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Dabigatran and Stroke Thrombolysis

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Dabigatran etexilate (Pradaxa) is the prodrug of the direct thrombin inhibitor dabigatran. Dabigatran directly inhibits both free and clot-bound thrombin; the inhibitory action is not dependent upon endogenous antithrombin. Peak plasma concentrations of the active drug dabigatran are reached 1.25–1.5 h after oral administration of dabigatran etexilate, and the half-life after a single dose is 7–9 h in healthy men [1]. In twice daily administration of the drug, a steady-state condition is reached after 2–3 days, and the elimination half-life is in the range of 12–14 h [2, 3].

Dabigatran has been shown to be effective for the prevention of stroke and systemic embolism in patients with atrial fibrillation. In the recently published phase III clinical trial RE-LY, 18,113 patients with atrial fibrillation either received 110 or 150 mg of dabigatran etexilate twice daily, or warfarin [4]. Stroke occurred in 171/6,015 patients (1.44% per year) treated with 110 mg, and 122/6,076 patients (1.01% per year) treated with 150 mg of dabigatran twice daily, and in 185/6,022 of patients (1.57% per year) receiving warfarin. Dabigatran has already been approved for prophylaxis of venous thromboembolism in elective hip and knee surgery, and clinical trials on treatment of venous thromboembolism and other clinical conditions are ongoing.

At present, fibrinolytic therapy is the only approved specific therapy for acute ischemic stroke. However, this treatment is associated with a significant increase in the risk of intracranial hemorrhage [5, 6].

So far, in all randomized clinical trials of fibrinolytic therapy in stroke, patients receiving therapeutic dose anticoagulants prior to stroke onset were excluded [7–9]. Thus, very few data are available concerning the effect of prior anticoagulant therapy on fibrinolytic therapy in acute ischemic stroke. Although it has been shown that prior treatment with antiplatelet agents increases the risk of intracranial hemorrhage in patients treated with tissue plasminogen activator for acute ischemic stroke [10–13], a recent meta-analysis suggests that antiplatelet agent therapy should not be considered a contraindication to thrombolysis [14]. This was a matter of serious concern when tissue plasminogen activator was approved by the European authorities.

Unfractionated heparin administered in parallel to fibrinolytic agents increases the risk of intracranial hemorrhage in a dose-dependent fashion [5]. Current treatment guidelines argue

against the use of therapeutic dose unfractionated or low-molecular-weight heparins in acute ischemic stroke, especially in patients treated with fibrinolytic agents [15, 16]. In patients with intracranial hemorrhage, prior medication with antiplatelet agents, as well as with warfarin, was associated with hematoma enlargement and early death [17]. Interestingly, warfarin in an international normalized ratio range of below 2.5, although leading to hematoma enlargement, was associated with a reduction in mortality. Furthermore, in patients with atrial fibrillation included in the RE-LY trial, the rate of intracranial hemorrhage was significantly lower in patients receiving dabigatran, compared to the patients treated with warfarin, with an odds ratio of 0.31 for 110 mg and 0.4 for 150 mg dabigatran twice daily ($p < 0.001$ for both) [4].

If patients treated with vitamin K antagonists (e.g. warfarin, phenprocoumon, acenocoumarol) experience an acute thromboembolic event, the anticoagulant effect may be antagonized instantly by use of prothrombin complex concentrate (PCC) [18, 19] in combination with intravenous vitamin K, making prompt thrombolytic therapy possible. Fresh frozen plasma (FFP) is less efficient for reversal of the anticoagulant effect and, due to the time needed for thawing and infusion, too slow to be useful under these circumstances.

In contrast, no reversal agent is currently available for dabigatran, and recommended strategies for treatment of acute bleeding events in patients treated with dabigatran include recombinant factor VIIa (Eptacog alfa, activated), FFP or PCC, although none of these options have been properly evaluated in vivo. Recombinant factor VIIa induces systemic coagulation activation which may overrun the anticoagulant effect of direct thrombin inhibitors [20], but the use of recombinant factor VIIa should be avoided in patients with acute ischemic events because of the prothrombotic effects of this drug. FFP causes dilution of the anticoagulant. PCCs increase the levels of prothrombin, factor X, factor IX and factor VII, leading to generation of more thrombin and a reduction of the dabigatran/thrombin ratio and the anticoagulant effect. Use of FFP, PCC or recombinant factor VIIa may be advisable in dabigatran-treated patients with acute hemorrhage, but not in dabigatran-anticoagulated patients with acute ischemic stroke.

The remaining option is to wait until the dabigatran level is below a functionally relevant threshold and then start. This requires measurement of the anticoagulant effect of dabigatran. Dabigatran affects all blood coagulation assays involving thrombin, including global assays prothrombin time (PT) and activated partial thromboplastin time (aPTT), as well as more specialized assays such as thrombin time or ecarin clotting time. If the requirement is that no anticoagulant effect be present when starting fibrinolytic therapy, the necessary time will probably exceed the 4.5-hour time frame for effective thrombolysis very often.

Direct thrombin inhibitors, such as dabigatran [21] or argatroban [22], enhance the effect of thrombolytic drugs by reducing the

generation of activated thrombin-activated fibrinolysis inhibitor, and by altering the fibrin structure of the clot [23]. In experiments with argatroban, reduction of clot lysis time was ascribed to a reduction of factor XIII activation in addition to reduced levels of activated thrombin-activated fibrinolysis inhibitor [24]. Treatment with the direct thrombin inhibitor argatroban in conjunction with tissue plasminogen activator in acute ischemic stroke led to a considerable increase in recanalization rate compared to tissue plasminogen activator alone, at the expense of a moderately increased rate of symptomatic intracranial hemorrhage [25]. In this study, the argatroban effect was monitored by use of the aPTT, with a target of a prolongation of 1.75 times the value of the control group not receiving argatroban. Similar levels are attained during dabigatran treatment with the doses used in the RE-LY trial [1].

What Actions Are to Be Taken?

First of all, laboratory assays for monitoring of the dabigatran effect need to be defined and evaluated. Direct thrombin inhibitors affect all coagulation assays based on thrombin activity, including PT, aPTT, thrombin time, ecarin clotting time and similar assays [26]. Clotting assays such as Heptest [27] or PiCT [28], developed for monitoring of unfractionated and low-molecular-weight heparins, are also useful for monitoring of direct thrombin inhibitors [28]. Assays need to be calibrated with a substance-specific calibrator. A normal PT, aPTT and thrombin time indicate that no relevant amounts of dabigatran are present in the blood. Of these assays, the thrombin time [29] is the most and the PT the least sensitive towards dabigatran effects [1]. A normal range thrombin time result thus excludes the presence of relevant amounts of dabigatran, which would be a contraindication for the administration of thrombolytics.

Secondly, investigations on the effect of dabigatran (and other direct thrombin inhibitors, such as argatroban) on the thrombolytic effect of recombinant tissue plasminogen activator are needed. A low concentration of dabigatran might actually be beneficial when combined with recombinant tissue plasminogen activator in acute ischemic stroke. In order to reduce the risk of intracranial hemorrhage, a lower dose of recombinant tissue plasminogen activator might be used, if dabigatran is present.

In view of the bleeding risks associated with both anticoagulants and antiplatelet agents, patients on combined therapy (dabigatran plus acetylsalicylic acid or clopidogrel) should at this point not be treated with thrombolytic drugs. In the RE-LY study, approximately 40% of patients received acetylsalicylic acid in addition to dabigatran or warfarin [4]. For all others, fibrinolytic therapy might be an option, as long as treatment can be performed within the established time frame and the anticoagulant effect of dabigatran does not exceed a certain limit, which still needs to be established.

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