IV thrombolysis for treatment of patients with stroke upon awakening

Yes? No?

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Summary

Current guidelines recommend IV administration of recombinant tissue plasminogen activator (rtPA) to carefully selected patients who can be treated within 4.5 hours of ischemic stroke onset. Patients whose neurologic symptoms are discovered upon awakening (wake-up stroke) generally are not given rtPA because of the uncertainty about the time of stroke onset. This group of patients may be relatively large. Preliminary reports suggest that patients with wake-up stroke who can be treated within 4.5 hours of discovery may respond similarly to patients with an established time of stroke onset. Clinical trials, which are selecting patients to treat primarily based on imaging surrogates, are under way. Pending the results of these trials, data about the utility of clinical or imaging findings that would identify those patients who could be treated and information about the safety and efficacy of IV rtPA in this situation are not available.

A 74-year-old woman with a history of atrial fibrillation is found by family members at 7 AM. She has aphasia and right hemiparesis. She was well when she went to bed at 10 PM the previous night. Based on the examination, her NIH Stroke Scale score is 18. A CT scan demonstrates a clot in the left middle cerebral artery. She was taking warfarin and her international normalized ratio is 1.3. It is now 8:30 AM. The family asks if she can be treated with IV recombinant tissue plasminogen activator (rtPA). How should the neurologist respond?

IV administration of rtPA aimed at restoring perfusion to the brain is the mainstay of emergency management of patients with acute ischemic stroke. Although this agent was approved by the US Food and Drug Administration almost 20 years ago, approximately 95%

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Disclaimer: The US Food and Drug Administration has not approved the IV administration of thrombolytic agents for treatment of patients more than 3 hours following stroke.

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of patients with stroke still are not being treated. A major hurdle to treatment is the short time period from onset of symptoms to therapy initiation. Current guidelines, which are based largely on the inclusion and exclusion criteria used in clinical trials, reinforce the maximal time window for treatment and recommend that the agent not be started more than 4.5 hours after stroke onset.¹ Because of the importance of the interval from stroke onset, the first question usually asked when assessing a patient for possible treatment is “When was the patient last in his or her usual state of health?” The answer is used as the time of onset of the vascular event, and if the time is beyond 3 or 4.5 hours, rtPA is not recommended. However, there are situations that make the determination of the time of onset difficult; for example, when a patient has aphasia or neglect and cannot provide history and no witness is available to describe the time of onset. Another such circumstance is when a patient awakens in the morning with neurologic impairments that developed during the night—the scenario of the “wake-up stroke.” Currently most patients with stroke upon awakening are not treated with rtPA. Epidemiologic studies report that approximately 10%–20% of patients with stroke have their symptoms first detected upon awakening; this figure reflects the established circadian pattern of stroke occurrence with a peak in the early morning.^{2–5} Thus, expanding the use of rtPA to those persons with stroke upon awakening could have important public health consequences.

There is some evidence that patients with wake-up stroke may be similar to patients with events with a known time of onset. Roveri et al.⁶ reported that patients with wake-up stroke seen within 3 hours of awakening have similar demographic features, risk factors, severity of neurologic impairments, subtypes of ischemic stroke, and findings on brain imaging as patients with a known time of stroke onset. On the other hand, Rimmele and Thomalla⁵ concluded that patients with stroke upon awakening or for whom the time of onset is not known have more severe events and poorer outcomes. These observations imply that patients with wake-up stroke could and should be treated with IV rtPA.

There may be circumstances in which some patients with wake-up stroke could be treated.^{5,7–10} For example, if evidence exists that the event happened shortly before awakening, the patient could receive reperfusion therapy.¹¹ A strategy that uses the time that the impairments were first detected (upon awakening) as the time that the stroke occurred could be used to make treatment decisions. Another potential approach would be to assume the halfway point during sleep as the time of stroke onset. In these situations, treatment of patients with wake-up stroke would be based on the traditional 3- or 4.5-hour time window from initial recognition until treatment.⁶ The utility of these strategies is not known.

Because crucial historical information is lacking, the results of brain imaging could be used as an alternative method for determining the likely time of stroke onset. Findings from both CT and MRI studies are being evaluated as surrogate markers for determining the time of onset and establishing the eligibility for treatment. Cortijo et al.¹² used CT angiography and perfusion to select thrombolytic treatment for patients with a stroke of unclear time of onset, including those with symptoms upon awakening. Those patients with a core area of infarcted tissue less than one-third of the territory of the middle cerebral artery, as demonstrated by cerebral blood volume (CBV), and a greater than 20% mismatch in volumes between the images of CBV and mean transit time were considered eligible for treatment. In comparison to 74 patients with known time of onset, the rates of early neurologic improvement and favorable outcomes at 3 months were similar among the 73 patients with unknown times of stroke onset.

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Another approach is to compare MRI findings detected by diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) sequences.¹¹ The assumption is that a discrepancy between the 2 sequences in visualization of the stroke (lesion seen on DWI but not clearly visualized on FLAIR) would represent an ischemic lesion that is less than 4.5–6 hours in age.¹³ Kim et al.¹⁴ compared DWI and FLAIR studies performed among patients with known time of stroke onset with those with stroke of undetermined age, including those with stroke upon awakening. The differences between the 2 sequences were most reliable when the studies were performed within the first 2 hours of initial recognition of the stroke. However, the detection of the subtle changes on FLAIR may be time-consuming and require special expertise and resources that may not be available in a community setting. The use of automated systems to detect the subtle nuances is not yet well-developed.¹⁵ While an imaging-based approach using either emergency CT or MRI to determine which patients with stroke of undetermined onset, including those with stroke upon awakening, could be used to select patients that can be treated; additional research is needed before clinicians should adapt this strategy into their clinical practice.

Unfortunately, definitive evidence about the efficacy and safety of IV rtPA for treatment of patients with stroke upon awakening is limited because these persons were excluded from the previous clinical trials. Most currently available data are from small series and observational reports that evaluated the use of IV thrombolysis, intra-arterial interventions, or the combination of IV and endovascular therapies.^{5,10,12} Most of these reports are retrospective reviews of experiences at clinical centers. Both imaging and clinical criteria for treatment vary considerably among the studies. Some studies used CT and others used MRI findings. The interval until treatment ranged from within 2 hours of clinical recognition to up to 24 hours after having last been observed as normal. In most instances, treatment was initiated within 3 hours. Given the nature of these studies, there are a large number of limitations and the results should be viewed with caution. The rates of symptomatic hemorrhage ranged from 0% to greater than 33%, with most reports describing a risk of bleeding of less than 6%. The percentages of favorable outcomes, usually measured by the modified Rankin Scale, varied from 10% to 50%, with most series describing an approximately 30% rate. Buck et al.¹⁶ have performed a detailed systemic review of these studies, and they provide detailed critiques of each study.

Some of the studies are described subsequently. In a single-center retrospective study using CT, Barreto et al.¹⁷ identified 80 patients who had strokes upon awakening; 46 were treated with IV or intra-arterial reperfusion therapies. They found that the interventions could be given with a reasonable degree of safety, and outcomes were similar to those noted in a comparison group treated within 3 hours of known stroke onset. Manawadu et al.¹⁸ compared 68 patients with wake-up strokes with 336 patients with known stroke onset <4.5 hours; all were treated with thrombolysis. After adjusting for age, severity of stroke, and the results of baseline imaging, they found outcomes and the risks of bleeding complications were similar in the 2 groups. In a subsequent report, the same group noted that advanced age did not result in poorer outcomes, although elderly patients (age >80 years) with wake-up stroke were less likely to be treated.¹⁹

On the other hand, Bai et al.²⁰ analyzed the outcomes of 70 patients with stroke upon awakening who had large artery occlusions. They found no differences in functional outcomes

among the 29 patients who had reperfusion therapy and the 41 patients receiving antiplatelet agents. Stampfl et al.²¹ reported their experience with the use of stent-retriever devices to restore perfusion among 19 patients with wake-up strokes. Although the intervention was successful in restoring perfusion, only 2 patients had favorable outcomes and 7 died. Although the Abciximab in Emergency Stroke Trial-II (AbESTT-II) did not test rtPA, it is the only randomized placebo-controlled trial that specifically tested the utility of an acutely administered perfusion therapy in patients with wake-up stroke.²² In the trial, patients with stroke upon awakening could be enrolled if treatment with the study agent (placebo or abciximab) could be initiated within 3 hours of awakening. Enrollment of this group of patients was difficult; only 43 patients were entered. Many of the patients had findings of acute stroke on the baseline CT. Recruitment was halted because of an unacceptably high rate of hemorrhagic complications. In addition, only 4 of 43 subjects with wake-up stroke had favorable outcomes, a rate that was much lower than that observed among patients with known time of stroke onset.

Thomalla et al.²³ are performing an international multicenter placebo-controlled trial (WAKE-UP) of IV rtPA using the DWI/FLAIR mismatch criteria among patients with stroke of undetermined onset. The trial will include both those patients who are found with a stroke and for whom no history is available and patients with symptoms identified upon awakening. Another randomized trial, Extending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND), is using the findings of perfusion mismatch on either MRI or CT to identify potentially eligible patients who could be treated with IV rtPA from 4.5 to 9 hours after stroke onset.²⁴ For those patients with wake-up stroke, the halfway point of the duration of sleep is calculated, and the treatment must be started within 9 hours of that point. Japanese investigators²⁵ are testing the utility of IV rtPA among carefully selected patients with stroke of undetermined onset. They are using the dosage of the medication (0.6 mg/kg) that is traditionally used in Japan, which is different from the dosage of rtPA used in the United States.

The neurologic community should support these trials, which are addressing an important question, but it may take considerable time before there are meaningful results. In a study evaluating the safety and efficacy of IV thrombolysis for patients with wake-up stroke, Hill et al.²⁶ were able to enroll only 20 of 89 screened patients; 19 patients were excluded because well-defined strokes were already present on the initial CT scan. Based on the experience at one EXTEND center, Dagonnier et al.²⁷ found that 70.5% of the 95 patients screened for the trial had wake-up strokes, but only 17 patients had no other exclusion criterion for treatment. Based on these experiences and that of the AbESTT-II, researchers should anticipate that the rates of recruitment in the trials will be slower than expected. Although expanding the use of thrombolytic treatment to patients with wake-up stroke would be welcomed, based on the ratio of patients with wake-up stroke to patients with stroke with known time of onset, clinicians may find the effect on the overall usage of IV thrombolysis to be relatively small.

Pending the results of these trials, the question is whether a physician should prescribe IV rtPA to a patient with stroke that is first detected upon awakening. Yes? No? This question currently cannot be answered with a reasonable degree of certainty. Management likely will vary from hospital to hospital. Although preliminary uncontrolled data are interesting, the risk of serious bleeding complications in this situation is not established. In addition, unequivocal data that the emergency IV administration of rtPA increases the likelihood of a favorable outcome are not yet available.¹⁶ Until the results of the ongoing trials become available, the most reasonable approach is to follow the recommendations contained in the national guidelines, which means most patients with stroke first discovered upon awakening cannot be treated with IV rtPA in a community setting. As a result, the patient described at the beginning of the article likely was not treated with IV thrombolysis.

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