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Pattern of use and Adverse Drug Reactions of Tramadol; A Review of 336, 610, 664 Insured Prescriptions During 5 Years

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Abstract: To compare the prescribing and usage pattern of all dosage forms of tramadol and to assess the type and frequency of tramadol-induced adverse drug reactions. All insured prescriptions which were collected in special software called Rx Analyst in the National Committee of Rational Drug Use were reviewed for prescriptions included at least one dosage form of tramadol. Data related to dispensing of tramadol were obtained from the official databank of national regulatory authority. All registered tramadol forms that induced adverse drug reactions in the database of Iranian Adverse Drug Reaction Monitoring Center were analyzed. The study period for all mentioned data was defined from 2006 to 2010. There were 291, 940 dosage forms of tramadol in 336, 610, 664 insured prescriptions in comparison to 1, 474, 680, 760 number of all dosage forms which dispensed from wholesaler to retail pharmacies during five years in the study. There were 461 different adverse reactions occurred in 249 patients. The most reported reactions included convulsion (73 items), nausea (56 items) and vomiting (47 items). We detected three death suspected to be induced by tramadol. Assessment of the trend of adverse reactions showed that the total number of reports was reduced from 89 cases in 2006 to 21 in 2010. There is a gap between number of tramadol prescribed and dispensed in the country that may be related to self-medication of this medicine. This has important value for priority setting in implementing interventions for promoting rational use of tramadol.

Key words: Tramadol, drug use pattern, adverse drug reactions, rational drug use, review

INTRODUCTION

Irrational use of drugs occurs for a variety of reasons. Appropriately prescribed medicines may be used inappropriately. Patients may not use the specified doses of medicines in appropriate intervals or for prescribed durations. In many developing countries, pharmacies dispense a range of drugs without physician's prescription. It is also part of another problem which is self-medication. In countries where the medicines market is not adequately regulated, patients may decide on what they need and obtain it freely from dispensers. The problem of irrational use of drugs may be the result of system failure.

On the other hand, the increase in abuse of marketed medications in the recent years has highlighted the need for abuse-liability assessment. As reported by The Substance Abuse and Mental Health Services Administration's (http://www.samhsa.gov), the numbers of new nonmedical users of four major classes of prescription-type drugs (pain relievers, tranquilizers, stimulants and sedatives) increased between 1991 and 2001, with the largest increase in pain relievers which increased from 628, 000 initiates in 1990 to 2.4 million in 2001. The number of primary treatment admissions for narcotic-analgesic abuse increased 76% between 1997 and 2000.

Tramadol is a central-acting analgesic which is used as a pain reliever for mild to moderate acute and chronic pain. The analgesic potency of tramadol is about 10% of morphine following parenteral administration and its abuse potential is low (Shadnia *et al*., 2007).

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Table 1: Number of evaluated prescribed and dispensed tramadol in various dosage forms

	Year				
	2006	2007	2008	2009	2010
Total number of evaluated prescriptions	49,415,728	71,027,535	84,889,274	93,407,063	37,871,064
Number of tramadol prescriptions	30277	25502	16802	17284	8725
Tramadol 50 mg tablet					
Dispensed by prescription or OTC	408,442,040	384,206,480	276,885,020	149,964,160	46,703,080
Dispensed by prescription only	72,772	33,469	16,664	14,348	8,913
Dispensed value (Rials)	167,544,485,870	154,555,945,400	111,505,024,000	76,610,195,910	38,501,688,500
Tramadol (ampoule)					
Dispensed by prescription or OTC	6,047,802	3,801,665	2,849,050	4,237,031	16,357,602
Dispensed by prescription only	27,378	20,641	12,122	18,164	7,877
Dispensed value (Rials)	9,218,834,286	5,696,620,000	5,173,077,500	7,374,456,500	11,951,531,500
Tramadol 50 mg (capsule)					
Dispensed by prescription or OTC	20,186,780	8,983,533	11,205,646	6,921,064	4,087,880
Dispensed by prescription only	43,714	7,580	1,827	2,745	1,197
Dispensed value (Rials)	10,015,370,589	3,692,586,789	5,134,720,945	3,654,686,353	1,035,328,000
Tramadol SR 100 mg tablet					
Dispensed by prescription or OTC	13,443,850	26,138,856	25,659,976	43,062,880	18,334,710
Dispensed by prescription only	516	379	547	1,010	50
Dispensed value (Rials)	10,492,699,100	17,765,355,520	12,642,081,500	26,767,173,500	20,633,856,000

In the present study, we aimed to assess the total number of tramadol which dispensed in comparison with the numbers that were prescribed. Also total number of tramadol-induced Adverse Drug Reactions (ADR) received by Iranian Adverse Drug Reaction Monitoring Center (IADRMC) is reported.

MATERIALS AND METHODS

In this cross-sectional study, all data on insured prescriptions included physician identification, dosage forms, strength and quantity of tramadol prescribed from 2006 to 2010 in the database of National Committee of Rational Drug Use, were analyzed. The number of prescriptions for mentioned period was 336, 610, 664. Data related to dispensing of tramadol were obtained from the official databank of national regulatory authority. All data were analyzed based on total number of different dosage forms and the price of tramadol. All registered ADR in the database of IADRMC from 2006 to 2010 were examined for tramadol-induced reactions. Extracted data were analyzed based on patient and reaction factors. World Health Organization (WHO, 1998) terminology was used for reported tramadol-induced ADR and system organ classification of reported ADRs. Route of administration, indication for tramadol use and outcome of reported reactions were assessed. Seriousness assessment was performed according to WHO criteria.

RESULTS

Table 1 shows the number of insured prescriptions evaluated in each year. As seen in this table, the total number of different dosage forms was 144, 380 out of 49, 415, 728 prescriptions in 2006, 62, 069 out of 71, 027, 535 prescriptions in 2007, 31, 160 out of 84, 889, 274 prescriptions in 2008, 36, 267 out of 93, 407, 063 prescriptions in 2009 and 18, 037 out of 37, 871, 064 prescriptions in 2010. Assessment of the trend of different dosage forms of tramadol that prescribed shows that the number of tramadol 50 mg capsule and tramadol tablet, decreased during this 5 year. While the number of prescribed tramadol Sustained Release (SR) 100 mg tablet was increased in the mentioned period. Evaluation of the pattern of prescription and dispensed injection dosage form shows a decrease in the first 3-year of the study and increase in the last 2-year (Table 2). Assessment of the

Table 2: Tramadol-related adverse reactions registered by IADRMC from 2006 to 2010

Adverse reaction	No.	Adverse reaction	No.	Adverse reaction	No.
Convulsion	73	Hallucination	4	Dysuria	1
Nausea	56	Diarrhea	3	Ear disorder	1
Vomiting	47	Malaise	3	Extrapyramidal reaction	1
Vertigo	44	Rash erythematous	3	Fever	1
Hypotension	26	Respiratory depression	3	Injection site necrosis	1
Dizziness	17	Stupor	3	Injection Site pain	1
Headache	17	Urticaria	3	Menstrual disorder	1
Confusion	13	Dry mouth	3	Paralysis flaccid	1
Pruritus	13	Chest pain	2	Polycythemia	1
Agitation	12	Hypertension	2	Ptosis	1
Dyspnea	12	Insomnia	2	Rash Postural	1
Asthenia	10	Myalgia	2	Rash	1
Somnolence	9	Euphoria	2	Serotonin syndrome	1
Sweating increased	8	Apnea	2	Tachypnea	1
Abnormal vision	7	Rigors	2	Torticollis	1
Fatigue	6	Abdominal pain	2	Vocal cord paralysis	1
Palpitation	5	Anaphylactic reaction	1	Arthralgia	1
Tachycardia	5	Anemia	1	Micturition frequency	1
Tremor	5	Angioedema	1	Delusion	1
Paraesthesia	5	Constipation	1	cardiac arrest	1
Flushing	4	Death	1	Ataxia	1

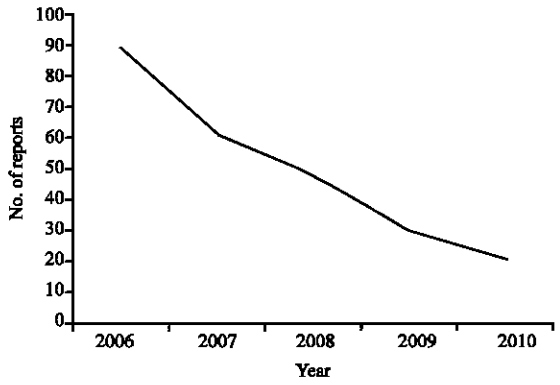

Fig. 1: The trend of tramadol-related adverse events from 2006 to 2010

Table 3: Route, indication and system organ classes involved in tramadol-induced adverse reactions

Factors	No.
Route of administration	
Per oral	165
Intramuscular injection	59
Unknown	18
Intravenous injection	7
Total	249
Indication	
Pain	72
Headache	30
Back pain	24
Abuse	22
Myalgia	7
Renal colic	7
Tooth pain	7
Influenza	2
Abdominal pain	1
Arthralgia	1
Arthrosis	1
Depression	1
Flank pain	1
Foot pain	1
Gastritis	1
Kidney carcinoma	1
Migraine	1
Total	249
System/Organ class	
Central and peripheral nervous system disorders	163
Gastrointestinal system disorder	72
Body as a whole-general disorders	32
Cardiovascular disorders, general	31
Skin and appendages disorders	21
Respiratory system disorder	15
Psychiatric disorders	12
Vision disorders	7
Musculoskeletal disorders	4
Heart rate and rhythm disorders	3
Application site disorders	2
Hearing and vestibular disorders	2
Red blood cell disorders	2
Reproductive disorder, female	1
Urinary system disorders	1
Vascular disorders	1

trend of reporting tramadol-induced ADRs showed that total number of reports was reduced from 89 cases in 2006 to 21 in 2010 (Fig. 1). A total of 461 different adverse reactions were registered in IADRMC database which was suspected resulting from tramadol use in 249 patients. These patients involved 122 females and 117 men. The most reported reactions included convulsion (73 items), nausea (56 items) and vomiting (47 items) (Table 2). The most involved system-organ classes were central and peripheral system and gastrointestinal system, respectively (Table 3). Three deaths were suspected to be induced by tramadol. Evaluating route of administration in reported cases revealed that most reactions occurred following oral consumption of tramadol (Table 3). In evaluation of known indications, we found that pain and headache were the most indications for use of tramadol in reported cases (Table 3). There were also 22 cases that used tramadol for abuse purposes. Seriousness assessment indicated that 33.3% of all reactions were serious ADRs.

DISCUSSION

Results show a huge gap between the number of tramadol prescribed and dispensed in the country that may be related to self-medication of tramadol. As described by WHO (1998), self-medication consists of the selection and use of medicines by people to treat self-diagnosed diseases or symptoms and should be understood as one of the elements of self-care". Irrational self-medication increases the risk of ADRs and masks real presentation of diseases and finally interferes with correct diagnosis of diseases. This results in further therapies that are almost more complex, invasive and expensive (Abdollahiasl *et al*., 2011a, b). Many factors lead to irrational use of medications, such as dispensing prescription-needed medications without prescription by pharmacies and cultural beliefs of patients to extra efficacy of injection dosage forms (Abdollahiasl *et al*., 2011b). Unfortunately in some cases, complete adherence to national rules of drug registration might be violated or missed (Nikfar *et al*., 2005).

Tramadol is associated with the development of physical dependence and a severe withdrawal syndrome (Barsotti *et al*., 2003), therefore irrational use of it has more adverse effect for users.

As shown in Fig. 1, trend of use of all dosage forms of tramadol, except for tablet 100 mg SR shows a decline. On the other hand, the reporting frequency of tramadol-induced ADR was obviously reduced during the study

period. We consider it as a result of interventions taken by IADRMC during 2003 to 2004, facing with the problem of high reporting frequency of severe ADR by tramadol (Gholami *et al*., 2007) or its poisoning cases (Taghaddosinejad *et al*., 2011; Talaie *et al*., 2009; Shadnia *et al*., 2008). Poisoning by tramadol is not that easy because it causes severe hypotension and it does not have special antidote (Nikfar *et al*., 2011). IADRMC issued alerting letters to healthcare professionals all around the country reminding them of positional hazards of tramadol and necessary precautions, limiting distribution of tramadol injection form to hospitals use only and reducing the potency of injectable tramadol from 100 to 50 mg by drug regulatory authority. Despite of reducing the reporting frequency, the results of this study shows that there are still problems in tramadol consumption in the society, e.g., it is used for abuse purposes in 22 cases registered in our database during the study period. Tramadol had been introduced as a medicine with no potential of abuse and dependency in early years of marketing, however, soon after the post-marketing reports showed some contrast data. Of course, several poisoning cases of tramadol occurred (Taghaddosinejad *et al*., 2011; Talaie *et al*., 2009; Shadnia *et al*., 2008). These data led to more limitations on distribution of this medicine in community pharmacies which was put on place by national drug regulatory authority.

The system organ classes of reported ADR in this study are in accordance with the nature of reported tramadol-induced adverse events in the literature. Central nervous system and gastro-intestinal system disorders are the most common involved system organ classes mentioned in the literature and in our study.

CONCLUSION

Regarding the gap between numbers of tramadol prescribed and dispensed in the country, the first think that comes to mind is self-medication of this medicine. This finding has important value for priority setting in implementing interventions for promoting rational use of tramadol. Therefore our final message to readers is that, use of tramadol should be limited to special cases and its prescription process and distribution to pharmacies should be highly limited.

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