REVISTA ONLINE DE PESQUISA

CUIDADO É FUNDAMENTAL

Universidade Federal do Estado do Rio de Janeiro • Escola de Enfermagem Alfredo Pinto

RESEARCH DOI: 10.9789/2175-5361.2019.v11i5.1312-1318

Drug Interactions in Elderly People Making use of oral Anticoagulants and Hospitalized in a Cardiology Hospital

Interações Medicamentosas nos Idosos em uso de Anticoagulantes Orais Internados num Hospital Cardiológico

Interacciones Medicamentosas en los Ancianos en uso de Anticoagulantes Orales Internados en un Hospital Cardiológico

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How to quote this article:
Cheno MY, Cardilli CVC, Kobayashi RM. Drug Interactions in Elderly People Making use of oral Anticoagulants and Hospitalized in a Cardiology Hospital. Rev Fund Care Online.2019. Oct./Dec.; 11(5):1312-1318. DOI: http://dx.doi.org/10.9789/2175-5361.2019.v11i5.1312-1318

ABSTRACT

Objective: The study's purpose has been to relate the drug interactions of oral anticoagulants with other medications used by elderly people hospitalized in a cardiology hospital. **Methods:** It is a prospective exploratory study with 16 elderly people taking oral anticoagulant, who were hospitalized at a governmental cardiology institution in *São Paulo* State over the period from November to December 2017. **Results:** Among 73 medicines prescribed and analyzed in the Micromedex 2.0, 24 (33.3%) interacted with Warfarin, the only prescribed oral anticoagulant. There were found Omeprazole (70; 97.2%); Dipyrone (68; 94.4%); Simvastatin (43; 59.72%); Enoxaparin (42; 58.33%); Amiodarone (29; 40.27%); Sertraline (28; 38.88%); Spironolactone (21; 29.16%); and Atenolol (11; 15.27%), whose interactions could either potentialize or inhibit the anticoagulant action. Considering the interactions, 14 (58.33%) were of moderate severity, 10 (41.66%) of high severity and 14 (58.33%) of fast effect. **Conclusion:** Polypharmacy and the use of oral anticoagulants in elderly patients bearing heart diseases are common events. Moreover, a better understanding about drug interactions is also required, bearing in mind that they can either potentialize or decrease the anticoagulant effect, with high or moderate severity.

Descriptors: Anticoagulation, Elderly People, Hospitalization, Drug Interactions.

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RESUMO

Objetivo: Relacionar as interações medicamentosas dos anticoagulantes orais com os medicamentos utilizados por idosos internados em hospital cardiológico. **Método:** Estudo exploratório, prospectivo, com 16 idosos em uso de anticoagulantes orais, internados numa instituição cardiológica governamental de São Paulo entre novembro e dezembro de 2017. **Resultados:** Dentre 73 medicamentos prescritos e analisados no Micromedex 2.0, 24 (33,3%) interagiam com a Varfarina, único anticoagulante oral prescrito. Encontrou-se Omeprazol (70;97,2%); Dipirona (68;94,4%); Sinvastatina (43;59,72%); Enoxaparina (42;58,33%); Amiodarona (29;40,27%); Sertralina (28;38,88%); Espironolactona (21;29,16%); e Atenolol (11;15,27%), cujas interações poderiam potencializar ou inibir a ação anticoagulante. Das interações, 14 (58,33%) eram de gravidade moderada, 10 (41,66%) maior e 14 (58,33%) de efeito rápido. **Conclusão:** A polifarmácia e o uso de anticoagulante oral em idosos cardiopatas é comum e, conhecer as interações medicamentosas, é imperativa, considerando que potencializam ou diminuem a ação anticoagulante, com gravidade maior ou moderada.

Descritores: Anticoagulação, Idoso, Hospitalização, Interações de Medicamentos .

RESUMEN

Objetivo: Relacionar las interacciones medicamentosas de los anticoagulantes orales con los medicamentos utilizados por ancianos internados em um hospital cardiológico. **Método:**Estudio exploratorio, prospectivo, con 16 ancianos en uso de anticoagulantes orales, internados en una institución cardiológica gubernamental de São Paulo entre noviembre y diciembre de 2017. **Resultados:**Entre 73 medicamentos prescritos y analizados en el Micromedex 2.0, 24 (33,3%) interactuaban con la Varfarina, único anticoagulante oral prescrito. Se encontró Omeprazol (70, 97,2%); Dipirona (68, 94,4%); Sinvastatina (43, 59,72%); Enoxaparina (42, 58,33%); Amiodarona (29, 40,27%); Sertralina (28, 38,88%); Espironolactona (21, 29,16%); y Atenolol (11, 15,27%), cuyas interacciones podrían potenciar o inhibir la acción anticoagulante. De las interacciones, 14 (58,33%) eran de gravedad moderada, 10 (41,66%) mayor y 14 (58,33%) de efecto rápido. **Conclusión:** La polifarmacia y el uso de anticoagulante oral en ancianos cardiopatas es común y, conocer las interacciones medicamentosas, es imperativa, considerando que potencian o disminuyen la acción anticoagulante, con gravedad mayor o moderada.

Descriptores: Anticoagulación, Ancianos, Hospitalización, Interacciones de medicamentos.

INTRODUCTION

The health profile of the Brazilian population has undergone several significant changes, such as a reduction in the birth rate and a reduction in mortality, a result of the prevalence of high fertility in the past in relation to the present and the improvement of living conditions and technological and scientific advances in the health area.[1] This population characteristic interferes with the epidemiological profile and justifies the prevalence of chronic respiratory diseases, diabetes mellitus, neoplasms, renal diseases, and cardiovascular diseases, the latter being the main cause of mortality in Brazil, totaling 34% of all deaths in 2013.[2,3]

This morbidity profile, in addition to degenerative diseases, common to the elderly phase, results in polypharmacy (consumption of five or more drugs) and, consequently, facilitating the occurrence of drug interactions.[4]

Drug interaction is defined as a detectable, measurable, quantitative clinical event or in which there is a change in the effect of a drug, by the presence of another drug, food, beverage or some chemical agent in the environment, being considered interactions that occur in vitro.[5,6]

Drug interactions can be real, when they can be proven from the clinical and laboratory evaluation; or potential, when there is the possibility of one drug changing the effect of the other. Interactions depend on several factors, such as the clinical condition of the patient and the amount of the drug and mechanism of action of the drugs.[7-9] Drug interactions can be further classified as follows: pharmacokinetics, pharmacodynamics, effect and pharmacy.[8,9]

In hospitalized individuals, the occurrence of drug interactions is greater due to polytherapy.[10] And, due to the current morbidity profile, over the years, an important increase in the use of anticoagulants for the prevention and treatment of thromboembolic events by cardiopathies, such as Atrial Fibrillation (AF); in Venous Thromboembolism (VTE) in the form of Deep Vein Thrombosis (DVT) or Pulmonary Thromboembolism (PTE); and in the use of heart valve prostheses.[11]

Anticoagulants may have the following presentations: oral, subcutaneous and intravenous. Among Oral Anticoagulants (OAC), vitamin K antagonists, Warfarin sodium (Marevan®) or crystalline and Femprocumone (Marcoumar®), and the new generation of OACs that act on other factors of the oral coagulation cascade - Rivaroxaban, Dabigatran, and Apixaban. The subcutaneous or intravenous form is represented mainly by low molecular weight heparins and unfractionated heparin.[12,13]

Warfarin is a vitamin K antagonist absorbed in the gastrointestinal tract whose onset occurs after 24 hours of oral administration and may last from 2 to 5 days. Its action peak is around 72 to 96 hours and its half-life time varies from 20 to 60 hours. After hepatic metabolism, the drug is eliminated via renal (92%). The main adverse effect of Warfarin is bleeding, especially as it is an anticoagulant and requires strict dose adjustment control.[14]

In the hospital environment, it is the nurse professional responsible for the medication scheduling and management of the care provided, thus, it is essential for them to be able to avoid drug interactions, through the appropriate scheduling of medication. The scheduling is the moment in which the nurse analyzes the medical prescription and, adding their knowledge about medicines, defines schedules for their administration according to the intervals prescribed by the doctor and the routine of the institution's scheduling.[15,16]

Considering that it is a competence of the registered nurse, in order to perform the scheduling of medications,

based on the technical-scientific knowledge, and to guarantee patient safety, a more detailed study of drug interactions in the pharmacological and pathophysiological dimensions is necessary.[17,18]

This study aimed to relate the drug interactions of oral anticoagulants to the medications used by elderly patients admitted to a cardiology hospital.

METHODS

It is a descriptive, prospective and documentary study that was carried out in a clinical-surgical hospitalization unit of a large hospital specialized in cardiology in *São Paulo - SP*, which has 130 beds in its infirmary.

The sample consisted of medical records of patients older than or equal to 60 years old, using oral anticoagulant, and admitted in clinical-surgical hospitalization units of the institution, from November to December 2016. Those excluded were those from the study whose records were not in the moment of data collection.

In order to standardize the study data, a form constructed by the researchers was used, consisting of identification data, clinical and prescribed medications, drug scheduling, nursing annotation on the signs and symptoms possibly derived from the use of these medications, and drug interaction with Oral Anticoagulant.

Data collection was daily, during the stipulated period, and for each medical record, the form was filled out. The analysis of drug interactions was done using the Micromedex 2.0 database, where all drugs were cross-checked with the oral anticoagulant, in order to identify drug interactions, articulating with the nursing schedule.

Micromedex 2.0 is an information database on medicines, bringing recommendations based on detailed assessments and reports. It provides information on diseases, drug interactions, intravenous compatibility, toxicology and also allows comparing the efficacy of medications.[19] It also classifies them as 1) contraindicated: Medicines are contraindicated for concomitant use; 2) important or high: The interaction may be life-threatening and/or require medical intervention to reduce or avoid serious adverse effects; 3) moderate: The interaction might result in exacerbation of the patient's health problem and/or require a change in treatment.; 4) secondary: The interaction would result in limited clinical effects. The manifestations may include an increase in the frequency or severity of the side effects but generally, do not require a major change in treatment; or 5) unknown. In addition to this classification, the interactions can be divided as to their speed of onset, such as 1) fast, when the effects of the interaction occur within 24 hours; 2) slow, late or delayed, when they occur after 24 hours; and 3) unspecified, when there is no documentation in the literature about the onset of the effects of drug interaction. (Bagatini F et al. apud Drugdex System, Greenwood Village: Thomson Micromedex® Healthcare Series 20: Interactions, 2010)[20,21]

For the analysis, eight drugs that were prescribed to a greater number of patients and that interacted with Warfarin were selected. These, although they were the most prescribed ones, are not necessarily those of greater severity (Table 1).

The project obeyed the ethical precepts of the research, and was developed after approval (Certificado de Apresentação para Apreciação Ética (CAAE) [Certificate of Presentation for Ethical Appreciation] No. 59405316.2.0000.5462) by the Research Ethics Committee from the institution and followed all the precepts addressed in the Resolution No. 466/2012 from the Comissão Nacional de Ética em Pesquisa (CONEP) [National Commission Ethics in Research].[22]

RESULTS AND DISCUSSION

A total of 74 medical prescriptions of 16 patients were analyzed, of which 10 (62.5%) were male and 6 (37.5%) were female, aged 60-77 years old. The clinical profile of these patients is characterized by 12 (75%) hypertensive, 7 (43.75%) dyslipidemic and 3 (18.75%) diabetic patients. With regards to comorbidities, 9 (56.25%) have arrhythmias; 7 (43.75%) are of the valve; 6 (37.5%) of the myocardium; 6 (37.5%) are former smokers; 5 (31.25%) are chronic renal; 4 (25%) have other comorbidities; 3 (18.75%) are of the pacemaker; 2 (12.5%) are of the coronary artery; 2 (12.5%) are of the vascular; 2 (12.5%) have some neoplasm; 1 (6.25%) are of the endovascular; and 1 (6.25%) is still smoking.

The main reasons for hospitalization and current diagnosis were valvular heart diseases - 9 (56.25%) and 7 (43.75%), respectively. There were 74 medical prescriptions with 73 drugs, with Warfarin sodium (Marevan®) being the only oral anticoagulant prescribed. Among medications, 24 (33.3%) presented potential interactions with Warfarin (**Table 2**).

Table 1. Characteristics of drug interaction

Drug	Class	Action	Interaction effect
Omeprazole	Proton pump inhibitors	It irreversibly inhibits the H+/K+ ATPase (proton pump), which constitutes the terminal step in the acid secretion pathway, thus inhibiting basal and stimulated gastric acid secretion.[43]	It potentializes the anticoagulant effect of Warfarin.[38]
Simvastatin	Statin	It inhibits the limitation of cholesterol biosynthesis rate by competitive inhibition of HMG-CoA reductase.[44]	It potentializes the anticoagulant effect of warfarin and increases the risk of rhabdomyolysis.[39]
Enoxaparin	Anticoagulant	It inhibits factor Xa by increasing the rate of inhibition of coagulation proteases that are activated by antithrombin III. Generally, it does not increase PT or PTT.[44]	It potentiates the anticoagulant effect of Warfarin.[39]
Amiodarone	Class III antiarrhythmic	Inhibition and adrenergic stimulation; affects the sodium, potassium and calcium channels; dramatically prolongs the potential for action and repolarization; decreases AV conduction and sinus node function.[44]	It potentiates the anticoagulant effect of Warfarin. [40]

Sertraline	Selective serotonin reuptake inhibitor	It has little or no affinity for alpha-adrenergic histamine or cholinergic receptor.[44]	It potentiates the anticoagulant effect of Warfarin. [41]
Spironolactone	Potassium-sparing diuretic	It competes for the intracellular aldosterone receptors in the distal tubule cells, resulting in inhibition of the aldosterone Na+ retention action, with a concomitant reduction in its K+ secretion stimulating effect. It also decreases the secretion of H+, as well as the excretion of uric acid.[30]	Reduces anticoagulant action. [30]
Atenolol	Beta-blockers	It blocks the response to beta-adrenergic stimulation; cardio selective for low dose beta1 receptors, with little or no effect on beta2 receptors.[44]	Risk of increased prothrombin time *vs* INR.[33]
Dipyrone	Nonsteroidal anti-inflammatory	Analgesic, antipyretic and spasmolytic without clearly defined mechanism of action.[45]	It potentiates the anticoagulant effect of Warfarin. [42]

Source: The authors

Table 2. Drugs that interact with Warfarin

Medicamento	Classe	Ação	Efeito de interação
Omeprazol	Inibidor da bomba de prótons	Inibe irreversivelmente a H+/K+ ATPase (bomba de prótons), que constitui a etapa terminal na via da secreção ácida, inibindo então, a secreção do ácido gástrico basal e estimulado.[43]	Potencializa o efeito anticoagulante da varfarina[38]
Sinvastatina	Estatina	Inibe a limitação da taxa debiossíntese de colesterol por inibição competitiva da HMG-CoA redutase.[44]	Potencializa o efeito anticoagulante da varfarina e aumenta o risco de rabdomiólise[39]
Enoxaparina	Anticoagulante	Inibe o fator Xa aumentando a taxa de inibição das proteases de coagulação que são ativadas pela antitrombina III. Geralmente não aumenta PT ou PTT.[44]	Potencializa o efeito anticoagulante da varfarina[39]
Amiodarona	tiarrítmico de classe	Inibe a estimulação adrenérgica; afeta os canais de sódio, potássio e cálcio; prolonga acentuadamente o potencial de ação e repolarização; diminui a condução AV e a função do nó sinusal[44]	Potencializa o efeito anticoagulante da varfarina[40]
Sertralina	Inibidor selectivo da recaptação da serotonina	Pouca ou nenhuma afinidade por histamina alfa-adrenérgica ou receptor colinérgico.[44]	Potencializa o efeito anticoagulante da varfarina[41]
Espironolactona	Diurético poupador de potássio	Compete pelos receptores intracelulares de aldosterona nas células do túbulo distal, resultando em inibição da ação de retenção de Na + da aldosterona, com redução concomitante no seu efeito de estimulação da secreção de K + . Também diminui a secreção de H + , bem como a excreção de ácido úrico.[30]	Reduz a ação anticoagulante[30]
Atenolol	Betabloqueador	Bloqueia a resposta à estimulação beta-adrenérgica; cardiosseletivo para receptores beta1 em doses baixas, com pouco ou nenhum efeito nos receptores beta2.[44]	Risco do aumento do tempo de protrombina vs INR[33]
Dipirona	Antiinflamatório não -esteroidal (AINES)	Analgésico, antipirético e espasmolítico sem mecanismo de ação claramente definido.[45]	Potencializa o efeito anticoagulante da varfarina[42]

Source: The authors

Among these, Omeprazole was present in 70 (97.2%) prescriptions; Dipyrone in 68 (94.4%); Simvastatin in 43 (59.72%); to Enoxaparin in 42 (58.33%); Amiodarone in 29 (40.27%); Sertraline in 28 (38.88%); Spironolactone in 21 (29.16%); and Atenolol in 11 (15.27%).

Among 24 drugs that interact with Warfarin, 14 (58.33%) correspond to the interaction of moderate severity, while 10 (41.66% are considered of greater severity. Regarding the effect, 14 (58.33%) are considered fast, and 10 (41.66%) are unspecified.

As for the schedule of all medications, there was a predominance of the following schedules: 6:00 a.m. (n=203), 10:00 a.m. (n=234) and 10:00 p.m. (n=315), which shows some standardization of the institution's schedule. For instance: the institution nurse has the custom to schedule the medications for 2:00 p.m., 10:00 p.m. and 6:00 a.m. when these are prescribed every 8 hours.

Warfarin was always used late afternoon, 13 times (17.56%) at 5:00 p.m. and 61 (82.43%) at 6:00 p.m. Furthermore, regarding the presence of adverse drug interaction events, only four (4) nursing records were identified. These records appeared on the nursing record sheet, such as back pain, haematuria, abdominal pain, and dizziness, all from different patients.

According to Rodrigues GHP et al. (2014)[23], the most frequent comorbidities in the elderly and cardiopathic population are in agreement with the findings in this study when it is stated that this population is commonly hypertensive, diabetic, dyslipidemic, obese, chronic renal, coronary disease, smokers, in addition to degenerative diseases characteristic of the age, such as cognitive deficit. This current morbidity and mortality profile leads to an increase in the number of hospitalizations of the elderly and cardiopathic population. It is common, therefore, to notice the increase of prescriptions of drugs in hospitalized patients, which favors, even more, the polypharmacy and the possibility of a drug interaction.[24]

In this study, all the prescriptions analyzed contained more than five prescribed drugs, thus constituting polypharmacy.[25] Among the 24 drugs that interact with Warfarin, the eight most prescribed drugs were Omeprazole, Dipyrone, Simvastatin, Enoxaparin, Amiodarone, Sertraline, and Atenolol.

During the collection of data, four signs or symptoms records presented by the patients were identified: lumbar pain, headache, distress sensation, and abdominal pain. Nevertheless, it is not possible to say with certainty if it was a drug interaction or not, since there are several factors that may have caused them. Therefore, in this study, we will refer to drug interactions as "potential".

Among the 24 drugs that interact with Warfarin in this study, two of them (Omeprazole and Spironolactone) were considered of moderate severity while six (Dipyrone, Simvastatin, Enoxaparin, Amiodarone, Sertraline, and Atenolol) were considered of greater severity. Regarding the effect, five are delayed (Omeprazole, Simvastatin, Amiodarone, Sertraline, and Atenolol) and three unspecified (Dipyrone, Enoxaparin and Spironolactone).

The study performed by Sconce et al. (2006)[26] has shown that concurrent use of Simvastatin and Warfarin results in changes in the pharmacokinetics of Warfarin, most likely through the inhibition of the P450 CYP3A4 and CYP2C9 enzymes responsible for the metabolism of R and S-Warfarin respectively, and not by action on pharmacodynamics. However, Westergren (2007)[27] confirms the interaction of Warfarin with Simvastatin. Nonetheless, despite not being sure of the mechanism of this interaction, the author concludes in his study that the potentiation of the anticoagulant effect is caused by the reduction of the elimination of Warfarin.

Santos et al (2014)[28] state in their study that Amiodarone interferes with the maintenance of the Warfarin dose; but, when anticoagulant therapy is already chronic, there is no association with adverse events. Although, caution should

be exercised in anticoagulant therapy concurrent with the use of amiodarone and that especially in the first few weeks, more attention is needed until the therapeutic dose is reached.

There are situations, such as pre and post-surgical procedures, in which Warfarin is discontinued, but due to the need to maintain anticoagulant therapy, it is decided the use of Enoxaparin, a type of low molecular weight and short-acting heparin, compared to Warfarin. Although it is an option of conduct with desirable effect, there can be serious consequences, such as an increased risk of bleeding, because it is another anticoagulant.[29]

There are few studies on the interaction between Warfarin and Spironolactone, but O'Reilly (1980)[30] suggests that the mechanism of this interaction is summarized by the diuretic effect of spironolactone whose product concentrates on coagulation factors, thereby decreasing the anticoagulant effect of Warfarin.

In the study made by Apseloff (1997)[31], it was found that the result of the interaction between Warfarin and Sertraline - the potentiation of the anticoagulant effect, is clinically insignificant. Nevertheless, regular care and monitoring of the International Normalized Ratio (INR) levels should be maintained. The same is true for the interaction between Warfarin and Omeprazole, according to Sutfin (1989)[32]. No studies were found to elucidate the interaction between Warfarin and Atenolol, nor between Warfarin and Dipyrone. Groia (2015)[33] that only affirms the possible first interaction whose result is the risk of increasing INR.

In this study, the combination of Paracetamol and Codeine was prescribed only twice and for two patients, but it was not known whether the prescriber and those who took and administered had knowledge about the potential drug interaction or was actually a risk-benefit assessment. Therefore, Paracetamol is a Nonsteroidal Anti-Inflammatory Drug (NSAID) with an analgesic and antipyretic effect, widely used domestically.[36] It is known from clinical practice that its concomitant use of Warfarin can cause considerable damage, such as bleeding. This interaction is considered of moderate severity and slow effect.[19-36] Mahé I (2005)[37] confirms that Paracetamol potentiates the anticoagulant effect of Warfarin, although this mechanism is still unclear.

At the institution where the study was conducted, Warfarin is generally scheduled in the late afternoon. And, in the present study, the only hours of scheduling were at 5:00 p.m. and 6:00 p.m. There is no documented scientific justification for this routine in the literature, but since routinely routine exams are collected in the morning until the time of the administration of Warfarin, the INR is likely to be ready. Hence, if necessary, it is possible to change the OAC dose at the time of its administration.[34,35]

CONCLUSIONS

Warfarin is an oral vitamin K antagonist with action duration of about two to five days and usually of continuous use. Therefore, prolonged action. Considering the high interaction power with several drugs, which may result in potentiation or inhibition of the anticoagulant action, it is important that the individual using oral anticoagulant periodically controls the INR, nor as directed for potential drug interactions, which may result in new treatments, hospitalizations and, consequently, the burden of health expenses, which can be avoided.

Nonetheless, it cannot be affirmed that nursing care is essential to avoid drug interactions in individuals who use Warfarin precisely because of the continuous action of it. However, regardless of the timing of Warfarin or any medications that interact with it, it is important to know the effects that the drug interaction can cause, in order to allow corrective action or immediate control, much more than to pay attention to the release itself, which may not be avoidable. Furthermore, it is vital that both physicians and nurses can identify the drugs that should not be concomitantly administered. The first, considering the prescription; and the second, with regards to the drug scheduling.

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Received on: 06/12/2018
Required Reviews: 07/19/2018
Approved on: 08/22/2018
Published on: 10/05/2019

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The authors claim to have no conflict of interest.