EDITORIAL

t-PA: A Cause for Tentative Celebration

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With the advent of t-PA as an approved therapeutic modality in acute ischemic stroke, Canada is about to enter a new and critical era in its approach to stroke, and the changes that will ensue will affect the public directly, identify changes needed in our health care delivery systems, and put pressure on neurologists to deal with stroke differently. The Canadian guidelines for the use of t-PA in acute stroke, developed by the Canadian Stroke Consortium and presented in this issue, are an important step in our orderly approach to stroke patients.

The advent of t-PA is a cause for celebration because it is the first drug proven effective after a stroke has occurred. Nonetheless, it is important to position this drug in the historical context of stroke research so that we could more reliably foresee other developments in the field of stroke. Our appreciation of the stroke process from the pathophysiologic and therapeutic points of view has gone through a number of phases, the first of which was the recognition that stroke was associated with certain medical risk factors. Without knowing very much at all about the CNS events associated with stroke, control of hypertension and more recently anticoagulation of patients with atrial fibrillation, led to a significant decrease in the incidence of stroke. Our aging population is neutralizing that benefit since the incidence of stroke has been rising again, but control of risk factors continues to be an important means of stroke prevention. The second phase was the appreciation that in the stroke setting, the brain was a target organ for events in the vascular compartment, including stenosis of blood vessels through atherosclerotic narrowing and emboli arising from vascular injury or cardiac abnormality. The therapeutic byproducts from this phase have had a major impact on our current approach to stroke. Canadian-led trials have for instance resulted in the widespread acceptance of carotid endarterectomy and aspirin as standard approaches in stroke prevention. t-PA is a therapeutic product of this "vascular" approach to stroke. As such, and despite all the hype, it is the outcome of research that started more than 40 years ago.

Stroke research has evolved well past this "vascular" thinking and our future therapeutic approach to stroke will likely change significantly. We now appreciate that certain brain regions affected by the ischemic process can, for a time, produce clinical deficits because they do not receive sufficient energy to function, yet blood supply to these regions is sufficient to maintain cellular integrity. This concept of ischemic penumbra became the antidote to the prevalent nihilistic attitude to stroke therapy. It led to the concept that *time is brain*, allowing us to believe that stroke may not only be preventable, but also treatable, if attended to rapidly. The NINCDS trial, by showing that t-PA compared to placebo results in 12% absolute increase in "cures" from stroke, 50% decrease in moderate disability, and 10% decrease in death or severe disability, destroyed the myth that stroke patients cannot benefit from any treatment post-event.

Significant additional inroads have been made into the metabolic, and more recently molecular mechanisms of ischemic brain damage. The appreciation of the roles of calcium and excitotoxic mechanisms that lead to ischemic cell death have resulted in the widely accepted notion that "neuroprotection" with drugs that block some of these processes will improve functional recovery from stroke, and while several clinical trials with calcium channel blockers and glutamate antagonists have not been successful, further research is bringing other neuroprotective agents that will undoubtedly provide additional therapies to our armamentarium against stroke. In the meantime, molecular neurosciences have shown that apoptosis may play a significant role in the development of ischemic damage. This is a process of cellular attrition that results from ischemic reactivation of suicide genes that were dormant following the conclusion of developmental remodelling of the CNS. Apoptosis is distinguished from the process of necrosis by the lack of an inflammatory response to the genetically-determined death of the cells, and the slowness of the death process which can stretch over several days. Thus, there are scientific reasons to believe that stroke will be treated in the future by a mixture of drugs that will include a thrombolytic agent, one or more neuroprotective drugs, and blockers of the apoptotic process.

t-PA is the first drug available for stroke therapy, but its significant hemorrhagic side-effects constrain its use. The benefits of t-PA listed above are achieved despite the 10-fold increase in intracerebral hemorrhage (ICH). Strict adherence to the protocol suggested by the CSC will limit the incidence of ICH. In addition, several points are worth studying further because clarifying them could limit the incidence of this very undesirable side effect. First, the risk of ICH increases in hypertensive patients, in those with higher NIH stroke scales (i.e., worse deficit), in those with large MCA infarcts, and those whose infarcts are associated with cerebral edema. In contrast, younger age, the absence of diabetes or cardiac disease and lower admission blood pressure appear to be predictors of good outcome. Can the dose of t-PA be tailored to the deficit? Can the particular distribution of the infarct be a reliable predictor of hemorrhage, and are there specific CT appearances that should lead to t-PA being withheld from some patients e.g., when there is CT evidence for thrombosis in the MCA? What is the influence of the interval from stroke to t-PA administration on the risk of hemorrhage? Until these determinants of risk/benefit ratio are studied, the attitude of physicians towards the use of t-PA in acute stroke will remain somewhat guarded.

Finally, t-PA will bring about significant changes to the health care delivery system in this country. Some of these have already started. Public education must be aimed at decreasing the ignorance regarding the warning signs and symptoms of stroke identified by recent surveys conducted by the Heart and Stroke Foundation of Ontario. Medical Centres that have, around the clock, CT scanning capability, neurologists on call, stroke teams, pharmacy and rapid access to neurosurgery, must be publicly identified so that patients can be transported to them directly. Such Centres should play a regional role in accommodating

stroke patients who are admitted to smaller satellite hospitals. Neurologists must accommodate the new reality that they now possess an effective therapeutic intervention where time is of the essence, when the absence of such scenarios may have contributed to their choice of specialization. A national database is essential if we are to monitor factors that impede rapid access of patients to stroke therapy, test the effectiveness of changes made to the education of the public and the physicians, and promote other needed changes to aspects of the health care system in this country.

t-PA should be the vehicle by which to bring hope to stroke patients.

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