Current Method of Monitoring Warfarinized Patients Using International Normalized Ratio (INR)

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INTRODUCTION

The effectiveness of any form of pharmacotherapy is heavily dependent on achieving an optimal therapeutic level. Every drug differs in respect to the pharmacokinetic or pharmacodynamic properties. Therefore, to ensure that a particular drug remains at the targeted optimal level, sometimes, a laboratory monitoring is employed. Warfarin, an oral anticoagulant, is an example of drug which commonly and routinely require clinical monitoring.Warfarin is widely prescribed for various clinical situations to prevent the risk of thromboembolism.

More than one million people in the United States are taking warfarin each year.[1] Any surgical dental treatment rendered on such patients poses the danger of significant haemorrhage post-operatively. On the other hand, partial or total withdrawal of warfarin from the patient risks the hazard of thrombosis and embolism.

Traditionally, the prothrombin time (PT) was the primary clinical indicator used by haematologists to assess the level of warfarin control.[2] Dental clinicians, in the past, were highly dependent on the PT values before deciding to attempt any surgical procedure on the patient concerned.

This paper shall highlight briefly the pharmacological properties of warfarin as an oral anticoagulant agent, review the newly accepted international normalized ratio(INR) to replace the PT test for monitoring anticoagulant status and discuss the advantages and disadvantages of utilizing INR.

PHARMACOLOGY OF WARFARIN

Warfarin sodium, which is a derivative of coumarin is one of the most popular drugs being prescribed.[3] The drug acts as a competitive-antagonist of enzyme Vitamin K epoxide to the active hydroquinone form. The active form of Vit. K is an essential cofactor for the gamma-carboxylation of clotting factors II, VII, IX, X as well as endogenous anticoagulant proteins C and S (Fig. 1).[3] This inhibition results in the failure of synthesis of physiologically functioning clotting factor proteins.

Warfarin has a half-life of 44 hours.[3] The effects of anticoagulant are delayed, until after four to five days of administration, to allow the normal clearance of previously synthesized active proteins.[4] Likewise,warfarin remains active for about the same length of time on cessation, both due to its mechanism of action and because it is strongly bound to plasma proteins.[5]

Uses of warfarin in clinical settings include prophylaxis of thromboembolic diseases, deep vein thrombosis, pulmonary embolism, preparation to cardioversion, atrial fibrillation and prosthetic heart valves. Patients with bleeding disorders, head injuries and diabetic retinopathy are absolute contraindications for warfarin therapy.[3]

MONITORING WARFARIN THERAPY

Since the early 1940s, the PT method developed by Quick had been the primary means of monitoring the level of oral anticoagulant control. The degree of anticoagulant recommended by haematologists were 1.5 - 3.0 times the control to prevent thromboembolism.[2] PT is the time required to form a plasma clot after adding calcium and thromboplastin to citrated patient's blood.[6] This, essentially, includes the extrinsic pathway and the common pathway of the coagulation cascade (Fig.

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2). Thromboplastins, are basically phospholipid-protein extracts of animal tissues such as brain, lung or placenta.

In the 1960s, the Manchester Comparative Reagent (MCR), a very sensitive thromboplastin derived from human tissue, was commercially available and widely-used throughout British laboratories.[2] For obvious reasons, all the thromboplastins used by the laboratories have different sensitivities due to varying species source, tissue used and the method of preparation.[7] The original recommendation of anticoagulant therapeutic range was a prothrombin ratio (PT/control) or PTR of 1.5 - 3.0 times.[2] In the early days, when there were wide differences of sensitivities using varying types of thromboplastins, the PT values became inconsistent. Many clinicians maintained the same target range even though the laboratories utilised different thromboplastins to test the PT ratio. When a less sensitive thromboplastin is being used but the target range remained the same, the level of anticoagulant used by physicians inadvertently became significantly higher, with markedly increased haemorrhagic potential. Because of this substandard medical care, the World Health Organization (WHO) in 1983, published the recommendations for reporting the level of anticoagulation using an international normalized ratio (INR).[6]

THE INR TEST: ADVANTAGES AND DISADVANTAGES

INR is a standardized PT, by using an additional adjustment for the reactivity of the reagents.[4] It is calculated based on the formula below:

$$INR = \left(\frac{\text{Patient's PT}}{\text{mean normal PT}}\right)^{ISI}$$

$$= PTR^{ISI}$$

International sensitivity index (ISI) corrects for the sensitivity of varying thromboplastins that laboratories use. The value is derived by an orthogonal regression line that rates the activity of a thromboplastin relative to the international reference preparation, a human brain thromboplastin, that has an ISI of 1.0[7] The less sensitive the thromboplastin, the higher the ISI value and vice versa. Currently, the values of ISI for commercial thromboplastins used in the North United States range from 1.8 - 2.8.[8] With such correction, an INR in one laboratory is equivalent to the INR in another laboratory even if a

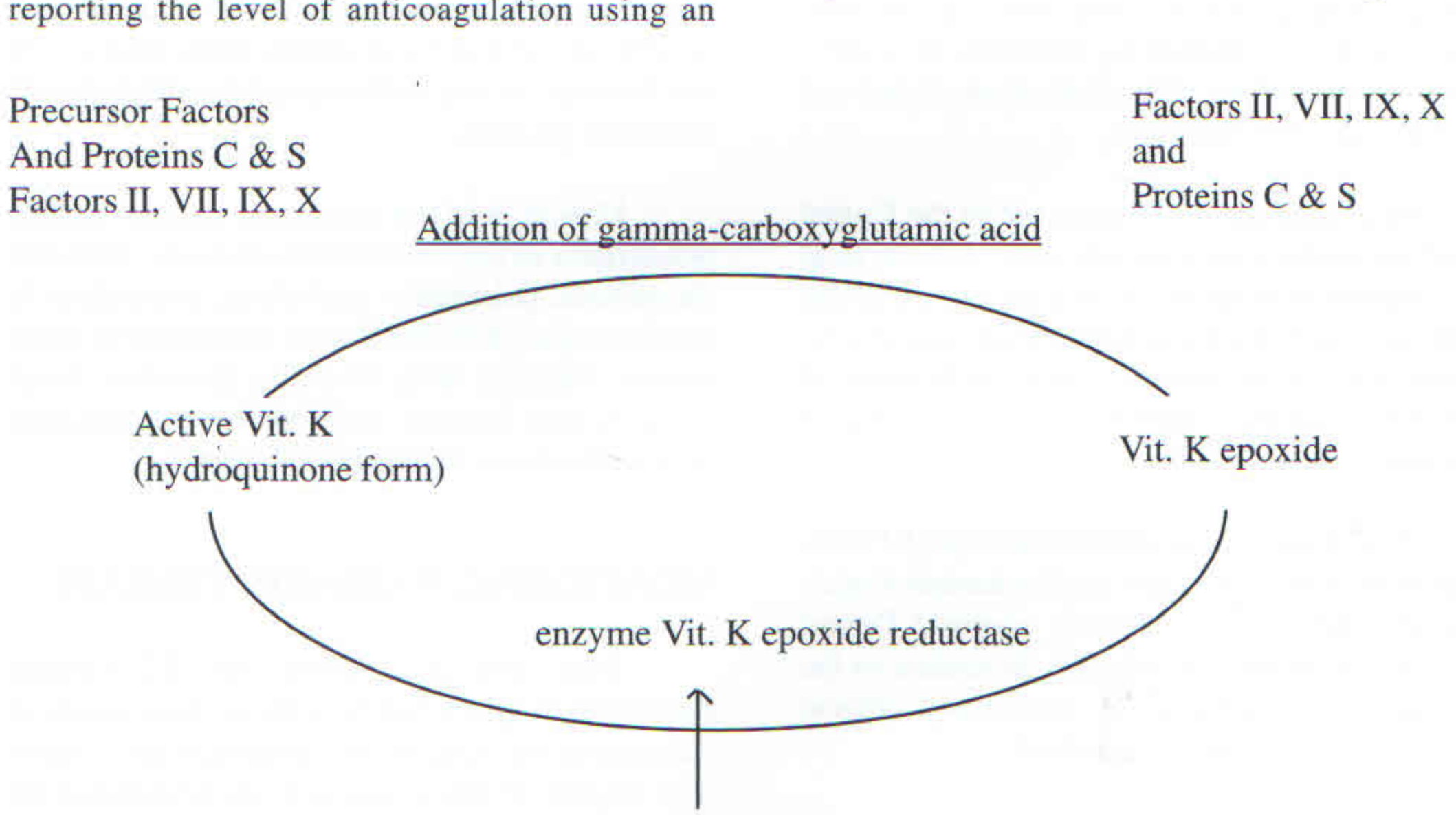

Fig. 1: Mechanism and site of action of warfarin

different thromboplastin was used to test patient's blood. The simplicity of using the INR can be illustrated below:

Example, the patient's PT ratio is 1.5 times if,
the ISI value is 2.0, then,
the INR=$1.5^{2.0}$ = 2.3
3.0 but,
if, the ISI value is 3.0,
then, the INR=$1.5^{2.0}$ = 3.4

The therapeutic range, generally accepted is between 2.0 and 4.0 when expressed as INR.[9] The INR test proved to be without flawless. It is not appropriate to assess the haemostatic function of patients suffering from liver diseases because other clotting factors, besides II, VII, IX, X, may be significantly affected.[10] Inconsistency, as a result of, different machines used between one laboratory to the other one remains an unsettled issue.[11] Even though the error is trivial, some clinical researchers suggested that the machine is calibrated prior to its function.[11] This is a necessary step to maintain internal quality and limit the systematic error.

Lastly, it has been reported that the coefficient of variation of the INR is equal to the coefficient of the PT ratio multiplied by the ISI value. Thus, a thromboplastin having a higher ISI value (less sensitive) will have higher coefficients of INR variations. Experiments have shown an estimated total error of 11% - 13.5% for INR values using a thromboplastin with an ISI value of 1.0. This error can be magnified for less sensitive thromboplastins with bigger ISI values.[7]

SUMMARY

This paper gives a brief account on the changing process of monitoring warfarinized patients and how INR is being derived from, together, with its shortcomings. The current method employing INR offers dental clinicians an accurate way to assess risk-benefit for each patient, prior to any surgical dental procedures. Treatment planning can, therefore, be accomplished with much safety and reliability.

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