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Review Article

Incorrect Anti-coagulant Treatment

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Abstract

Rivaroxaban, sold under the trade name Xarelto, is heavily promoted as an effective alternative to warfarin to reduce the risk of life-threatening blood clots. However, its potential side effects include death, bleeding into the brain and other internal organs and tissues. It is concerning that this new and heavily promoted drug is being rapidly and widely used when there are still unforeseen and serious side effects. The fundamental error is the use of single doses not normalised for body mass, and lack of monitoring tests.

Keywords: *Anti-Coagulant Treatment ; Rivaroxaban ; Warfarin*

Introduction

There is a long history of attempts to control diseases featuring abnormal clotting of blood such as venous thrombosis, pulmonary embolus, atrial thrombosis in atrial fibrillation and thrombosis within arteries. As the latter is characterised by thrombi rich in platelets, drug development for this problem has focused on so called dual antiplatelet therapy. In the other conditions in which fibrin dominates the pathology of the clots, anticoagulation has been the way forward. However, all the drugs used for all these anti-thrombotic effects have the side effect of excess bleeding, which can cause serious disability and death if not rigorously controlled.

The drug rivaroxaban is one such anticoagulant of which the adverse results have hit the headlines of the lay press, e.g. [1], in which Matthew Davies and Lucy Johnston reported that this BLOOD-thinning drug prescribed to thousands of NHS patients has been linked to severe side effects that have led to more than one death a week.

Plant materials

The traditional methods were the use of heparin (which has to be injected and therefore used mainly for acute thrombosis) and warfarin which was given orally in graded doses according to the patient's prothrombin time, assessed in more recent times by the INR test [2]. Since the focus of this article is on the problem of long term chronic anti-thrombotic therapy, one needs first to understand what happened with warfarin. Warfarin was the most widely used anticoagulant in the world. 8% of the over-80s were taking it regularly [3]. It was discovered because previously healthy cattle began dying of internal bleeding with no obvious precipitating cause. This was a devastating blow for the farmers' livelihoods. The cattle and sheep had grazed on sweet clover hay (*Melilotus alba* and *Melilotus officinalis*) and the incidence of bleeding occurred most frequently when the climate, and therefore the hay, was damp. Such damp hay became infected by moulds such as *Penicillium nigricans* and *Penicillium jensi,* which appeared to be integral in the disease process occurring in the cattle -sweet clover disease [4-6].

Although the sweet clover clearly caused the haemorrhage, it was found that a natural substance became oxidised in mouldy hay, to form the substance that would become better known as dicoumarol [6-9] a member of a family of substances called coumarins. This was originally exploited as a rat poison [2]. For clinical application the principal advantages of the coumarin warfarin was high water solubility and high oral bioavailability, and it was more potent than dicoumarol while retaining the ability to have its effect reversed by vitamin K [10].

Controlling warfarin doses in patients

Was dosing in the UK too low, increasing the incidence of thromboses, or was the dosing in the USA excessive, leading to unacceptable bleeding risks? A randomised trial was carried out in which patients with venous thrombo-embolism were assigned to target the different doses and prothrombin times used in the two countries. The incidence of recurrent thrombosis was 2% in both groups but bleeding rates were five times higher if the North American thromboplastin was used [11]. The adoption of the Brit-

ish reagent led to the widespread adoption of an INR target of 2 - 3. The importance of regular INR testing and dose adjustment cannot be over- emphasised. Unfortunately, the cost and time involved by the increasing requirement for anticoagulation in an increasing ageing population, led some misguided drug developers to imagine that single dosing of different kinds of anticoagulant without control would solve the logistic problem. In a way it did, as the patients who died as a result were no longer a burden on health provision services.

New anticoagulants

In the last few years, the FDA has approved three new oral anticoagulant drugs- Pradaxa (dabigatran), Xarelto (rivaroxaban), and Eliquis (apixaban). Like warfarin, all three are 'blood thinners' that reduce the overall risk of stroke related to atrial fibrillation, preventing pulmonary embolus and venous thrombosis, but they also cause bleeding.

As I have pointed out elsewhere [12] the first error made by the pharma industry was to use the same dose in mg to some people who are of normal, increased or decreased mass. This inevitably means that patients with increased mass will be under-treated, being too low on the effect/drug blood concentration curve [13]. A patient with lower body mass is over treated because he/she is too high on the effect/drug blood concentration curve and is very likely to bleed. The fundamental error perpetrated by the drug industry is to develop fixed dose tablets without monitoring and titration of dose. ALL drugs should be administered in mg/Kg and be available in a sufficient number of strength of tablets to enable the physician to prescribe by mg/ Kg. Patient prospects were much superior in the days of warfarin in which the dose was titrated against the INR. The same safety might easily have been obtained with rivaroxaban treatment if the doses had been titrated against the plasma rivaroxaban concentration for which an assay is available [13].

Drug sensitivity

Unfortunately for such a simple method of control, every human individual is unique; they are not all identical to the average. The same drug dose should not be applied to all patients, even after normalisation for body mass and the correct blood concentration of the drug checked, because the receptor mechanisms of actions vary from individual to individual. In order for correct dosage to be achieved, each patient should have the effect and the blood concentration measured, using the appropriate blood tests, assays or bleeding time. Factor Xa effect monitoring [14], should be been mandatory for factor Xa antagonists.

A further complication occurs in the presence of contra-indications such as diverticular disease. Diverticulitis intestinal haemorrhagic is found among people who take rivaroxaban, especially for people who are male, over 60 years old , and have been taking the drug for 1 - 6 months. The FDA eHealthMe report [15] states that 87,540 people have side effects when taking rivaroxaban, a number which is updated regularly.

Interactions

A total of 375 drugs (1466 brand and generic names) are known to interact with rivaroxaban. Using rivaroxaban together with ibuprofen may increase the risk of bleeding, including severe and sometimes fatal hemorrhage [16]. This list includes many commonly prescribed and over-the-counter available medications. The frequency of rivaroxaban side effects and interactions with other commonly used drugs would justify, in my opinion, the withdrawal of rivaroxaban from the pharmacopoeia.

Dual Anti-platelet therapy

Arterial disease is treated by anti-platelet therapy which has all the same problems as anti-coagulants and is associated with many bleeding complications. Consideration of the pathophysiology of the disease [17] shows that thrombotic occlusion occurs within arterial stenoses caused by convective acceleration and shear stress induced activation of platelets, followed by thrombus growth due to activation of more platelets via the serotonin $5HT_{2A}$ platelet receptor, a positive feedback phenomenon. This process is completely abolished by $5HT_{2A}$ antagonists [18] with no effect on bleeding time as confirmed in human patients [19]. The consistent refusal of the pharmaceutical industry to develop a 5HT2A antagonist for treatment of arterial disease is not understandable.

Conclusion

Anticoagulation treatment as currently practiced with new drugs is incorrect (same single dose for every patient), in that (1) dosage is not normalised for body mass, (2) the sensitivity of each individual patient to the drug is not determined, (3) the dose is not titrated for each individual patient until the correct optimal blood concentration of the drug is achieved, (4) there is no regular blood test monitoring of the patients as occurs with warfarin, (5) the drugs are administered without checking for contra-indications (e.g., diverticular disease and rivaroxaban), (6) the drugs are not checked for interactions with other drugs (e.g., ibuprofen and rivaroxaban).

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