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Tramadol-induced hiccups: a case–noncase study in the European pharmacovigilance database

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Abstract

Background: Hiccups are usually benign and self-limiting, but can sometimes be persistent. If left untreated, they can provoke severe discomfort, and even death. Hiccups can be idiopathic, organic, psychogenic, and caused by drugs. Although some case reports have suggested a possible association between tramadol and hiccups, to our knowledge, no study has analyzed this possible relationship. The aim of this study was to analyze whether a disproportionate number of cases of hiccups are reported for tramadol in the EudraVigilance database.

Methods: A case–noncase study was conducted to assess the association between hiccups and tramadol, calculating reporting odds ratios (RORs) from 1 January 1995 to 11 September 2020. Cases were selected using the preferred term 'Hiccups'. The noncases used as controls were all other adverse drug reaction reports recorded in EudraVigilance during the same period. Exposure was defined as exposure to tramadol among cases and noncases. To reduce the risk of confounding by indication, the RORs for tramadol compared with other opioids were obtained. Additionally, we performed a confirmatory analysis in the World Health Organization pharmacovigilance database, VigiBase®.

Results: There were 3089 cases of hiccups in the 7,213,623 reports. Tramadol was involved in 50 cases. The ROR for tramadol exposure was 3.35 [95% confidence interval (CI) 2.53–4.43]. This association persisted when comparing tramadol with other opioids; ROR: 2.13 (95% CI 1.52–2.99). Disproportionality was also observed in VigiBase®: ROR 1.69 (95% CI 1.47–1.93).

Conclusion: Our study confirms, for the first time, a possible signal for a tramadol–hiccups association. Nevertheless, observational analytical studies are needed to confirm these results

Plain Language Summary

Evaluation of the relationship between the tramadol and the risk of hiccups

Introduction: Hiccups are sudden involuntary contractions of the diaphragm. This involuntary contraction causes the vocal cords to close very briefly, which produces the characteristic sound of a hiccup. Hiccups are usually benign and self-limiting, but can sometimes be persistent. If left untreated, they can provoke severe discomfort, depression, disability, and in the most extreme cases, even death. Drugs are a rare cause of hiccups.

Methods: This study investigated the possible association between tramadol and hiccups (an unmentioned adverse drug reaction in the Summary of Product Characteristics) in the European pharmacovigilance database (EudraVigilance) and a confirming analysis in the World Health Organization pharmacovigilance database (VigiBase).

Results: Our analysis shows that hiccups is relatively more frequently reported in association with tramadol than with other medicinal products, with EudraVigilance and VigiBase confirming this association.

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Conclusion: Tramadol is an opioid analgesic indicated, alone or in combination with dexketoprofen or paracetamol for pain with various causes, so healthcare professionals and patients should be aware of this possible association.

Keywords: drug safety surveillance, EudraVigilance, hiccups, spontaneous reporting system, tramadol

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Introduction

Hiccups are sudden involuntary contractions of the diaphragm and, in many cases, of the intercostal musculature, followed by an abrupt closure of the glottis causing the interruption of airflow. The classification of hiccups is by their duration: acute attack (<48 h), persistent hiccups (>2 days) and intractable hiccups (>1 month). Intractable hiccups can cause severe discomfort, depression, disability, and in the most extreme cases, it can lead to severe medical problems, including sleep deprivation, respiratory muscle fatigue, nutritional depletion, aspiration pneumonia, and can be fatal.[1] Despite being observed for centuries, the exact pathogenesis of hiccups remains a mystery. A phylogenetic hypothesis for its origin suggests that the ventilator central pattern generator of lower vertebrates (e.g. gills) provides the base upon which central pattern generators of higher vertebrates such as hiccups develop.[2]

The neural pathways of the reflex arc of hiccups are composed of three components: (1) an afferent branch that includes the phrenic, vagus, and sympathetic nerves; (2) the 'central unit' of hiccups, which includes the respiratory center, phrenic nerve nuclei, reticular formation, and hypothalamus; and (3) an efferent branch that carries motor fibers to the diaphragm and intercostal muscles.[3]

Hiccups can be idiopathic, organic, psychogenic or caused by drugs. The frequent causes of persistent or intractable hiccups are medical (including cerebrovascular disease, brain tumor, gastroesophageal reflux disease, hiatus hernia, myocardial infarction, pericarditis, aortic aneurysms, psychogenic and other causes) and surgical (pharyngeal intubation, endoscopy, thoracic and upper abdominal surgical).[4]

Drugs are a rare cause of hiccups. So far, the drugs that have been most frequently associated with hiccups are corticosteroids (particularly dexamethasone), antineoplastic drugs (e.g. cisplatin), diazepam, midazolam, barbiturates, and dopamine agonists.[3,4] Until now, healthcare authorities have published no safety signal associating this adverse reaction with any drug.

Tramadol is a centrally acting opioid analgesic indicated in the treatment of moderate to severe pain, first marketed by Grunenthal in Germany more than 40 years ago.[5] Worldwide tramadol use has increased rapidly over the past decades. In the United States, data from Truven Health Analytics MarketScan showed that prescriptions of tramadol increased by 22.8% between 2012 and 2015.[6] Its most common adverse reactions include: nausea, vomiting, constipation, dry mouth, headache, and hyperhidrosis. Respiratory depression can occur with high doses or when administered concomitantly with other drugs with central depressant actions. As far as we are concerned, so far, no study has analyzed the possible relationship between hiccups and tramadol. Also, in the Summary of Product Characteristics of tramadol brands, hiccups is not mentioned as adverse drug reaction. A better understanding of this phenomenon might help earlier recognition of this adverse effect, allowing treatment as soon as possible.

The aim of this study was to analyze the possible relationship between tramadol and the risk of hiccups, using the case–noncase method in the European pharmacovigilance database (EudraVigilance), as well as to describe the characteristics of the cases.

Methods

Data source

In this study, we used EudraVigilance as the data source. EudraVigilance is the centralized European

database of suspected adverse reactions to medicinal products that are authorized in the European Economic Area. EudraVigilance receives data from case reports filed by national drug regulatory agencies and pharmaceutical companies. EudraVigilance first operated in December 2001,[7] although there are cases from 1 January 1995 onwards. Taken into account that tramadol has been available since 1977, in this study collected the spontaneous reports recorded in EudraVigilance between 1 January 1995 and 11 September 2020. Suspected adverse reactions are recorded in EudraVigilance according to the Medical Dictionary for Regulatory Activities (MedDRA). For each individual case safety report, we retrieved demographic and clinical characteristics of the case, comorbidities, and pharmacological treatment (including dose, route of administration, start date and duration, and indication). Additionally, it is possible to retrieve information on adverse reactions (seriousness, date of start of reaction, duration, and outcome), the country that reported the case, and the professional qualification of the reporter.

Furthermore, for each individual case safety report, we evaluated the temporal and biological plausibility, taking into account demographic and clinical characteristics of the case and the time to onset (time in days from the drug administration start date to the reaction start date). Second, we analyzed reported comorbidities to assess whether existing clinical conditions might be associated with the development of hiccups. Third, we looked at whether the patient was on any other drug that could be associated with hiccups, even if it was not considered suspicious in the report. If considered as not sufficiently informative after careful evaluation, the case was excluded.

In order to assess the quality of available information for each case, we used VigiGrade, a tool developed by the Uppsala Monitoring Center. This tool assesses the following data for each individual report: time to onset, age, sex, indication, outcome, report type, dose, country, primary reporter, and comments. Calculation is carried out by assigning penalties according to the availability of information and its clinical relevance for each item. A case is considered well documented when the score is greater than 0.8.[8]

Disproportionality analysis

A case–noncase analysis was performed to evaluate the association between exposure to tramadol and hiccups. To that end, cases were selected using the preferred term 'hiccups' (from MedDRA, version 23.0). The noncases used as controls were all the remaining adverse drug reaction reports recorded in EudraVigilance during the same period. Exposure was defined as exposure to tramadol among cases and noncases.

The case–noncase analysis calculated reporting odds ratios (RORs) and their 95% confidence intervals (CIs) as a measure of disproportionality between a drug and a particular adverse drug reaction. The ROR was calculated using a two-by-two table, ROR = ad/cb (where a = exposed cases; b = exposed noncases; c = nonexposed cases; and d = nonexposed noncases). According to the European Medicines Agency recommendations, to generate a safety signal, the lower bound of the 95% CI of the ROR is required to be $\geqslant 1$ and the number of individual cases to be $\geqslant 3$.

We carried out analysis in which tramadol was compared with all the other drugs listed in the entire EudraVigilance database. Additionally, a similar analysis was performed for each combination separately. We also conducted a confirmatory analysis in the World Health Organization (WHO) pharmacovigilance database, VigiBase®.

Subsequently, in order to mitigate confounding by indication (opioids might be prescribed for conditions associated with hiccups *per se*) the ROR for tramadol compared with other opioids was obtained. For that purpose, opioids were defined as any drug from the N02A group in the Anatomical Therapeutic Chemical classification system.[9] Finally, in order to exclude a notoriety bias, the evolution of the ROR over time (dynamic ROR) was analyzed.

Review of the literature

A systematic review following the steps recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes checklist[10] was performed to find out published cases of tramadol-associated hiccups.

A search for published reports in *Embase* and *PubMed* electronic databases was carried out in October 2020, using the following keywords: 'hiccup/si' (side effect) in *Embase*, and 'hiccup/chemically induced' (MeSH terms) in *PubMed*. The search was restricted to articles having abstracts and comprising human data, but no

Table 1. General characteristics of cases of hiccups associated with tramadol in EudraVigilance.

Drug	Cases (*n*)	Sex (M/F)	Age (years) mean ± SD	Latency (days) mean ± SD	Outcome	*n* cases (only suspect)	Considered serious by EU criteria
Tramadol	39	26M, 13F	52.2 ± 18.1 NS in 4 cases	9.4 ± 29.8 NS in 5 cases	Recovered 53.8% (21/39) Not recovered 23.1% (9/39) Unknown 23.1% (9/39)	35	11 cases hospitalization (2), disability (1), medically significant (8)
Tramadol + paracetamol	8[a]	6M, 2F	46.0 ± 19.8	2.5 ± 2.8	Recovered 62.5% (5/8) Not recovered 12.5% (1/8), Unknown 25% (2/8)	8	Three cases hospitalization (1)[a], medically significant (2)
Tramadol + dexketoprofen	4[a]	4M	36.5 ± 6.8	1.7 ± 1.2 NS in 1 case	Recovered 75% (3/4), Unknown 25% (1/4)	3	1 case hospitalization (1)[a]

[a]One patient having taken both tramadol + paracetamol and tramadol + dexketoprofen.
EU, European Union; F, female; M, male; NS, not specified; SD, standard deviation.

language or temporal limits were established. Then, duplicates were excluded manually. A complementary search with the same terms was also performed in *Google Scholar* to increase sensitivity. Only studies where the title or abstract contained the term 'tramadol' were selected. The titles and abstracts were independently reviewed and compared against the selection criteria by two authors. Subsequently, this list was further reduced by accessing the full text to ensure that the hiccups were associated with tramadol. All papers that fulfilled the selection criteria were retrieved in full text and examined for relevant citations.

Results

Disproportionality analysis

During the study period, 7,213,623 spontaneous cases of adverse reactions were registered in EudraVigilance, of which 3089 (0.04%) were hiccups. Opioids were involved in 151 cases. Of these, 50 cases implicated tramadol (tramadol, $n = 39$; tramadol + paracetamol, $n = 8$; tramadol + dexketoprofen, $n = 4$; one patient having taken both tramadol + paracetamol and tramadol + dexketoprofen). Two duplicate cases were detected and eliminated. In addition, using the VigiGrade tool, 26 of the 50 cases (52%) had an information quality score > 0.8.

The majority of cases were reported in the Netherlands ($n = 16$; 31.4%), followed by France, Germany, and Spain ($n = 5$; 9.8% each). Approximately half of the 50 cases were reported by consumers 21 (42%); 17 (34%) by doctors; 6 (12%) by pharmacists, and 6 (12%) by other healthcare professionals.

The general characteristics of cases are summarized in Table 1. Of the 50 patients, 35 (70%) were male. The mean age was 50.0 ± 18.2 years (24–85), and the mean latency period until the appearance of hiccups was 1.7–9.4 days. Tramadol daily dose was ⩾150 mg/day in 24 cases, and <150 mg/day in 17 cases (in 9 cases the dose was unknown). Fourteen cases were classified as serious according to EU criteria (12 of them were reported by healthcare professionals). At the time of the report, 28 (55%) cases were recovered. Tramadol was present as the only suspect drug in 45 cases, whereas other suspect drugs (in addition to tramadol) were present in 5 cases: gabapentin, insulin, oxycodone, fentanyl, and varenicline. Comorbidities described in the report were: no comorbidities (7), myocardial infarction (2), diabetes mellitus (2),

Table 2. RORs for tramadol and hiccups in EudraVigilance and WHO VigiBase®.

Exposure	EudraVigilance			WHO VigiBase®		
	Cases, *n*	Noncases, *n*	ROR (95% CI)	Cases, *n*	Noncases, *n*	ROR (95% CI)
All drugs	3089	7,210,534	Reference	16,087	23,243,426	Reference
Tramadol (alone or in combinations)	50	35,257	3.35 (2.53–4.43)	214	185,286	1.69 (1.47–1.93)
Tramadol	39	27,770	3.31 (2.41–4.54)	109	135,934	1.16 (0.96–1.41)
Tramadol + paracetamol	8[a]	6847	2.73 (1.36–5.47)	102[b]	49,168	3.02 (2.49–3.67)
Tramadol + dexketoprofen	4[a]	640	14.61 (5.46–39.06)	5	982	7.39 (3.07–17.80)

[a,b]One patient having taken both tramadol + paracetamol and tramadol + dexketoprofen.
[b]One patient having taken both tramadol and paracetamol + tramadol.
CI, confidence interval; RORs, reporting odds ratios.

Table 3. ROR for tramadol and hiccups compared to other opioids in EudraVigilance.

Exposure	Cases, *n*	Noncases, *n*	ROR (95% CI)
All opioids	151	187,020	Reference
Tramadol (alone or in combinations)	50	35,257	2.13 (1.52–2.99)
Tramadol	39	27,770	2.00 (1.39–2.88)
Tramadol + paracetamol	8[a]	6847	1.47 (0.72–3.00)
Tramadol + dexketoprofen	4[a]	640	7.92 (2.93–21.46)

[a]One patient having taken both tramadol + paracetamol and tramadol + dexketoprofen.
CI, confidence interval; ROR, reporting odds ratio.

gastroesophageal reflux disease (1), asthma (1), and chronic bronchitis (1); for 26 cases, no information was provided.

Hiccups was reported relatively more frequently in association with tramadol than with other medicinal products in EudraVigilance database. The ROR for tramadol (alone or in combination) exposure was 3.35 (95% CI 2.53–4.43). Disproportionality was also observed for each combination separately. On the other hand, disproportionality was also observed in VigiBase®; the ROR was 1.69 (95% CI 1.47–1.93) for tramadol (Table 2).

Disproportionality was still observed when comparing tramadol with other opioid drugs, with a ROR of 2.13 (95% CI 1.52–2.99) (Table 3).

The evolution of ROR over time (dynamic ROR) shows that the disproportionality remains constant for the association of tramadol and hiccups (Figure 1).

Review of the literature

Only five of the 1152 identified studies were included in the qualitative analysis. Four of them reported data from clinical trials and the other one was a report of two cases. The flowchart of identification, screening, and eligibility of studies for final inclusion is presented in Figure 2.

The first was an open-label phase I trial comparing the pharmacokinetic profile of the co-crystal of tramadol–celecoxib (29 patients) with tramadol (30 patients), celecoxib (28 patients), and tramadol + celecoxib (28 patients). Tolerability

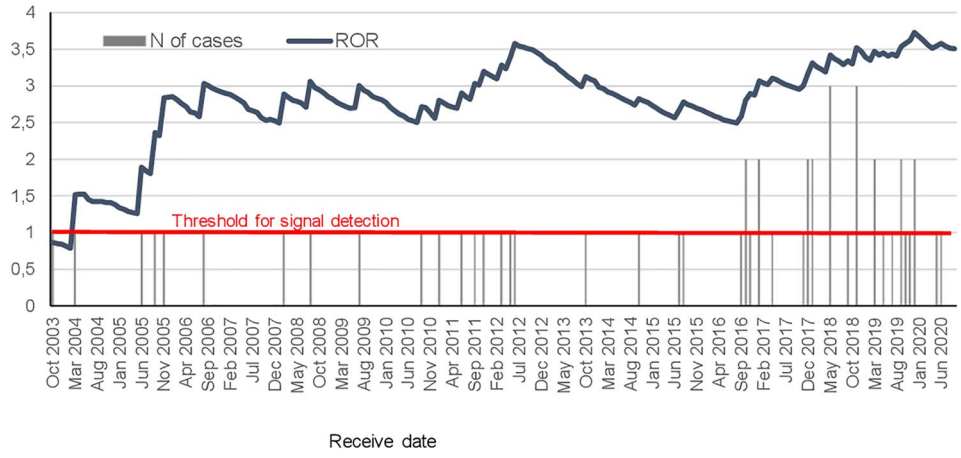

Figure 1. Number of reported cases and RORs for tramadol and hiccups.
RORs, reporting odds ratios.

and safety was also evaluated. Three of the 28 patients in the tramadol + celecoxib group suffered from hiccups. No additional cases were reported in any of the other treatment arms.[11] The second study was a double-blinded phase I, four-way crossover study, controlled with placebo, which aimed to measure the impact of therapeutic and supra-therapeutic doses of tramadol on the QTc interval in healthy volunteers (aged 15–55 years). Of the 63 patients receiving 400 mg/day of tramadol, 4.8% reported hiccups. This proportion was higher in those on 600 mg/day, with 7.8% of them suffering from hiccups.[12]

The third clinical trial compared the efficacy and safety of tramadol *versus* fentanyl in pediatric patients undergoing upper gastrointestinal endoscopy. Patients were divided into three subgroups: 0–2 years, 2–12 years, and >12 years. One of the 16 patients aged 2–12 years reported hiccups.[13] In the fourth trial, a multicenter, double-blind study, the analgesic efficacy of intravenous tramadol *versus* intravenous morphine was compared in postoperative pain. A high incidence of gastrointestinal adverse effects was observed with both treatments, consisting mainly of nausea, dry mouth, dyspepsia, and hiccups.[14]

The last report details two patients presenting hiccups 1 h and 2 h, respectively, after the administration of tramadol for cellulitis-related pain. Both patients recovered with withdrawal of tramadol and treatment with baclofen.[15]

Discussion

The disproportionality analyses in this case–non-case study based on the EudraVigilance and WHO VigiBase® databases confirm a signal between tramadol exposure and hiccups. An indication bias does not seem a likely explanation of our results, considering the signal persisted after comparing tramadol with opioid drugs.

Besides, we believe that a notoriety bias can be discarded based on two facts. First, until now, there are no safety signal published by healthcare authorities associating hiccups with any drug. Second, the dynamic ROR showed no clear variation over time.

Available evidence relating tramadol with hiccups is scarce. We only found five published articles of tramadol-associated hiccups, and a detailed description of the adverse reaction was exclusively available in the publication including the two case reports. The clinical trials only reported aggregate data on the number of patients with hiccups, with no individual information. However, it is remarkable that the four clinical trials collected cases of hiccups, which validates the signal detected in EudraVigilance and VigiBase®.

Nevertheless, opioid-related hiccups has been reported in several articles. A 63-year-old man with severe neck pain associated with a tonsil carcinoma developed persistent hiccups after taking oral sustained-release morphine. Hiccups

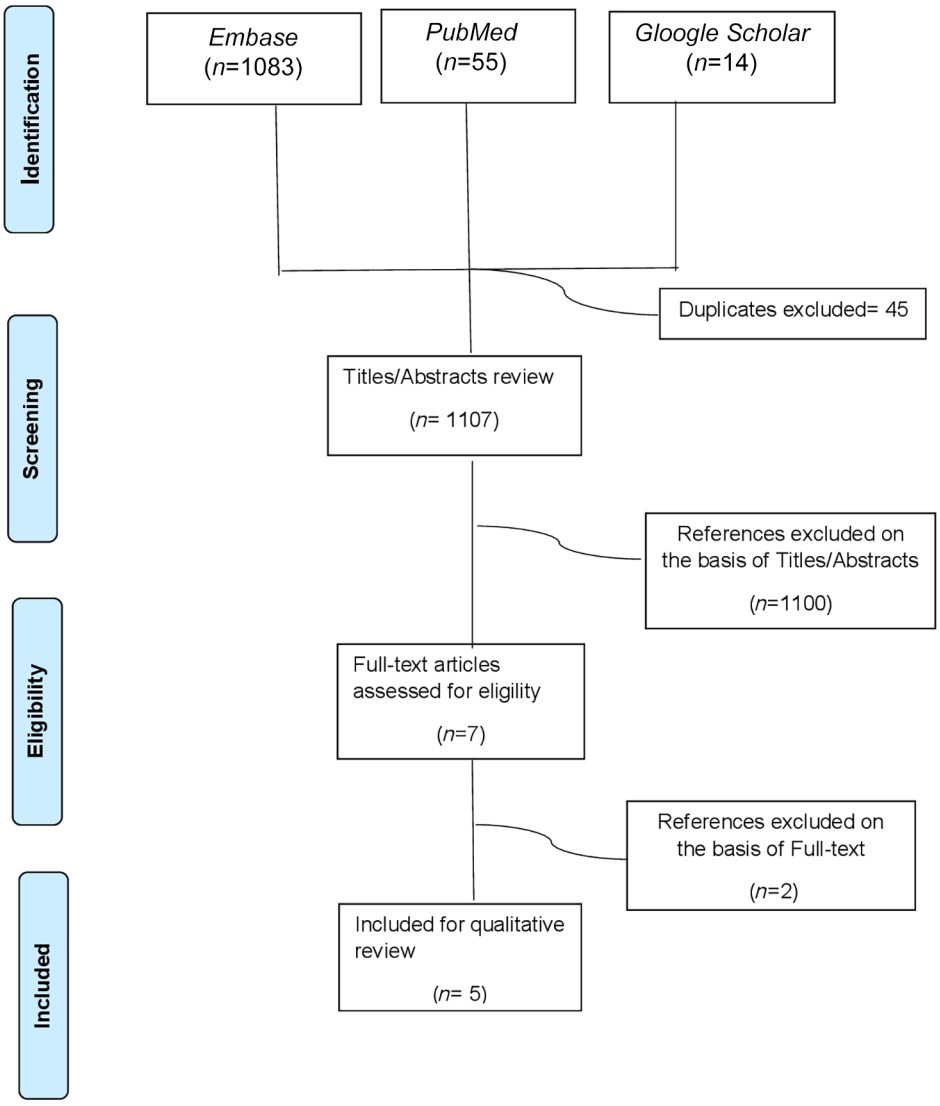

Figure 2. Flow diagram of a systematic review of the literature.

resolved, without recurrence, substituting morphine for fentanyl and oxycodone patches.[16] A 55-year-old patient experienced persistent hiccups for 4 days after receiving hydrocodone (5 mg/4 h) for a dental problem, which resolved after withdrawal.[17] Finally, two cases of persistent hiccups with intrathecal morphine were reported. In both, hiccups appeared 12 h after starting treatment with morphine and resolved when it was replaced by hydromorphone.[18,19] Bagheri *et al.*[20] showed that opioids represented 6% of the 53 cases of drug-associated hiccups in the French pharmacovigilance database, between 1985 and 1997. However, due to the small sample size, 6% would correspond to three cases in 12 years in France. In our study, of the 3089 drug-induced hiccups cases, 151 (4.9%) implicated opioids. In 101 of them, the suspicious drug was other than tramadol.

In this study, approximately half of the cases were patient-reported. The participation of patients in the notification of adverse drug reactions is important, as it adds new clinical and subjective information.[21] In addition, it has also allowed the identification of previously unknown adverse reactions, leading to the strengthening of safety signals,[22] such as in this study.

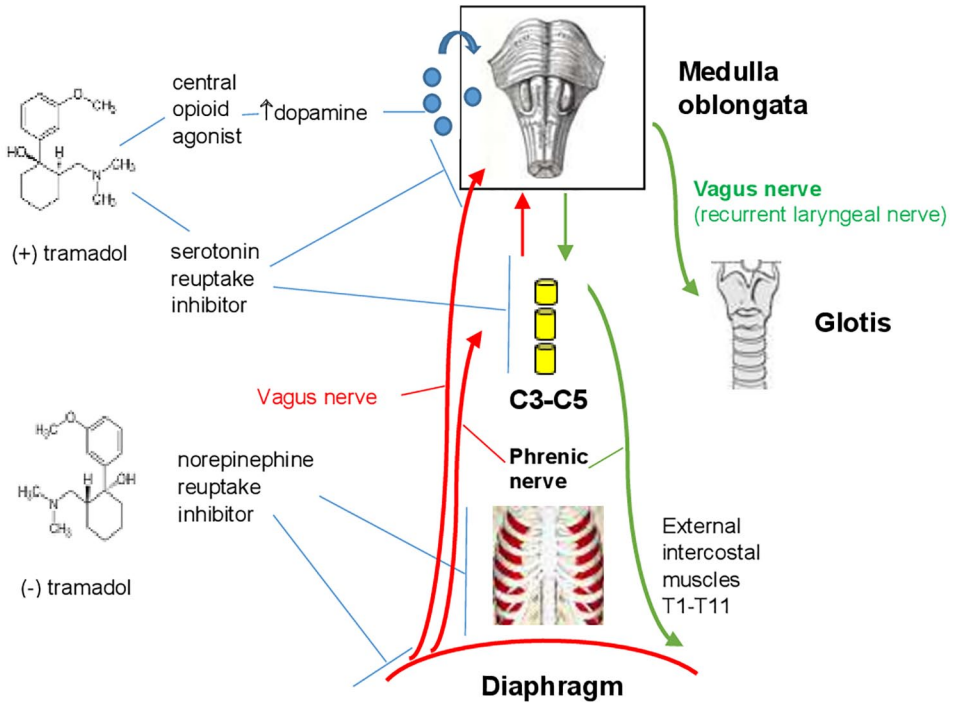

Figure 3. Possible mechanism of tramadol in the pathophysiology of hiccups.

Numerous studies describe higher incidence of hiccups in men.[20,23] A systematic review and meta-analysis of case–control studies and case reports whose objective was to identify differences in sex in patients with hiccups, showed a male predominance [odds ratio (OR) = 2.42 (95% IC 1.40–4.17)]. This finding was particularly significant when the hiccups were not of central origin (non-CNS origin) (i.e. peripheral or drug-related causes): OR 11.72 (95% CI 3.16–43.50).[24] Our results are in line with these studies, since 70% of tramadol-associated hiccups cases (35) occurred in male patients. The cause of this difference in sex is unknown. Male susceptibility to hiccups could be attributed to a lower synaptic threshold and easier excitability of the afferent or efferent nerves, in the reflex arc of hiccups.[24] Some authors have suggested differences between male and female in the regulation of corticosteroid receptors and their coactivators in the brain and pituitary gland in hiccups cases associated with dexamethasone.[25]

The study using supra-therapeutic doses of tramadol in health volunteers showed a relatively high proportion of patients suffering from hiccups, suggesting that this adverse reaction might be dose related.[12] Accordingly, of the 50 available cases in EudraVigilance, the dose of tramadol was ⩾150 mg/day in 24 cases (48%) and <150 mg/day in 17 cases (dose was unknown for 9 cases).

In five cases reported in our study, an additional drug (apart from tramadol) was considered suspicious. Of the five involved drugs, hiccups have only been described for oxycodone and fentanyl. Gabapentin, indeed, is used to treat hiccups. On the other hand, seven cases had comorbidities that have been associated with the development of hiccups.[4]

The onset of hiccups can range from minutes to several hours after parenteral administration of drugs, and from hours to a few days after oral administration.[26] In our study, the mean latency ranged from 1.7 to 9.4 days (in 40 cases tramadol was administered orally, 2 intravenously, and 9 unknown).

The exact mechanism behind tramadol-associated hiccups is unknown. The reflex arc of hiccups has been reported to be regulated by central (serotonin, dopamine, and GABA) and

peripheral (epinephrine, norepinephrine, acetylcholine, and histamine) neurotransmitters. Tramadol is a weak selective μ-opioid receptor agonist and, at the same time, a weak inhibitor of serotonin and norepinephrine reuptake. This dual action can be attributed to the two enantiomers of the racemic mixture. The cis-enantiomer has a higher affinity for the μ-opioid receptor and is a more effective inhibitor of serotonin reuptake.[27] This inhibition in serotonin reuptake could stimulate the central component of the hiccup reflex arc, while stimulation of opioid receptors decreases the release of GABA, therefore increasing dopamine release. The trans-enantiomer of tramadol is a more effective inhibitor of norepinephrine reuptake and increases its release by activation of α_2 autoreceptors. Consequently, the increase in norepinephrine could also stimulate the reflex arc of hiccups and could lead to contractions of skeletal muscle, including the diaphragm[15] (Figure 3).

Strength and limitations

The use of EudraVigilance, a database covering the entire European Union population in terms of reporting adverse reactions (7,213,623 spontaneous cases in total), can be considered a strength. Systematic collection of individual safety case safety reports in large pharmacovigilance electronic databases has allowed data mining and statistical screening (such as reporting ORs) for the detection of safety signals relevant for public health and therapeutic strategies.[28] In addition, disproportionality studies allow the study of rare adverse reactions (such as hiccups), since few exposed cases are necessary to perform the analysis. A validated method was used for the detection of signals in pharmacovigilance.[29] However, using data from spontaneous notification systems has important limitations that should not be neglected. Biases such as underreporting, lack of denominator, and the irregular quality of case information cannot be ruled out (in our study, only 52% were classified as well documented). Another weakness of spontaneous reporting databases is report duplication. Duplicates may mislead clinical assessment or distort statistical screening.[28] In our study, duplicate cases were detected by individual case review of all reports and then removed. The lack of detailed information for each individual case is another major bias both in EudraVigilance and VigiBase®. This is in contrast with some national pharmacovigilance databases, where each case is individually assessed by pharmacovigilance experts.[30] On the other hand, EudraVigilance and VigiBase® are not independent sources of information and a certain overlap of cases between these two databases should also be considered, as reports to EudraVigilance may be included in VigiBase®. Finally, the RORs could not be adjusted by age and sex due to limitations in the extraction of data from the noncases from the databases, so it was not possible to establish whether advanced age is associated with a higher risk of hiccups.

Conclusion

To the authors' knowledge, this is the first study to show a relationship between tramadol and hiccups. Our findings showed high disproportionality for hiccups in patients treated with tramadol in EudraVigilance and VigiBase® databases. Tramadol is an analgesic used for pain with various causes. Furthermore, as many prescribers believe that this drug has a lower risk of addiction and a more favorable safety profile compared with other opioids, its use has increased around the world in recent years. In definitive, it is important that healthcare professionals and patients should be aware of this possible association. However, observational analytical studies will be needed to confirm these results.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Research ethics and patient consent

The authors state that no ethical approval was needed. As all data from EudraVigilance and VigiBase were deidentified, patient informed consent was not necessary.

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Availability and data and material

EudraVigilance data are available subject to the EudraVigilance access policy for medicines for human use, available at http://EudraVigilance.ema.europa.eu/human/EudraVigilanceAccessPolicy.asp.

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