

PHARMACO THERAPEUTIC FOLLOW- UP BEFORE THE USE OF ANTITHROMBOTICS, ANTICOAGULANTS AND ANTIPLATETARYS: A REVIEW

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Abstract: Knowing that cardiovascular diseases have a high mortality in Brazil and in the world, thrombosis is a pathology that stands out in this system for triggering different complications. To mitigate these risks, drugs such as anticoagulants and antiplatelet agents are widely used, and these modulators need a lot of attention. The pharmaceutical professional is trained to assist in this therapy through different interventions, resulting directly in better adherence and in the minimization of possible DRPs evidenced by patients. As a result, this study aimed to emphasize the importance of the clinical pharmacist in the face of the pharmacotherapy that is protocolled in cases of thrombosis. It is a narrative literature review using articles indexed in academic research databases within a time frame of 10 years (2011-2021). Thrombosis, in turn, occurs due to inappropriate activation of clotting factors without hemorrhagic evidence, and anticoagulant and antiplatelet drugs are used, which will act at some point in the coagulation cascade aiming at the treatment and prevention of thrombi. As they need special attention, the literature points out that the presence of the pharmacist in the follow-up of patients on anticoagulant therapy is essential to improve adherence, pharmacotherapy results, reduce the intrinsic risks of medicines, as well as provide a better quality of life for patients. From the results found in the literature, it is noted that the clinical pharmacist is relevant in the therapy of thrombotic diseases, and their role is to minimize the risks and increase the success of the treatment.

Keywords: Thrombosis; pharmacotherapy; Anticoagulants; Antiplatelet agents.

INTRODUCTION

Among the pathologies, cardiovascular diseases are the ones with the highest mortality in Brazil and in the world (SBC, 2021a; WHO,

2021). In Brazil, in particular, ischemic heart diseases occupies a prominent position as the main cause of cardiovascular death (SBC, 2021b) acute myocardial infarction has a mortality rate of 9.06% in the year 2021 (SBC, 2021c; W.H.O, 2021).

According to the W.H.O., it is estimated that in 2030 about 23.6 million people will die from cardiovascular diseases. In view of this, due to the high rate of cardiovascular diseases in the world, the consumption of medicines to treat this pathology is high, with this, the pharmacist can guide the patient on the right way to use the medicines and solve problems related to the use of the medicine, with the objective of preventing all the risks that the pathology can cause and consequently improving the patient's quality of life (MENDIS, 2011; RIBEIRO, 2020).

Regarding cardiovascular diseases, thrombosis stands out, which can be defined as a sequence of pathophysiological events that lead to the formation of thrombi, which basically have their genesis in vascular endothelial injury, abnormal blood flow and blood hypercoagulability. The thrombus is made up of a solid portion of blood that has undergone the clotting process within the circulatory system (KOUPENOVA et al., 2017).

Regarding their classification, thrombi can be divided into venous or arterial, which in general can generate systemic complications, mainly due to the formation of emboli, which can be carried by the blood, and can obstruct vessels of important organs (PRANDONI; PIOVELLA, PESAVENTO), 2012; BEVIS; SMITH, 2016).

In the pharmacological treatment of thrombotic diseases, antiplatelet drugs, oral or injectable anticoagulants are commonly used. Of which, we can mention warfarin, vitamin K antagonists, heparin and clopidogrel that act on clotting factors, in addition, there are

fibrinolytic drugs and fibrinolysis inhibitors. In addition, acetylsalicylic acid is also used for the clinical management of the disease, for example, it is one of the oldest and most effective in the treatment of thrombosis (FIGUEIREDO et al., 2018; LEME; SGUIZZATTO, 2012).

The inappropriate use of anticoagulants can lead to complications for the individual's health. For example, warfarin, a vitamin K antagonist, has dose-response variability, that is, its therapeutic dose is very close to the toxic dose. Another drug with similar characteristics is heparin, as its response may vary from individual to individual, thus requiring constant monitoring of users of these drugs (O'DONNELL, 2012; TRAN et al., 2013).

According to Lorga Filho and employees (2013), the clinical use of anticoagulants and antiplatelet agents has increased significantly in the last ten years. Therefore, due to the epidemiological issues associated with the incidence and complications caused by thrombi, as well as the enormous use of these drugs, which can lead to DRPs (Drug Related Problems), the objective of this work is to show the importance of the clinical pharmacist in pharmacotherapy with anticoagulants. and antiplatelet agents in thrombotic diseases.

In this context, it is noted that professional interventions become relevant, including that of the pharmacist, given their contribution, for example, to identifying, preventing and solving problems related to drugs associated with pharmacotherapy (CESARZ et al., 2013).

This assignment is in line with Resolution No. 585, of 2013, of the Federal Council of Pharmacy, which enables the pharmacist to monitor and follow pharmacotherapeutic measures that result in direct patient care, providing the safe use of medications and improving pharmacotherapy. (MIRANDA et al., 2012; BRASIL, 2013).

Based on these premises, the objective of this review is to elucidate, through a narrative literature review, the main scientific evidence of pharmaceutical intervention in the pharmacotherapy of patients who use drugs involved in the coagulation cascade.

METHODOLOGY

This work consists of a narrative literature review, a descriptive and explanatory text modality that gathers information considered relevant to elucidate or address a subject of scientific interest (MARIANO; ROCHA, 2017). For its development, a research was carried out by consulting academic health research databases, among which we can mention: SciELO (Scientific Electronic Library Online), ScienceDirect and PubMed (US National Library of Medicine – NLM).

To carry out an active search for these materials in these databases, the following descriptors were used: Thrombosis; anticoagulants/anticoagulants; Pharmacotherapy/pharmacotherapy and pharmaceutical assistance, these words were used in combination or isolated using Boolean operators and filter resources intrinsic to the databases.

Finally, 36 articles were included within a time window of 10 years (2011 to 2021), taking into account updates on the proposed topic and relevance. Furthermore, works that consist of abstracts, incomplete or methodologically irrelevant articles were excluded from the scope of the manuscript. To complement the discussion, clinical protocols and therapeutic guidelines that guide the use of anticoagulants were also included for the construction of the work.

RESULTS AND DISCUSSION

In normal hemostatic processes, after an aggression and consequent endothelial injury that results in hemorrhage, there is

activation of the coagulation cascade, in which platelet aggregation events and fibrin formation occur to contain the outflow of blood from the vessels. On the other hand, when this aggression occurs without apparent hemorrhage, thrombus formation may occur, due to inappropriate activation of coagulation processes. This is related to changes in blood flow, deterioration of the vascular wall and changes in blood or platelet composition (CUGNO et al., 2014; PALTA; SAROA; PALTA, 2014; BRANDÃO et al., 2018).

PHARMACOTHERAPY OF THROMBOTIC DISEASES

In order to prevent or treat thrombotic diseases and their consequences, drugs that act at some point in the coagulation cascade or on platelet aggregation are used. The main characteristics of these drugs are described in the following topics.

Anticoagulant drugs

Heparin, an anticoagulant, which is used to treat and/or prevent thrombotic diseases or other problems resulting from blood clotting, acts mainly through the inhibition of thrombin, in relation to its route of administration, unfractionated heparin (UFH) is usually used intravenously, while low molecular weight heparin (LMWH) is applied subcutaneously. Other routes of administration, such as the oral route, are not used due to pharmacokinetic characteristics (HUNTINGTON, 2011; ONISHI et al., 2016).

LMWH is preferentially used due to its effectiveness and ease of administration, but in patients with renal failure UFH must be used, as LMWH is mostly eliminated through the urine. Regarding unwanted effects, bleeding is present, which can be influenced by the dose regimen used (COSTANTINO et al., 2012; WELLS; FORGIE; RODGER, 2014; VORISEK et al., 2019).

Within the oral anticoagulants, we have warfarin, which acts by antagonizing vitamin K through the carboxylation reaction. This occurs at glutamate residues in coagulation factors II, VII, IX and X, inhibiting the reduction of vitamin K epoxide to its active hydroquinone form. Due to this broad action on clotting factors, prothrombin time (PT) must always be controlled and measured in patients who use it (TELES; FUKUDA; FEDER, 2012).

This drug is rapidly absorbed from the intestine, has a half-life of 40 h and reaches its peak action 48 h and 72 h after administration, being excreted in feces and urine after fulfilling its action (MEGA; SIMON, 2015).

Platelet antiaggregating drugs

The use of acetylsalicylic acid (ASA) is effective in preventing thrombi by inhibiting the COX1 isoenzyme, mainly preventing the formation of the important mediators for platelet aggregation, thromboxane A₂ (TXA₂) (FUSTER, 2011; UNDAS, 2014).

According to Miser (2011), aspirin contains absolute and relative contraindications, the first being related to peptic ulcer, aspirin allergies, bleeding disorders, renal failure, among others, regarding relative contraindications, under 21 years of age stands out, as there is an increased risk of Reye's syndrome, the simultaneous use of anticoagulant therapy, its use associated with non-steroidal anti-inflammatory drugs and hypertension outside the therapeutic goals. Among the adverse effects related to the use of ASA, there are listed, prolonged bleeding, gastrointestinal complications, which can vary from superior to mild, peptic ulcers, among others (VALKHOFF, 2012).

Another platelet antiaggregant is Clopidogrel, a prodrug with a mechanism of action through inhibition of platelet aggregation through antagonization of P2Y₁₂ receptors present on platelets, thus preventing

its activation through ADP. Regarding the kinetic aspects, this drug has a peak of action of 2 to 6 hours and its frequency of administration is once a day at a dose of 75 mg. Clopidogrel may have dyspnea as an adverse effect (HULOT, 2011; PATRONO, 2017).

Fibrinolytic drugs

In antithrombotic therapy, fibrinolytic agents may also be present, which act by stimulating activation of plasminogen into plasmin which will hydrolyze insoluble fibrin into soluble polypeptide fragments resulting in thrombus elimination (STEWART; KLINE, 2020).

Among the main agents are first-generation agents such as streptokinase extracted from streptococcal cultures, associating with plasminogen to form streptokinase-plasminogen and urokinase synthesized in the kidneys and excreted through the urine (STEWART; KLINE, 2020).

Alteplase is classified as a second-generation agent, being a fibrin-specific drug. Entering the third generation are tenecteplase and reteplase, both genetically modified to extend the half-life (STEWART; KLINE, 2020). The main adverse reactions associated with the use of these drugs are intracranial and non-intracranial hemorrhagic events (BUNDHUN; JANOO; CHEN, 2016).

IMPORTANT DRUG INTERACTIONS INVOLVING DRUGS THAT ACT ON THE CLOTTING PATHWAYS

A study aimed at investigating the nature and determinants of drug therapy alerts showed that the drugs that led to the most interactions were antithrombotic agents. In addition, these drugs for thrombotic treatment presented a greater amount of alerts in relation to duplicate medication (HERINGA et al., 2016).

Warfarin is composed of a racemic mixture, where its most potent form is the

S isomer, but both the S and R enantiomers are metabolized by cytochrome P450 CYP enzymes. Therefore, the most significant interactions are those that inhibit CYP pathways. Interactions with several antibiotics are quite recurrent due to changes in the bacterial flora and modification of warfarin clearance (NUTESCU; CHUATRISORN; HELLENBART, 2011; AGENO et al, 2012).

Conditions in which it interferes with CYP2C19 enzymes, which are related to clopidogrel metabolism, may provide pharmacologically relevant impacts on the action of this drug. As in the case of proton pump inhibitors, which are also metabolized by these cytochrome P450 enzymes, thus causing a competition, in which clopidogrel's antiplatelet effect can be reduced (D'UGO; ROSSI; DE CATERINA, 2014).

ROLE OF THE CLINICAL PHARMACIST IN MONITORING PATIENTS WITH THROMBOTIC DISEASES AND IN TRANSIENT ANTICOAGULANT THERAPY

Among the clinical duties of the pharmacist, there is the pharmacotherapeutic monitoring and review of the pharmacotherapy, in order to ensure the rational use of medicines through direct action in patient care. Regarding venous thromboembolism (VTE) care, the pharmacist has a fundamental role, contributing in a way that can improve VTE prophylaxis and treatment (BRASIL, 2013; DOBESH; TRUJILLO; FINKS, 2013).

According to Piazza and employees (2012), individualized education programs carried out by pharmacists allow an increase in medication adherence in the prophylaxis of venous thromboembolism.

In a systematic review and meta-analysis study addressing the benefits of pharmacist-led anticoagulant management, it demonstrated favorable results as a result of pharmacist

leadership in anticoagulation management, in which patients on anticoagulant treatment under the pharmacist's supervision had lower probability of occurrence of bleeding as well as lower chances of thrombotic events. In this case, also enabling a decrease in medical costs (HOU et al, 2017).

Ashjian and colleagues (2017) emphasized in a retrospective study a comparative analysis between the performance of the clinical pharmacist and the usual treatment followed by a physician in a service of therapy with direct oral anticoagulants. In the study, results showed that pharmacist-led patients were more likely to receive both the prescribed anticoagulant drugs and the appropriate dosages (93%) compared with the usual therapy group (79.1%). Given that the pharmacist actively participates not only in the pharmacotherapeutic follow-up of patients, but also permeates assertive guidance on the therapy in question, ensuring them greater understanding (ASHJIAN et al., 2017).

In addition, the clinical pharmacist can still act as an intermediary in the prevention of thrombotic diseases, as in a study carried out by Haga et al. Therefore, the preventive measures adopted were: inclusion of drug therapy, mechanical methods, dose/dosage adjustments and route of administration. That said, the results showed that of the 77 interventions carried out in a period of 5 months (January to May), 71 had adherence and were accepted by the medical team, while only 6 interventions were not accepted (HAGA et al., 2014).

Regarding pharmaceutical intervention in the context of antithrombotic drugs, table 1 brings together some of the main studies found in the databases listed in the review, and the results and main outcomes are described below.

Title (in Portuguese)	Goals	Kind of study	Main results	Reference
Patients and physicians with a pharmacist-administered anticoagulation program at a family medicine clinic	To describe patients' satisfaction with the warfarin education and management they received from the pharmacist, and to describe physicians' satisfaction with the level of care provided by the pharmacist to their patients using warfarin.	Descriptive Approach Survey Survey	Patients were highly satisfied with the education provided by the pharmacist about warfarin. They agreed with the pharmacist's teachings on warfarin adherence, INR tests, and bleeding risks. Regarding physicians, all those who received the survey show that they are satisfied with the program administered by the pharmacist.	Bishop and employees (2015).
Clinical pharmacist led hospital-wide direct oral anticoagulant delivery program	Describe the types of drug-related issues addressed and program performance in terms of physician consultation and acceptance rates.	Retrospective evaluation	From the consultations carried out by the pharmacist, the main recommendations were, 23% to monitor the levels of direct-acting oral anticoagulants (DOAC) and anti-Xa, 23% to increase and 5% to decrease DOAC doses, 20% to discontinue the drugs. concomitant antiplatelet agents, and 20% for other recommendations on DOAC therapy.	Perlman and Employees (2019)
A prospective multicenter study that evaluated the impact of clinical pharmacist-physician advice on the management of warfarin therapy in Lebanon	To assess patients' knowledge of warfarin and to assess the impact of healthcare professionals' advice on increasing patients' knowledge of warfarin therapeutic outcomes	Prospective multicenter study	It was possible to observe a higher mean knowledge after counseling in the warfarin score. Possessing greater knowledge about dose, toxicity, interactions, therapeutic INR and general knowledge of the drug. Patients achieved therapeutic INR values of 74.4% after counseling versus 37.2% before counseling.	Choumane and employees (2018)
Title (in Portuguese)	Goals	Kind of study	Main results	Reference
Efficacy and safety of a pharmacist-administered hospital anticoagulation service for warfarin initiation and titration	To assess the effect of implementing a pharmacist-administered hospital anticoagulation service	Unicentric cohort study	Therapeutic International Normalized Ratio (INR) values increased from 38% to 88% in a 5-day period and INRs greater than 4 were reduced from 27% to 2%. At discharge, subtherapeutic low-molecular-weight heparin-free INRs decreased from 15% to 0%.	Wong and employees (2011)
Time in the therapeutic range as a marker of thrombosis with bleeding outcomes in Fontan patients	To determine, through a cardiology specialist pharmacist, the exact time of the therapeutic range when warfarin is administered to patients who have undergone Fontan therapy	Observational study	The study demonstrated for the first time that it is possible to obtain very high proportions of time in the therapeutic range for Fontan patients. This therapeutic time was associated with excellent clinical outcomes.	Faircloth and employees (2017)
Pharmaceutical care increases time in the therapeutic range of patients with poor quality of warfarin anticoagulation	To prospectively evaluate the management of warfarin by a pharmacist in patients with poor quality of anticoagulant therapy (Time in Therapeutic Range - TTR <50%)	Cohort study	The results were the percentages of TTR (Time in Therapeutic Range) were higher after 12 weeks of pharmacist-directed treatment than one year before treatment. In addition, the results showed that the probability of	Marcatto and employees (2018)

Title (in Portuguese)	Goals	Kind of study	Main results	Reference
Assessment of a pharmacist's anticoagulation management compared to a physician's coagulation management in Qatar	The primary objective of this research was to assess the impact of pharmacist versus physician-based anticoagulation management on percentage of time on therapeutic INR (International Normalized Ratio; TTR)	Retrospective cross-sectional study	Individuals followed at the clinic and managed by a pharmacist had a higher TTR compared to those administered at the clinic administered by a physician (81.8% vs. 69.8%). The extreme subtherapeutic INR range ratio was lower in the pharmacist-managed group compared to the physician group. And according to the supratherapeutic INR there were no significant differences between the groups.	Elewa and employees (2016)
Impact of High Anticoagulation Education by Emergency Department Pharmacists at a Medical Center Tertiary Academic	Identify the impact of pharmaceutical education, defined as the need for callback intervention, versus medical and nursing discharge measures on patient understanding and appropriate use of anticoagulant medications	Unicentric retrospective analysis	Patients who did not receive pharmaceutical education before the intervention had a greater need for interventions during callback compared to those who did (36.4% vs. 12.9%). Patients who did not receive pharmaceutical counseling were at greater risk of being readmitted to a hospital or returned to an emergency room due to an anticoagulation-related problem compared to those who received counseling (12.12% vs 1.85%).	Zdyb and employees (2017)
Title (in Portuguese)	Goals	Kind of study	Main Results	Reference
The Impact of Implementing an Advanced Practice Pharmacist Conducted Anticoagulation Clinic in a Correctional Center	To describe the implementation of a pharmacist-run anticoagulation clinic at the Los Angeles County Jail	Descriptive study	The main indication for warfarin in the present study was for deep vein thrombosis or pulmonary embolism (67%). The INR within the mean therapeutic range was 74.1 after management by the pharmacist and the time in the therapeutic range was 67%, thus indicating good control.	Employees (2019)
Impact of education on patients on anticoagulation regimens by pharmacists and telephone follow-up on care transition: A randomized clinical trial	To evaluate the impact of pharmaceutical intervention in the follow-up of patients who use anticoagulants.	Randomized Clinical Trial	A total of 200 patients from a hospital participated in the study, who were divided into a control and intervention group, and these patients were admitted who were receiving anticoagulant therapy and who need to continue their medication. In the intervention group, the pharmacists provided guidance on how to proceed with the therapy and, despite not having a direct influence on the bleeding time, it was observed that most patients returned to the doctor to continue the treatment.	Karaoui e employees (2021).

Table 1: Main articles published in the researched databases on the role of pharmacists in antithrombotic pharmacotherapy.

FINAL CONSIDERATIONS

The scientific evidence narrated in this review demonstrates that the pharmacist's intervention in the therapy with these drugs was crucial in the positive outcomes cited in each study. Among the pharmacist's attributions in this context, it is possible to mention medication conciliation, observation, identification and resolution of problems related to the medication, of which the most common and recurrent are potential drug interactions, adverse reactions. Thus, this mediation makes it possible to minimize risks associated with medications.

In addition, pharmaceutical activity was noted in patient-oriented guidance and, consequently, in a better adherence, which can be noticed in the monitoring of coagulation tests through laboratory tests, which the pharmacist can request in the context of monitoring.

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