

## Obstacles to the use of intravenous tissue plasminogen activator for acute ischemic stroke. Is time the only barrier ?

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### Abstract

**Background and aims :** The short time window is frequently cited as the main reason for exclusion of intravenous tissue plasminogen activator (tPA) in acute stroke. Identifying and circumventing barriers to thrombolysis other than time could increase the frequency of treatment. The goal of this study was to identify whether the rate of treatment with tPA would increase if time window was not an obstacle to treatment.

**Methods :** In four hospitals we prospectively recorded the rate of tPA use in consecutive patients admitted with acute ischemic stroke and in those admitted within 3 hours, the reasons why thrombolysis was not given, and the potential gain in the rate of tPA use if all patients had been admitted within 3 hours considering all exclusion criteria other than time.

**Results :** We recruited 486 patients (258 men ; mean age,  $70.4 \pm 13.5$  years), of whom 154 (31.7%) were admitted within 3 hours. The time of stroke onset was unknown in 28 (5.8%). The rate of tPA use was 11.1% in the whole study population and 35.1% in those admitted within 3 hours. In 'eligible' patients, TIA in 33 patients (21.4%), age > 80 years in 27 (17.5%), mild stroke in 27 (17.5%), rapidly recovering stroke in 9 (5.8%), a too long door-to-needle time in 8 (5.2%), and severe hypertension in 5 (3.2%) were the main reasons for not to treat. Two patients were not treated despite the absence of documented reasons. If all patients had hypothetically been admitted within 3 hours, the rate of tPA use would have increased from 11.1% up to 27.9% of the whole population and up to 37.4% if aged patients and those with no documented reasons or with a rapidly recovering stroke had also been considered for treatment.

**Conclusions :** Delayed presentation to hospital is the main factor limiting the use of thrombolysis in acute stroke, but additional patients would be treated if those with no contraindication, advanced age or rapidly recovering stroke were considered as eligible.

**Key words :** Stroke ; thrombolytic therapy ; tissue plasminogen activator ; time ; therapy.

### Introduction

The National Institute of Neurological Disorders and Stroke (NINDS) study showed that intravenous

(IV) tissue plasminogen activator (tPA) benefited acute stroke patients treated within 3 hours from the onset of symptoms (Marler *et al.*, 1995). Intravenous tPA therapy within this short time frame was approved in Belgium in 2003. However, few patients receive this treatment, and the rate of tPA use in the whole Belgian population of ischemic stroke patients remains unknown. The short therapeutic time window is frequently presented as the main reason for exclusion, but identifying barriers to thrombolysis other than time could help increase the rate of tPA delivery. Yet, there remains a number of patients who will never be treated even though they should be admitted within 3 hours because they present true contraindications to tPA other than delayed admission.

The aim of this study was to collect prospective data about the tPA use in a Belgian population of consecutive patients admitted in an emergency department for acute ischemic stroke and determine the maximal rate of tPA use which could be reached. For this purpose, we first measured the current rate of IV tPA use in four Belgian stroke centres, identified the reasons why thrombolysis was not given in those admitted within 3 hours, and estimated the potential gain in the rate of tPA use if all patients had virtually been admitted within 3 hours considering all exclusion criteria other than time.

### Methods

The study was performed using a prospective internet registry of ischemic stroke patients admitted between June 2005 and July 2006 in four Belgian hospitals covering a different catchment area. This registry was approved by each hospital's ethics committee. All patients with suspected acute stroke attended the emergency department of each hospital and were seen by a neurologist. They were further referred to the on site department of neurology. The registry consisted in a standardized electronic questionnaire collecting data on demographic characteristics, admission time, use

of intravenous tPA, and the reasons for exclusion from tPA (30 items). Demographic data were age and gender. Stroke onset time, admission time, IV tPA use, time of thrombolytic therapy, and the initial National Institutes of Health Stroke Scale (NIHSS) score were first recorded in the patients' chart. Time at stroke onset was defined as the time at which the patient or a witness first noted a recent acute neurological deficit. If the symptoms were first observed on awakening, the time at onset was recorded as when the patient was last seen normal. Stroke onset time was considered as unknown if the patient or a witness could not provide information on the time at which there was no neurological deficit. Door-to-needle time was defined as the time elapsed between hospital admission and start of thrombolytic therapy. According to the patient's chart, each participating center was asked to code in the registry whether the stroke-to-admission time was within or beyond 3 hours and whether the door-to-needle time was too long for thrombolysis within the 3-hour time frame. Transient ischemic attack (TIA) was defined by a neurological deficit fully recovering within 3 hours.

All patients underwent a brain computed tomography (CT) scan or multimodal magnetic resonance imaging (MRI) to ascertain the diagnosis of ischemic cerebrovascular disease. A diffusion/perfusion mismatch was searched in patients who had a MRI scan. Patients with cerebral or subarachnoid hemorrhage on the initial scan were excluded from the registry. Ischemic stroke patients admitted to hospital within 3 hours of symptom onset were considered as 'eligible' to tPA therapy according to the NINDS protocol (Marler *et al.*, 1995). Each tPA treated patient was recorded in the registry. The reasons for exclusion from tPA as defined by the NINDS trial in 'eligible' patients were documented. Mild or severe stroke was defined by an initial NIHSS score  $\leq 5$  without aphasia or  $\geq 22$ , respectively. Rapidly recovering stroke as an exclusion criterion to tPA was left to the neurologist's judgment and the NIHSS score at that decision time was recorded. Other exclusion reasons were also entered into the registry: a CT ASPECT score  $\leq 7$  (Barber *et al.*, 2000) or the absence of diffusion/perfusion MRI mismatch when performed, history of cerebral hemorrhage, early hemorrhagic transformation, neurological disease mimicking stroke, or any other reasons. Age over 80 years was considered as a possible reason for exclusion since tPA has been licensed in Belgium with this restriction. 'No documented reason' was coded for patients who did not receive intravenous tPA despite the absence of physician-documented exclusion criteria. In the end of the questionnaire, the virtual tPA use was assessed for each patient admitted beyond the 3-hour time point, asking the participating center to code whether they would have treated this patient if the stroke-to-admission

time had virtually been within 3 hours. In case of exclusion, they were asked to record the appropriate NINDS criteria.

#### STATISTICAL ANALYSES

For demographic data, we used the mean or median values with SD and range.

### Results

Four hundred and eighty-six patients (258 men, 53.1%) with acute ischemic cerebrovascular disease presenting at the emergency room were recorded during the study period. Mean age was  $70.4 \pm 13.5$  years (median, 74.0 years; range, 19-96). Age was higher than 80 years in 112 patients. Stroke-to-admission time was within 3 hours in 154 patients (31.7%), beyond 3 hours in 304 (62.5%), and unknown in 28 (5.8%). Intravenous tPA was administered in 54 patients. Therefore, the rate of tPA use was 11.1% of the whole population of stroke patients and 35.1% of the 154 patients admitted within 3 hours. In these 'eligible' patients, the main exclusion criteria for thrombolysis were TIA in 33 (21.4%), age  $> 80$  years in 27 (17.5%), mild stroke in 27 (17.5%), rapidly recovering stroke in 9 (5.8%), a too long door-to-needle time in 8 (5.2%), and severe hypertension requiring IV antihypertensive treatment in 5 (3.2%). Some of these exclusion criteria were cumulative in the same patient. The other reasons for exclusion were less frequent and are listed in the table. Two patients (1.3%) were not treated despite the absence of documented reasons. Considering the number of patients having only one single exclusion criterion, advanced age or rapidly recovering stroke was recorded in 3 (1.9%) and 6 (3.9%) patients, respectively. Thus, 11 additional patients could have been treated if these criteria had not been used and if the two patients with no documented reasons for exclusion had been treated. This would have increased the tPA use from 11.1% to 13.4% of the whole population and from 35.1 to 42.2% of patients admitted within 3 hours.

In addition to the 54 patients who received tPA, 82 additional patients without any contraindication other than time would have been treated if they had been admitted within the 3-hour therapeutic window, leading to a total of 136 treated patients among the 486 admitted for acute ischemic stroke. Thus, the rate of tPA use would have increased from 11.1% up to 27.9% of the whole population. Using this virtual assessment, the main exclusion reasons would have been mild stroke in 157 (32.3%), age  $> 80$  years in 100 (20.6%), and TIA in 83 (17.1%) (Table I). Five patients (1.0%) would not have been treated despite the absence of documented criteria. Advanced age or rapidly recovering stroke would have been considered as

Table I  
Exclusion criteria for thrombolysis

Exclusion criteria	Admission $\leq$ 3 h. n = 154 n (%)	Virtual admission $\leq$ 3 h. n = 486 n (%)
Age > 80 years	27 (17.5)	100 (20.6)
TIA	33 (21.4)	83 (17.1)
Rapidly recovering stroke	9 (5.8)	12 (2.5)
No documented reason	2 (1.3)	5 (1.0)
Door-to-needle time	8 (5.2)	–
Mild stroke	27 (17.5)	157 (32.3)
Severe stroke	3 (1.9)	6 (1.2)
Severe hypertension	5 (3.2)	14 (2.9)
CT ASPECT score $\leq$ 7	4 (2.6)	–
No MRI mismatch	2 (1.3)	–
Disease mimicking stroke	4 (2.6)	13 (2.7)
Prothrombine time > 15 sec.	0 (0)	1 (0.2)
Previous dependency	3 (1.9)	16 (3.3)
Severe trauma at the time of stroke	2 (1.3)	3 (0.6)
Glucose < 50 or > 400 mg/dl	2 (1.3)	4 (0.8)
Other reasons	2 (1.3)	4 (0.8)
History of intracranial hemorrhage	2 (1.3)	6 (1.2)
Early hemorrhagic transformation	1 (0.6)	–

Virtual admission : all patients of the studied population were considered to be admitted within 3 hours. Door-to-needle time, CT ASPECT score, MRI mismatch, and early hemorrhagic transformation only apply for the group of patients admitted within 3 hours. The table only reports the exclusion criteria with a frequency higher than 1%.

the single reason for exclusion in 33 (6.8%) and 8 (1.6%) patients, respectively. Thus, the rate of tPA use might reach 37.4% of the whole population if aged patients and those with no documented reasons or with a rapidly recovering stroke were treated.

### Discussion

The rate of tPA use is known to be disappointingly low, between 1.2% and 8.7% of all stroke patients whatever the admission time (Chiu *et al.*, 1998 ; Wang *et al.*, 2000 ; Barber *et al.*, 2001 ; Grotta *et al.*, 2001 ; Johnston *et al.*, 2001 ; Heuschmann *et al.*, 2003 ; Katzan *et al.*, 2004 ; Brown *et al.*, 2004 ; Birbeck *et al.*, 2004 ; California Acute Stroke Pilot Registry (CASPR) Investigators, 2005 ; Cocho *et al.*, 2005 ; Qureshi *et al.*, 2005 ; Deng *et al.*, 2006) and between 6.8% and 26.7% of those admitted within 3 hours (Barber *et al.*, 2001 ; Johnston *et al.*, 2001 ; Heuschmann *et al.*, 2003 ; Katzan *et al.*, 2004 ; Cocho *et al.*, 2005 ; Qureshi *et al.*, 2005 ; Deng *et al.*, 2006 ; Huang *et al.*, 2006 ; Weimar *et al.*, 2006). Some differences may appear between the different studies depending on whether hemorrhagic stroke or TIA are included in the studied population, thereby yielding a lower rate of tPA use. Our study calculated the percentage of tPA use from the whole population admitted for ischemic stroke or TIA, being excluded from the registry patients with cerebral hemorrhage. The treatment rates, 11% in the whole population and 35% in the subgroup admitted within 3 hours, are slightly higher than

those reported in the previous studies. This result does not probably reflect the true rate of tPA use in Belgium, because there may have been a recruiting bias. Indeed, this registry involved four hospitals which have organized an active stroke clinical pathway in their respective catchment area, and in Belgium stroke care is not centralized. Besides, this study was not externally controlled to check if all patients were consecutively included in the central registry. The contribution of our study is however to demonstrate that this level of tPA use can be reachable by any hospital organizing a stroke care pathway reducing the time interval for acute intervention.

Admission time beyond 3 hours or unknown is the main reason for exclusion in our study (68.3%). This is in concordance with the rates observed in other studies (73-85%) (Barber *et al.*, 2001 ; Johnston *et al.*, 2001 ; Katzan *et al.*, 2004 ; California Acute Stroke Pilot Registry (CASPR) Investigators, 2005 ; Cocho *et al.*, 2005 ; Qureshi *et al.*, 2005). Delayed presentation as a factor limiting the use of thrombolysis in acute stroke is also shown by the virtual calculation of the number of treated patients if all had been admitted within 3 hours. On that condition and considering all the other possible exclusion criteria, the IV tPA use would have increased from 11.1% to 27.9% of the whole population. This rate probably reflects the maximal potentially reachable target for IV thrombolysis, many patients being excluded for other reasons than time. Other limiting factors are unavoidable such as severe hypertension (3.2%) or TIA (21.4%). In contrast, others are either

avoidable or questionable. Cocho *et al.* (Cocho *et al.*, 2005) found that the tPA use could be increased from 7% to 37% if avoidable reasons were circumvented. Our study shows that a significant minority of stroke patients (1.3%) were not treated, or would not have been treated in our virtual scenario (1.0%), despite the absence of documented reasons. A too long door-to-needle time precluded thrombolysis in 5.2% in our series and 12% in that of Cocho (Cocho *et al.*, 2005). This may be due to an avoidable delayed diagnostic workup or unavoidable emergent admissions just minutes before the 3-hour time point. Age  $\geq$  80 years is often considered as a contraindication to tPA which has been licensed with this restriction in Europe. In our study, advanced age was the single exclusion criterion in 1.9% of patients admitted within 3 hours and 6.8% of the whole population of patients who might have been treated if they had been admitted within 3 hours. However, some studies (Engelter *et al.*, 2005 ; Vatankhah *et al.*, 2005), but not all (Berrouschot *et al.*, 2005), have shown that patients aged over 80 years can also benefit from IV thrombolysis without a significantly higher risk of hemorrhage. This suggests that tPA might be administered in old patients in good medical condition and without a severe neurological deficit, but randomized trials are still lacking (Hemphill and Lyden, 2005). Mild or rapidly recovering stroke (23.3%) is one of the most frequent exclusion criterion, ranging from 19% to 31% in other prospective studies (Barber *et al.*, 2001 ; Cocho *et al.*, 2005). In our study, rapidly recovering stroke was the single exclusion factor in 3.9% of the eligible patients and 1.6% of the total population in our virtual scenario. If these patients are usually excluded from tPA treatment, about 30% of them can die or not be discharged home because of neurological worsening or persistent 'mild' neurological deficit (Barber *et al.*, 2001 ; Smith *et al.*, 2005). Another study reported that 10% of patients eligible for thrombolysis and who were not treated owing to recovering stroke showed early neurological deterioration with infarct expansion within 48 hours, and about 20% had poor outcome at discharge (Rajajee *et al.*, 2006). More data about the efficacy and safety of tPA in this particular subgroup of patients are needed.

In conclusion, delayed presentation to hospital remains the main factor limiting the use of thrombolysis in acute stroke, but additional patients would be treated if those with no contraindication, advanced age and rapidly recovering stroke were considered as eligible.

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