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Electroencephalogram and Brain CT-Scan Changes in Tramadol Associated Seizures

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Abstract: Objective: Drug-induced convulsions are the main causes of new-onset seizures and tramadol is one of the commonest drugs that can induced seizure. Methods: In a cross-sectional prospective survey, we assessed the predisposing factors, electroencephalogram (EEG) and brain computed tomography (CT) findings in tramadol-associated seizures cases. Results: of total of 126 drug-induced seizures, 26.2% were purely due to tramadol. Convulsion occurred after using a mean dose of 422 mg. Nearly 94% experienced only one single tonic-clonic convulsion. Brain CT scan was normal in all patients and non-epileptiform pattern were detected in eighty percent on EEG. Insomnia was the main risk factor related to convulsion. Conclusion: Although, head CT Scan has no rule in early treatment of drug induced seizure at ED, imaging is essential for rule out the concomitant trauma and other probable causes of new case of seizure even though in drug associated seizure.

Keywords: Tramadol, Seizure, Brain CT Scan, Electroencephalogram

1. Introduction

Tramadol as a centrally acting analgesic is extensively used in the management of moderate to severe pain in all over the world. It may also be abused by juveniles because of its euphoric and analgesic effects or as a substitute for opioid detoxification. Seizures are serious complication associated with tramadol that may occur with both therapeutic doses or overdose [1]. Tramadol associated seizure (TAS) are usually single and self-limited and most of them need no additional specific treatments, but there is no standard protocol for evaluation of the drug-induced seizures. Some authors believe that these patients need to be completely evaluated. We aimed to find the EEG and head CT Scan changing, to assess the predisposing factors that contributed to recurrent seizures, and argument about the work up of drugs-related seizure and the role of imaging in these patients.

2. Materials and Methods

In a prospective, cross-sectional survey over a 6-months period in 2015, all tramadol-associated seizures that presented at emergency department (ED) of two general teaching hospitals in Tehran were evaluated. We assessed factors that predisposed tramadol users to seizures, electroencephalogram, and head computed tomography scan changings.

Inclusion criteria: Patients with a first seizures after use of tramadol in the last 24 hours prior to seizures episode with age over 12 years were included. The use of tramadol confirmed by patient assertion and presence of tramadol in urine sample by rapid qualitative test.

Information including ingested doses of tramadol, time elapsed between ingestion and seizure, previous history of head injury, history of seizure in the patient's family, and prolonged use or recent tapering or discontinuation of tramadol was gathered by interview with patients or their families. Tramadol exposure was confirmed by positive history of recent ingestion of tramadol by patients and positive quantitative urine tests. Occurrence of seizure was determined by the history taken from patient's relatives or paramedics who brought the patient to hospital or by observation of convulsion at ED by emergency physicians. Blood sugar, serum sodium, calcium, magnesium, and routine tests measured on presentation. All subjects were hospitalized for at least 48 hours. Non-contrast head CT scan

were performed at first six hours and EEG was also performed 24 to 36 hours after presentation at ED.

Exclusion criteria: Patients with history of concurrent use of other drugs that could induce seizures (m, history of previous seizure or epilepsy in patient, positive history of idiopathic epilepsy in patients' family, history of previous head trauma and those with concomitant recently head trauma due to loss of consciousness, and history of confirmed underlying brain pathology were excluded from the study.

The data was analyzed with SPSS version 20 and a "P value" less than 0.05 was considered to be statistically significant. The study was approved by the local ethics committee in Iran University of Medical Sciences.

3. Results

A total of 126 cases of drugs-related seizures were registered in our emergency department during the study period, of whom, tramadol was the most common drug (33 cases or 26.2%) that led to seizures followed by antidepressants (23 cases or 18.3% of the patients). Table 1 shows the drugs that induced seizures. Exposure to tramadol was through ingestion in all cases. Table 2 shows the purposes of tramadol use. All patients were male with a mean age of 24.5±12.7 years. Hypoglycemia, hypocalcemia, hypomagnesemia, and hyponatremia was not seen in any of our cases. Seizure had happened prior to arrival in the ED in 94% of cases and in 2 cases another episode of seizure at ED.

In 31 cases (94%) a single generalized tonic-clonic seizure occurred at prehospital and none of them did not need anticonvulsant medications. Two cases (6%) experienced 2 episodes of seizures (one before hospital and the other one at hospital). No case of status epilepticus or prolonged seizure was observed. Table 3 shows the types of seizures. In physical examination at ED, twenty patients (60.6%) had a transient postictal confusion and 4 (12.1%) had hypotension (systolic blood pressure <100 mmHg) as a side effect of tramadol that treated simply with normal saline. Twenty-four of 33 patients (72.7%) had willfully used tramadol recreationally or continuously in therapeutic ranges for pain relief and three cases (9%) had overdosed on tramadol to attempt suicide. In our cases convulsion occurred after using a dose ranging between 200-700 mg (mean dose; 422 mg) and within 11 to 26 hours after tramadol use (mean time; 7.2± 2.2 hours). Eighteen patients (54.5%) gave a history of recent severe insomnia. Non-contrast head CT Scans were normal in all cases. In EEG, non-epileptiform pattern were detected in eighty percent of cases.

Table 1. *Kinds of drugs-induced convulsion.*

Kind of drugs	Number/Percent
Tramadol	33 (26.19)
Tricyclic antidepressant	11 (8.73)
Other antidepressant	12 (9.52)
Antipsychotics	6 (4.76)
NSAIDs	7 (5.55)
Opioids	10 (7.93)
CNS stimulants	3 (2.38)
Mixed drugs	39 (30.95)
Unknown	5 (3.96)

Table 2. *The causes of tramadol use by patients (N: 33).*

Causes of overdose	No (percent)
Increased daily dose	18 (54.5)
Decreased daily dose	3 (9.0)
Acute intentional overdose	3 (9.0)
Recent use for pain management	9 (69.7)

Table 3. *Types of seizures at ED (total: 33).*

Type of seizure	No (percent)
Single Tonic-Colonic Convulsion	31 (94%)
Status epilepticus	0 (0.0%)
Prolonged Seizures	0 (0.0%)
Recurrent Seizures	2 (6%)

4. Discussion

Seizures are serious complications associated with tramadol that may occur with both therapeutic doses or overdose [1]. Tramadol (Ultram) is a synthetic analgesic, opioid-like drug widely used to relieve pain in all over the world [2]. Tramadol has been one of the eighteen most commonly prescribed drugs from 2002 to 2012 in the USA [3]. Some authors [4, 5] believe that drug-induced seizures are an uncommon cause of new-onset seizures, but many recent articles [1, 23] demonstrated it is about eight percent and in our study, it was forty-five percent.

In one study [6] about seven percent of drug-induced seizure were related to tramadol. The maximum therapeutic daily dose of tramadol is 300-400mg/day for treatment of moderate to severe pain and chronic cancer pain in adults. Tramadol is pain relief drug with a dual mechanism of inhibiting reuptake of norepinephrine and serotonine and stimulating opioid receptors in the CNS. Tramadol may be abused, especially by juveniles because of its euphoric effects or as a substitute for opioid detoxification while its use for patients younger than 16 years of age is not approved [7, 14].

4.1. Type of Seizure Related to Tramadol

Seizures is the most common potential side effect of tramadol even in therapeutic doses, but may also happen after abuse or overdose [8]. Few authors said, tramadol-associated seizure (TAS) is not dose-dependent [8] but some other studies [9, 10] showed that TAS is dose dependent. Tagaddosinejad's study showed that, although higher doses of tramadol were related to higher blood concentration, blood tramadol concentrations were not associated with seizures. In this study, in nearly sixty percent of the cases were willing chronic users of tramadol and seizure was happened after increasing or decreasing their previous daily doses. In the literature, many authors have reported TAS. Some of them reported single tonic-clonic and some reported recurrent seizures [11]. In a study [2], on one hundred patients with the

diagnosis of TAS, they showed that the risk of recurrent seizures in tramadol users is low (nearly seven percent) and all of those with recurrent seizures recovered without sequelae. In another study [1], one third of cases experienced recurrent seizures and 3.6 percent status epilepticus because the most of them has been overdosed after suicidal attempted while in our study only two patients had more than one seizure without status epilepticus. Tramadol abuse not suicidal attempts in our patients explain this difference. In our study, ninety-four percent of patients had only a single self-limited generalized tonic-colonic convulsion before hospital presentation that did not need benzodiazepines at ED or during hospitalization and only six percent (2 of 33 cases) experienced another one episode of seizure during hospitalization that controlled by a single dose of diazepam (0.1mg/kg iv.). Prolonged and recurrent seizures or status epilepticus were not seen in our subjects, either. In our cases like as other studies [12, 13], seizures mostly occurred during the first 24 hours after taking tramadol.

4.2. Aggravating and Predisposing Factors Related to Drugs Induced Seizures

Tramadol can induce seizure in patients with underlying diseases; it may aggravate preexisting seizures and/ or trigger new seizures by lowering its threshold in the brain [15]. Seizure risk is also greater in patients with underlying disease such as preexisting neurologic illness (especially epilepsy) and concurrent medical illness [16, 17].

In another studies [1, 23] tramadol with nearly eight percent was the leading cause of seizures while the most leading cause of seizures due to drug was bupropion in twenty-tree percent [1]. However, in our study, nearly forty-five percent of total 280 new-cases of seizures seized due to drugs, of whom, twenty-six percent were related to tramadol. This result shows that tramadol broadly misused by Iranian's juvenile in compare to west countries (33 to 8 percent respectively). Some researches [15, 18] showed that some drugs such as antipsychotics, antidepressant such as bupropion, selective serotonin reuptake inhibitors (SSRIs) and TCAs, and monoamine oxidase inhibitors also may provoke seizures. These drugs may increase the neuro-excitatory effects of tramadol and the risk of seizures even in patients who were not predisposed to it [5]. Although, naloxone can reverse respiratory depression related to tramadol overdose, but it will increase the risk of seizures [2, 15]. So, tramadol should be prescribed with caution in patients who are at risk of seizures or taking other medications that lower the threshold of seizures. In our study, we only assessed pure tramadol users and we could not assessment the effects and interactions between above drugs and tramadol. In most of our cases seizures occurred when the patients suddenly increased tramadol doses and also in those persons who used tramadol for the first time regardless to it doses. There are many others important factors such as positive family history of epilepsy, age, sleep deprivation, stress, and alcohol use that can predispose patients to seizures related to drugs like tramadol [12]. In our study, sleep deprivation was the most common predisposing factor seen in more than fifty percent of the subjects. However, the potential risk for seizures should also be kept in mind, even when tramadol was used within the therapeutic ranges. Hypoglycemia and serotonin syndrome have been reported to be associated with tramadol use or overdose but these side effects were not detected in our cases.

4.3. EEG and Drugs-Induced Seizures

In another study [19], tramadol user who had seizures was assessed by both EEG at first day and delayed EEG on week later. At first EEG on first day, nearly forty-tree percent of subjects had abnormality and only one delayed EEG showed abnormality. One study in Iran [8] showed that thirty-five percent of patients with TAS had abnormal EEG. Some authors [20] believed that EEG should be requested for children presenting with a first seizure but CT scan for adults, or those with risk factors such as concomitant head trauma and presence of neurologic deficits. In another study in Iran [21], the EEG was performed in the first hours and one week after seizure related to tramadol. They fund out abnormal EEG at first day after seizure in nearly fifty percent of them in comparison to one case in later EEG.

In our study, nearly eighty percent showed non-specific abnormality but not epileptiform pattern on EEG that was done 24 to 36 hours after seizures episode. We, however, did not evaluate the patients' EEG later. So, a few of above authors believe that EEG is not crucial for early management of tramadol or drugs-induced seizures and it also has no benefit in treatment of these patients and will not change our approach to drugs-induced seizures.

4.4. Brain CT Scan and Drugs-Induced Seizures

In one study on sixteen cases of tramadol overdose [22], brain CT changes were seen only in one patient due to concomitant trauma. They said, one probable risk for obtaining CT-scan in unconscious patients is transporting the patient from ED to CT room. Thus overdose alone do not seem to be an indication to obtain CT-scan. In another study on 2003 in Australia [23], nearly eight percent of seizures related to drugs belonged to tramadol and all of them had normal head CT scan. In our study, non-contrast head CT scan, in all 33 cases was normal. Therefore, although based on above results, it seems that head CT Scan may not be indicated in the early work-up of definite tramadol-associated seizures or even other drugs-related seizures with single self-limited feature, many authors believe that, brain CT scan should be consider for all drug-induced seizures like TAS who have sings of head trauma such as focal neurologic signs or who have history of recent head trauma, positive previous history of seizures or epilepsy in patient or in patient's family, and in those with prolonged seizures, recurrent seizures, and in those with status epilepticus.

Finally, it should be keep in mind that the role of non-

contrast head CT scan and scalp EEG for evaluation of new-onset of seizures with un-known origin appears to be novel and appropriate. Also, when a patient present to the ED with seizures without known origin specially in an altered state with limited ability to provide a history and reportedly has had a seizure in the field, the emergency physician may order a non-contrast head CT Scan to rule-out other causes than drugs for new-onset seizures that require immediate intervention (i.e. intracerebral hemorrhage). The yield of non-contrast head CT scan is low; the cost of finding an acute intracerebral hemorrhage is high. Therefore, the cost-benefit ratio may still favor non-contrast head imaging in patients presenting with new-onset seizures.

5. Conclusion

Although, it seems that head CT scan has no benefit for early treatment of definite, pure, single, self-limited, and uncomplicated drugs-induced seizures, because of drug-induced seizures are a diagnosis of exclusion, head CT scan is crucial for rule out of other causes of seizures or concomitant head trauma and it recommended after performing basic treatment and patient stabilization especially in presence of predisposing factors. We strongly recommend Brain CT scan and EEG especially for drug-induced seizure with criteria's of; two or more than two times convulsion, prolonged seizure, and positive history of previous seizure, Idiopathic epilepsy in patient and his or her family, and positive history of recent head trauma.

Limitations of Study

Firstly, we could not to measure the level of tramadol in serum by quantitative tests and we could not compare the relation between serum level of tramadol and seizure. Secondly, this study did not compare it results to a relevant control group.

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Declaration

The authors declare that there are no financial and conflict of interests.

Abbreviations

ED; Emergency department, EEG; Electroencephalogram, TAS; Tramadol-associated seizures, CT; Computed tomography

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