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FULL PAPER

Evaluation of tramadol use in Ibn Sena General Hospital in Mukalla City, hadhramout governorate, Yemen

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Tramadol is a synthetic centrally-acting analgesic. It is effective in the treatment of moderate to severe pain. Potential implications or consequences of dependence to tramadol may occur. To evaluate the rational use of tramadol among patients admitted to Ibn Sena General Hospital (ISGH) in Mukalla City, Hadhramout, Yemen. A retrospective, cross-sectional analytical study was conducted on patient files in Ibn Sena General Hospital to investigate the rational use of tramadol. 363 files were reviewed for patients admitted between 1st of June and 31st of December, 2017. Data were collected and analyzed from patients' files according to a checklist. Tramadol was estimated to be rationally used in 64.7% of patients. The irrational use covered mainly the topics of indications and safety (drug-drug interactions and contraindications). The improvement in the use of tramadol should be addressed through education of medical staff. The issue of potential drug interactions and contraindications associated with tramadol use should not be left unaware.

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KEYWORDS

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Introduction

Historically, evaluation of drug use had served as a traditional tool to evaluate whether medications were prescribed and used, safely and rationally [1]. Evaluation can include a single agent, a therapeutic class of drugs, a defined disease state, or a selected outcome [2]. Tramadol hydrochloride is an appropriate drug for medication-use evaluation [3]. Overall, the ultimate goal of an evaluation process is to optimize drug therapy, improve patient safety, and minimize needless expenditures [4]. Tramadol hydrochloride is a synthetic opioid analgesic; it has an analgesic efficacy and potency ranging between weak opioids and morphine. It is administered orally, rectally or parenterally (intravenous, intramuscular, and subcutaneous) [5]. It is effective in the treatment of moderate pain and has been used as an adjunct to opioids in chronic pain syndrome [6]. Tramadol has been successful in the treatment of postoperative pain. A dose of 50 to 100 mg may be given every 4 to 6 hours by intramuscular or intravenous injection over 2 to 3 minutes, or by

intravenous infusion. For the treatment of postoperative pain, the initial dose is 100 mg followed by 50 mg every 10 to 20 minutes if necessary to a total maximum (including the initial dose) of 250 mg in the first hour. Usual rectal doses by a suppository are 100 mg up to 4 times daily [7]. Drug-drug interactions may occur, for example, with enzyme inducers, those that have the potential to lower the seizure threshold, and those that affect neurotransmission [3]. The incidence of adverse effects depends on the dose and the mode of administration [8]. Sustained-release preparations showed a better tolerability profile [9]. Studies, in recent years, on tramadol prescribing patterns in France and Germany revealed a decrease in overall tramadol prescribing in Germany and an increase followed by a plateau in France. Higher prescribing rates were observed among females [10]. In the USA, a study on tramadol prescription patterns over a 4-year period from 2012 to 2015 showed a notable national increase by 22.8%, with regional variations [11]. In Denmark, tramadol consumption increased significantly from 2001 to 2013, with tramadol being the most utilized opioid in the country [12]. On the other hand, in Africa, postoperative pain management is substantially more common, and inadequate pain management is attributed to inadequate assessment of postoperative pain, knowledge gaps among medical professionals, patients' misconceptions, scarcity of resources, and lack of medications [13]. In South Africa, tramadol hydrochloride prescriptions were analyzed, with a compliance rate of 70.1% to the Standard Treatment Guidelines and Essential Medicines List [14]. Despite its widespread prescription for managing diverse types of pain, inconsistencies in prescribing practices have been observed, prompting concerns regarding its appropriate utilization [15]. Patient demographics, notably age, and comorbidities, play a significant role in shaping tramadol prescription trends, with elderly individuals and those with underlying medical conditions often facing increased risks of adverse effects [16]. Safety considerations extend to a spectrum of side effects, including nausea, dizziness, and the potential for serotonin syndrome, necessitating vigilant monitoring by healthcare providers. Moreover, the escalating rates of tramadol misuse globally underscore the importance of implementing strict regulatory measures to prevent its abuse [17]. While existing literature offers valuable insights into prescribing practices and safety concerns, knowledge gaps persist, particularly in resource-constrained settings such as Yemen. Based on the above-cited studies, it seems that investigating the rational use of tramadol in Yemen is worthwhile to address critical gaps in understanding of tramadol utilization and optimizing patient care within the context of Ibn Sena General Hospital.

Methods

Study design

The study design employed in this research endeavor was a retrospective cross-sectional analytical study conducted at Ibn Sena General Hospital in Mukalla, Hadhramout. All patient files from the year 2017 were scrutinized, and those containing tramadol and meeting the predefined study criteria were included in the analysis. This study design facilitated the examination of tramadol utilization patterns and associated factors within a specific timeframe and patient population, allowing for valuable insights into prescribing practices and patient outcomes.

Inclusion criteria

The inclusion criteria for patient files in the study were established to ensure comprehensive data collection. Specifically, only patient files containing complete information were selected for analysis. Tramadol use was deemed rational if it met specific criteria outlined in the study protocol.

These criteria included adherence to proper indications for tramadol usage, appropriate doses, and frequency of administration. Furthermore, tramadol use was considered rational only in the absence of contraindications and drug-drug interactions, as delineated by the guidelines provided by the World Health Organization (WHO) [18]. By applying stringent inclusion criteria, the study aimed to maintain the integrity and reliability of the data collected, facilitating accurate analysis of tramadol utilization patterns and associated outcomes.

Sample size estimation

The sample size was calculated using the following formula:

$$N = \frac{(Z)^2 Pq}{(d)^2}$$

Where, P = proportion of characteristic in the population (p= 50 %; 0.5) because there is no study found about this problem, q=1-p (0.5), z is the confidence interval (95%) and d= precision or error allowable (5%). The sample size required = 384 files

Sampling method

The sample selection process involved isolating and labeling patient files from those admitted between June and December 2017, containing tramadol among their medications. These selected files were then stratified based on whether they pertained to surgery or internal medicine cases. The required number of files was determined considering the total number of files available, the specified sample size for the study, and the distribution of files across wards. After calculation, it was determined that 291 surgery files and 93 internal medicine files were needed for the study (Table 1). However, out of 384 files, data from 363 files were collected and analyzed. Other 21 files were excluded, because of incomplete information.

Systematic random sampling, specifically selecting every third file, was then conducted within each stratum to ensure a representative sample from both surgery and internal medicine cases. This sampling approach aimed to provide a balanced representation of patient cases across different medical specialties while ensuring efficiency in sample selection.

TABLE 1 Distribution of sample size among the hospital wards

Name of the ward	Number of files	Percentage	Sample size
Surgery	1063	75.8%	291
Internal Medicine	339	24.2%	93
Total	1402	100%	384

Data collection methods

For data collection process, two main tools were utilized as follow: patient files and a checklist. The checklist served as a structured tool for systematically gathering information from the patient files, organized into seven sections, each comprising specific items for evaluation by the research group. These sections include:

1. *Sociodemographic characteristics and medical information*: This section encompassed details such as patient demographics and pertinent medical history.
2. *Indications for tramadol use*: A comprehensive list of potential indications for tramadol administration was provided, with space for documenting unlisted indications.
3. *Dosage administration*: Information on the doses of tramadol administered to patients was recorded in this section.
4. *Frequency of administration*: The frequency of tramadol administration was documented to assess adherence to prescribing guidelines.

5. *Contraindications*: A list of contraindications for tramadol use was included to evaluate patient safety.
6. *Drug-drug interactions*: This section identified potential interactions between tramadol and other medications, ensuring the avoidance of adverse drug interactions.
7. *Overall evaluation summary*: A summary section allowed for the comprehensive evaluation of the patient file, integrating findings from the preceding sections.

By employing this structured checklist, the research team systematically evaluated patient files to assess the appropriateness of tramadol use, adherence to prescribing guidelines, and patient safety considerations.

Data analysis

The data were entered and analyzed using Statistical Package for Social Sciences (SPSS version 23) software program. Percentage and frequencies were determined for categorical variables. The data were presented in tables and graphs using computer applications (excel and word).

Ethical considerations

The ethical considerations for conducting the study on tramadol use in Ibn Sena General Hospital are of paramount importance and have been addressed in accordance with ethical guidelines. Approval was obtained from the Hospital University Committee of the Clinical Pharmacy Department (HUCOM) to conduct the study. In addition, written permission was obtained from the administration of Ibn Sena General Hospital (ISGH) to conduct the research within their facility. It is essential to note that all information collected during the study were treated with the utmost confidentiality and used exclusively for scientific purposes and for the benefit of the community. Adherence to these ethical principles ensures the integrity of the research process and upholds the rights and welfare of the participants involved.

Results

Global evaluation of tramadol prescription

Data from 363 inpatient files from ISGH wards had been collected and analyzed. Other 21 files were excluded, because of incomplete information. By overall global evaluation, 235 (64.7%) patients were found to have appropriate tramadol prescriptions (Table 2).

TABLE 2 Global evaluation of tramadol prescription

General Evaluation	Frequency	Valid Percent	Cumulative Percent
Appropriate	235	64.7	64.7
Inappropriate	128	35.3	100.0
Total	363	100.0	

Tramadol indications

When the indication for tramadol was considered, 314 (86.5%) patients were prescribed tramadol appropriately according to the guidelines, while 49 (13.5%) patients did not meet the criteria (inappropriate prescription). The most frequent indications of tramadol were appendectomy and bone fracture, hernia followed by cancer (Table 2). The most frequent inappropriate indication was the use of tramadol for mild pain.

Tramadol dose

For appropriateness of the tramadol dose, 326 (89.8%) patients were prescribed a dose that

meets the guidelines, while 37(10.2%) patients were not. The most frequently used single doses were 50 mg (18.5%) and 100mg (79.3%) injections.

Frequency of tramadol administration

For the appropriateness of frequency, 348 (95.9%) patients were given tramadol inappropriate frequency, while 15 (4.1%) patients received tramadol in inappropriate frequency.

Safe use of tramadol evaluated through drug-drug interactions and absence of contraindications

Of the total of 363 patients, 307(84.6%), and 317(87.3%) patients had no drug-drug interactions and no contraindications, respectively. 56 (15.4%), and 46 (12.7%) patients had drug-drug interactions and contraindications, respectively.

TABLE 2 Indications for tramadol use

Appropriate indications	Frequency	Per cent
Appendectomy	86	23.7
Bone fracture	48	13.2
Cancer	36	9.9
Wound	20	5.5
Hernia	16	4.4
Trauma	13	3.6
Piles	12	3.3
Gun shot	10	2.8
Abdominal obstruction	8	2.2
Snake bite	8	2.2
Diabetic foot	7	1.9
Fistula	7	1.9
Chronic Pancreatitis	5	1.4
Other indications	87	23.9
Total	363	100.0

Discussion

Global evaluation of tramadol prescription and Tramadol indications

The study provides valuable insights into tramadol utilization patterns and adherence to prescribing guidelines in a hospital setting. The observed higher utilization of tramadol in surgical wards compared to internal medicine wards reflects the diverse patient populations and pain management needs across different medical specialties. The finding that approximately 65% of tramadol prescriptions were probably appropriate according to established guidelines highlights both strengths and areas for improvement in clinical practice. While the majority of prescriptions adhered to guidelines, deviations were observed in key areas such as drug-drug interactions, indications for use, and contraindications. These deviations raise concerns regarding patient safety and underscore the need for ongoing education and training initiatives targeting healthcare providers. In terms of indications of tramadol, 86.5% patients were prescribed tramadol according to the guidelines. The most frequent inappropriate indication was the use of tramadol for mild pain where paracetamol or one of the NSAIDs may be more appropriate.

Tramadol dose and frequency of tramadol administration

The findings regarding deviations in tramadol dosing, particularly in cases of renal and hepatic impairment, highlight significant concerns regarding patient safety and adherence to prescribing guidelines.

Specifically, the observation that the most frequent deviations pertained to the unadjusted dose for patients with renal and hepatic impairment underscores the importance of individualized dosing regimens based on patients' specific clinical characteristics and comorbidities. In addition, the discovery that 4.1% of patients did not receive the recommended frequency of tramadol administration, suggests potential gaps in healthcare providers' understanding or implementation of dosing protocols. This deviation may increase the risk of inadequate pain relief or adverse effects associated with suboptimal dosing regimens and their potential consequences. These could include exacerbation of pain symptoms and potentially compromised patient outcomes. Therefore, addressing and rectifying these deviations in dosing protocols is crucial to ensuring optimal pain management and patient safety.

Drug-drug interactions and contraindications

The CNS identification depressants as the most frequent drug-drug interactions with tramadol is of concern, as it may potentiate the risk of central nervous system (CNS) and respiratory depression, leading to severe adverse effects or overdose. Similarly, interactions with CYP3A4 inducers and inhibitors highlight the importance of considering pharmacokinetic interactions that can alter tramadol metabolism and efficacy. The presence of acute intoxication with opioids, uncontrolled epilepsy, and acute intoxication with other analgesics represent the most frequent contraindications for tramadol use and underscores critical safety considerations. These contraindications reflect situations where tramadol administration could exacerbate underlying medical conditions or increase the risk of adverse events, necessitating cautious prescribing practices and consideration of alternative pain management strategies.

Our findings align with a study carried out in South Africa [14]. The study collected 415 tramadol HCl prescriptions over a 2-month period, with a compliance rate of 70.1% to the Standard Treatment Guidelines and Essential Medicines List. This study from South Africa also found an increase in the hospital's tramadol expenditure over previous financial years, indicating a growing utilization of tramadol in the hospital setting [14]. Moreover, it was found that tramadol misuse in treatment-seeking adolescents may be a risk factor for non-completion of treatment [19]. A study in Ghana highlighted the misuse of tramadol among commercial vehicle operators, leading to various adverse effects, including physical, psychological, and social effects [20]. Additionally, the prescription of tramadol was compared with codeine and found that tramadol dispensation was significantly associated with a higher risk of all-cause mortality, cardiovascular events, and fractures compared with codeine [21,22]. This highlights the importance of understanding the risks associated with different opioids in the management of pain.

Moreover, another study focused on the clinical and economic burden of prescribing tramadol and other opioids for patients with osteoarthritis in the United States; this study revealed that tramadol patients had lower all-cause total healthcare costs during the follow-up period compared to non-tramadol patients but incurred higher prescription costs [23]. Furthermore, a Danish nationwide drug utilization study reported a decrease in the incidence and prevalence of tramadol use coinciding with media attention and regulatory actions, suggesting changes in opioid prescribing patterns over time [24]. These studies collectively emphasized the complexities and varied outcomes associated with tramadol prescribing practices, highlighting the need for continued research to optimize pain management strategies while considering the safety and economic implications of opioid use. Furthermore,

several studies have focused on the pharmacokinetics of tramadol, comparing different formulations and dosing regimens. The safety, tolerability, and pharmacokinetics of therapeutic and supratherapeutic oral dose regimens of tramadol have been investigated [25,26]. Those studies collectively contributed to a comprehensive understanding of tramadol's pharmacokinetics, safety profile, and potential risks associated with its use in different populations. Awareness of surgical and medical teams about the rational improvement of tramadol use.

Conclusion

Tramadol is one of the most commonly prescribed drugs for the management of pain in ISGH. Although the use of the drug was appropriate in a significant number of cases and according to the guidelines. However, drug-drug interactions, indications and contraindications were the main aspects in which noncompliance with the guidelines was frequently noted. There was more use of tramadol in surgical wards than in internal medical wards. Compliance with prescribing guidelines needs to be improved in both types of wards through educating medical staff or activating clinical pharmacy programs in the hospital.

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Authors' Contributions

All Authors equally contributed.

Conflict of Interest

The authors declared no conflict of interest.

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