Thrombolytic Solutions for Peripheral Vascular Disease: Summary and Conclusions

Kenneth Ouriel, MD

Department of Vascular Surgery, Cleveland Clinic Foundation, Cleveland, OH

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Peripheral vascular occlusions remain the source of significant patient morbidity, whether they occur on the arterial or venous side of the circulation or in catheters and dialysis access grafts. Arterial occlusions are associated with significant risks to life and limb. With the notable exception of pulmonary embolism, the complications from venous occlusions are seldom associated with limb loss or death; they are associated with significant long-term morbidity in the form of the post-thrombotic syndrome. Although reestablishing flow in a thrombosed dialysis access grafts may not be as dramatic as an arterial or venous procedure, the sheer volume of failed access grafts underscores the clinical importance of the problem.

Irrespective of the anatomic location of a vascular occlusion, treatment options span a spectrum, from observation alone to pharmacological intervention to open surgical revascularization. The limitations of surgery and anticoagulation and the benefits of thrombolysis with an agent such as urokinase require that we better understand the role of these approaches. Treatment of acute arterial occlusion with surgery is associated with high mortality rates to achieve limb salvage,[1] whereas heparinization alone does little to restore arterial perfusion to the extremity. Similarly, anticoagulation for deep venous thrombosis is associated with an unacceptably high incidence of post-thrombotic complications.[2] Against this background, peripheral arterial and venous thrombolysis emerged as a promising alternative, with the ability to achieve recanalization of the obstructed vascular segments with the hope of minimizing the risks of major surgery that are so common in this fragile patient population.[3]

Until the last part of the 1990s, peripheral thrombolysis was synonymous with catheter-directed urokinase administration. Clinicians were comfortable with the safety and efficacy profile of the agent, with its predictable dose–response relationships and relatively low frequency of complications. In early 1999, Abbokinase™ (Abbott Laboratories, Abbott Park, IL), the brand of urokinase used in the United States, was no longer available when Abbott Laboratories withdrew Abbokinase to focus on concerns regarding current Good Manufacturing Practice (cGMP).[4] The U.S. Food and Drug Administration (FDA) was concerned about the potential risk of viral contamination. This theoretical risk, although possible, was thought very unlikely by the informed medical community. Clinicians were forced to either abandon thrombolytic treatment strategies altogether and resort to more invasive modalities or to use alternative agents, such as recombinant tissue plasminogen activator (rt-PA) or reteplase. These needs spawned the organization of small pilot dose-ranging trials in attempts to arrive at thrombolytic regimens that would achieve the safety and efficacy of catheter-directed urokinase therapy. This goal was never completely achieved, and clinicians never gained the comfort level to which they had been accustomed when urokinase was first available.

This supplement to *Reviews in Cardiovascular Medicine* has sought to provide a basic understanding of the principles that underlie the use of thrombolytic agents, both from the standpoint of the pharmacology and underlying scientific characteristics of the agents as well as from the perspective of clinical strategies for optimal use. Each author was chosen on the basis of his long commitment to investigation, and with the goal of encompassing both the basic science and clinical aspects of the care of patients with vascular disease. Most have been integral to the design and conduct of thrombolytic investigations. They have each devoted their career to acquiring sound data—data that has provided the foundation for the contemporary care of the patient with vascular disease.

Clinicians have assumed that the various thrombolytic agents differ in their respective risks of bleeding complications. Also, differing rates of efficacy of thrombolytic dissolution have been assumed to exist when one agent is compared with another. A scientific basis for these anecdotal observations is provided in the reviews within this supplement. The pioneering work of Weitz, originally directed at explaining the observed differences between the decreased rates of distant bleeding complications with streptokinase as compared with rt-PA,[5] can be applied to the observed benefit of urokinase over either rt-PA or reteplase. Differences in the generation of fragment X may underlie the worrisome observation of delayed intracranial bleeding in patients treated with either rt-PA or its analogues. The fact that a diminished rate of hemorrhage is observed with urokinase over the other agents is reiterated in the clinical reviews contrasting the assorted thrombolytic agents.[6] In the absence of blinded, randomized comparison studies, disparate dosing regimens cannot be completely excluded as a primary cause of the observed differences. Nevertheless, pharmacological distinctions between the agents, as well outlined by Weitz[7] and by Bell,[8] provide a rational explanation for the observed reduced rate of hemorrhage associated with the use of urokinase. The review of thrombolytic pharmacologic principles by Deitcher and Jaff[9] further delineates the differences between available thrombolytic agents and those presently under investigation. In their very complete analysis, the authors review the theory underlying the development of novel thrombolytic agents. The long hoped-for link between fibrin specificity and safety never materialized in clinical practice. In fact, newer plasminogen activators empirically offer no safety advantages over older, better-established agents.

Utilizing the diagnostic principles outlined by Katzen[10] in his review of the basics of recognizing, categorizing, and treating patients with peripheral arterial occlusion, the rapid and appropriate management of patients should be attainable by primary care physicians and special-

ists alike. Physicians must be alert to the signs and symptoms of acute arterial occlusion, and categorization into subgroups initially outlined by Rutherford and colleagues provides a rational basis for the timing of intervention.[11] Yet, although no adequately powered clinical studies exist that compare the available thrombolytic agents, there exist several prospective comparisons of thrombolysis versus traditional open surgery for peripheral arterial occlusions. The data from such trials, outlined in the review by Ouriel,[12] suggest that significant benefit is accrued from thrombolysis. The Rochester trial was the only study to compare thrombolysis and open surgery as primary interventions in a very ill group of patients.[13] In this trial, significant reductions in mortality were observed when comparing thrombolysis with urokinase to open surgery. This difference was attributable to an increased rate of cardiopulmonary complications when patients were taken directly to the operating room for surgical revascularization. There were no significant mortality differences documented in two other large, randomized clinical trials,[14,15] but a reduction in amputation rate and in the need for open surgical revascularization over long-term follow-up was observed. On the arterial side of the circulation just as on the venous side, the wealth of published clinical data on the safety and efficacy of thrombolysis regards the use of urokinase.

On the venous side of the circulation, thrombolysis offers the potential to recanalize the obstructed venous segments as well as the opportunity to preserve valve function, the two physiologic derangements that underlie symptomatic chronic post-thrombotic symptoms. Meissner[16] has provided a well-rounded review of upper extremity venous problems and the interface between initial thrombolytic recanalization and subsequent operative decompression of the thoracic outlet. He also reviews the use of thrombolytic agents for lower extremity venous thrombosis,[17] outlining the excellent mid-term results with catheter-directed urokinase therapy in the Venous Registry published by Mewissen et al.[18] This promising data should lead to randomized clinical trials comparing thrombolysis with anticoagulation. Comerota has further analyzed the results of this study,[19] assessing quality of life in a subgroup of patients from the Registry and comparing them to a similar group of patients treated with anticoagulation alone. Significant improvements were observed in the patients who received thrombolysis. Again, this analysis reiterates the link between an open vessel and the resolution of clinical symptoms—an association that rings true irrespective of the location of the thrombosis.

Olin[20] aptly characterizes the treatment of pulmonary embolism, providing a concise review of the diagnosis and treatment of this common but all too often unrecognized disorder. Data support the use of a thrombolytic agent such as urokinase for pulmonary embolism when the event is severe enough to cause right heart dysfunction. In fact, the FDA has recognized pulmonary embolism as one of the indications for clinical use of urokinase, originally stemming from the urokinase-streptokinase pulmonary embolism trial.

Lastly, an ever-increasing number of dialysis-dependent patients underlie the dramatic rise in the frequency of dialysis graft failure. Cynamon[21] describes the use of thrombolytic techniques to restore patency of such grafts, identifying the importance of rapid and economically efficient recanalization ("lyse-and-wait" technique) followed by percutaneous management of the almost ubiquitous venous outflow stenosis. Haskal[22] contrasts the pharmacological management of dialysis graft failure with the use of mechanical thrombectomy, describing the myriad devices available to clear the thrombotic occlusion. Although pharmacological and mechanical techniques have their distinct advantages and shortcomings, the modern interventionalist should be adept at the use of each.

The recent reintroduction of urokinase in the United States (as Abbokinase) provides incentive to review the pharmacology of the thrombolytic agents in general, as well as the available clinical data gathered from anecdotal reviews and clinical trials. As of this writing, most of the clinical data acquired so far on the safety and efficacy of thrombolytic therapy in the treatment of peripheral vascular disorders deals with urokinase. Whether the results of an experience with one thrombolytic agent can be extrapolated to another agent is doubtful due to their very different pharmacologic properties. As such, the publication of this supplement is timely. The appropriate management of peripheral arterial, venous, and dialysis graft occlusions is possible only after acquiring a basic fund of knowledge of scientific principles and clinical caveats. In this regard, it is hoped that this supplement has provided a concise and up-to-date compendium for the practicing clinician involved in the care of patients with peripheral vascular disease. ■

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