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Article

Bleeding associated with self-medication in warfarin users: A prospective observational study in Ijuí (Brazil)

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Warfarin has been associated with bleeding and venous thromboembolism. Objective: This study aimed to estimate the association between bleeding and concomitant self-medication, and the incidence of adverse drug reactions in patients using warfarin. Setting: the public health network of Ijuí, a municipality in southern Brazil. This was an open prospective cohort, conducted for a period of 18 months with users of warfarin, treated at the public health service. The association between bleeding and self-medication was evaluated by means of the Cox Model with left truncation, using the time variable. Main outcome measurement: bleeding reported in the follow-up. Cases of thromboembolism and death were also registered. All patients treated with warfarin in the public health system of the municipality (98) were identified. Sixty-eight were interviewed and followed up, of whom 63 completed follow-up and five died during the study. Bleeding rates of 37.7 /100 patients/year, thromboembolism of 4.8/100 patients / year and deaths of 4.8 /100 patients / year were observed. The results showed that patients, who take warfarin and self-medicated present a two-fold increased bleeding, compared with those who do not self-medicate. The bleeding risk associated with self-medication ranged from 2.001 to 2.685; those values maintained their significance even when adjusted for number of interactions, CYP polymorphism, TTR and age in COX analysis. These results greatly suggest the need for providing greater assistance to patients who take anticoagulant medications with the purpose of reducing self-medication and consequently, adverse reactions.

Keywords: Bleeding. self-medication. Warfarin. Adverse effects. primary care. Brazil.

INTRODUCTION

The incidence of bleeding and thromboembolism in anticoagulated patients varies according to the heterogeneity and duration of the studies, as well as the number of patients and the characteristics of the included population. Being woman, instability of optimal INR range, advanced age, concomitant diseases, type of oral anticoagulant (OAC), genetic polymorphisms and use of other drugs are some of the well-defined risk factors. Other factors are therapeutic indications of anticoagulants, time in the target INR (International Normalized Ratio), adherence to treatment, and the use of associated medications, including those administered by self-medication (Palareti *et al.*, 1996; Castro, Heineck, 2012; Jorgensen *et al.*, 2012; Jover *et al.*, 2012; Hallinen *et al.*, 2014; Ghousain *et al.*, 2014; Teklay *et al.*, 2014; Jun *et al.*, 2017).

According to the literature the incidence rates for bleeding events varies of 4.6 to 15.4 events/100 patients/year and for embolic events of 0.75 to 2.57 events/100 patients/year (Benhamou *et al.*, 2009; Deitelzweig *et al.*, 2013; Labaf

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et al., 2014; Cressman *et al*., 2015; Pastori *et al*., 2015). Major bleedings cause emergency department visits or hospital admission, and rise the costs of health care.

This study aimed to estimate the association between bleeding and concomitant self-medication in primary health care warfarin users, as well as to estimate the incidence of adverse reactions related to this OAC, which is still the most used for treatment of venous thromboembolism in many countries.

MATERIAL AND METHOD

Study Design and participants

This open, prospective cohort included all users of warfarin linked to the public health network of a municipality in Rio Grande do Sul (RS, southern Brazil). Ijuí is a municipality with an estimated population of 82,833 inhabitants in 2015 and 15 places where medicines are dispensed.

Warfarin users were identified through access to the copy of dispensed prescriptions. Participants were identified in February 2014 and followed up for at least 12-month period between April 2014 and October 2015. In the first six months (until October 2014), new patients were enrolled when they began to use warfarin. Monthly interviews were conducted in the participants' homes.

Regarding the eligibility criteria, all the patients residing in the city of Ijuí, RS, who used oral warfarin for chronic treatments, assessed by medical records, were included in the study. Patients from other municipalities using other anticoagulants and who purchased their medications from private drug stores were excluded.

Data collected and study procedures

For the first interview, a structured questionnaire was prepared, which included information on the socioeconomic and demographic characteristics of patients, as well as the use of warfarin and other drugs prescribed or used for self-medication. Regarding the monthly patient follow-up, a specific instrument was developed including questions related to the prescription of new drugs, new health problems and adverse drug reactions (ADR) that occurred during that month. This instrument was completed every month in the households of the interviewees, and the data were checked in the Health Unit or Hospitals, in the case of reports of use of these services.

Reports of ADR were confirmed by checking the medical record each time a patient sought medical or hospital care.

In the 3rd, 10th and 18th months, blood tests were performed for INR and renal function analysis, by assessing the clearance of creatinine, urea and uric acid.

Data Organization and Analysis

Outcomes*:* The main outcome of this study was "bleeding" reported in the follow-up, without classification by severity, but classified by place of occurrence. We also registered cases of "thromboembolism", if reported in the follow-up and checked in medical records; and also "death" considered if reported in the follow-up and confirmed by death certificate.

Exposition*:* "Self-medication use" was considered each time patients reported the use of a medicine without the prescription of a physician.

Variables of interest*:* a) Number of drug interactions: Micromedex® database was used to verify the possibility of drug interactions (Micromedex® Healthcare Series, 2018). b) CHA2DS2-Vasc score: was a score to quantify the thromboembolic risk. For each factor presented by the patient, a score was assigned. "High risk" was considered when patients had four or more points, and "low risk" when they reached 1 to 3 points (CHA_2DS_2-VASc Score for Atrial Fibrillations Stroke Risk, 2016). c) "Renal impairment" was the alteration of one or more of the following parameters: urea, uric acid and creatinine. d) To identify genetic polymorphisms, the CYP2C9 and VKO2C9 genes were analyzed. Genotypes of the polymorphisms -1639G> A (rs9923231) in the gene VKORC1, CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910) in the CYP2C9 gene were performed by the real-time PCR technique. For the present study, the presence or absence of polymorphism was considered for the above-mentioned genes. The analyses were performed by the Human Genetics Laboratory of UFRGS. e) "Time in Therapeutic Range" (TTR) was

calculated by using INR data collected during follow-up, according to the method validated and adapted by Schimidt, Speckman and Ansell (2003). The median value was used to present the data.

Statistical Methods

The data were analyzed by the SAS Studio program. Descriptive statistics were performed using measures of central tendency and data dispersion. Bleeding as an adverse drug reaction was evaluated by means of the Cox Model with left truncation, using the time variable (duration of warfarin use before the patient entered the study, in which the patient was already at risk, but not relative to whether or not bleeding occurred in this period). Several Cox models were adjusted to estimate the association (hazard ratio) between bleeding and use of self-medication in the absence and presence of the following adjustment variables: number of interactions; CYP2C9 genetic polymorphism; time in therapeutic range (TTR); age; weekly dose; change in renal function; CHA2DS2-Vasc. The significance level considered was 5%.

All procedures performed involving the participants were in accordance with the ethical standards of the Research Ethics Committee of the Federal University of Rio Grande do Sul (Report No. 336.259 / 2013) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

RESULTS AND DISCUSSION

Up to 98 warfarin users were identified through the prescriptions. Of these, 11 were not found due to problems with their home address, seven were excluded due to the early replacement of warfarin with another anticoagulant, five refused to participate, three died before the first interview; two moved from the municipality, and one did not receive warfarin from the Public Health System. Therefore, 68 patients were interviewed and followed up (study sample). Sixty-three (92.6%) completed follow-up and five (7.4%) died during the study. Up to 17 had a follow-up time of at least one year, and were classified as 'starting treatment'.

The 68 patients followed up had mean age of 64.3 ± 13.7 years; 55.1% were female, and 63.2% had incomplete elementary education. The most frequent age group was 60 to 79 years (n=38; 55.9%). In the present study, 40 users (58%) reported self-medication with one to nine different medications during follow-up. Table I shows the characteristics of the exposure groups of interest.

TABLE I - Characteristics of exposure groups of interest. Ijuí/Brazil n=68

	Self-medication	
	Yes (40)	**No (28)**
Age mean (SD)	66.05±13,06	61.31±17.46
Number of interactions mean (SD)	5.16±2.59	3.87±1.51
CYP_ Polymorphism n (%)	9 (22,5%)	10 (35,7%)
Time in Therapeutic Range (TTR) mean (SD)	32.5±39.9	44.5±18.90
Weekly dosage (mg) mean (SD)	30.02±15.48	31.81±12.53
Renal alteration n (%)	26 (65%)	23 (82%)
CHA2DS2-Vasc. n (%)	22 (55%)	16 (57%)

Thirty-four patients (49.3%) presented bleeding, with a mean of 1.5 ± 0.4 events during follow-up. The most frequent bleeding sites were nose and mouth (55.6%); gastrointestinal tract [except mouth] (17.8%); extremities (14.4%); eyes and ears, cerebral and vaginal (4.4%, each). The incidence of bleeding was 37.7 / 100 patients / year, while that of thromboembolism was 4.8 / 100 patients / year. The number of deaths was also 4.8 / 100 patients / year. Four deaths occurred due to thromboembolism and one due to bleeding, in the months: 2, 3, 4, 6 and 10. Fifteen patients (21.8%) required hospitalization for the resolution of their bleeding. Eight patients (11.6%) discontinued the use of warfarin at some point along the treatment due to some hematological ADR. In addition to bleeding, dermatological adverse reactions (rash) and gastric discomfort were reported.

Regarding bleeding, the COX model showed an association with reported self-medication, and statistical significance was maintained when the model was adjusted for number of interactions (p=0.0438), CYP2C9 polymorphism, low percentages of TTR, old age, weekly dose (mg), renal alteration and CHA2DS2-Vasc (see Table II).

TABLE II - Association between bleeding and self-medication among patients taking warfarin in a cohort of patients from the city of Ijuí/Brazil n=68

***Hazard ratio* self-measurement in relation to the occurrence of bleeding.**			
Model	**Hazard ratio**	**IC95%**	**Value p**
Self-medication[a]	2.164	(1.022 ;4.583)	0.0438
Self-medication[b]	2.001	(0.931 ;4.299)	0.0755
Self-medication[c]	2.210	(0.986 ;4.957)	0.0543
Self-medication[d]	2.304	(1.104 ;5.234)	0.0461
Self-medication[e]	2.308	(1.019 ;5.229)	0.0449
Self-medication[f]	2.281	(1.005 ;5.179)	0.0487
Self-medication[g]	2.685	(1.158 ;6.228)	0.0214
Self-medication[h]	2.606	(1.105 ;6.147)	0.0286

a. self-medication (reference: no)
b. adjusted by number of interactions
c. adjusted by number of interactions + CYP_ Polymorphism
d. adjusted by number of interactions + CYP_ Polymorphism + Time in Therapeutic Range (TTR)
e. adjusted by number of interactions + CYP_ Polymorphism + Time in Therapeutic Range (TTR) + Age
f. adjusted by number of interactions + CYP_ Polymorphism + Time in Therapeutic Range (TTR) + Age + weekly dosage (mg)
g. adjusted by number of interactions + CYP_ Polymorphism + Time in Therapeutic Range (TTR) + Age + weekly dosage (mg) + renal alteration
h. adjusted by number of interactions + CYP_ Polymorphism + Time in Therapeutic Range (TTR) + Age + weekly dosage (mg) + renal alteration + CHA2DS2-Vasc

The results showed that patients taking warfarin who self-medicated were approximately twice as likely to develop bleeding compared with those who did not self-medicate.

Some of the active ingredients reported as being taken for self-medication produced potential drug-drug interactions associated with bleeding (see Table III). The most frequently reported self-medication drug was paracetamol, used by 75% of the interviewees, and 66.7% of them actually presented bleeding.

TABLE III - Frequency of self-medication with drugs that increase the risk of bleeding among users of warfarin. Ijuí/Brazil n = 40

Drugs	Patients n (%)	Bleeding n (%)
Paracetamol and associations	30 (75)	20 (66.7)
Omeprazole	7 (17.5)	5 (71.4)
Vitamins	7 (17.5)	3 (42.9)
Salicylic Acid and associations	7 (17.5)	5 (71.4)
Ibuprofen	5 (12.5)	3 (60)
Diclofenac	5 (12.5)	4 (80)
Picosulfate, *Cassia Senna* and associations	3 (7.5)	1 (30)

Close follow-up of a cohort of warfarin-treated patients for 18 months showed that half of them (49.3%) had at least a bleeding episode; more than 20% required one or more hospitalizations, and 11% discontinued their treatment because of an adverse drug reaction. The analysis of the results showed that the risk of bleeding doubled if the patient self-medicated with other commonly consumed drugs, including anti-inflammatories, paracetamol or irrational fixed-dose combinations used for symptomatic treatment of common cold and flu.

The data on bleeding incidence and embolic events found in the present study were higher than those of other studies which described bleeding incidence (Labaf *et al.*, 2014; Cressman *et al.*, 2015; Pastori *et al.*, 2015; Jun *et al.*, 2017). In the present study, all types of bleeding were considered and the included warfarin users received community health care in a Health Unit. According to Palareti *et al.* (1996), patients treated by an anticoagulation outpatient team may present better results than those who receive conventional care. A close follow-up by the team allows early identification of problems and prevents the manifestation of some ADR (Lee, Davis, Kielly, 2016). In theory, providing patients with guidance on avoiding falls and injuries; ingestion of certain foods; use of injectable drugs or on self-medication, among others, usually form part of these services (Esmerio *et al.*, 2009).

The bleeding risk associated with self-medication observed in the present study ranged from 2.001 to 2.685; those values maintained their significance even when adjusted for number of interactions, CYP polymorphism, TTR and age in COX analysis. This means that despite the adjustments considering different combinations of factors, the risk value remained close to 2. The consistency of these results presented in Table I indicates that the apparent small number of patients was sufficient to show statistical difference between the groups.

Despite being considered an important form of self-care, self-medication is among the risk factors for bleeding in patients taking anticoagulants. The frequency of self-medication observed among users of warfarin in our study (58%) was within the range showed by a systematic review which included studies conducted with different groups of patients in Brazil (22.9% to 75.3%) (Domingues *et al.*, 2015). Other authors observed lower prevalence values ranging from 12.7% to 39.2% (Awad, Eltayeb, Capps, 2006; Suleman, Ketsela, Mekonnen, 2009; Carrasco-Garrido *et al.*, 2010). On the other hand, in rural communities in Slovenia the observed proportion was higher (80.9%) (Klemenc-Ketis, Mitrovic, 2017) indicating that the distance from health centres stimulated this practice.

Among the most commonly used drugs for self-medication, non-steroidal anti-inflammatory drugs are prominent (Zamir, Nadeem, 2016; Ayalew, 2017) whose relationship with bleeding is well established [26]. In the present study, we emphasized paracetamol, as well as omeprazole and the anti-inflammatory medicines diclofenac sodium and ibuprofen. Kotirum *et al.* (2007) and Palareti *et al.* (1996) also pointed out paracetamol as the most frequently used drug among those with interactions with warfarin.

When patients on warfarin require the use paracetamol, it is advisable to inform them about the limits of their intake, considering that INR elevations may occur within 1-2 weeks of starting moderate to high doses (2 and 4 g / day, respectively) (Leiria *et al.,* 2010). It is recommended to monitor the INR and change the dose or discontinue the drug in order to maintain the desired level of anticoagulation (Castro, Heineck, 2012). It is important to emphasize that this medicine is part of the composition of other medicines; such as fixed-dose combinations used in colds, thus increasing the possibility of exposure to the drug and the use of high doses.

The consumption of some medications such as paracetamol, omeprazole, and anti-inflammatories has been pointed out in studies as excessive and irrational (Jain et al., 2015) and some authors have suggested an evaluation of the possibility of deprescribing them (Kimmel et al., 2007; Gavillán-Moral et al., 2012). In Brazil, omeprazole and diclofenac are use under medical prescription. However, it is possible to acquire them without the prescription, because in several pharmaceutical establishments commercial interests prevail over the sanitary issues. Because of the difficulty of changes in this regard, health professionals should alert users to the risks related to self-medication, especially in the case of users of a potentially dangerous drug, such as warfarin. Perhaps the priority should be to analyze some of the underlying causes of self-medication, such as indiscriminate sale of medicines, difficult access to the health care system, or high costs of private medical plans and consultations (Eticha, Mesfin, 2014). Understanding the impact of this practice on the safety of anticoagulated patients is still incipient. Published studies have addressed hospital (Castro, Heineck, 2012; Merli *et al*., 2016) or outpatient use (Leitia *et al*., 2010; Deitelzweig *et al*., 2013) of warfarin, but there are still few studies in primary care (Hallinen *et al*., 2014) especially in countries with less structured health services such as Brazil.

The association of bleeding with the other factors included in the multivariate analysis and bleeding has previously been observed in several studies (Schimidt, Spechman, Ansell, 2003; Suh *et al*., 2013; Jun *et al*., 2017). Regardless of the presence of other risk factors, self-medication should be discouraged among users of warfarin, since most drug interactions increase the chances of episodes of severe or even fatal bleeding. It is noteworthy that only 11.6% of the patients discontinued the use of anticoagulants as a consequence of some ADR. This value was lower than the 51.7% found in a previous study (Suh *et al*., 2013).

One limitation of the present study is the number of patients treated with an AC and not located due to inaccurate registry of their home address (11 out of 98). Despite reducing the number of participants, the difficulty of locating patients showed problems with the follow-up of chronic patients, a situation which can be common in Brazil and other countries, and should be improved. On the other hand, cohort studies are subject to bias inherent to observational studies, but the results relative to the factors related to adverse reactions and the observed incidence showed the real health aspects of anticoagulated patients attended at healthcare units. An additional limitation is that outcomes were self-reported. However, data collection was done with monthly intervals, thus reducing recall bias. Additionally, reports of ADR were confirmed by consulting the medical record, each time a patient sought medical or hospital care.

Primary care patients on anticoagulants are more prone to self-medicate than those from hospitals or outpatient's settings and may consequently have a higher incidence of adverse reactions. Better knowledge about individuals who self-medicate and the associated factors may help to identify groups that are more susceptible and to find strategies to minimize avoidable harm.

The most important finding of the present analysis of patients using anticoagulants showed that self-medication with common medicines increased the risk of a common and potentially severe adverse effect such as bleeding, thus drawing attention on the importance of carefully reviewing drug therapy by health professionals to prevent avoidable toxicity.

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