Target INR after mitral valve replacement with a mechanical prosthesis: time interval and warfarin dose

Thesis

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Taha Ali Ahmed Mahmoud

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List of Abbreviations

Abbr.	Full-term
AAs	: African-Americans
aPTT	: Activated Partial Thromboplastin Time
Gla	: Glutamate residues
INR	: International Normalized Ratio
ISI	: International sensitivity index
MVR	: Mitral valve replacement
OA	: Oral anticoagulant
PT	: Prothrombin time
PTT	: Partial thromboplastin time
SD	: Standard deviation
SPSS	: Statistical package for Social Science
TWD	: Total weekly dose
VKORC1	: Vitamin K epoxide Reductase Complex subunit 1
WHO	: World Health Organization

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Introduction

Valvular heart disease's burden is growing worldwide due to the high incidence of rheumatic heart disease in developing countries and the increase in degenerative etiologies in those industrial once. Valvular heart replacement is a milestone in the management of patients with However, significant improvements, the quest for the ideal valvular prosthesis is still ongoing.[1]

Advancement in valve repair and replacement surgeries has improved the symptoms, quality of life and life expectancy of the cardiac patients.

However, postoperatively all patients with valve replacement are required to take oral anticoagulation either temporarily or for life according to the type of the valve prosthesis to avoid the risk of valve thrombosis.[2]

Oral anticoagulant (OA) therapy provides the best thromboprophylaxis for patients with heart valve prosthesis. Since oral anticoagulants (OAs) increases the risk of bleeding, the therapy requires a careful attention to the balance between the risks of these two outcomes.[3]

Warfarin is one of the most widely used oral anticoagulant. Mechanism of action is by interfering with the conversion of vitamin K to its 2,3-epoxide, which results in inhibition of the synthesis of biologically active vitamin K–dependent clotting factors (II, VII, IX, X).[4]

The extent of action is governed by pharmacokinetic effects (mainly the drug's unbound concentration in plasma, which is dependent on daily dose and intrinsic hepatic clearance) and pharmacodynamic effects (i.e., the sensitivity of the target organ) [(5)].

Safety and effectiveness of warfarin therapy are critically dependent on a dose-response relationship, which is extremely individualized and can be influenced by several, different factors: age, body mass index, nutritional status, concomitant drug therapy and diet. Another factor that make warfarin dosage is challenging is the narrow therapeutic index of Warfarin. [(6-7)]

Thrombotic and embolic complications and anti-coagulation-related bleeding are the most common cause of morbidity and mortality after valve surgeries. So all patients after mechanical heart valves must receive lifelong oral anticoagulation therapy [(8)].

One of the causes for excessive anticoagulation is dosing error during initiation of warfarin therapy; thus, selecting an appropriate initial dose is important. In order to avoid early excessive anticoagulation, most patients currently receive an initial dose of 5 mg.[(5)]

In order to optimize the therapeutic effect without the dangerous risk, close monitoring of the degree of anticoagulation is required by blood testing through measuring the International Normalized Ratio (INR) [9].

Aim of the Work

To define independent predictor of reaching target INR after mechanical mitral valve replacement.

Antithrombotic Therapy

Antithrombotic agent:

Is a drug that reduces thrombus formation. It can be used therapeutically for primary prevention, secondary prevention, or treatment of an acute thrombosis.

Antithrombotic agents are divided into four major groups:

1. **Antiplatelet drugs:**
   - Glycoprotein IIb IIIa inhibitors : Tirofiban.
   - Cyclooxygenase inhibitors : Aspirin.
   - Thromboxane inhibitors : Dipyridamole.
   - Phosphodiesterase inhibitors : Cilostazol.
   - Prostaglandin analogues : Prostacyclin.

2. Anticoagulant drugs:

- Vitamin k antagonist: warfarin – Phenindione.
- Factor Xa inhibitor with some factor II inhibition: Heparin group.
- Direct thrombin inhibitors: -Lepirudin,Rivaroxaban.
- Other: protein C.

3.Thrombolytic drugs"fibrinolytic drugs":

- Plasminogen activator, urokinase plasminogen activator:
- Urokinase, streptokinase, fibrinolysin.

4. Non medical: EDTA, citrate.

Warfarin

Warfarin (also known under the brand names Coumadin, Jantoven, Marevan, Lawarin, Waran) is an anticoagulant normally used in the prevention of thrombosis and thromboembolism, the formation of blood clots in the blood vessels and their migration elsewhere in the body respectively (figure 1).

It was initially introduced in 1948 as a pesticide against rats and mice and is still used for this purpose, although more potent poisons such as Brodifacoum have been developed. In the early 1950s warfarin was found to be effective and relatively safe for preventing thrombosis and embolism (abnormal formation and migration of blood clots) in many disorders. It was approved for use as a medication in 1954 and has remained popular ever since; warfarin is the most widely prescribed oral anticoagulant drug in North America [(10)].

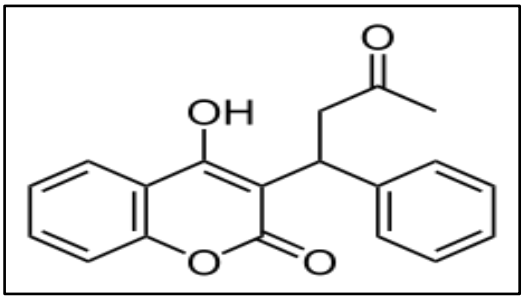

Figure (1): Warfarin structure [(11)]

Pharmacology of warfarin

Warfarin produce their anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide), thereby modulating the gamma carboxylation of glutamate residues (Gla) on the N-terminal regions of vitamin K-dependent proteins (Fig 2).[12]

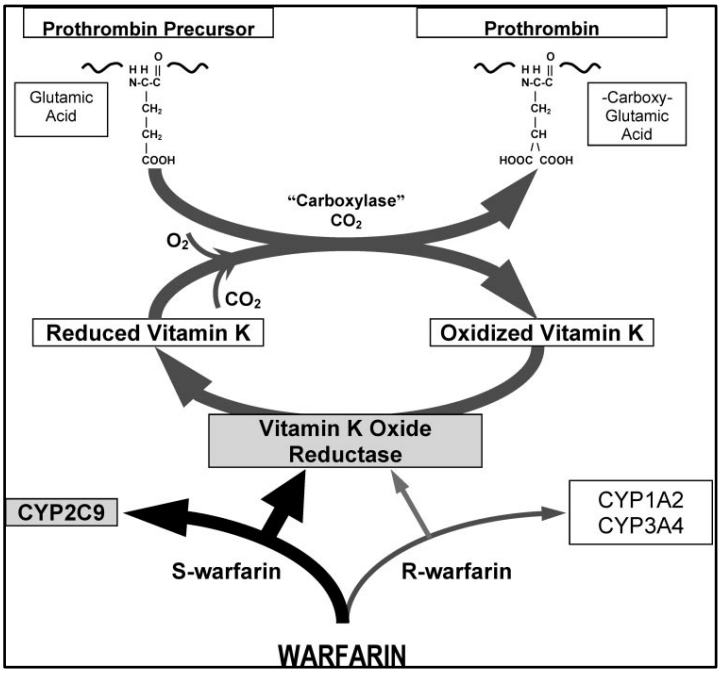

Figure (2): Mechanism of action of Warfarin [13]

The vitamin K dependent coagulation factors II, VII, IX, and X require gamma-carboxylation for their procoagulant activity, and treatment with Warfarin results in the hepatic production of partially carboxylated and decarboxylated proteins with reduced coagulant activity.[14-15]

Carboxylation promotes binding of the vitamin K–dependent coagulation factors to phospholipid surfaces, thereby accelerating blood coagulation. gamma-carboxylation requires the reduced form of vitamin K (vitamin KH_2). Coumarins block the formation of vitamin $KH_2$by inhibiting the enzyme vitamin K epoxide reductase, thereby limiting the gamma-carboxylation of the vitamin K–dependent coagulant proteins. In addition, the vitamin K antagonists inhibit carboxylation of the regulatory anticoagulant proteins C and S. The anticoagulant effect of coumarins can be overcome by low doses of vitamin K_1 (phytonadione) because vitamin K_1bypasses vitamin K epoxide reductase. Patients treated with large doses of vitamin K_1 (usually >5 mg) can become resistant to warfarin for up to a week because vitamin K_1 accumulating in the liver is available to bypass vitamin K epoxide reductase.[16]

Pharmacokinetics of Warfarin.

It is a racemic mixture of two optically active isomers, the R and S enantiomers. Warfarin is highly water soluble, rapidly absorbed from the GI tract, has high bioavailability [17,18] and reaches maximal blood concentrations about 90 min after oral administration [19,20].

Racemic warfarin has a half-life of 36 to 42 h24 (R-warfarin, 45 h; S-warfarin, 29 h); circulates bound to plasma proteins (mainly albumin); and accumulates in the liver,