

Wake-Up to Wake-Up Stroke!

Can J Neurol Sci. 2014; 41: 137-138

Here is a typical story. A patient arrives at the emergency room. He was well when he went to bed and then he woke up with symptoms suggestive of stroke several hours later. Even without further scrutiny, the clinician determines that intravenous thrombolytic therapy is contraindicated. End of story.

Such is the plight of patients with wake-up stroke. Can we do more? Can we do better?

Wake-up stroke is not rare. About 5 to 30% of patients who presents to the emergency room for presumed acute stroke have wake-up stroke. Because of uncertainty regarding the time of symptoms onset, these patients are routinely excluded from intravenous thrombolytic therapy. In a population-based study, 14% of ischemic strokes presented to an emergency department were wake-up stroke. Among these patients, more than one third would have been eligible for thrombolysis if arrival time were not a factor.¹ If the same pattern holds true for Canada, that would translate to thousands of additional patients eligible for thrombolytic therapy.

When one deals with wake-up stroke, one needs to re-visit the concept of “last seen well”. The time “last seen well” is a good and objective way to time the onset of stroke symptoms. When symptom onset is unwitnessed, such as patients who are aphasic and alone at the time, “last seen well” may become an obstacle to thrombolysis. In the case of wake-up stroke, “last seen well” often puts the patient outside the conventional therapeutic time window. Although well-intentioned, we may not be right to assume that the time of symptom onset is close to the time of “last seen well”.

Let us assume that the onset of stroke symptoms occurs in a random fashion during sleep hours. For a patient who was well when he went to bed eight hours earlier, the chances of stroke occurring during the final four hours will be the same as the chance of it starting during the first four hours, or 50%. That means that 50% of these patients are potential candidates for intravenous thrombolytic therapy. Of course, the assumption that the chance of stroke occurring equally at every time point during sleep is questionable at best. Other vascular events, particularly acute myocardial infarction in which the onset is marked by the development of chest pain, tend to occur in the final hour before arousal. Ischemic strokes likely follow the same diurnal pattern.² Several studies compared the clinical and radiological features between patients with wake-up stroke and patients with strokes that occurred within the therapeutic windows of alteplase. The two groups of patients were essentially identical in these studies.^{3,4} The evidence suggests that wake-up strokes more likely occur in the early morning hours just before arousal.

Clinicians involved in thrombolytic therapy for acute stroke know that some patients presenting within 4.5 hours of symptoms onset will show well defined infarct on cranial computed tomogram (CT) scan. We also have examples of patients who have normal cranial CT scan even though their symptoms occurred more than 4.5 hours. The progression from

ischemia to infarct is not linear in any given patient. The progression rate also varies from patient to patient, explained at least in part by the status of collateral circulation, presence of inflammatory mediators, and the metabolic demand of the brain tissues.⁵ When viewed in this context, “time window” is merely a surrogate marker for the “tissue window”.

Conceptually speaking, “tissue window” refers to a state where brain tissues in the penumbra zone may be salvaged but without increasing the risk of hemorrhage or other unfavorable outcome. Many radiological techniques allow us to visualize and quantify the penumbra. Unfortunately, we do not yet have the ability to predict accurately the risk of hemorrhage following thrombolysis, although the infarct volume appears to be an important factor. Patients with the correct tissue characteristics will benefit from thrombolysis even if the time of symptom onset is unknown or beyond the conventional time window.

Unlike time window, tissue window is somewhat more difficult to define. Clinical and radiological features are being used concurrently to define a favorable tissue window. The presence of measurable focal neurological deficits is a prerequisite to defining the tissue window. Severity may be related to the volume of tissue in the penumbra or infarcted tissue. Stroke subtype may also be an important factor. The radiological appearances are, by far, the most direct way to visualize the tissue at risk. Current research activities utilize either magnetic resonance imaging (MRI) or CT for this purpose. In CT, non-contrast study has been used to look for acute infarction and changes of early ischemia. The addition of perfusion study allows clinicians to estimate the size of the penumbra. Using the diffusion-weighted sequence, MRI can identify infarcted tissue early in its course of evolution. The MR perfusion study not only shows the perfusion status of brain tissue, the penumbra is defined by the presence of perfusion-diffusion mismatch, which can be mapped accurately. Without any doubt, MR study is more sensitive than CT. However, the immediate availability of MR facilities remains a major hindrance.

Several studies investigating the safety of thrombolysis therapy in the setting of wake-up stroke are either on-going or completed. So far, the safety data looks promising. The potential benefit of thrombolytic therapy is being investigated in two phase 3 clinical trials. Project WAKE-UP (NCT01525290) is a multicenter randomized clinical trials that will enroll 800 patients from several European countries with wake-up stroke.⁶ The study will use findings from the baseline MRI to identify patients who will likely benefit from intravenous thrombolytic therapy. Another clinical trial, EXTEND (NCT01580839), looks to extending the time for thrombolytic therapy from the conventional time window to nine hours.⁷ The study will include patients with wake-up stroke, using the midpoint of sleep duration as the presumed onset time. Unlike WAKE-UP, the EXTEND investigators will use either MRI or CT to determine the perfusion-infarct mismatch. Patients with large infarct core

volume (≥ 70 mL) or small mismatch volume (≤ 10 mL) are excluded.

In this issue, Bal *et al* reports their CT-based approach to the problem of reperfusion therapy for patients with wake-up stroke.⁸ In this retrospective study, 70 patients with wake-up stroke were identified. About 40% of the patients with wake-up stroke received thrombolysis. The mean last seen well to thrombolysis time was in excess of eight hours. The small sample size precludes any efficacy analysis, but the study shows that the approach was safe, with no symptomatic hemorrhage in the treatment group. The incidence of asymptomatic hemorrhage was not statistically different compared to patients treated conservatively. The remarkable aspect of the approach is its simplicity. They used CT which is widely available. Unlike studies such as EXTEND, there is no need to quantify volumes of infarcted and at-risk tissue. In my reading, the authors defined patients with favorable tissue window by: (1) clinically not a stroke due to small vessel disease; (2) demonstration of occlusion in a proximal large- or medium-sized artery; and (3) an ASPECT score > 7 . The simple approach, plus the wide availability of CT scanner, may transform the way we treat wake-up stroke.

However, this approach is not without problems. A key component of the selection criteria is the absence of radiological signs to suggest significant tissue damage. The Calgary investigators used the ASPECTS score to do this. This tool has been developed by researchers in Calgary and it is used to quantify the degree of ischemic damage. In the study, a score of >7 was used. This usually means no or minor ischemic change in the cerebral parenchyma. Despite its apparent objectivity, the reliability of the score is put in doubt in the study. Although all the thrombolysed patients were rated to have score of > 7 at the time of patient presentation, the score was revised to ≤ 7 in 50% of patients during subsequent review. If ASPECTS score is ultimately used to select patient for thrombolysis in the future, ways to improve inter-rater validity must be devised unless an alternate method is found. The apparent deficit raised another important question. The cut off value for the ASPECTS score may be too stringent in the study. In fact, a study headed by the senior author of the current article had previously reported the result of a prospective safety study using similar criteria, except for the ASPECTS score of > 5 .⁹ Given the overall outcome, thrombolysis can probably be administered safely in patients with lower ASPECTS score, although further analyses will be needed to determine the optimum cut off value.

This is not the first study to suggest the safety of thrombolytic therapy in patients with wake-up stroke.¹⁰ Some studies even provide tantalizing evidence of benefit over conservative treatment.¹¹ So what should the treating clinician do when confronted with such a patient? There is good evidence that the time last seen well is not likely the time of symptom onset. There is also compelling evidence to suggest that stroke usually occurs in the final hours before arousal. Thrombolysis appears to be safe in these patients, as noted in the study published in this issue of the journal. Should the clinician just take the chance and offer reperfusion therapy?

Personally, I think not. While it is tempting to believe in the beneficial effect of alteplase, there is no evidence to suggest sure success with thrombolysis. Besides, although the risk of intracerebral hemorrhage appears to be low in the phase II studies, it can significantly worsen patient outcome. Until more

evidence becomes available, such off-label treatment is not to be encouraged. On the other hand, if the patient with signs of a devastating stroke and his cerebral CT scan is completely normal, when there is nothing to lose, thrombolysis could be justified on compassionate ground. However, the patient and their kin must be informed of the uncertainty surrounding the treatment option beforehand.

The benefit of thrombolytic therapy in acute ischemic stroke was established in 1995. The development of intra-arterial thrombolysis and various endovascular interventions appears promising but no formal efficacy study has been performed. Because of the need for specialized facilities and specialist, these invasive procedures are not likely to have a major impact on stroke treatment worldwide. In the last two decades, the only significant improvement in acute ischemic stroke therapy was the extension of the treatment window from 3 to 4 ½ hours. We may be at the threshold of the next development in reperfusion therapy. The interest in wake-up stroke in recent years may prove interesting. If thrombolysis can be safely administered to this group of patients and with favorable outcome, the concept of tissue window would be validated. With that, we may be able to offer thrombolysis to a much larger group of patients that are currently being excluded. Perhaps by then, we will see the full potential of the thrombolytic therapy unleashed.

Richard K. Chan

Department of Clinical Neurological Sciences
Western University / London Health Sciences Centre
London, Ontario, Canada. Email: richard.chan@lhsc.on.ca

REFERENCES

1. Mackey J, Kleindorfer D, Sucharew H, et al. Population-based study of wake-up strokes. *Neurology*. 2011;76:1662-7.
2. Elliott WJ. Circadian variation in the timing of stroke onset. *Stroke*. 1998;29:992-6.
3. Fink JN, Kumar S, Horkan C, et al. The stroke patient who woke up: clinical and radiological features, including diffusion and perfusion MRI. *Stroke*. 2002;33:988-93.
4. Todo K, Moriwaki H, Saito K, Tanaka M, Oe H, Naritomi H. Early CT findings in unknown-onset and wake-up strokes. *Cerebrovasc Dis*. 2006;21:367-71.
5. Krakauer JW. The complex dynamics of stroke onset and progression. *Curr Opin Neurol*. 2007;20:47-50.
6. Thomalla G, Fiebich JB, Østergaard L, et al. A multicenter, randomized, double-blind, placebo-controlled trial to test efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke (WAKE-UP). *Int J Stroke*. Epub 2013 Mar 12.
7. Ma H, Parsons MW, Christensen S, et al. A multicenter, randomized, double-blind, placebo-controlled phase III study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND). *Int J Stroke*. 2011;7:74-80.
8. Bal S, Bhatia R, Shobha N, et al. Stroke-on-awakening: safety of CT-CTA based selection for reperfusion therapy. *Can J Neurol Sci*. 2014;41(2):182-6.
9. Hill MD, Kenney C, Dzialowski U, et al. Tissue Window In Stroke Thrombolysis study (TWIST): a safety study. *Can J Neurol Sci*. 2013;40:17-20.
10. Barreto AD, Martin-Schild S, Halleivi H, et al. Thrombolytic therapy for patients who wake-up with stroke. *Stroke*. 2009;40:827-32.
11. Manawadu D, Boida S, Keep J, Jarosz J, Kalra L. An observational study of thrombolysis outcomes in wake-up ischemic stroke patients. *Stroke*. 2013;44:427-31.