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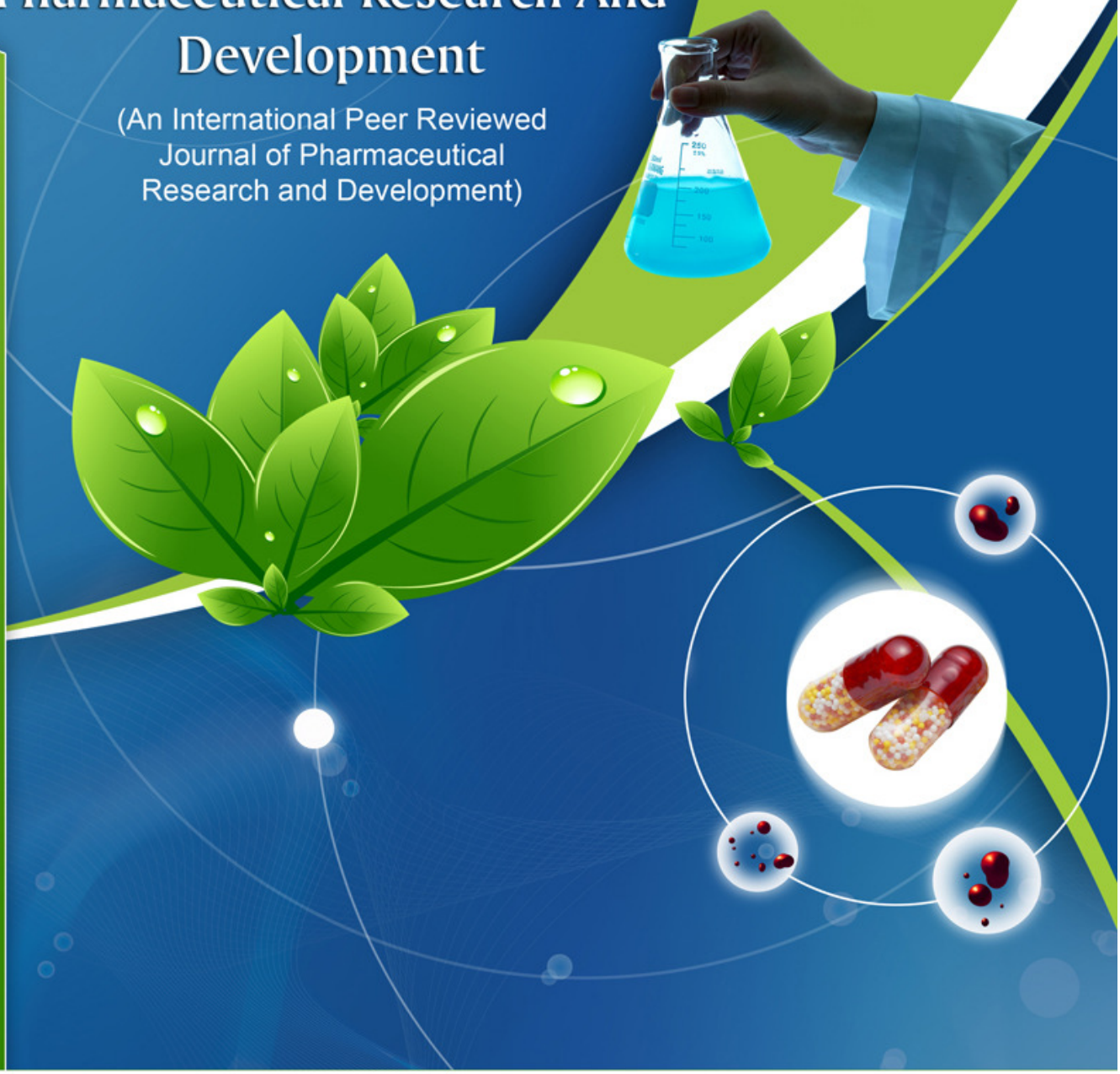

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Research Article

INDICATIONS FOR USE OF VITAMIN K AND IDENTIFICATION OF ADVERSE REACTIONS TO ORAL ANTICOAGULANT THERAPY IN HOSPITALIZED PATIENTS: A DESCRIPTIVE STUDY

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ABASTRACT

Vitamin K is a substance found at low concentrations in the human body, where it plays important roles in coagulation and calcium retention. The objective was to identify indications for use of vitamin K in a sample of hospitalized patients. In this descriptive, case-finding study, inpatients prescribed vitamin K during their hospital stays were assessed to identify the indications for vitamin K administration (thrombocytopenia due to oral anticoagulation or other drugs, vitamin K deficiency, or dietary deficiency). Patients from the Emergency Department and neonates were excluded. Overall, 161 cases were followed. In 73.3% of cases, the indication for vitamin K use was thrombocytopenia due to vitamin K deficiency. Seven patients (4.4%) had INRs outside the target range; of these, four (57%) developed bleeding, which was identified as an ADR. In the majority of patients given vitamin K, the indication was vitamin K deficiency.

Key words: *Drug utilization, Drug toxicity, Pharmacovigilance, Vitamin K*

INTRODUCTION

Vitamin K, a fat-soluble vitamin, plays several roles in the human body and can be found in a variety of dietary sources, particularly vegetables and leafy greens [1]. Vitamin K deficiency may lead to coagulation problems. This deficiency may be hereditary, but most cases are acquired, due to liver disease, deficient dietary intake, or excessive oral anticoagulant therapy; treatment, which consists of vitamin K supplementation, is required to ensure proper regulation of the coagulation cascade [2]. Neonates often receive intramuscular vitamin K within the first few days of life to prevent hemorrhagic diseases due to reduced levels of vitamin K-dependent clotting factors [3]. In adults, vitamin K is administered to patients with absence of biliary secretion, celiac disease, nutritional deficiencies (malabsorption), liver disease, hemodialysis, or destruction of the intestinal microflora after antibiotic therapy. Furthermore, vitamin K administration is considered a trigger for detection of adverse drug events due to excessive use of oral anticoagulants, a situation where

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intervention is required to prevent harm [4,5].The present study was prompted by a need to identify indications for use of vitamin K in hospitalized patients at our center, particularly as a red flag for excessive anticoagulation.

MATERIALS AND METHODS

Pharmacovigilance practices were implemented at our center (Hospital de Clínicas de Porto Alegre, state of Rio Grande do Sul, Brazil) in 2002 and have since been carried out by the Clinical Pharmacy Service. The hospital's Drug Information Center is in charge of all such activities, and conducts drug utilization studies and active case-finding of adverse drug reactions (ADRs) with the primary objective of fostering rational use of medicines. The present descriptive study, conducted from June through August 2012, included patients who were prescribed intravenous, intramuscular, or subcutaneous vitamin K. Patients as were neonates (due to routine prophylactic administration of vitamin K) [3]. Patients were identified by means of daily reports of patient prescriptions, issued by the hospital electronic medical records (EMR) system, and by means of active case-finding, which consisted of a daily review of the EMR and contact with staff physicians. The identified patients were followed until discontinuation of vitamin K therapy or until hospital discharge so as to assess the profile of vitamin K prescription at our center. Vitamin K was selected as a trigger for identification of adverse events (AEs) associated with excessive use or insufficient monitoring of therapy with oral anticoagulants, such as warfarin [4,5]. All AEs thus identified were treated as ADRs, as all therapeutic doses were individualized. Patients on oral anticoagulant therapy were monitored by means of the prothrombin time (PT), as expressed by the International Normalized Ratio (INR) (reference range 2–3); INR values >4 were flagged due to risk of bleeding and/or hemorrhage. The Naranjo et al. algorithm was used to determine the probability of a causal relationship between the prescribed medications and the suspected ADR, which was classified as definite, probable, possible, or doubtful [6]. ADRs were further classified by predictability as predictable or unpredictable, as per Thompson & Rawlins [7]; and by severity as mild, moderate, or severe, as per World Health Organization recommendations [8]. On detection of an ADR, the presence of drug-drug interactions involving warfarin and the other drugs prescribed on the day of the event was assessed using the Micromedex® database, thus enabling identification of potential increases in ADR severity due to INR changes and, in this case, the drug interactions were reported to the physician staff [9]. This study project was approved by the local Research Ethics Committee. All data were stored and analyzed in PASW Statistics 18.0.

RESULTS

During the study period, vitamin K was prescribed to 820 patients. Of these, 75.6% were excluded in accordance with the aforementioned criteria and a further 4.7% were excluded because they were discharged before pharmacovigilance could begin. Therefore, the final sample comprised 161 cases (19.6%). The indications for use of vitamin K are shown in Table 1. The most common route of administration was intravenous, which is consistent with the indications observed; intramuscular vitamin K was most commonly prescribed in emergency settings and in neonates. Seven patients (4.4%) had INRs outside the target range; of these, four (57%) presented with bleeding, which was recorded as an ADR. All four of these patients were admitted at risk of bleeding due to lack of INR monitoring during home therapy. Their INR values ranged from 5.74 to 9.81. Half of ADRs occurred in female patients (mean age 66 years), and 75% of cases had neoplasms as the primary comorbidity. Regarding the association between dosage and adverse effects, we found that, independently of dose, all patients with ADRs had moderate to severe reactions. There were no cases of warfarin allergy or allergy to any other prescribed drugs. Regarding causality and predictability, 100% of reports were classified as possible ADR and as Type A (well characterized in the literature) respectively. Drug-drug interactions that could enhance the anticoagulant effect of warfarin, thus increasing the risk of bleeding, were found in 100% of patients who developed ADRs. Overall, 20 interactions were identified, with a mean of five interactions per prescription

(Table 2). The mean number of drugs per prescription was 9.5. In one case (25%) of ADR, the attending team chose to continue warfarin and administer vitamin K therapy. In the remaining cases, the attending physician chose to discontinue warfarin and institute vitamin K therapy. All patients recovered uneventfully.

DISCUSSION

Drug utilization studies, whether conducted in a hospital or outpatient setting, have a major, relevant role to play in improving our understanding of drug use practices and promoting patient safety. In the inpatient setting, vitamin K is indicated for the reversal of excessive anticoagulation in patients receiving oral anticoagulants such as warfarin, which exert their effects by competitive inhibition of the enzyme vitamin K epoxide reductase and consequently impede production of clotting factors [2]. When used for this purpose, vitamin K prescription can be employed as a pharmacovigilance trigger for identification of AEs associated with excessive warfarin use; this information, in turn, can be used as an input for AEs prevention strategies, such as implementation of warfarin use protocols, and help avoid preventable harms [8,10]. Regarding the use of vitamin K for reversal of bleeding events caused by oral anticoagulant use, pharmacists should warn medical teams of the potential for AEs and the presence of drug-drug interactions that might affect the outcome of therapy, exposing patients to risk of harm or treatment failure [11]. Likewise, patients should be instructed to watch out for signs and symptoms that might denote adverse reactions to their current prescriptions [12]. The effect of anti-vitamin K anticoagulants can be monitored by assessment of the PT, as expressed by the INR. Values <2 suggest risk of thrombosis, whereas INR >4 is associated with bleeding risk [2,13]. Management of oral anticoagulation is still fraught with difficulty, as many variables influence anticoagulation levels; studies have shown that polypharmacy increases the risk of bleeding, and that monitoring of serum levels should be performed more frequently in these patients [11]. Low-dose vitamin K supplementation of patients on oral anticoagulant therapy has proven effective for INR management as compared with placebo [14]. Both intravenous and oral vitamin K may be used for warfarin reversal, although the intravenous route is associated with faster onset of action, correcting INR within 6 to 8 hours. However, both routes appear equally effective in correcting INR within 24 hours. The intramuscular and subcutaneous routes are not recommended. Subcutaneous injection is no more effective than placebo, and intramuscular administration of vitamin K in anticoagulated patients may cause hematoma and bleeding; due to its variable absorption, it may also produce an erratic increase in plasma levels and, consequently, may hinder re-anticoagulation. The greatest potential hazard of intravenous vitamin K administration is anaphylaxis. Although there is no convincing evidence for an association between anaphylaxis and dose, concentration, or route of administration, the literature recommends that formulations with mixed micelles of lecithin and glycol be used, as they are considered safer than preparations containing polyethylated castor oil [15]. This study includes some limitations including that we did not quantify the interventions performed by treating physicians or their outcomes.

CONCLUSION

The majority of patients in this sample were prescribed vitamin K due to vitamin K deficiency, which constituted the main indication for use. The widespread use of vitamin K identified herein also suggests that greater care and improved monitoring and guidance of patients on chronic home-based anticoagulant therapy are required; oral anticoagulant use must be monitored regularly, particularly with respect to drug-drug interactions, so as to prevent and address potentially reversible harms.

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