Differentiating Pharmacologic Agents Used In Catheter-Directed Thrombolysis

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ABSTRACT

The use of catheter-directed thrombolysis is a proven treatment for arterial ischemia, deep vein thrombosis, and severe pulmonary embolism. For arterial ischemia, thrombolysis has resulted in improved amputation-free survival and fewer subsequent surgeries to reestablish blood flow to the ischemic limb. The management of patients with thromboembolic diseases is complex, and the multiple thrombolytic drugs available to choose from compound this complexity. Although some believe the available thrombolytic agents are interchangeable, real biochemical differences exist that may prove otherwise. This article describes these pharmacologic differences and how they may affect the clinical practice of catheter-directed thrombolysis.

KEYWORDS: Thrombolysis, catheter-directed thrombolysis, pharmacology, bleeding complications

Objectives: Upon completion of this article, the reader will understand pharmacologic differences of agents used in catheter-directed thrombolysis and how they may affect clinical practice.

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Percutaneous catheter-directed thrombolysis has become the standard of care as the initial treatment for many forms of thromboembolic disease including arterial, venous, and pulmonary vascular thromboembolic events. Landmark studies such as the Rochester,¹ Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE),² and Thrombolysis or Peripheral Arterial Surgery (TOPAS)^{3,4} studies have established catheter-directed thrombolysis as the preferred initial treatment for most cases of acute peripheral arterial occlusive disease. Collectively, these studies show that when compared with surgical methods, catheter-directed thrombolysis results in improved 30-day ampu-

tation-free survival rates and reduces the number of subsequent surgical procedures.¹⁻⁴

Historically, urokinase (UK) was the preferred agent for catheter-directed thrombolysis until 1998, when the Food and Drug Administration raised questions about tissue-derived production methods for UK. This concern led to the voluntary withdrawal of Abbotkinase (Abbott Laboratories, Abbott Park, Illinois) by Abbott Laboratories in early 1999, forcing many physicians to use alternative thrombolytic agents in the treatment of thromboembolic disease.

With time, most practitioners have become familiar with newer thrombolytic agents, incorporating

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them into their day-to-day practice. To some, the different agents seem interchangeable; however, to others there are clinical differences in treatment outcomes and safety that require alterations in the techniques formerly used with UK. Accordingly, the following describes the different thrombolytic agents currently available, the pharmacologic differences between them, and how these differences may be manifest clinically.

THE THROMBOLYTIC AGENTS

As previously stated, UK became the overwhelming agent of choice for catheter-directed thrombolysis in the United States. Since then, we have seen the withdrawal and the reintroduction of this drug in the thrombolytic market. As a consequence, many physicians have been faced with the task of choosing which agent or agents are best suited for the management of thromboembolic disease. Although some of the thrombolytic drugs currently available were available prior to the departure of UK, others have been introduced more recently. The choice of thrombolytic drugs has never been greater, and the understanding of the pharmacology of these agents, specifically in the interventional community, has increased as well. Still, for many the implications of these differences are unclear, and therefore it seems prudent to begin with a description of the pharmacologic properties of each of the available agents.

Agents are classified as either non-fibrin specific or fibrin specific. Non-fibrin-specific agents are those that are indiscriminate in their ability to cause both fibrinolysis and fibrinogenolysis. Fibrin-specific agents are those that cause fibrinolysis while having no significant lytic action experimentally when exposed to fibrinogen in the presence of plasminogen.

Streptokinase

An exogenous plasminogen activator isolated from β -hemolytic streptococci was first described in 1933⁵ and named streptokinase (SK) in 1945.⁶ It is a non-fibrin-specific agent which is, in fact, an indirect plasminogen activator that must complex with plasminogen first to become active. This complex then converts both complexed and free plasminogen to plasmin.⁷ Of interest is that SK is the only thrombolytic agent approved for the treatment of peripheral arterial thromboembolic disease, although this approval is for intravenous (IV) administration only.

As an exogenous agent, SK is antigenic, leading to the production of antistreptokinase antibodies. Consequently, SK has been associated with febrile reactions and unpredictable efficacy because of antigen-antibody formation. Furthermore, SK, when compared with other agents, can lead to significant bleeding

complications. As a result, SK is rarely used in current practice.⁸⁻¹⁰

Urokinase

First identified and isolated from human urine in 1951,¹¹ UK was named in 1952 by Sobel et al.¹² Original preparations were urine derived, with ~1500 L of urine needed to produce enough drug to treat a single patient. In the early 1970s tissue culture techniques were developed as a practical method of UK production.^{13,14} Interestingly, UK that is marketed outside the United States is still produced from human urine.

UK is a non-fibrin-specific agent that directly activates plasminogen to plasmin. Tissue culture methods of producing UK result in the formation of both high-molecular-weight and low-molecular-weight forms of the drug. Both forms activate plasminogen similarly, but it is the latter form that is found predominantly in commercially available preparations. UK is primarily cleared from the circulation by the liver with a half-life of ~13 minutes when administered intravenously. Currently, the only approved indication for UK is for the treatment of symptomatic pulmonary embolism by an IV route of administration.

Nonetheless, the use of UK for catheter-directed thrombolysis for both venous and arterial thromboembolic disease is well supported in the literature.^{1,2,15} Reported dosing is widespread; however, typical dosing protocols range from 100,000 to 240,000 IU/hr. Although no prospective dose-ranging studies have been performed to investigate thoroughly the lower threshold of efficacy for the catheter-directed administration of UK, doses as low as 50,000 IU/hr have been reported as efficacious.¹⁶ Currently, we routinely use doses in the 60,000–80,000 IU/hr range to treat arterial disease and higher doses, 80,000–120,000 IU/hr, to treat venous disease. Our recent use of lower infusions rates is an effort to address cost concerns while maintaining efficacy and safety.

There are other forms of UK-related drugs that have been clinically evaluated but are currently not commercially available. These include recombinant prourokinase (r-pro-UK) and recombinant UK (r-UK). Prourokinase is a precursor to UK; however, r-pro-UK is a potent plasminogen activator itself in the presence of insoluble fibrin without first being converted to UK. Because of this, r-pro-UK is considered more fibrin specific than UK with a theoretical safety advantage over UK in regard to bleeding¹⁷ complications. Unfortunately, the prourokinase versus urokinase for recanalization of peripheral occlusions, safety and efficacy (PURPOSE) study, a dose-ranging trial evaluating r-pro-UK, did not substantiate this theory.¹⁸ Recombinant UK (r-PA) is structurally very similar to the high-molecular-weight version of UK, is produced using

recombinant technology, and is the agent used in the TOPAS trials.

Tissue Plasminogen Activator

Human tissue plasminogen activator (t-PA) is secreted by a variety of cells in the body including vascular endothelial cells, presumably to keep the thrombotic system in check. The commercially available form of t-PA is produced using recombinant technology and is called alteplase or recombinant t-PA (rt-PA). It is only slightly different in structure from the naturally occurring form of the molecule. There are five domains in the t-PA molecule that are of pharmacological significance. These are worth mention as changes to or the elimination of these domains is responsible for the different plasminogen activators that are discussed subsequently.

The finger domain is located at the amino terminal. This domain contains one of the two binding sites for plasminogen and is responsible for the drug's strong affinity for cross-linked fibrin. The epidermal growth factor and kringle-1 domains are two regions containing binding sites responsible for plasma clearance of the drug by the liver. The kringle-2 domain contains the other binding site for plasminogen and is responsible for the drug's specificity in activating plasminogen in the presence of fibrin. Finally, the protease domain is the catalytic portion of the molecule where the actual activation of plasminogen occurs.

Recombinant t-PA has a long history in the treatment of acute myocardial infarction (AMI) and has more recently become the most commonly used lytic agent in the periphery since the withdrawal and reintroduction of UK. The drug currently has several approved indications including the IV administration of the drug for AMI, pulmonary embolism, and stroke. It also has an approval for central venous catheter clearance. The use of rt-PA for catheter-directed lysis of arterial and venous thrombus represents an off-label use, as is the case with all lytic agents. We use doses of less than 1.0 mg/hr, with the most common doses being 0.25–0.5 mg/hr. In addition, we limit the use of IV heparin to a subtherapeutic dose of 300–500 IU/hr. We do not use doses above 1.5 mg/hr because they have been linked to significant bleeding complications.¹⁹

Reteplase

Recombinant plasminogen activator (r-PA) is a deletion mutation form of the t-PA molecule in that the finger, epidermal growth factor, and kringle-1 domains are missing from the molecule. Because these domains are responsible for fibrin affinity (finger domain) and clearance of the drug by the liver (epidermal growth factor, and kringle-2), r-PA has less fibrin affinity and a longer

half-life than rt-PA. The drug maintains the kringle-2 domain; thus, it is considered to be fibrin specific.

The decreased fibrin affinity of r-PA has been cited as the reason that r-PA has improved clot penetration compared with rt-PA. It is thought that the strong fibrin affinity or binding properties of rt-PA do not allow this agent to penetrate into the deeper layers of the thrombus, whereas r-PA, with its relatively weak fibrin affinity, can penetrate deeper, increasing the amount of thrombus exposed to the lytic agent.²⁰ As a result, it has been suggested that lysis occurs faster with r-PA than with rt-PA. This theory has been supported by studies that evaluate angiographic endpoints in both animals and humans^{21,22}; however, this has not translated into improved clinical endpoints when treating AMI.²³ The impact of this difference has not been evaluated in the catheter-directed use of this agent for peripheral thromboembolic diseases.

Currently, r-PA has a single indication for the IV treatment of AMI, and any use of the drug for catheter-directed peripheral lysis is off label. As stated previously, r-PA has a longer half-life than rt-PA at 15–20 minutes. Our own study shows that doses ranging from 0.125 to 0.5 IU/hr are effective and safe in the catheter-directed treatment of acute peripheral arterial thromboembolic disease. The most common doses that we employ for arterial thrombus are 0.25–0.5 IU/hr with slightly higher doses of up to 1.0 IU/hr used for venous disease. As with rt-PA, we use subtherapeutic doses of IV heparin at 300–500 IU/hr during r-PA infusions.

Tenecteplase

Tenecteplase (TNK-t-PA) is a bioengineered triple point mutation of t-PA with a reported longer half-life and improved fibrin specificity compared with rt-PA. The longer half-life occurs because of a shift in a glycosylation site from amino acid 117 (N117, abbreviated N) to amino acid 103 (T103, abbreviated T) within the kringle-1 domain, decreasing the efficiency of hepatic clearance. Also, there is a point mutation at the K site in the protease domain that causes resistance to plasminogen activator inhibitor 1. Furthermore, these changes increase the fibrin specificity of the drug by 15-fold compared with that of rt-PA, making this drug less efficient at causing fibrinogenolysis, as discussed in more detail later.²⁴

TNK-t-PA is indicated only for the IV treatment of AMI and its use as a catheter-directed thrombolytic agent in the periphery is considered off label. The plasma half-life of the drug is 20–24 minutes. Dosing regimens for catheter-directed thrombolysis have been reported to be similar to those used with rt-PA.^{25,26} Currently, reports on the use of this agent in the peripheral system are few, and these studies are not well controlled.

EFFICACY

Although well-established criteria are not published regarding measures of efficacy when performing catheter-directed arterial or venous thrombolysis, a few endpoints seem to be relatively consistent in more recent publications. For arterial disease, perhaps the most common measure of thrombolytic success is the 30-day amputation-free survival rate. Although this is not a direct measure of thrombus dissolutions, it is a clinical endpoint that has no ambiguity. The patient is either alive with limb intact or not. Another arterial endpoint often cited is thrombolytic success. This is usually defined as greater than 95% lysis with some degree of antegrade flow.^{3,4,18,19,27}

As for venous disease, some endpoints such as thrombolytic success are pertinent; however, because one of the main goals of venous thrombolysis is to prevent the long-term sequelae of chronic venous obstruction, acute endpoints such as 30-day limb salvage or amputation-free survival have less clinical relevance. In fact, clinical endpoints measuring the benefit of lytic therapy in the prevention of chronic venous insufficiency are difficult to reach because of the prolonged length of time it takes to manifest these clinical findings.

In general, all of the currently available lytic agents (UK, rt-PA, r-PA, and TNK-t-PA) are effective. In fact, there are no reports on the use of any of these agents at any dose that has been shown to be ineffective. Moreover, it can be said that when infusion rates decrease, total dose used decreases, and the length of infusion increases. When performing catheter-directed arterial thrombolysis, amputation-free survival rates from 75 to 95% have been reported, and thrombolytic success rates are usually slightly lower, ranging from 67 to 87% regardless of the agent used.^{3,4,19,26,27} Thrombolytic success when treating venous disease is typically lower; however, with careful selection of patients (i.e., those with iliac vein involvement) success is improved upon, especially when lysis is combined with angioplasty and stenting.¹⁵ This strategy allows reasonable short-term patency rates that have been speculated to contribute to improved long-term clinical success.

HEMORRHAGIC COMPLICATIONS

The most significant complication encountered when performing catheter-directed thrombolysis is bleeding, the most feared form being intracranial hemorrhage. Bleeding complications associated with lytic therapy can lead to extended hospital stays, surgery, transfusions, stroke, and death. No agent is immune, and even though some agents are known to be more fibrin or clot specific, this has not translated into improved safety. In the late 1980s when rt-PA was emerging as a potent drug in the treatment of AMI, there was much speculation that this more fibrin-specific drug (when compared with SK and

UK) may have the benefit of being a potent fibrinolytic agent while causing less fibrinogenolysis in the systemic circulation. It was hoped that this would lead to less distant bleeding.

Early large-scale AMI studies proved that this was not the case, and although fibrinogenolysis is seen to a lesser extent with rt-PA than with SK,²⁸ the bleeding rates associated with the use of rt-PA for this indication were at best comparable to those with SK.²⁹ In fact, some early cardiac studies showed an increased incidence of intracranial hemorrhage with rt-PA compared with SK.^{30,31} For many, the explanation was easy—rt-PA, like any other lytic agent, was simply causing fibrinolysis at a remote hemostatic thrombus—and to some extent this is true. Thrombolysis is probably occurring at a remote site because of the activation of plasminogen by the lytic agent. However, to suggest that free drug in the circulation is the sole reason that remote bleeding occurs is probably an oversimplification of the chain of events leading to hemorrhagic complications.

In general, catheter-directed thrombolysis is associated with higher rates of bleeding. Major bleeding rates associated with the treatment of AMI are routinely less than 5%,^{32–34} whereas bleeding rates associated with longer catheter-directed techniques are most often greater than 5%.^{3,4,19,35} This in spite of the fact that during catheter-directed lysis, the total lytic dose is often much less than the total dose given for the treatment of AMI. Furthermore, during catheter-directed infusions, with the relatively small amounts of drug given, plasminogen inhibitors such as α_2 -antiplasmin should quickly neutralize any free lytic drug that enters the circulation.

As a further explanation for remote site bleeding, one must look beyond fibrinolysis to the events that surround fibrinogenolysis. All lytic agents used in current practice, whether fibrin or non-fibrin specific, cause some degree of fibrinogen depletion. Although no absolute fibrinogen level predicts bleeding, landmark studies show that bleeding complications occur in patients with more significant drops in fibrinogen.^{2,36,37} As a result, fibrinogenolysis is probably an important component in the turn of events leading to hemorrhagic complications.

First, a distinction must be made between fibrinolysis and fibrinogenolysis. The former represents the breakdown of cross-linked fibrin, whereas the latter represents the breakdown of freely circulating fibrinogen. Many who have reported on thrombolytic therapy and the associated bleeding complications often use these terms interchangeably. The terms are not interchangeable, and this distinction is not trivial. A significant difference is that the breakdown products from these two processes are distinct, and the roles they play in determining distant bleeding are likewise distinct.

Perhaps the most exhaustively studied interaction of a lytic agent with cross-linked fibrin, fibrinogen, and

their related breakdown products with regard to hemorrhagic complications is rt-PA. This is in part due to the success of the drug in treating AMI and the fact that the improved fibrin specificity of the drug has not led to improved rates of bleeding complications. As discussed earlier, fibrinogenolysis probably plays a role, and this leads to the question, how does a drug with a limited capacity to activate plasminogen in the presence of fibrinogen cause fibrinogenolysis?

First, rt-PA, like all other lytic agents, causes fibrinolysis, the breakdown of insoluble cross-linked fibrin into various soluble fibrin degradation products (FDPs). The predominant fragment produced is the (DD)E fragment,³⁸ which is then free to enter the circulation. Furthermore, reports show that the (DD)E fragment is as potent as fibrin in stimulating the rt-PA-mediated activation of plasminogen.³⁹ The soluble nature of the (DD)E fragment provides a freely circulating substrate allowing rt-PA and plasminogen to come into vital molecular proximity, allowing systemic plasminogen activation. The rt-PA/(DD)E/plasmin complex is now able to break down freely circulating fibrinogen, resulting in fibrinogenolysis.

A valid question remains: what is the link between fibrinogenolysis and bleeding complications? During fibrinogenolysis, various degradation products are produced. The initial fragment produced, regardless of agent, is fragment X. Unfortunately, for many the very name fragment X suggests that this fragment is an enigma. This could not be further from the truth; descriptions of fragment X occur in the literature as early as the late 1960s. This fragment is actually a family of fragments with a molecular mass of $\sim 260,000$ daltons⁴⁰ and is produced when plasmin cleaves the small B β 1–42 amino peptide fragment from the parent fibrinogen molecule.⁴¹ Interestingly, fragment X also contains two D domains and one E domain; however, it is distinct from the (DD)E fragment resulting from fibrinolysis mentioned earlier. Fragment X is simply a subfragment of a single parent fibrinogen molecule, whereas the (DD)E fragment is a product of cross-linked fibrin with the D and E fragments arising from neighboring fibrin molecules in the parent thrombus. Fragment X can be further degraded into fragments Y, D, and E.⁴⁰

The importance of fragment X is somewhat controversial; however, there is substantial experimental and clinical evidence to suggest that fragment X plays a significant role in the occurrence of bleeding associated with catheter-directed thrombolysis. In vitro studies show that fragment X, unlike the smaller Y, D, and E fragments, retains the ability to form clot.⁴² Furthermore, fragment X has been shown to decrease the tensile strength of thrombus in a concentration-dependent fashion in that increasing amounts of fragment X within a clot accelerate clot lysis.^{43,44} Given that thrombus is a dynamic entity, it is reasonable to believe that fragment

X, produced during lysis, may be incorporated into any existing thrombus, including a distant hemostatic plug. It could be said that regardless of agent, fragment X plays a role in the occurrence of distant bleeding by lowering the integrity of distant hemostatic thrombi.

That said, it is relevant to look at the differences in how some of the lytic agents behave during fibrinogenolysis. For instance, SK and UK are indiscriminate lytic agents. Initially during fibrinogenolysis, these agents produce fragment X, and with time (i.e., several hours) fragment X is broken down into fragment Y and then fragments D and E.^{40,45} On the other hand, rt-PA behaves differently. In vitro human and in vivo animal and human studies show that rt-PA, a more fibrin-specific drug, causes an accumulation of fragment X with less subsequent breakdown of fragment X into the smaller Y, D, and E fragments.^{38,44,45} Central to this finding is the study by Owen et al.⁴⁵ This sophisticated study compared two groups of patients treated for AMI with IV thrombolytics, one group being treated with SK and the other with rt-PA. The study showed that fibrinogenolysis occurs earlier with SK than with rt-PA owing to the fact that SK causes fibrinogenolysis immediately upon the administration of the drug whereas rt-PA requires the production of FDPs such as (DD)E to commence fibrinogenolysis.⁴⁵

In addition, SK causes more significant levels of fibrinogen depletion and therefore more fragment X production than seen with rt-PA. One important comment on this study is that most of the time-activity assays that are used to compare fragment X production between the two agents are just that, assays that measure production and not accumulation. This measure of production is achieved by using immunoblot techniques to measure the small B β 1–42 fragment, which, as mentioned earlier, is initially cleaved from fibrinogen to form fragment X.⁴⁵ Measuring the B β 1–42 fragment is, therefore, a one-to-one indirect measurement of the formation of fragment X but obviously not a direct measurement of fragment X itself. The difference is that when production or formation of a molecule is measured it tells nothing of what happens to that molecule subsequent to its formation, such as whether the fragment is degraded into smaller fragments.

For this, the study includes an immunoblot evaluation of the serum and plasma of treated patients with antibodies targeted to the D domain of fibrinogen and its degradation products (collectively termed fibrinogen-related antigens). Here the investigators show that although twice as much fragment X is formed by SK compared with rt-PA, similar amounts of fragment X accumulation are seen with both agents. The reason for this is that SK, unlike rt-PA, goes on to degrade fragment X further into the smaller Y, D, and E fragments, whereas rt-PA does not. The authors conclude that comparable levels of fragment X explain why

similar bleeding rates were seen in the two groups despite the decreased levels of fibrinogenolysis seen with rt-PA.⁴⁵

For the peripheral angiographer, obvious limitations of the preceding study are that these findings were seen in patients who were treated for AMI using high-dose short-bolus IV infusions. Perhaps one of the most surprising findings is that these events happen to the extent that they do during the treatment of AMI when only very small amounts of thrombus are the target for lysis. Considering this, one could speculate that during peripheral thrombolysis, the impact of these differences may be accentuated, resulting in higher rates of hemorrhage. This is due to the fact that during peripheral catheter-directed infusions, thrombus burden is higher and lytic infusions are longer. This would prolong the production of FDPs and increase the time during which rt-PA can cause systemic plasminogen activation and therefore fibrinogenolysis.

More important, fragment X production would also persist for more extended periods of time. For the non-fibrin-specific drugs (SK and UK), fragment X would continue to degrade throughout the infusion, whereas fragment X would continue to accumulate during infusions with rt-PA. This is perhaps the most significant biochemical difference between lytic agents. It is especially significant given that the study by Owen et al also shows that fragment X continues to be present in the plasma of treated patients 24 hours following the lytic infusion,⁴⁵ which may further compound the potential for fragment X accumulation. Whether the same phenomenon happens with the other fibrin-specific drugs (r-PA and TNK-t-PA) has yet to be studied; however, given that both of these drugs carry the binding site for the (DD)E fragment and fibrinogen, the potential exists for the same turn of events. On the other hand, TNK-t-PA has been shown to be more fibrin specific than rt-PA in that TNK-t-PA is 15 times less likely to activate plasminogen in the presence of the (DD)E fragment.²⁴ Theoretically, this could translate into a safety benefit, but only if the increased specificity is sufficient to temper fibrinogenolysis and therefore fragment X accumulation during the typically long infusion times encountered in the periphery.

Considering the foregoing, it is perhaps best to think of fibrinogenolysis qualitatively rather than quantitatively. Measuring fibrinogen tells of only the initial event in a cascade of events occurring at the molecular level that contributes to bleeding. It is not just the amount of fibrinogen that is degraded but also the extent to which it is degraded that is important. This may explain the dubious nature of using absolute fibrinogen levels to predict bleeding complications. Unfortunately, measuring specific fibrinogen degradation products is not a realistic approach in the typical hospital setting, and therefore we are left with following a laboratory

value (fibrinogen) that at times seems meaningless. At the same time, this information can be used to realize that fibrinogen depletion may have variable significance depending on which lytic agent is being utilized.

CLINICAL SIGNIFICANCE

Clearly, the difference in how the various lytic agents deplete fibrinogen goes to the core of what differentiates the lytic agents at the molecular level, but the question remains, what is its impact on the clinical management of a patient with limb ischemia or acute deep venous thrombosis (DVT)? Both UK and the more fibrin-specific agents can be used safely, as shown by clinical data that are currently available.^{1,2,25-27,46,47} Nonetheless, this does not negate the possibility that there may be a safety advantage with the use of UK versus the other more fibrin-specific agents. Unfortunately, there are very few studies that compare UK with other agents, and those that do exist compare UK almost exclusively with rt-PA.^{2,35,46-49} Furthermore, most of these studies are retrospective and nonrandomized with the exception of the STILE trial.² These studies also suffer from dosing protocols that often compare a relatively low dose of one agent with a relatively high dose of another. In addition, the use of heparin is nonuniform.

Despite this, our experience suggests that certain precautions are to be taken when using the newer more fibrin-specific drugs. Our studies on the early use of rt-PA following the withdrawal of UK from the market show that using rt-PA in doses greater than 1.5 mg/hr with full heparinization leads to unacceptable rates of major bleeding.¹⁹ Our subsequent report on the use of r-PA in a prospective nonrandomized dose-ranging study shows that using lower doses and subtherapeutic heparinization significantly reduces bleeding. It is our opinion that there are clinical manifestations that result from the differences between UK and the more fibrin-specific agents such as rt-PA and r-PA. First, the newer drugs appear to have a relatively narrower window of dosing safety,^{19,27} and second, subtherapeutic doses of heparin (or less) should be used during infusions with these newer drugs. In other words, care should be taken with rt-PA and r-PA to keep dosing protocols low and limit concomitant anticoagulation. Interestingly, this approach to the newer lytic agents is in accordance with recommendations made by the Society of Interventional Radiology Advisory Panel on Catheter-Directed Thrombolytic Therapy when using rt-PA as an alternative to UK.⁵⁰ Currently our experience with TNK-t-PA is limited, and this third-generation lytic agent may, as stated previously, offer some safety advantages as a result of its increased fibrin specificity compared with rt-PA.

In our practice we employ both UK and rt-PA, with the slight majority of patients being treated with

rt-PA. The point is not to advocate one drug over another but rather to indicate that we follow a treatment strategy that includes the use of both UK and another newer generation lytic agent. Patients who have an increased risk of bleeding, such as those with relatively recent gastrointestinal bleeding, previous stroke, relatively recent surgery, and advanced age, and patients for whom full anticoagulation is desired tend to be treated with UK. All other patients are treated with rt-PA (or potentially r-PA) and subtherapeutic heparinization with heparin doses of 300–500 units/hr. This approach is the result of multiple factors including our previous anecdotal experience using UK with full anticoagulation, retrospective experiences using rt-PA with both full and subtherapeutic anticoagulation, prospective dose-ranging experience using r-PA with subtherapeutic anticoagulation, and an understanding of the potential for safety differences based on the pharmacological differences that have been described here. We feel that this approach allows us to best tailor catheter-directed thrombolysis to each patient's specific needs.

In addition, our decision to use multiple lytic agents is driven by cost concerns. Nonrandomized studies comparing the retrospective use of rt-PA and UK in similar groups of patients treated for arterial ischemia and DVT show that the only significant difference between treatment groups is an increased drug expense when using UK.^{46,47} Obvious limitations of these studies are that they are retrospective and nonrandomized. In addition, these types of studies lend themselves to a decision-making process in which one drug is chosen over another and do not explore the possibility that patients may be best served by using a multidrug approach as has been described previously.

CONCLUSION

Catheter-directed thrombolysis represents one of the most challenging clinical scenarios that a physician may face. These cases most often last multiple days, are labor intensive, and consume a great deal of hospital resources. Furthermore, patients requiring this type of treatment are often complex, with medical comorbidities that can lead to significant complications and even death. Considering this, the approach that strives to utilize a single thrombolytic agent may be one that is oversimplified and does not take into consideration the well-described pharmacological differences that exist between the different agents. The approach to thrombolysis as described here is the result of careful consideration of the risk of bleeding, potential need for full anticoagulation, and drug expense. With this in mind, we feel that we can enhance the well-documented beneficial results of catheter-directed thrombolysis when treating patients suffering from various forms of thromboembolic disease.

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