specific antidotes for controlling seizure in some forms of intoxication, including naloxone, pyridoxine, and glucose in poisoning with propoxiphen, isoniazid, and hypoglycemia, respectively. Moreover, they should know the indications and proper time of hospital discharge in the patients to avoid its untoward morbidities and mortality.

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