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Research Article

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Consequences of Restricting Tramadol Dispensing in Iraqi Private Healthcare Facilities

Samer Shukur Mohammed[1*], Wael Waleed Mustafa[1], Manal Mohammed Younus[2]

[1]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Rafidain University College, 10052 Baghdad, Iraq;*
[2]*Iraqi Pharmacovigilance Center, Ministry of Health, Baghdad, Iraq*

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Abstract

Background and aim: Tramadol is a codeine analogue with less analgesic power than morphine but with better abuse potential. However, chronic use is associated with different adverse effects like anxiety, euphoria, nervousness, insomnia, depression, and agitation. In this study, we assessed the outcome behind the restriction on dispensing Tramadol in private health sectors in Iraq. ***Methods***: We look at tramadol data from VigiBase data searches and the Individual Case Safety Reports (ICSR) that are formally supported by the WHO worldwide database. All complaints were evaluated using Vigilyze data mining and computing IC25 to assess the strength of the link between Tramadol and the adverse reactions it causes, as well as to compare them to other records from around the world. ***Results***: For patients who used tramadol in a variety of dose forms, 184 instances were gathered over the course of seven years by the Iraqi Pharmacovigilance Center. There were 32 cases of hyperhidrosis, which occurred when tramadol was used alone, 47 incidents of vomiting, and 67 cases of nausea. Many adverse effects, including chest pain, hyperhidrosis, headache, dyspnea, and constipation, are more common in Iraqi records than in internationally known instances. Other side effects, such as vomiting, hallucination, vertigo, respiratory depression, and chills, were found to be milder than previously reported. There were no deaths in any of the instances that were recorded during this time period. ***Conclusion***: The number of reported tramadol-induced adverse events has fallen significantly, which can be attributed to the ministry of health restricting tramadol dispensing and enabling public hospitals to only dispense it under medical monitoring.

***Keywords*:** Tramadol, VigiBase, VigiLyze, Iraqi pharmacovigilance system.

عواقب تقييد صرف الترامادول في مرافق الرعاية الصحية الخاصة العراقية

الخلاصة

الخلفية والهدف: الترامادول هو احد نظائر الكوديين مع قوة مسكنة للألم أقل من المورفين ولكن مع إمكانية إساءة استخدام اقل. ومع ذلك ، يرتبط الاستخدام المزمن بآثار ضارة مختلفة مثل القلق والنشوة والعصبية والأرق والاكتئاب والإثارة. في هذه الدراسة، قمنا بتقييم النتائج الكامنة وراء القيود المفروضة على صرف الترامادول في القطاعات الصحية الخاصة في العراق. **الطرائق**: تمت مراجعة البيانات الخاصة بالترامادول من خلال عمليات البحث في بيانات VigiBase وتقارير سلامة الحالات الفردية التي تدعمها رسميا قاعدة بيانات منظمة الصحة العالمية في جميع أنحاء العالم. تم تقييم جميع الشكاوى باستخدام استخراج بيانات Vigilyze وحوسبة IC25 لتقييم قوة الصلة بين الترامادول وردود الفعل السلبية التي يسببها ، وكذلك لمقارنتها بسجلات أخرى من جميع أنحاء العالم. **النتائج**: بالنسبة للمرضى الذين استخدموا الترامادول في مجموعة متنوعة من أشكال الجرعات، تم جمع 184 حالة على مدار سبع سنوات من قبل المركز العراقي للتيقظ الدوائي. كانت هناك 32 حالة من فرط التعرق، والتي حدثت عندما تم استخدام الترامادول وحده، و 47 حالة من القيء، و 67 حالة من الغثيان. العديد من الآثار الضارة، بما في ذلك ألم الصدر وفرط التعرق والصداع وضيق التنفس والإمساك، هي أكثر شيوعا في السجلات العراقية مما كانت عليه في الحالات المعروفة دوليا. أثبتت الآثار الجانبية الأخرى مثل القيء والهلوسة والدوار والاكتئاب التنفسي والقشعريرة أنها أكثر اعتدالا من تلك المبلغ عنها في جميع أنحاء العالم. ولم تسجل أي وفيات في أي من الحالات التي سجلت خلال هذه الفترة الزمنية. **الاستنتاج**: انخفضت وتيرة حدوث الآثار الضارة الناجمة عن الترامادول المبلغ عنها انخفاضا كبيرا، وهو ما يمكن أن يعزى إلى قيام وزارة الصحة بتقييد صرف الترامادول وتمكين المستشفيات العامة من صرفه فقط تحت المراقبة الطبية.

* Corresponding author: Samer S. Mohammed, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Rafidain University College, 10052 Baghdad, Iraq; Email: samer.shukur@ruc.edu.iq

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INTRODUCTION

Tramadol is 2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexanol. It is a 4-phenyl-piperidine-group analogue of the opioid medication codeine [1]. Tramadol has a lower analgesic potency than morphine, but it is more likely to be safe in the long run. Tramadol is deemed safe because it does not produce respiratory depression or addiction like other opiate analgesics [2]. It works by activating μ-opioid receptors, central GABA receptors, and serotonin receptors to provide analgesia. The (+) Dextro tramadol enantiomer binds to the μ-opioid receptor and enhances dopamine activity in the central nervous system [3]. Tramadol is completely absorbed into the gut and shows bioavailability of approximately 75% when taken orally [4]. Approximately 30% of tramadol is excreted in the urine and 60% in metabolite form. Tramadol and its M1 metabolite have 6.3 and 7.4 hours of plasma half-lives, respectively [5]. Orally, the lethal dose (LD50) for rats is approximately 300-350 mg/kg orally [6]. Tramadol is primarily used as an analgesic to manage moderate to severe muscular and wound pain. Also, in combination with non-opioid analgesics such as paracetamol, it is often prescribed for moderate to severe pain [7].

Patients with a medical history of drug addiction, alcoholism, epilepsy, headaches, or metabolic disruption are more likely to experience tramadol-induced seizures. It is not recommended for patients who have kidney, liver, stomach, mental health, or depression, as well as those who are at high risk of suicidal ideation, as it may worsen their condition. Its use in pregnant women and mothers is restricted since it can cause birth abnormalities and harm the fetus and breastfeeding offspring. The American Food and Medication Administration classifies tramadol as a high-risk drug in Category C [8]. Overdoses and the abrupt combination with other drugs that interact are the main causes of tramadol side effects [9]. During anesthesia, intramuscular tramadol injection inhibits stomach acid secretion [10]. Patients having a history of seizures or other neurological disorders during tramadol usage (head trauma, brain injury, or CNS malignancies) should be treated with caution because tramadol overdose increases the risk of seizures. Naloxone may also enhance the risk of tramadol overdose-related convulsions [11], that is why Tramadol use is also not recommended. Respiratory depression and death are two things that can happen.

Tramadol-induced respiratory depression is treated with Naloxone as an antidote [12]. CNS stimulation, anxiety, euphoria, nervousness, sleep problem, insomnia, sadness, agitation, apathy, and, in rare circumstances, nightmares, dependency, and withdrawal syndrome are all prevalent psychological symptoms of long-term tramadol use. Menopause symptoms, urinary tract infections, micturition, hematuria, dysuria, and cystitis are all caused by it. The goal of this study is to assess the outcomes of Tramadol dispensing restrictions in private health sectors in Iraq, which has forbidden it through community pharmacies since 2014 [13].

METHODS

This was a descriptive assessment of Tramadol and its potential disorders during its use, based on data from VigiBase, the world's largest database of more than 20 million ICSRs submitted by members of the WHO Program for International Drug Monitoring since 1968, and the risk of multiple disorders occurring at the same time. This database is created and maintained by the Uppsala Surveillance Center (UMC) in Sweden. VigiBase data mining using search parameters was conducted on February 3rd, 2021: "Tramadol" as a medicinal drug. During the investigation, which lasted from 2014 to January 2021, some unpleasant things that happened in Iraq were examined. VigiLyze was used to retrieve the reaction outcome, disproportionality measure (information component – IC value), and other relevant variables. VigiLyze is a data mining and analytics tool developed for VigiBase. Drug adverse reaction (ADR) pair disproportionality is measured by IC. IC is used to evaluate the strength of the association between a drug and ADR. It is mathematically expressed as:

$$IC=Log^2 p(x,y)/p(x), p(y)$$

Where p(x) denotes the likelihood of a specific drug 'x' being listed in a case report; p(y) denotes the likelihood of a specific ADR 'Y' being listed in a case report; and p(x,y) denotes the likelihood of a specific drug-ADR combination being listed in a case report. IC value indicates that certain drug-induced adverse reactions are reported at a higher rate than the expected rate based on the rest of the reports in the database. An IC value of zero indicates no quantitative dependency, while a negative IC value indicates the combination is reported less commonly than statistically expected in the database. In the present study, we included all adverse events with high IC values that appear as Iraqi IC_{25}/global $IC_{25} > 1.0$ value, which can be defined as "a traditional threshold that indicates a correlation between drug-ADR more than expected globally based on all reported cases found in VigiBase." The exclusion criteria include all adverse events that have the same or lower IC value compared to that globally found in VigiBase. The literature search on this article includes the following keywords in Google scholar, PubMed, and search engine: "Tramadol", "Hyperhidrosis", "chest discomfort", "constipation", "dizziness", "vomiting", "hallucination", "headache", "respiratory depression", "vertigo", and "dyspnea".

RESULTS

The Iraqi Pharmacovigilance Center has assessed and documented 184 cases in VigiBase over the last seven years. All instances are quantitatively screened and compared to adverse events that have been reported globally in the same database. Table 1 compares the Iraqi IC_{25}/Global IC_{25} ratio, gender, seriousness, patient age, concurrent drug use, and multiple adverse drug reactions among the most common adverse drug responses stated in the summary of product features. All instances had gender differences noted, with

females accounting for roughly 59 percent of the overall cases. The bulk of those surveyed were between the ages of 18 and 44, with 58.7% falling into this category. In 19% of cases, tramadol was utilized concurrently. Ceftriaxone, metoclopramide, paracetamol, acetyl salicylic acid, and clopidogrel were the most regularly utilized concomitant medications. Tramadol has also been reported to be used with sodium chloride, heparin, amikacin, atorvastatin, and isosorbide dinitrate. In addition, records suggest that nausea is the most common adverse event, accounting for roughly 36.4% of all cases, while vomiting accounts for 25.5 percent of all reports.

Table 1: The most common adverse drug reactions of tramadol reported by Iraqi Pharmacovigilance Center

Adverse Drug Reaction	Cases (No.)	Iraqi IC_{25}/Global IC_{25} ratio	Gender n(%)	Seriousness n(%)	Age	Concomitant drug use (%)	Co-reported reaction term
Hyperhidrosis	32	3.7/2.3	M=15(46.9) F=17(53.1)	8(25)	18-44yr (40%)	100%	90% with sweating
Chest discomfort	8	1.6/0.4	M=4(50) F=4(50)	6(75)	18-44yr (62.5%)	100%	62.5% with hyperhidrosis
Constipation	14	1.5/1	M=5 (35.7) F=9 (64.3)	3(21.4)	18-44yr (64.3%)	78%	28.6% with sweating
Headache	17	0.7/-0.4	M=5(29.4) F=12(70.6)	3(17.6)	18-44yr (70.6%)	70.5%	47% with nausea
Nausea	67	2.4/2.7	M=23(65.7) F=44(34.3)	16(23.9)	18-44yr (68.7%)	65.7%	40% with vomiting
Gastric disorder	8	1.5/-1.8	M=4(50) F=4(50)	1(12.5)	18-44yr (25%)	100%	100% alone
Constipation	14	1.5/1.0	M=9(64.3) F=5(35.7)	3(21.4)	18-44yr (64.3%)	78.7%	7% with absent bowel movement
Dizziness	20	1.5/1.7	M=8(40) F=12(60)	3(15)	18-44yr (75%)	100%	55% with nausea
Vomiting	47	1.3/2.7	M=13(27.7) F=32(68.1)	13(27.7)	18-44yr (68.1%)	70.2%	57.4% with nausea
Hallucination	4	0.7/1.6	M=1(25) F=3(75)	4(100)	18-44yr (50%)	100 %	50% with nausea
Dyspnea	20	0.3/-0.4	M=4(20) F=15(75)	14(70)	18-44yr (55%)	80%	25% with nausea
Vertigo	3	-0.2/1.5	M=2 (66.7) F=1(33.3)	2 66.7)	18-44yr (33.3%)	100%	66.7% with nausea, dizziness, constipation
Respiratory depression	2	-0.5/2.4	F=2(100)	1(50)	18-44yr (50%)	100%	100% with nausea and dizziness
Chills	3	-0.9/-1.4	M=2(66.7) F=1(33.3)	1(33.3)	18-44yr (66.7%)	100%	100% with hyperhidrosis 66.7% with nausea

Serious instances were reported in 31% of cases, with one fatality (0.5%) and 10.3% of cases being life threatening. The same percentage of people had to stay in the hospital for an extended period of time.

DISCUSSION

The cases reported to the Iraqi pharmacovigilance center include several concurrent drug usages, making it impossible to determine whether tramadol is to blame for these side effects. In contrast to that, many reported cases show that tramadol is the only used medicine (as in hyperhidrosis, chest discomfort, gastric disorder, dizziness, hallucination, vertigo, respiratory depression, and chills), and this confirms that tramadol is responsible for those effects. According to the global data of the WHO, the majority of those effects have small differences between their percentages, and some of them show negative correlations, which indicates that the expected reports are higher than those actually reported. Some of the adverse effects reported showed a great difference in IC_{25} between cases reported in Iraq and those globally recorded as in hyperhidrosis, chest discomfort, headaches, and gastric disorder. During the survey, more attention is paid to people who use tramadol as a monotherapy than people who use it with other drugs. Tramadol-induced hyperhidrosis is one of these events caused by tramadol when used as sole therapy, and it shows a higher incidence when compared to global reports. Tramadol causes hyperhidrosis commonly in about 17% of cases, which occurs through the monoaminergic effect of tramadol. It rarely affects their usage, but this side effect may affect patient adherence, especially in countries with a hot climate like Iraq. Chest discomfort is one of the less common adverse effects of tramadol and it appeared in only 8 patients (4%) out of 184 cases, and its IC_{25} does not reflect the real number when compared to globally reported cases. Nausea and vomiting appeared commonly with tramadol usage, and they appeared in about 37% and 25% of the Iraqi reported cases, IC_{25} for nausea, which is comparable to that globally reported, while for vomiting, it is less than that recorded by WHO. This may be due to fewer cases reported by healthcare professionals from Iraq or to low dose usage of tramadol, which cannot be approved through those reports. Dizziness appeared in about 10% of reported cases, more than half of them accompanied by nausea and comparable IC_{25}

between Iraqi and globally reported cases. In contrast to those previously mentioned, serious adverse events associated with higher doses of Tramadol, such as hallucination and respiratory depression, are much lower in Iraq than those reported globally. Also, severe adverse events that are reported globally are not recorded in Iraq. This may be due to the restricted use of tramadol in Iraq for hospitalized patients in the governmental sector and the prohibition of its use in the private sector, which led to a decrease in tramadol poisoning cases reported through the Iraq Pharmacovigilance center.

CONCLUSION

The number and frequency of the reported adverse events were decreased, which can be attributed to the restriction of tramadol use by the Iraqi Ministry of Health and authorized dispensing it only in public hospitals and under medical supervision.

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Conflict of interests

No conflict of interests declared by the authors.

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Data sharing statement

The corresponding author can provide the data source in response to a reasonable request.

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