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Research Paper

Pharmacokinetics And Pharmacodynamics of Warfarin in Critically Ill Hematological Patients

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ABSTRACT

Background: Warfarin is an anticoagulant that comes in two forms, S-warfarin and R-warfarin, the former being five times more potent and responsible for its anticoagulant effect. Genetic variants in the CYP2C9 gene, such as CYP2C9*2 and CYP2C9*3, may reduce the effectiveness of the enzyme that metabolizes S- warfarin, leading to people with these variants needing lower doses of the drug. Methodology: A bibliographic review was carried out through various databases from 2018 to 2024; The search and selection of articles was carried out in indexed journals in English and Spanish. The following keywords were used: pharmacokinetics, pharmacodynamics, warfarin, patients, hematological. Results: In patients with chronic hematological disorders, the pharmacodynamics of Warfarin is influenced by alterations in coagulation, drug metabolism, response and drug interactions, making the management of anticoagulation more delicate, with a balance between the prevention of thrombosis and the minimization of the risk of bleeding, rigid monitoring of INR, by customizing treatment to the patient's condition, high-risk complications are avoided. Conclusion: Warfarin as a treatment in patients with chronic hematological pathologies can present significant risks as benefits, on the one hand, when we refer to pathologies with a high thrombotic predisposition, Warfarin is a fundamental option for the prevention of serious thrombotic events, in these cases, the ability it has to inhibit the formation of coagulability is crucial.

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INTRODUCTION

It is very important to mention that Warfarin is defined as an oral anticoagulant that is widely used in the treatment and prevention of different thromboembolic pathologies, its mechanism of action is based on the inhibition of vitamin K epoxide reductase, which interferes in the synthesis of coagulation factors II, VII; LX and X, however, although it has been shown to be effective in hematologically critical patients, it still presents a series of significant challenges due to the variability of its pharmacodynamics and pharmacokinetics in this specific population. (1) Since we are referring to critically ill patients, specifically to patients with hematological disorders, which are those that produce pathophysiological alterations that directly affect the adsorption, distribution, metabolism and excretion of Warfarin. Many factors such as hepatic or renal dysfunction, hypoalbuminemia, problems with the natural production of vitamin K, drug interactions or underlying coagulopathies have a direct impact on the Warfarin profile, which generates difficulties in the control and increases the risk of bleeding and thrombotic events. (2,3)

On the other hand, the existence of multiple comorbidities and the use of drugs that interfere in the metabolism of Warfarin through cytochrome P450 enzymes and the need for frequent medical interventions further complicate anticoagulant management, which means that these characteristics mean that treatment with Warfarin in critical hematological patients requires exhaustive monitoring and dose adjustment based on the dynamic changes in the patient's clinical status. In the following article, reference will be made to the pharmacokinetics and pharmacodynamics of Warfarin specifically in hematological critical patients, its interaction, advantages and disadvantages.

MATERIALS AND METHODS

A literature review was conducted, searching PubMed, Scielo and ScienceDirect databases, among others. The collection and selection of articles was carried out in indexed journals in English and Spanish language from the years 2018 to 2023. As keywords, the following terms were used in the databases according to DeCS and MeSH methodology: "pharmacokinetics, pharmacodynamics, Warfarin, patients, hematological". In this review, 102 original and review publications related to the subject studied were identified, of which, 18 articles met the specified inclusion requirements, such as, articles that were in a range not less than 2018, that were full-text, indexed and original articles reporting on the "Pharmacokinetics and pharmacodynamics of Warfarin in hematological critically ill patients."

RESULTS

Warfarin is an anticoagulant that comes in two forms, S-warfarin and R-warfarin, the former being five times more potent and responsible for its anticoagulant effect. Genetic variants in the CYP2C9 gene, such as CYP2C9*2 and CYP2C9*3, can reduce the efficacy of the enzyme that metabolizes S-warfarin, which leads people with these variants to require lower doses of the drug. (4,5) In addition, warfarin acts by inhibiting the enzyme vitamin K epoxide reductase (VKORC1), which is key to activating vitamin K and thus to clotting. People with the VKORC1 -1639GG variant require higher doses of warfarin than those with GA or AA variants. Although there are studies showing variations in response to warfarin according to race, African American and Latin American populations have been underrepresented in these investigations. This is relevant because these populations may face a higher risk of complications due to inadequate warfarin management.(6,7)

Warfarin Pharmacokinetics

Warfarin is an oral anticoagulant that acts by interfering with the synthesis of vitamin K-dependent coagulation factors, which pharmacokinetics may present significant variations due to several specific factors in hematologic critically ill patients, here the following key points: Absorption: Warfarin is absorbed in the gastrointestinal tract; in critically ill patients, absorption tends to be affected by changes in gastrointestinal motility, the use of intravenous drugs and alterations in health status. (8) Distribution: it generally binds to plasma proteins, mainly albumin, which means that it has a fairly low volume of distribution and in hematological patients protein levels may be affected, leading to an increase in the free fraction of the drug and therefore its anticoagulant effect.

Metabolism: it is metabolized mainly in the liver, through cytochrome P450 isoenzymes, liver function may be compromised, which may lead to a decrease in the metabolism of Warfarin, increasing the risk of accumulation and adverse effects (9). Elimination: Warfarin circulates in the body for 20 to 60 hours, which allows long-term control of coagulation. In patients with renal insufficiency, elimination may be affected, generating higher levels of Warfarin in the blood.

Interaction: Warfarin response may be influenced by genetic factors, drug- drug interactions that may alter pharmacokinetics, such as changes in metabolism by other drugs or alterations in absorption (10).

Warfarin Pharmacodynamics

It refers to its mechanism of action on the coagulation system and how this is converted into therapeutic or adverse effects, especially when referring to hematologically compromised patients. Warfarin inhibits the enzyme vitamin K epoxide reductase (VKORC1) which reduces the regeneration of active vitamin K, which is necessary for the carboxylation and activation of vitamin K-dependent clotting factors II, VII, IX and X, as well as anticoagulant proteins C and S, which are blood proteins that work together to prevent the blood from clotting too much. (11)

Relevance of Warfarin pharmacodynamics in chronic hematologic patients;

Coagulation disorders	Patients with chronic hematological disorders, such as hemophilia, leukemias, myelodysplasias or myeloproliferative syndromes, already have intrinsic alterations in their coagulation system. Adding Warfarin further impairs the body's ability to maintain a balance between thrombosis and bleeding. These patients are at increased risk of bleeding complications due to decreased vitamin K-dependent clotting factors, adding to pre-existing coagulopathies.
Interference with proteins C and S	In chronic patients, the reduction of proteins C and S (natural anticoagulants) can be exacerbated by the use of warfarin. This is particularly relevant in hematological pathologies such as hereditary thrombophilias or antiphospholipid syndrome, where the balance between procoagulant and anticoagulant factors is already altered. The initial inhibition of proteins C and S by warfarin may induce a paradoxical procoagulant state, especially at the beginning of treatment, which increases the risk of thrombotic complications such as skin necrosis or deep vein thrombosis (12).
Variability in treatment response	In chronic hematologic patients, the response to warfarin can be

	unpredictable due to factors such as impaired liver function, concomitant use of drugs (such as chemotherapies or immunosuppressants), and possible nutritional deficiencies, such as vitamin K, which is common in these patients. In addition, genetic polymorphisms, such as variants in the VKORC1 or CYP2C9 gene, may make some patients more sensitive or resistant to warfarin, requiring more frequent dose adjustments and close INR monitoring.
Increased risk of bleeding	Patients with chronic hematologic diseases are usually at increased risk of bleeding due to thrombocytopenia, platelet dysfunction or coagulopathies secondary to their underlying pathology. Administration of warfarin in this setting may aggravate the risk of bleeding, especially if strict INR control is not maintained. Warfarin, by further reducing the levels of active clotting factors, increases the risk of serious bleeding, which can be fatal if not detected and treated in time.
Pharmacological interaction	Chronic hematologic patients are often medicated with various medications, and many of the drugs they receive can interfere with the metabolism of warfarin, altering its anticoagulant effect. For example, immunosuppressants, antibiotics and antifungals common in these patients can inhibit the liver enzymes responsible for metabolizing warfarin (CYP2C9), increasing its effect and the risk of bleeding. In contrast, enzyme inducers such as certain chemotherapeutics may reduce the efficacy of warfarin, increasing the risk of thrombosis.(13)
INR monitoring	Chronic hematologic patients require more frequent and adjusted INR monitoring due to the instability of their response to treatment, to avoid both thrombosis and bleeding.

Chronic hematological pathologies and their interactions with Warfarin.

The following table shows the positive and negative interaction that occurs in patients with different chronic hematological pathologies, when treated with warfarin, in some cases this can become a risk of complications such as bleeding, however, in other conditions it can be beneficial as an option in preventive management with INR control and constant monitoring. (14,15)

Chronic hematologic pathology	Negative interactions	Positive interactions
Chronic myeloid leukemia	● Increased risk of hemorrhage due to bone marrow alterations and thrombocytopenia. ● Interactions with chemotherapies (imatinib) that inhibit	● It may be useful in the prevention of deep vein thrombosis (DVT) or pulmonary thromboembolism (PTE) in advanced stages or in
	or potentiate warfarin metabolism.	treatments with thrombogenic agents.
Chronic lymphocytic leukemia	● Increased risk of bleeding due to disease- or treatment- induced thrombocytopenia. ● Interactions with immunosuppressants and chemotherapies.	● It can help in the prevention of thrombotic events in patients with reactive thrombocytosis or hypercoagulability secondary to

		immunosuppressive treatments.
Hodgkin's lymphoma	● Increased risk of bleeding due to thrombocytopenia induced by the disease or by chemotherapy treatments. teraction with immunosuppressive and chemotherapeutic drugs.	● Possible use to prevent thrombosis in patients with antiphospholipid syndrome (APS) secondary to lymphoma.
Myelodysplastic Syndrome	● Elevated risk of bleeding due to thrombocytopenia and coagulation alterations. ● Variability in response to warfarin due to bone marrow instability.	● It may be useful in the prevention of thrombotic events in patients with mutations that predispose to thrombosis (e.g., JAK2 in some forms of MDS).
Polycythemia vera	● Difficulty controlling INR due to overproduction of blood cells, which may	● Indicated for the prevention of arterial and venous thrombosis, since patients with PV have
	alter the distribution of warfarin.	a high thrombotic risk due to hyperviscosity.
Essential thrombocytopenia	● Risk of bleeding due to platelet dysfunction, despite thrombocytosis. ● Fluctuations in INR due to variability in platelet number and function.	● Effective in the prevention of venous and arterial thrombosis, especially in patients with high platelet levels that generate a state of hypercoagulability.
Antiphospholipid syndrome	● Elevated risk of bleeding if INR is not adequately controlled (highest recommended range, 2.5-3.5). ● Variability in the anticoagulant effect due to drug interactions.	● Warfarin is the treatment of choice for the prevention of arterial and venous thromboembolic events in patients with APS, reducing the risk of recurrence
Aplastic anemia	● Increased risk of bleeding due to pancytopenia (anemia, thrombocytopenia and leukopenia). ● Interactions with immunosuppressive treatments, such as cyclosporine and antithymoglobulin.	● It is used with great caution in some patients where there is a risk of thrombosis due to immunosuppressive treatments or transitory situations that increase coagulation.
Hemophilia	● Contraindicated due to the extremely high risk of spontaneous bleeding, especially	● In hemophiliac patients, warfarin is rarely used; other anticoagulants that
	joint and cerebral hemorrhages. ● Any level of INR imbalance can be fatal.	are easier to reverse are preferred if temporary anticoagulation for clots is necessary.

Hereditary thrombophilia	• Possible complications if INR is not properly managed, risk of bleeding in some subgroups. • Warfarin resistance may occur in patients with certain mutations.	• Warfarin is highly effective in preventing recurrent thrombosis in patients with factor V Leiden mutations, prothrombin G20210A, and protein C or S deficiencies.

DISCUSSION

It is important to mention that, in critical patients with hematological pathologies, management represents a significant challenge, due to the variability in the response of the drug in the patient and the high susceptibility to generate hemorrhagic or thrombotic complications, since, in general, these patients suffer from complex coagulopathies and alterations in the metabolic pathways that affect the pharmacokinetics and pharmacodynamics of Warfarin, generating unpredictable fluctuations in INR (International Normalized Ratio) levels, which is a blood test that indicates the time it takes for the blood to clot, being used for the evaluation of the effectiveness of anticoagulants, increasing the risk of bleeding. (16) Warfarin can have effects in critical hematological patients as well as mentioned by the researcher Abel Berrios Arando et al, in his report of a clinical case where he indicates that Warfarin can cause fatal bleeding due to overdose in a patient under treatment with oral anticoagulants which is associated with an underlying pathology, since the 75 year old patient has a history of alcoholism making treatment more complicated, Warfarin 5mg orally for 18 days was started with Warfarin, An event such as the one mentioned above can put the patient at vital risk. Vitamin K and fresh frozen plasma can be effective in reversing anticoagulation and preventing hemorrhage; on the other hand, heparinization can also be a valid option until Warfarin is reestablished, but it can further prolong the hospitalization time. (17) On the other hand, there are also cases where patients may present resistance to drugs such as Warfarin due to drug interaction, as in the case presented by the researcher Rebeca Riva Pelegrin et al, the case of an 81 year old patient who was initially treated with anticoagulants with LMWH (fraxiheparin) of 0.6 mg every 12 hours SC and with Warfarin 2 mg 3 tablets daily, after that, it was decided to increase the dose to 5 tablets daily, since the expected results were not obtained, it was started with ciprofloxacin every 12 hours for 7 days, when following up and without achieving the expected INR values, it was decided to suspend carbamazepine and after 72 hours the patient underwent INR and PT, obtaining therapeutic limits. (18)

CONCLUSION

It is very important to say that Warfarin as a treatment in patients with chronic hematological pathologies can present significant risks as well as benefits, on the one hand, when we refer to pathologies with high thrombotic predisposition Warfarin is a fundamental option for the prevention of serious thrombotic events, in these cases, its capacity to inhibit the formation of coagulability is crucial. On the other hand, its use is also limited or contraindicated in patients with conditions such as thrombocytopenia, coagulopathies or platelet dysfunction, where the risk of bleeding is higher than the potential benefits, in addition to taking into account the possible pharmacological interactions that complicate its management, requiring continuous INR monitoring and personalized dose adjustment. In conclusion, it should be used with great care in chronic hematological patients individualizing the

treatment according to the patient's condition, the risk of thrombosis and bleeding complications, having a strict follow-up with a multidisciplinary approach to improve its benefits and minimize the risks in this specific population.

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