Original Article

Chlordiazepoxide Preventive Effect on Tramadol Overdose Induced Serotonin Syndrome Evaluated by Hunter and Radomski Criteria: A Clinical Trial

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ABSTRACT

Introduction: Tramadol is an analgesic medication that is frequently abused. It has two functions; mu-opioid receptors agonism, as well as, serotonergic activities. It has shown that tramadol overdose may induce serotonin syndrome (SS). This study evaluates whether early treatment with chlordiazepoxide could prevent SS in admitted tramadol overdoses. **Materials and Methods:** In this single blind randomized control trial, 50% of admitted tramadol overdoses in Imam Reza (p) Hospital from 21 September 2011 to 21 January 2012 were recruited. Cases received chlordiazepoxide and controls received placebo. Clinical findings were recorded in a pre-designed spread sheet every 6 hours in the first 24 hours of admission. SS was determined by two independent methods; Hunter Criteria (HC) and Radomski Criteria (RC). **Results:** In total, five patients developed SS when HC or RC was taken into account. Among them, four cases were shared. None of the SS cases diagnosed with HC received chlordiazepoxide. However, just one SS case diagnosed with RC was from the case group. Based on HC, chlordiazepoxide decreased the Risk Ratio (CI 95%) of SS to 0.80 (0.66-0.97) ($P = 0.025$). This effect did not reach statistically significant levels when SS was diagnosed with RC. **Conclusion:** This study supports the fact that pre-treatment with chlordiazepoxide could prevent tramadol overdose induced SS.

Key words: Hunter criteria, radomski criteria, serotonin syndrome, tramadol

INTRODUCTION

Tramadol, a synthetic analogue of codeine, is an analgesic medication frequently used as an illicit drug.[1] This drug has two functions: Mu-opioid receptors agonism, as well as, serotonergic and noradrenergic activities.[2,3]

Opioid overdose and abuse including tramadol is rather common in Iran. Tramadol overdose may induce seizure, increased Creatinine Phosphokinase (CPK), and acute renal failure.[4-8] In addition, serotonin syndrome (SS) has been reported due to its overdose.[4,9,10] SS has been known as an adverse side-effect of serotonergic agents since 1960. Its clinical course is wide-ranged from very mild to fatal.[11]

This syndrome has three main clinical features: (a) neuromuscular hyperactivity, such as tremor, myoclonus, and hyperreflexia; (b) autonomic hyperactivity including diaphoresis, fever, and tachycardia; (c) altered mental status that could present with agitation and confusion.[1,11,12] Activation of the central 5-hydroxytryptamine1A receptors (5-HT1A) in the nervous system can explain the clinical features of SS.[11,13,14]

Management of SS is mainly supportive. It includes discontinuation of the serotonergic agents and external cooling. Sometimes patients need to be admitted to the

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ICU. Anti-serotonergic agents such as cyproheptadine and chlorpromazine that block 5HT1A and 5HT2 can be effective in the treatment of SS.[5] Chlordiazepoxide has also been used to manage tramadol overdose-induced SS.[4]

We hypothesized that chlordiazepoxide could prevent the occurrence of this syndrome in admitted tramadol overdoses.

MATERIALS AND METHODS

In this study, 50% of admitted tramadol overdoses in the Medical Toxicology Center, Imam Reza (p) Hospital, Mashhad, Iran were prospectively included from 21 September 2011 to 21 January 2012. This center is a 41-bed Toxicology Ward which receives around 12,000 referrals each year. Mashhad is the second major city of Iran with a population of approximately 3,000,000.

Eligibility criteria

Eligible patients were aged between 15 and 60 years and were referred for tramadol overdose. Exclusion criteria included mixed overdoses and history of epilepsy.

Ethics approval was obtained from the regional Ethics Committee, Mashhad University of Medical Sciences (2011-6710). An informed consent form was completed on arrival by one of the adult companions of each patient and was repeated retrospectively by the patient 24 hours after admission. Process of clinical evaluation and data gathering did not influence patient's medical treatment.

A previously used questionnaire[4] was modified to document demographics (number and strength of tramadol tablets, age, gender, history of addiction, and type of addiction) and clinical findings (vital signs and size of pupils). Observations were recorded in this sheet every 6 hours during the first 24 hours after admission.

Outcome measures

Serotonin Syndrome (SS) was determined by two independent methods. SS was diagnosed via Hunter Criteria (HC),[15] if one of the following events happened: (1) Spontaneous clonus; (2) Inducible clonus plus agitation or diaphoresis; (3) Ocular clonus plus agitation or diaphoresis; (4) Tremor and hyperreflexia; (5) Hypertonia; (6) Temperature above 38°C plus ocular clonus or inducible clonus.

SS was also diagnosed via Radomski Criteria (RC),[11] if at least four major or three major plus two minor variables (listed below) developed. Major criteria include (a) mental findings (consciousness impairment, elevated mood, and semicoma/coma); (b) neurological symptoms (myoclonus, tremor, shivering, rigidity, and hyper-reflexia); (c) vegetative symptoms (fever and sweating). Minor criteria include (a) mental findings (restlessness and insomnia); (b) neurological symptoms (incoordination, dilated pupils, and akathisia); (c) vegetative symptoms (tachycardia, tachy/dyspnea, diarrhoea, and hyper/hypotension). The SS diagnosis via RC was withdrawn if (1) clinical features described in the first criterion were an integral part of the underlying psychiatric disorder prior to commencing the serotonergic agent; (2) Other aetiologies (e.g., infectious, metabolic or endocrine, substance abuse or withdrawal) had not been ruled out; (3) A neuroleptic drug had been started or increased in dosage prior to the onset of the signs and symptoms listed above.[11]

Randomization

After assessing for eligibility criteria and to avoid selection bias, patients were consecutively recruited and randomly divided into two single blind groups. Equal randomization was used (1:1 for two groups). The method used to generate the random allocation was based on the random-number table. The first author (SMM) performed the randomization. The first case was selected by chance. The random allocation sequence was generated by moving to the next number from the random-number table. In the case group, chlordiazepoxide (10 mg every 8 hours) (n = 25) and in the control group placebo tablets were administered every 8 hours (n = 25). No cases or controls were dropped out within 24 hours of follow-up.

Treatment

All patients received fluids and symptomatic treatment. In the case group, chlordiazepoxide (10 mg as soon as possible and repeated every 8 hours) and in the control group, placebo tablets were orally administered on admission. When SS developed, cyproheptadine (4 mg every 8 hours) was also administered to treat patients.

Statistical analysis was performed using SPSS 11.5 (Chicago, Illinois, USA). The Chi-square test was used to compare the observed and expected frequencies of SS in both groups. $P < 0.05$ were considered to be statistically significant. Moreover, to indicate the reliability of some estimates and their directions, 95% confidence intervals for their risk estimates (Risk Ratios, 95% CI) were also calculated.

RESULTS

Socio-demographic

Overall, 50 cases were included. Tramadol overdose was male dominant (74%). Mean age (standard deviation, min-max) was 23.4 years (6.0, 15.0-40.0). Among them,

20 cases (40%) were addicts. Almost all of them (95%) were tramadol abusers. The alleged ingested dose was 1212.0 mg (973.7, 100.0-5000.0) [Table 1].

Clinical findings

Examining the pupils revealed 7 cases (14%) of miosis, 25 cases (50%) of mid-sized pupils, and 18 cases (36%) of mydriasis on admission. Patient systolic blood pressure was 120 mm Hg (14, 100-160). Pulse rate was 99 beats per minute (18, 64-140). Respiratory rate was 16 breaths per minute (3, 10-30), and temperature was 36.9°C (0.2°C, 36.0-37.8°C).

Serotonin syndrome

Among 25 patients who received the study drug, one developed SS by RC, but no cases were developed by HC. Out of the 25 patients who received the placebo, 5 developed SS by HC, and 4 developed SS by RC (4 of them shared). As a result, there was one case diagnosed with HC but not with RC, and also one case diagnosed with RC but not with HC.

Frequency of signs and symptoms in patients based on HC [Table 2 and Figure 1].

Among these 50 patients, 10% presented with spontaneous colonus in the first six hours. This sign decreased to 8% in 6-11 h, 2% in 12-17 h, and 0% in 18-24 h. However, no patient was presented with inducible colonus. Frequency of agitation was 6% in the first six hours. It decreased to 4% in 6-11 h, 2% in 12-17 h, and remained 2% in 18-24 h. 14% of patients experienced diaphoresis in the first six hours. It decreased to 10% in 6-11 h, 6% in 12-17 h, and 2% in 18-24 h. However, no patient was presented with ocular colonus.

Frequency of tremor was 16% in the first six hours. It remained 16% in 6-11 h, decreased to 4% in 12-17 h, and decreased further to 0% in 18-24 h. Frequency of hyperreflexia was 12% in the first six hours. It decreased to 10% in 6-11 h, 6% in 12-17 h, and 2% in 18-24 h. No patient presented with hypertonia. Temperatures above 38°C were observed in 2% of patients in the first six hours.

Frequency of signs and symptoms in patients based on RC [Table 2 and Figure 2].

In the first six hours, 34% of patients were manifested with altered consciousness levels. This percentage decreased to 12% in 6-11 h, 2% in 12-17 h, and remained 2% in 18-24 h. No patient was unconscious. None of them manifested with elevated mood. Frequency of myoclonus was 10% within the first six hours. It decreased to 8% in 6-11 h, 2% in 12-17 h, and 0% in 18-24 h.

Within the first twelve hours, 16% of patients were presented with tremors. This sign decreased to 4% in 12-17 h and 0% in 18-24 h. 14% of patients complained of shivering in the first six hours. This percentage decreased to 6% in 6-11 h, 4% in 12-17 h, and 0% in 18-24 h. No patient had rigidity. Frequency of hyperreflexia was 12% in the first six hours. It decreased to 10% in 6-11 h, 6% in 12-17 h, and 2% in 17-24 h.

Just 2% of patients experienced fever in the first six hours. 14% of patients experienced diaphoresis in the first six hours.

Table 1: The demographic data related to cases and controls

Groups variables	Case $n=25$	Control $n=25$	Total $n=50$
Age year (SD)	24.1 (5.9)	22.7 (6.1)	23.4 (6.0)
Male *n* (%)	19 (76)	18 (72)	37 (74)
History of addiction *n* (%)	10 (40)	10 (40)	20 (40)
Alleged tramadol dose (mean (SD)) mg	1236 (1185)	1188 (727)	1212 (973.7)
Type of addiction (tramadol-other opioids)	10-0	9-1	19-1

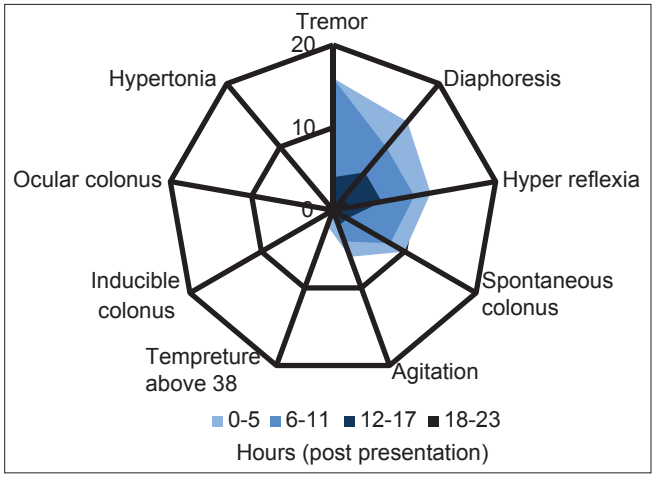

Figure 1: Frequency of sign and symptoms based on Hunter criteria

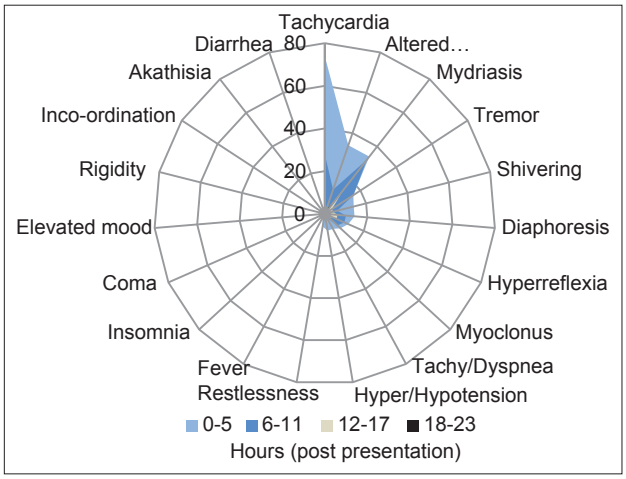

Figure 2: Frequency of sign and symptoms based on Radomski criteria

Table 2: Frequency of sign and symptoms in patients based on (a) Hunter criteria (b) Radomski criteria (*n*=50)

Time elapsed from exposure (hours)	0-5			6-11			12-17			18-24		
	Case	Control	All	Case	Control	All	Case	Control	All	Case	Control	All
Hunter Criteria *n* (%)												
Spontaneous colonus	0 (0)	5 (10)	5 (10)	1 (2)	3 (6)	4 (8)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Inducible colonus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Agitation	0 (0)	3 (6)	3 (6)	0 (0)	2 (4)	2 (4)	0 (0)	1 (2)	1 (2)	1 (2)	0 (0)	1 (2)
Diaphoresis	1 (2)	6 (12)	7 (14)	0 (0)	5 (10)	5 (10)	0 (0)	3 (6)	3 (6)	0 (0)	1 (2)	1 (2)
Ocular colonus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tremor	4 (8)	4 (8)	8 (16)	4 (8)	4 (8)	8 (16)	2 (4)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
hyper reflexia	1 (2)	5 (10)	6 (12)	1 (2)	4 (8)	5 (10)	0 (0)	3 (6)	3 (6)	0 (0)	1 (2)	1 (2)
Hypertonia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Temperature above 38	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Radomski criteria												
Major *n* (%)												
Altered consciousness	4 (8)	13 (26)	17 (34)	2 (4)	4 (8)	6 (12)	0 (0)	1 (2)	1 (2)	0 (0)	1 (2)	1 (2)
Coma	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Elevated mood	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myoclonus	0 (0)	5 (10)	5 (10)	1 (2)	3 (6)	4 (8)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Tremor	4 (8)	4 (8)	8 (16)	4 (8)	4 (8)	8 (16)	2 (4)	0 (0)	2 (4)	0 (0)	0 (0)	0 (0)
Shivering	5 (10)	2 (4)	7 (14)	2 (4)	1 (2)	3 (6)	1 (2)	1 (2)	2 (4)	0 (0)	0 (0)	0 (0)
Rigidity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hyperreflexia	1 (2)	5 (10)	6 (12)	1 (2)	4 (8)	5 (10)	0 (0)	3 (6)	3 (6)	0 (0)	1 (2)	1 (2)
Fever (Hyperthermia)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0(0)	0 (0)	0 (0)
Diaphoresis	1 (2)	6 (12)	7 (14)	0 (0)	5 (10)	5 (10)	0 (0)	3 (6)	3 (6)	0 (0)	1 (2)	1 (2)
Minor *n* (%)												
Restlessness	0 (0)	3 (6)	3 (6)	0 (0)	2 (4)	2 (4)	0 (0)	1 (2)	1 (2)	1 (2)	0 (0)	1 (2)
Insomnia	0 (0)	1 (2)	1 (2)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Inco-ordination	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mydriasis	7 (14)	10 (20)	17 (34)	6 (12)	10 (20)	16 (32)	1 (2)	6 (12)	7 (14)	1 (2)	4 (8)	5 (10)
Akathisia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tachycardia	17 (34)	20 (40)	37 (74)	4 (8)	10 (20)	14 (28)	0 (0)	2 (4)	2 (4)	0 (0)	0 (0)	0 (0)
Tachy/dyspnea	2 (4)	2 (4)	4 (8)	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hyper/hypotension	2 (4)	2 (4)	4 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

This figure decreased to 10% in 6-11 h, 6% in 12-17 h, and 2% in 18-24 h. Frequency of restlessness was 6% in the first six hours. It decreased to 4% in 6-11 h, 2% in 12-17 h, and 2% in 18-24 h. 2% of patients experienced insomnia in the first six hours. This symptom remained 2% in 6-11 h. It decreased to 0% in 12-17 h and 0% in 18-24 h. No patients presented with in-coordination. 34% of patients had mydriasis in the first six hours. It decreased to 32% in 6-11 h, 14% in 12-17 h, and 10% in 18-24 h. No patient experienced akathisia. Frequency of tachycardia was 74% in first six hours. It decreased to 28% in 6-11 h, 4% in 12-17 h, and 0% in 18-24 h. Frequency of tachypnea or dyspnea was 8% in first six hours. It decreased to 2% in 6-11 h, 0% in 12-17 h, and 0% in 18-24 h. No patient complained of diarrhea. 8% of patients presented with a change in blood pressure within the first 6 hours.

Patients who developed SS based on HC

In total, 5 patients developed SS when HC was taken into account. None of them received chlordiazepoxide.

- Patient 1 HC (P1HC): Presented with spontaneous colonus (resolved in 12 hours following cyproheptadine administration) and diaphoresis (18 h)
- Patient 2 HC (P2HC): Presented with spontaneous colonus (resolved in 12 hours following cyproheptadine administration), tremor (12 h), and hyperreflexia (6 h)
- Patient 3 HC (P3HC): Presented with spontaneous colonus (resolved in 6 hours following cyproheptadine administration), tremor (12 h), hyperreflexia (12 h), and diaphoresis (6 h)
- Patient 4 HC (P4HC): Presented with spontaneous colonus (resolved in 18 hours following cyproheptadine administration), tremor (12 h), and hyperreflexia (18 h)
- Patient 5 HC (P5HC): Presented with spontaneous colonus (resolved in 12 hours following cyproheptadine administration), hyper reflexia (12 h), and tremor (12 h).

P1HC, P2HC, P3HC, and P4HC except P5HC were also diagnosed with SS based on RC.

Patients who developed serotonin syndrome based on RC

In total, 5 patients developed SS based on RC. Among them, one case (P1RC) received chlordiazepoxide.

- Patient 1 RC (P1RC): Presented with altered consciousness (resolved in 12 hours following cyproheptadine administration), hyperreflexia (24 h), diaphoresis (24 h) (3 major criteria) plus tachycardia, (6 h) and agitation (24h) (2 minor criteria)
- Patient 2 RC (P2RC): Presented with altered consciousness (resolved in 6 hours following cyproheptadine administration), myoclonus (12 h), diaphoresis (18 h) (3 major criteria) plus mydriasis, (12 h) and tachycardia (12 h) (2 minor criteria)
- Patient 3 RC (P3RC): Presented with altered consciousness (resolved in 6 hours following cyproheptadine administration), myoclonus (12 h), tremor (12 h), shivering (12 h), hyperreflexia (6 h) (5 major criteria) plus agitation, (6 h) and tachycardia (18 h) (2 minor criteria)
- Patient 4 RC (P4RC): Presented with myoclonus (resolved in 6 hours following cyproheptadine administration), shivering (6 h), tremor (12 h), diaphoresis (6 h), and hyperreflexia (12 h) (5 major criteria) plus insomnia (12 h), tachycardia (6 h), and increased blood pressure (6 h) (3 minor criteria)
- Patient 5 RC (P5RC): Presented with myoclonus (resolved in 18 hours following cyproheptadine administration), tremor (12 h), hyperreflexia (18 h) (3major criteria) plus mydriasis, (12 h) and tachycardia (12 h) (2 minor criteria). P2RC, P3RC, P4RC, and P5RC except P1RC, were also diagnosed with SS based on HC.

Risk ratios

Based on HC, administration of chlordiazepoxide decreased the Risk Ratio (CI 95%) of SS (n = 5) to 0.80 (0.66-0.97) (P = 0.025). (No case of SS developed in the study group and five cases of SS developed in the control group) [Figure 3].

This effect did not reach statistically significant levels when RC was taken into account 0.22 (0.02-2.11) (P = 0.174). (One case of SS developed in the study group and four cases of SS developed in the control group) [Figure 3].

Chlordiazepoxide impact

Chlordiazepoxide administration in cases significantly decreased myoclonus (P = 0.025) and diaphoresis (P = 0.049), but not in other variables.

DISCUSSION

In this study, tramadol overdose mainly occurred in young males, in which the outcome was similar to our previous findings.[4] This could be related to a higher prevalence of drug abuse in young men. Older opioid addicts are probably less familiar with Tramadol as it has been popularized in recent years. In addition, tramadol could be used to treat premature ejaculation, which is more common in younger cases.[16] Frequency of mid-sized pupils was also similar to our previous experience.[4]

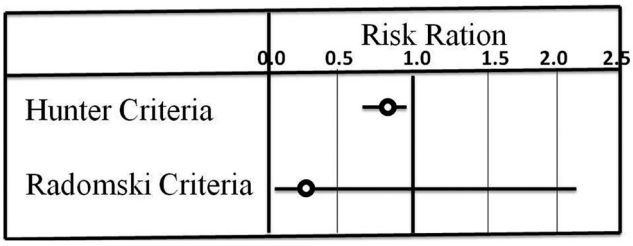

Figure 3: Administration of chlordiazepoxide on frequency development of Serotonin Syndrome (Risk Ratio (CI 95%) (n = 50))V

Frequency of SS in the current study was relatively higher in comparison with previous studies.[4] Tramadol induced SS was treated with cyproheptadine, as well as, fluids within 24 hours, which is similar to previous studies.[17] Cyproheptadine efficacy could be related to its inhibitory effects of 5-hydroxytryptamine 2a (5HT2a). 5HT is one of serotonin receptor families (5-HT_1 to 5-HT7) and 5-HT2A receptor is a subtype of it.[18-20] The efficacy of external cooling, supportive therapies, chlordiazepoxide, and cyproheptadine has been shown in many other studies.[4,17,21,22]

It has been previously shown that benzodiazepines may be used to treat agitation and tremor in SS.[23] This study demonstrated that chlordiazepoxide can decrease the risk of SS based on HC. In addition, it decreased the frequency of spontaneous clonus and diaphoresis, which was probably the reason for no SS occurrences among the case group. Unlike previous findings,[23] agitation and tremor in these subjects were not controlled with chlordiazepoxide.

Although spontaneous clonus and diaphoresis decreased in cases, the frequency of SS diagnosed by RC was not affected. This could be related to the method of measurement of the Radomski scale, in which at least 3 major criteria should be observed. Based on these data, HC is more sensitive when intervention is taken into account, which is consistent with previous reports.[15]

Radomski and colleagues revised Sternbach Criteria and developed RC to diagnose SS in 2000.[11] In later stages, a new set of decision rules, "the Hunter Serotonin Toxicity Criteria", was developed. It is suggested that HC are simpler, more sensitive, and more specific than Sternbach's criteria.[15] Evaluating SS with these two methods in the current research (HC and RC) will also provide evidence for future validation of these criteria.

This study confirms the previous hypothesis[4] that chlordiazepoxide could be effective in prevention of tramadol overdose induced SS.

Limitation

The number of cases diagnosed with SS were limited ($n = 5$). This research could be under-powered to detect potential impacts of chlordiazepoxide when SS is evaluated via RC. In this setting, administration of activated charcoal followed by gastric lavage was performed in some cases. This could have interfered with the study of chlordiazepoxide effectiveness.

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