REVIEW ARTICLE

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Thrombolytics
Drug Interactions of Clinical Significance

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Contents

Abstract

Thrombolytic agents activate plasminogen and induce a systemic fibrinolytic and anticoagulant state. Interaction of fibrinolysis with coagulation and platelet aggregation might be important for synergistic interactions with other antiplatelet or anticoagulant drugs. Thrombolytic agents are most often used in patients with coexisting cardiovascular medication, including various antihypertensives, β-blocking agents, nitrates and aspirin (acetylsalicylic acid). In acute coronary syndromes, anticoagulants and antiplatelet compounds such as clopidogrel or glycoprotein IIb/IIIa receptor antagonists might be given.

Inducers or inhibitors of the cytochrome P450 system are not reported to affect the pharmacokinetics of any thrombolytic agent. Since the elimination of the recombinant plasminogen activators saruplase and alteplase is dependent on liver blood flow, drugs affecting hepatic blood flow could theoretically affect the hepatic clearance of these agents. In fact, a reduction in thrombolytic activity has only been demonstrated for alteplase with nitroglycerin (glyceryl trinitrate).

Pharmacodynamic interactions occur more often. The additive and beneficial effect of aspirin as concomitant therapy to thrombolysis has been demonstrated without excessive bleeding rates. No data are available on the interaction between ticlopidine or clopidogrel and thrombolytic agents in humans. Anticoagulation by heparin concomitantly with thrombolysis improves the patency rate of the occluded coronary vessel, but bleeding complications are seen more frequently. Although there has been no controlled study on the interaction between oral anticoagulants and thrombolytic agents, patients with myocardial infarction who

were taking an oral anticoagulant before admission seem to be at higher risk for intracranial haemorrhage during thrombolytic therapy.

Currently, no recommendations can be given for possible dose adjustment of thrombolytic therapy in patients receiving antiplatelet comedication. For comedication with heparin, it has been advised to monitor activated partial thromboplastin time frequently and to avoid values >2.5-fold normal. Patients receiving thrombolytic treatment should be monitored frequently for bleeding and the physician should be aware of any comedication exerting antiplatelet (e.g. aspirin, clopidogrel and ticlopidine) or anticoagulant (e.g. warfarin) effects.

Thrombolytic agents are widely used in the active dissolution of thrombi and emboli and the prevention of clot apposition. Optimal thrombolytic therapy in acute myocardial infarction (MI) must aim to achieve early and complete reperfusion of the infarct-related coronary artery.[1] Although the pivotal role of thrombolysis in acute MI has been challenged by the expanding use of invasive revascularisation procedures, a considerable proportion of patients with acute MI will not have access to, or are not eligible for, primary percutaneous transluminal angioplasty (PTCA). Furthermore, the combination of thrombolysis and PTCA has undergone initial successful studies, as has the combination of thrombolytic agents with powerful antiplatelet glycoprotein (GP) IIb/IIIa-inhibitors instead of PTCA.[2] Another expanding area for the use of thrombolytic agents is the treatment of acute stroke, paralleled by the increasing role of stroke units.[3] As well as the most commonly used thrombolytic agents, streptokinase and the recombinant tissue-type plasminogen activator alteplase, a variety of other agents are in use (e.g. anistreplase, urokinase, reteplase) or in different stages of clinical development (e.g. tenecteplase, staphylokinase).[4] Although the value of the use of thrombolytic agents in the treatment of deep vein thrombosis is still being discussed,[5,6] high dose, short duration regimens of alteplase are currently being evaluated, and in cases of fulminant pulmonary embolism thrombolysis remains first-line treatment.

In this heterogenous field of clinical situations, a variety of other drugs will be given routinely as concomitant treatment.[7] Since the therapeutic range of thrombolytics is narrow and limited by potentially life-threatening bleeding episodes or failure of clot lysis, interactions between thrombolytic agents and concomitant treatment might influence the treatment outcome. As well as drugs, contrast media used in arteriography might be the source of interactions.[8] However, additive pharmacodynamic effects of concomitant drugs might also contribute to the efficacy of thrombolytic therapy.[9] In this review, we will give a short overview on the relevant pharmacokinetic and pharmacodynamic properties of thrombolytic agents, describe the possible sources of interactions in the clinical situation, and report on proven and potential interactions and possible strategies to avoid unwanted interactions. Unlike many other drug interactions, for example those arising from metabolic interactions, interactions with thrombolytic agents have hardly been investigated under controlled conditions in human volunteer studies because of possible risks and the lack of assessment of clinical relevance. Animal models on experimental thrombosis might in part serve as a surrogate,[10-12] but most of the knowledge regarding drug interactions with thrombolytics comes from clinical observations.

The literature search for this article was conducted using the Medline and the Micromedex® databases.

1. Principles of Thrombolysis

Thrombolytic drugs act by converting the proenyme plasminogen to the active enzyme plasmin by cleavage of an Arg-Val peptide bond.[4,13] Plasmin is a nonspecific serum protease that not only lyses the fibrin clot but also is capable of breaking down clotting factors (e.g. factors II, V or VIII). Physiologically, fibrinolysis is effected by tissue-type plasmin-

ogen activator (tPA) which is synthesised and secreted by endothelial cells and which activates plasminogen in the presence of fibrin. Once activated, the action of plasmin is regulated by circulating plasma inhibitors, primarily α_2-antiplasmin. However, plasmin formed at fibrin surfaces is only slowly inactivated by α_2-antiplasmin, whereas free plasmin is rapidly inhibited.[14] Endogenous thrombolysis by tPA activity is limited by the rapid hepatic clearance of tPA and inactivation of tPA by plasminogen activator inhibitor (PAI). The half-life of tP7A in circulation is less than 5 minutes.[4,15] Other naturally occurring fibrinolytics are urokinase and pro-urokinase, enzymes produced by the kidneys and vascular endothelium.[16]

Thrombolytic drugs may act as direct activators of plasminogen (e.g. urokinase or alteplase) or, after forming a complex with plasminogen, indirectly by inducing a conformational change of plasminogen which leads to its activation (streptokinase, anistreplase). Experimentally, the activity of alteplase is fibrin-specific and exerts its activity mainly at the clot site, whereas urokinase and streptokinase act systemically and induce a systemic fibrinolytic state and reduction of other clotting factors, including factor V, factor VIII and prothrombin.[14] Although differences in the bleeding risk have been claimed from these differing properties, the clot specificity of alteplase appears to be dose-related, and concentrations similar to those achieved in recent clinical trials have been associated with haemostatic defects.[13] Furthermore, bleeding risks observed so far in comparative clinical trials are similar, e.g. for streptokinase and alteplase.[17] Paradoxically, it has been shown that plasmin, the final step of thrombolysis, activates the intrinsic pathway of coagulation, predisposing to the formation of thrombin. Furthermore, during clot lysis thrombin bound in the clot might be released. On the other hand, fibrin degradation products which occur during thrombolysis as a result of the breakdown of fibrin are capable to inhibit fibrin polymerisation, thus exhibiting an anticoagulant effect.[14] These interferences with coagulation and platelet aggregation might be important for synergistic interactions with antiplatelet or anticoagulant drugs.[7]

Figure 1 provides an overview of the basic mechanism of fibrinolysis and its interaction with the coagulation cascade and platelet aggregation.

2. Thrombolytic Agents

Streptokinase binds plasminogen in 1 : 1 ratio, and this 'activator complex' catalyses the conversion of further plasminogen molecules into plasmin. Its pharmacological profile is characterised by a rapid degradation of the circulating fibrinogen and accumulation of fibrinogen degradation products. Streptokinase exhibits 2 disappearance rates: a fast half-life (18 minutes) attributable to the action of antibodies, and a slow half-life (83 minutes) which is operative in the absence of antibodies. After prolonged infusion of streptokinase, the fibrinolytic effect disappears within a few hours, but the effect on coagulation may persist for 12 to 24 hours.[4,7,13,15]

Anistreplase is an acylated form of the streptokinase-plasminogen complex which contains streptokinase and human Lys-plasminogen in equimolar amounts. Acylation makes the complex temporarily inactive but protects it from neutralisation by plasmin inhibitors. After deacylation, which begins immediately after injection, the streptokinase-plasminogen complex promotes thrombolysis. Like other thrombolytic agents, anistreplase induces a systemic fibrinogenolytic state. The plasma half-life of anistreplase is 88 to 112 minutes, which allows for a bolus administration without prolonged infusion.[4,13,14]

Urokinase acts directly on the endogenous fibrinolytic system to convert plasminogen into the proteolytic enzyme plasmin. Following intravenous administration of urokinase, fibrinolytic activity begins promptly and may last for several hours after discontinuation. The drug is cleared by the liver with a small fraction of the dose appearing in the bile and urine. The serum half-life is 20 minutes or less.[4,13,14]

Saruplase (pro-urokinase), or single-chain urokinase, is the precursor of urokinase. Saruplase is

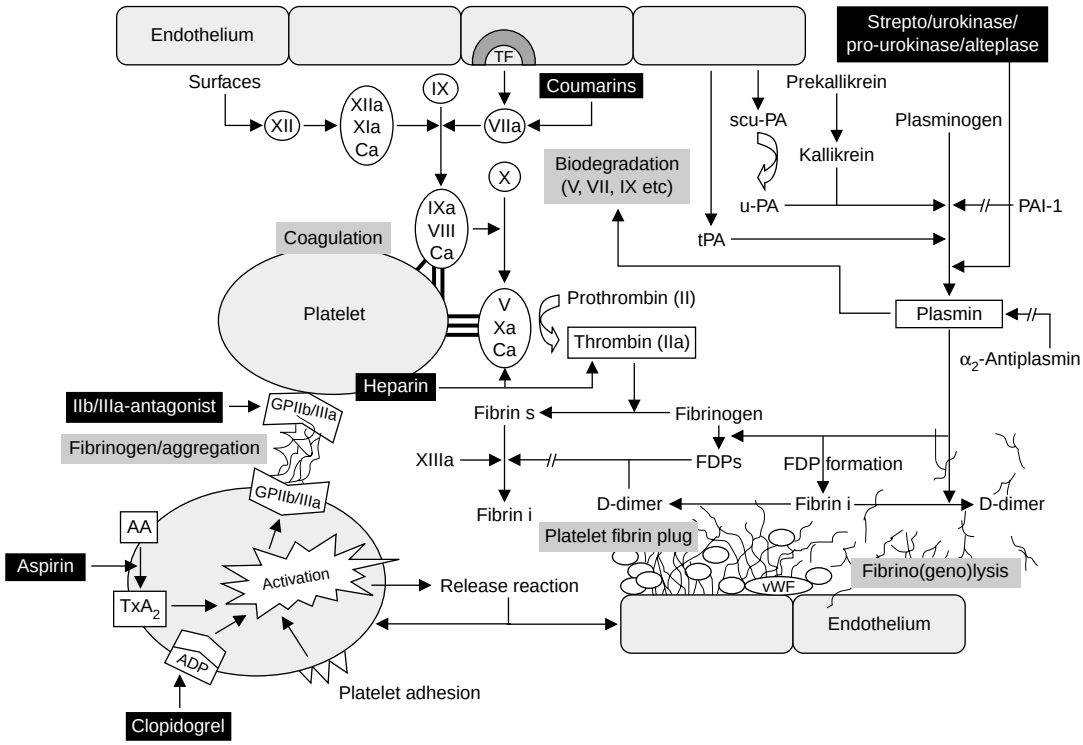

Fig. 1. Basic mechanism of fibrinolysis and interaction with the coagulation cascade (fibrin formation) and platelet thrombus formation. The site of action of different thrombolytic agents, anticoagulants and antiplatelet agents is indicated. The physiology of the fibrinolytic system is simplified and interferences with coagulation and platelet aggregation/thrombus formation are only partially illustrated. **AA** = arachidonic acid; **ADP** = adenosine diphosphate; **Ca** = calcium; **FDPs** = fibrin degradation products; **GP** = glycoprotein; **fibrin i** = insoluble fibrin; **fibrin s** = soluble fibrin; **PAI-1** = plasminogen activator inhibitor; **scu-PA/u-PA** = pro-urokinase/urokinase; **TF** = tissue factor; **tPA** = tissue plasminogen activator; **TxA_2** = thromboxane; **V**, **VIIa**, **VIII**, etc = factors V, VIIa, VIII, etc where **a** = activated.

activated to high-molecular-weight urokinase for fibrinolytic activity. Saruplase itself can also convert plasminogen to plasmin. This activity appears to be selective at sites of fibrin deposition,[13] but the clot selectivity of saruplase is partially lost during administration of clinically effective doses, with associated declines in fibrinogen plasma levels. Clearance of saruplase from plasma occurs primarily via the liver with an elimination half-life of 3 to 7 minutes. It is suggested that hepatic blood flow is the rate limiting step of saruplase clearance.[7,18]

Alteplase is a human tPA produced by recombinant DNA technology. It is a relatively fibrin-specific thrombolytic agent. Alteplase is eliminated primarily by rapid hepatic metabolism with an elimination half-life of 5 to 10 minutes.[4,7,13] The recommended dose to produce recanalisation following myocardial infarction is 100mg given as a 'front-loaded' infusion.[13,14] As for saruplase, hepatic blood flow is the rate limiting step of alteplase clearance.[7,19]

Reteplase is the most recent approved thrombolytic agent derived from human tissue plasminogen activator. Its mechanism of action is similar to that of alteplase, but it differs in pharmacokinetic and pharmacodynamic properties.[20] The main metabolic organs of reteplase are the kidneys, liver and blood. Certain structural changes contribute to dif-

ferences in pharmacokinetic properties such as a prolonged half-life (15 minutes), which allows it to be administered as two 10MU bolus injections. Despite evidence that use of reteplase results in an improved coronary artery patency rate versus accelerated infusion of alteplase, an improvement in mortality rate with reteplase was not shown.[21] Reteplase may have an advantage over alteplase because of a more rapid and simpler administration regimen, but the significance of this difference is yet to be determined.

Tenecteplase is a fibrin-specific recombinant tPA with increased resistance to inhibition by PAI and a slower systemic clearance that allows a single intravenous bolus administration.[14,17] Following intravenous bolus administration in patients with MI, there was a biphasic elimination of tenecteplase from plasma. The initial phase had a mean half-life that ranged from 11 to 20 minutes and was followed by a terminal phase with a mean half-life that ranged from 41 to 138 minutes. A decrease in tenecteplase plasma clearance with increasing tenecteplase dose was noted. In addition, women and patients with lower bodyweight or older age had a slower plasma clearance.[22]

3. Clinical Situation and Concomitant Treatment

Thrombolytic agents will be most often used in patients with coexisting cardiovascular and metabolic diseases. A 'standard' situation describes a patient with hypertension, dyslipidaemia and pre-existing coronary artery disease and/or MI in their history, who is admitted to the hospital with acute MI. The patient will already be treated with various antihypertensives (calcium antagonists, ACE inhibitors or angiotensin II receptor antagonists, or thiazide diuretics), as well as with β-blockers and aspirin (acetylsalicylic acid) and perhaps an HMG-CoA reductase inhibitor for secondary prevention. Acute treatment will include β-blockers and aspirin. Nitrates might also be given long term or in the acute situation. Heparin or (in case of a history of thrombocytopenia) hirudin will be given routinely as an infusion, or at least after clot lysis or in the presence of large anterior MI. Within 24 hours after admittance, ACE inhibitor therapy will be initiated.[1] Contrast media will be administered during coronary angiography. Patients who have experienced stroke will receive very similar medication upon admittance, and acute treatment will include aspirin.[3] The use of streptokinase or alteplase in acute myocardial infarction has been shown to reduce the rate of early mortality (up to 4 weeks) by 25% when compared with aspirin and heparin alone.[14] In patients who have had a stroke, alteplase yields a symptomatic benefit of 30% when given within 3 hours after stroke onset, while mortality is not affected.[23]

4. Pharmacokinetic Interactions with Thrombolytics

None of the thrombolytic agents is metabolised by the cytochrome P450 system, and common inhibitors or inducers of this metabolic pathway are not reported to affect the pharmacokinetics of any thrombolytic agents. However, since reduction of hepatic blood flow decreases the clearance of highly extracted drugs and might enhance their systemic availability, high-clearance drugs such as alteplase and saruplase might be susceptible to this type of interaction.[7] Although β-blockers, calcium antagonists, nitroglycerin (glyceryl trinitrite) and opioids, which will presumably be given together with alteplase during acute thrombotic events, might theoretically exhibit this type of interaction, clinical data have only been reported for alteplase/nitroglycerin[24] and indicate a diminished thrombolytic activity under nitroglycerin.

In this study,[24] 60 patients with acute MI were randomised to 2 groups. Group A (33 patients) received alteplase 100mg infusion over 3 hours; group B (27 patients) received the same alteplase dose plus nitroglycerin 100 μg/min for 8 hours. Electrocardiogram (ECG) evidence of reperfusion was 76% versus 56%, and reperfusion time was 19.6 minutes versus 37.8 minutes, for groups A and group B, respectively. ECG evidence of reocclusion was 24% in group A and 53% in group B. An earlier study by some of the same researchers produced similar results in patients with acute MI who received

nitroglycerin plus alteplase.[25] No statement was provided on the possible clinical consequences of this interaction.

An increase in hepatic blood flow induced by calcium antagonists (nifedipine, diltiazem) might theoretically enhance the extraction of alteplase or saruplase, therefore diminishing the thrombolytic efficacy. However, a controlled study in healthy participants showed that nifedipine, despite a 95% increase in hepatic blood flow, did not influence the plasma concentrations and activity of alteplase.[26]

5. Pharmacodynamic Interactions with Thrombolytics

5.1 Platelet Inhibitors

The independent additive effect of aspirin used as concomitant therapy with thrombolysis on mortality in patients with MI has been demonstrated by, for example, the Third International Study of Infarct Survival (ISIS-3) trial.[9,27] Such comedication does not cause additional bleeding events. Even under aspirin comedication, platelet function may be impaired during thrombolysis in patients with an acute MI. The effects of reteplase and alteplase on platelet aggregation and major surface antigen expression (CD62) during the first 24 hours of infarction therapy have been investigated. Although similar patterns of platelet aggregation and surface receptor expression occurred during the first 24 hours of coronary thrombolysis with reteplase and alteplase, indicators of platelet activity were higher at 24 hours after thrombolysis with reteplase than with alteplase.[28] These data suggest that additional (to aspirin) antiplatelet strategies may be particularly advantageous when used 12 to 24 hours after thrombolysis, especially after reteplase therapy.

Early studies with full dose fibrinolytics and glycoprotein IIb/IIIa inhibitors [abciximab or eptifibatide (integrilin)] have been promising,[29,30] but concern about bleeding has hindered this strategy.[31] Several recent trials have evaluated full dose abciximab with reduced dose fibrinolytic therapy (alteplase) and have yielded promising results without higher bleeding rates.[2] In an animal model, it has been shown that platelet ADP receptor blockers (ticlopidine or clopidogrel) enhance the thrombolytic effect of tPA, whereas aspirin did not.[32] No data are available on the possible interactions between ticlopidine or clopidogrel and thrombolytic agents in humans.

An antiplatelet effect has been discussed for several calcium antagonists, e.g. verapamil,[33] and reinforcing of bleeding has been demonstrated for alteplase when given together with diltiazem in an animal model.[11] There is so far no clinical evidence that the use of calcium antagonists is a risk factor for bleeding during thrombolysis.

5.2 Activation of Saruplase by Alteplase

Alteplase has been demonstrated to bind directly to fibrin[34] and activates different forms of available fibrin-bound plasminogen than saruplase.[35] The differing actions of alteplase and saruplase have led to their combined use in lower doses; a synergistic effect on enhancing thrombolysis has been observed with a combination of saruplase and alteplase in animal models[36] and in patients with acute MI.[37,38] However, this approach has not become a generally adopted policy in the treatment of MI.[1]

5.3 Heparin

Anticoagulation by heparin concomitant to thrombolysis improves the patency of the occluded coronary vessel. In a subgroup of patients in the European Cooperative Study Group, coronary artery patency rate was higher in patients allocated to heparin therapy than in those allocated to placebo (80 and 71%, respectively).[39] In contrast, bleeding complications, especially intracerebral haemorrhage, are seen more frequently with heparin (and also hirudin) comedication. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) I trial, intracerebral bleeding rates were 0.5% with streptokinase and 0.7% with alteplase, respectively.[14] In the GUSTO II trial,[40] intracerebral bleeding in the different treatment groups varied between 0.9% (alteplase + heparin) to 3.6%

(streptokinase + hirudin) and was correlated with the extent of prolongation of activated partial thromboplastin time (aPTT). It has been advocated to initiate heparin when the aPTT – which is elevated during thrombolysis – returns to twice the control values (approximately 70 sec).[14] Data on the combination of thrombolytic agents and low-molecular-weight heparins[41] did not indicate differences in bleeding risks, but a trend towards a better patency rate when compared with conventional heparin.

One study has indicated that streptokinase may cause partial resistance to anticoagulation by heparin. Zahger et al.[42] described a retrospective, non-randomised study in which 50 patients who received heparin and warfarin plus streptokinase (group 1) were compared with 35 patients who received heparin and warfarin only (group 2). Group 1 consisted of patients with MI, and group 2 consisted of patients with MI, deep vein thrombosis or pulmonary embolism. Group 1 was treated with streptokinase and heparin 5000U followed by 24 000 to 30 000 U/day; oral warfarin was begun on day 7 and regulated to maintain prothrombin time at twice the control value. A 24% higher heparin dosage and a longer time to therapeutic aPTT (5 *vs* 3 days) was required in group 1 compared with group 2. However, the aPTT value was 15% lower in group 1 than in group 2, and the time required to reach the target prothrombin time was longer (5 *vs* 4 days) in group 1 than in group 2. The authors conclude that streptokinase might cause a partial resistance to anticoagulation; higher heparin dosages and more frequent dosage adjustments may be required. The clinical consequences of these finding have not been elucidated.

5.4 Oral Anticoagulants

Although there are no controlled studies on the interactions between oral anticoagulants and thrombolytic agents, data from a Dutch registry on patients with MI who underwent thrombolysis (mainly with streptokinase) indicated that pretreatment with oral anticoagulants is an independent risk factor for cerebral haemorrhage.[43] Altogether, 2469 patients with acute MI treated with a thrombolytic agent were prospectively registered. Intracranial haemorrhage was observed in 24 patients. The results of multivariate logistic regression analysis indicate that patients taking an oral anticoagulant before admission, patients with a bodyweight less than 70kg and those more than 65 years old are at higher risk for intracranial haemorrhage during thrombolytic therapy.

There is little clinical information concerning concurrent use of streptokinase and warfarin in the treatment of deep vein thrombosis; in 1 study, 8 of 44 patients (18%) experienced haemorrhage that required discontinuation of streptokinase.[44] Both the anticoagulant and streptokinase were begun at the same time. Since 3 to 5 days is required before hypoprothrombinaemia is obtained, these patients might not have experienced the true interaction of the thrombolytic effect of streptokinase and the hypoprothrombinaemia attributable to warfarin.

5.5 Contrast Media

Contrast media inhibit fibrinolysis in vitro and interact with endothelial cells, platelets and the coagulation system.[45] Case reports and 1 clinical study in patients with unstable angina undergoing PTCA[46] have reported an increased risk of thrombosis with the use of nonionic contrast media. The *in vivo* effects of contrast media on thrombolysis have so far only been investigated *ex vivo-in vitro*[47,48] or in animal experiments. A study in dogs[8] showed that after induction of occlusive coronary artery thrombosis and treatment with alteplase, aspirin and heparin, application of a low-osmolar nonionic contrast medium (iohexol) as well as a high-osmolar ionic contrast medium (amidotrizoate) was associated with longer reperfusion delays and shorter periods of coronary perfusion. No such effect was seen with a low-osmolar ionic contrast medium (ioxaglate). The authors concluded that this interaction should be considered in the design of clinical trials of thrombolytic therapy, but no clinical recommendations were given.

6. Conclusions

Any influence of drug-drug interactions affecting the pharmacokinetics of thrombolytic agents (e.g. organic nitrates) has no proven clinical relevance. Regarding pharmacodynamic interactions, the possible synergistic or additive interactions of thrombolytics with anticoagulant and/or antiplatelet drugs have been considered in current guidelines for the treatment of acute MI,[1] but no clear guidelines exist for the avoidance of bleeding complications caused by unwanted deterioration of the coagulation system during treatment with this combination of agents. In general, patients receiving thrombolytic treatment should be monitored frequently for signs of bleeding, and the physician should be aware of any comedication exerting antiplatelet or anticoagulant effects. However, there is no validated 'point of care' monitoring parameter to assess whether thrombolytic efficacy is maintained in the therapeutic range or exceeds it.

During comedication with unfractionated heparin, it has been advised to monitor aPTT frequently and to avoid values of aPTT >2.5-fold normal.[14] Currently, no recommendations can be given for possible dose adjustments or monitoring of thrombolytic therapy in patients receiving ticlopidine or clopidogrel comedication. Treatment with oral anticoagulants is regarded as a relative, but not absolute, contraindication to thrombolysis.

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