

Thrombolysis in ischaemic stroke

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Intravenous tissue plasminogen activator (rt-PA) is the only drug currently approved for the treatment of acute ischemic stroke in the first 3 hours after onset of symptoms. However, only a small percentage of stroke patients are candidates for rt-PA therapy. Newer imaging techniques, particularly magnetic resonance imaging, offer essential tools for selecting patients who would benefit from thrombolysis more than 3 hours after the onset of symptoms. Intra-arterial techniques will also play an important role in treating acute stroke in the future. [Emergencias 2008;20:419-427]

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None

The recombinant tissue plasminogen activator (rt-PA) is currently the only approved treatment for ischaemic stroke of less than 3 hours of evolution. In the United States this treatment was approved in 1996 in view of the results of the study by the National Institute of Neurology Disorders and Stroke (NINDS)¹ while approval was initially only conditionally given in Europe after the non conclusive results obtained in the European trials of the European Cooperative Acute Stroke Study-1 (ECASS I)² and ECASS II³ and was pending the phase IV results collected in the SITS-MOST (State Implementation of Thrombolysis in Stroke-Monitoring Study). However, the real impact of thrombolysis in the usual clinical practice is scarce since less than 5% of the patients with stroke receive treatment with rt-PA⁴.

Endovenous thrombolysis. Clinical studies

The rt-PA is a drug currently used in endovenous fibrinolysis in ischaemic stroke (Table 1). It is a relatively specific drug for fibrin with a half life of 4-8 minutes and, as such, it is used in endovenous perfusion during one hour after an initial bolus of 10% of the dose.

The ECASS-12 was the first study published which evaluated the efficacy of rt-PA in acute is-

chaemic stroke. This drug was used at a dose of 1.1 mg/Kg or placebo in patients with ischaemic stroke of less than 6 hours of evolution and the degree of functional independence was assessed at 90 days using the Rankin functional scale. In this study, a favourable non significant trend for rt-PA was observed on presenting null or minimum disability (Rankin 0-1) compared to placebo. This difference was significant after excluding 109 patients in whom some inclusion criteria had been violated, mainly the presence of signs of extensive infarction on cranial computerised tomography (CT). The intracranial haemorrhagic complications and mortality were greater in patients treated with rt-PA.

Initial approval of the use of rt-PA in ischaemic stroke was based on the results of the NINDS¹ study. The dose of rt-PA was lower than that used in the ECASS-1 study (0.9 mg/Kg, maximum 90 mg) and the patients were treated within the first 3 hours after the onset of the symptoms. Half of the patients received treatment in the first 90 minutes. The study was developed in two phases. In the first phase, initial clinical improvement was assessed at 24 hours of treatment according to the NIH scale score (Table 2). Of the patients treated with rt-PA and those treated with placebo, 47% and 39%, respectively presented initial improvement (complete resolution of the symptoms or a

Table 1. Inclusion and exclusion criteria for treatment with rt-PA**Inclusion criteria:**

Patients with acute ischaemic stroke of less than 3 hours of evolution with none of the following exclusion criteria.

Exclusion criteria for treatment with rt-PA

1. Stroke of craniocerebral traumatism in the previous 3 months.
2. Major surgery in the last 14 days
3. History of intracranial haemorrhage.
4. Systolic blood pressure > 185 mm Hg.
5. Diastolic blood pressure > 110 mm Hg.
6. Minor symptoms of improvement.
7. Intracranial haemorrhage demonstrated in CT or early signs of ischaemia in > one third of the middle cerebral artery.
8. Digestive or gastrointestinal haemorrhage in the last 21 days.
9. Arterial puncture in a site not accessible for compression.
10. Epileptic seizures at the beginning of the stroke.
11. Treatment with oral anticoagulants with PT > 15 sec.
12. Treatment with heparin in the previous 48 hours and elevated TPaT.
13. Treatment with aspirin in the previous hours is considered risk of haemorrhage.
14. Platelet count less than 100,000 m³.
15. Glycaemia less than 50 mg/dL.
16. Glycaemia greater than 400 mg/DL.
17. Needs for aggressive measures to lower blood pressure.
18. Treatment with aspirin.

Administration schedule of rt-PA

- 0.9 mg/Kg (maximum dose 90 mg).
- 10% of the total dose administered in one minute bolus.
- The remainder of the dose administered in continuous infusion during one hour.
- Heparin, aspirin or oral anticoagulants not administered in the following 24 hours.

CT: computerised tomography; TP: Prothrombin time; TPaT: time of partial activated thromboplastin.

fall of more than 4 points in the NIHSS scale). Recovery was complete in the first 24 hours in 16.8% and 2.7%, respectively. In the second phase of the study, the number of patients who were asymptomatic or presented a minimum deficit which had no impact on daily activities (Rankin 0-1) at 3 months of treatment was evaluated. The study was favourable for the use of rt-PA. For every 100 treatments with rt-PA, 13 more patients benefited from a degree of Rankin 0-1 recovery compared to patients treated with placebo. The incidence of symptomatic cerebral haemorrhage in patients treated with rt-PA or placebo was 7% and 2%, respectively.

The benefits of rt-PA were independent of age, risk factors, severity of the stroke, stroke subtypes, and the presence of hyperacute signs of ischaemic on cranial CT⁵. The patients with moderate baseline neurological involvement (NIHSS 10-14) were those who most benefited from treatment.

In the ECASS II³ study the dose of rt-PA used in the NINDS study and the inclusion and exclusion criteria of the ECASSI were applied and strict control of blood pressure and identification of early

signs of acute infarction in the cranial CT were insisted upon. The therapeutic window was 6 hours. Null or minimum disability was evaluated at 3 months (Rankin 0-1) and the results were similar between the treated and placebo groups. The differences were significantly in favour of rt-PA when the incidence of null to moderate disability (Rankin 0-2) was taken into account. The incidence of symptomatic cerebral haemorrhage was significantly greater in the treated patients.

In view of these results, rt-PA was conditionally approved in Europe in 2002 while awaiting the results of the SITS-MOST registry. This registry collected the data of 6,493 patients treated with rt-PA from 2002 to 2006 in 14 European countries. The aim was to determine the efficacy and safety of rt-PA as a thrombolytic treatment in the first 3 hours after stroke in the usual clinical practice. The results of this registry were compared with those obtained in the joint clinical trials and demonstrated that rt-PA is an effective and safe drug in the treatment of ischaemic stroke administered by qualified personnel in the first 3 hours of clinical manifestations⁷. The number of patients to be treated with intravenous rt-PA to avoid death or dependence would be 11 if treated in the first 6 hours, or 7 if treatment were administered in the first 3 hours⁸.

Factors associated with haemorrhagic complications after the administration of intravenous rt-PA

Intracranial haemorrhage is probably the most feared complication following treatment with rt-PA. Tanne et al analysed 1,205 patients treated with rt-PA in the first 3 hours. The frequencies of symptomatic and asymptomatic intracranial haemorrhage were 6 and 7%, respectively. Baseline glycaemia, history of diabetes mellitus, stroke severity (basal NIH), low platelet count and ischaemic involvement of more than one third of the territory of the middle cerebral artery on cranial CT were independent predictor factors of symptomatic cerebral haemorrhage⁹. In the NINDS study, only basal clinical severity and the presence of cerebral oedema or mass effect in the cranial CT were independent variables associated with a greater risk of cerebral haemorrhage¹⁰. Whether age or previous use of platelet antiaggregants is associated with an increase of cerebral haemorrhage as concluded from the data of the ECASS II¹¹ study remains under debate since posterior studies do not seem to corroborate these results^{12,41}. In the ca-

Table 2. NIH scale

	Score
Level of consciousness	
Alert	0
Responds to minimum verbal stimuli	1
Requires repeated or painful stimuli	2
Reflex responses or lack of response	3
Level of consciousness. Oral questions	
<i>What month is it? How old are you?</i>	
Both answers correct.	0
One correct answer.	1
Neither answer correct.	2
Level of consciousness. Motor orders	
<i>"Close your eyes". "Make a fist with your hand"</i>	
Both orders correct	0
One order correct	1
Neither order correct	2
Ocular coordination	
Normal	0
Partial paresis in looking	1
Total paresis or forced deviation of coordinated looking	2
Visual	
No visual alteration	0
Partial hemianopsy	1
Complete hemianopsy	2
Total blindness	3
Facial paresis	
Normal symmetric movement	0
Nasogenian furrow or minimum asymmetry on smiling	1
Total or almost total paralysis of inferior area of the hemiface	2
Complete paralysis of superior and inferior area of the hemiface	3
Upper extremity paresis (order to raise and extend arm)	
<i>(Score each arm separately)</i>	
Holds arm up for 10 seconds	0
Gives up in less than 10 sec., does not touch the bed	1
Gives up in less than 10 sec., touches the bed	2
Minimum movement	3
Total absence of movement	4
Lower extremity paresis (order to raise and extend 30°)	
<i>(Score each leg separately)</i>	
Maintains the position for 5 sec.	0
Gives up in less than 5 sec., does not touch the bed	1
Gives up in less than 5 sec., touches the bed	2
Minimum movement	3
Total absence of movement	4
Dysmetry	
Absent	0
Present in one extremity	1
Present in 2 extremities	2
Sensitivity	
Normal	0
Mild or moderate hyposthenia	1
Severe hyposthenia or anaesthesia	2
Language	
Normal	0
Mild aphasia	1
Severe aphasia (communication impossible)	2
Mute	3
Dysarthria	
Normal	0
Mild or moderate, understandable	1
Severe or unintelligible	2
Visual, tactile, special neglect	
No alterations	0
Extinction of one	1
Extinction of more than one	2

sec.; seconds.

ses in which the inclusion criteria of the NINDS protocol were violated, the presence of symptomatic haemorrhage may increase up to 38%¹³.

Thrombolysis in stroke after more than 3 hours?

The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS)¹⁴ study, evaluated the efficacy and safety of rt-PA in a 3 to 5 hour window after the onset of symptoms, a time not included in the NINDS study. In this study a dose of 0.9 mg/Kg was used and patients presenting signs of ischaemia in more than one third of the territory of the middle cerebral artery were excluded similar to what was done in the ECASS II study. No differences were observed in the disability presented by the patients at 3 months of treatment and thus did not support the use of rt-PA more than 3 hours after the initiation of the symptoms when cranial CT is used as the baseline neuroimaging technique.

The benefit of the treatment gradually reduces over time even within the first 3 hours after the stroke¹⁵. However, analysis of all the previously mentioned data of the NINDS, ECASS I and II and ATLANTIS studies seems to demonstrate that the benefits of rt-PA could be extended up to 4 hours and a half after the initiation of the symptoms¹⁶.

Taking this into account, the ECASS III study was initiated on behalf of the European Agency of Medication. This study evaluated the role of rt-PA (0.9 mg/Kg) versus placebo in patients with ischaemic stroke of 3 to 4 and one half hours of evolution. The inclusion period has finished and the results will soon be available.

Selection of candidates for thrombolysis by diffusion-perfusion magnetic resonance

The diffusion and perfusion sequences of magnetic resonance (MR) may detect cerebral areas with alterations in perfusion without alterations of diffusion (diffusion-perfusion uncoupling) which may represent areas with cerebral flow alterations (determined by the perfusion sequences) but without irreversible damage of the cerebral parenchyma (diffusion sequence) and thus, potentially salvable if cerebral flow can be reestablished¹⁷. Thus, persistence of this uncoupling beyond 3 hours after the stroke would allow individual identification of candidates to receive recanalization treatment¹⁸.

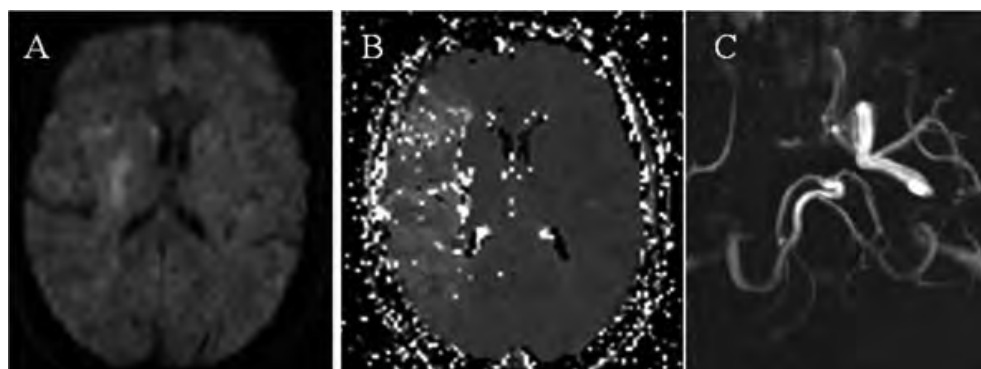


Figure 1. Important uncoupling between the diffusion image (A) and that of perfusion (B) in a patient in whom the angiography demonstrates occlusion of the right internal carotid artery (C).

With this objective the DEFUSE study analysed the pre-treatment and post treatment MR of 74 patients treated with rt-PA from 3 to 6 hours after the onset of the symptoms. It was observed that early reperfusion in patients presenting diffusion-perfusion uncoupling (perfusion $\geq 120\%$ of the diffusion) (Figure 1) was associated with a favourable clinical response, in contrast to what occurred in patients without diffusion-perfusion uncoupling. This study also identified that despite diffusion-perfusion with early reperfusion, patients presenting a large initial diffusion volume or altered perfusion (≥ 100 mL) had a worse prognosis. Indeed, early reperfusion in this subgroup of patients was associated with more symptomatic intracranial haemorrhages¹⁹.

Another recent analysis of 1,210 patients receiving different treatment modalities (less than 3 h with CT, less than 3 h with MR, more than 3 h with MR) showed that the use of MR reduces the frequency of symptomatic intracranial haemorrhages and when used beyond 3 hours MR was associated with a better prognosis²⁰.

However, no data from randomised, double-blind studies are available which justify the use of MR in current clinical practice. The DIAS and DEDAS trials evaluated whether patients presenting perfusion-diffusion uncoupling between 3 and 9 hours after the beginning of symptoms might benefit from thrombolysis. The drug used was desmoteplase, a thrombolytic agent derived from saliva of the vampire *Desmodus rotundus* and is characterised by its high affinity for fibrin and a longer half life than rt-PA. In both studies the patients receiving treatment with desmoteplase presented a better recovery at 3 months than those treated with placebo, especially with the highest doses of the drug. Likewise, in the DIAS study the patients treated with desmoteplase presented higher arterial reperfusion rates, which correlated with

a better final prognosis. Nonetheless, this greater rate of reperfusion in the patients treated with desmoteplase was not statistically significant in the DEDAS study, which may be related to a high reperfusion rate in the patients treated with placebo^{21,22}. However, these results have not been confirmed in a posterior phase III study (DIAS-II)²³.

Thrombolytic action of ultrasound

A higher incidence of arterial recanalization has been described in patients monitored with ultrasound during the administration of thrombolytic drugs²⁴. This greater recanalization may be because ultrasounds facilitate greater cavitation of the thrombus which allows a greater concentration of the lysing agent in the thrombosed arterial segment. The CLOTBUST study demonstrated that the use of ultrasound by transcranial Doppler associated with rt-PA increase arterial recanalization and improved the clinical response in the first two hours after the initiation of treatment with rt-PA. Similarly, the patients treated with rt-PA and ultrasounds presented better functional recovery at 3 months although future studies are required to confirm this²⁵.

Arterial thrombolysis

Arterial administration of thrombolytic agents benefits the mechanical thrombolytic effect of the introduction of the catheter itself and achieves a greater local concentration of the drug. This is translated into a greater percentage of recanalization, being 66% in the PROACT II trial versus 27-70% of endovenous thrombolysis²⁶. The greatest inconvenience of arterial administration was the need for interventional neuroradiological equip-

ment and the additional delay of 1.5 to 2 hours until the initiation of treatment.

The Prolyse in Acute cerebral Thromboembolism (PROACT-I)²⁷ study included 40 patients, 26 of whom received 6 mg of recombinant pro-urokinase (rpro-UK, 6 mg) and non fractionated heparin (NFH dose 1,000 u/h) and 14 received only NFH. A statistically significant greater recanalization was observed in patients treated with rpro-UK with a trend towards a better functional situation (Rankin 0-1) and lower mortality.

In the PROACT-II²¹ study 180 patients were included with the same criteria as in PROACT-I, with greater doses of rpro-UK (9 mg) and lower doses of NFH (500 U/h) being administered. The percentage of recanalization at 2 hours in the group receiving rpro-UK and in the group treated only with NFH was 66% and 18%, respectively. The mortality was similar in both groups and the percentage of asymptomatic or slight disability at 3 months (Rankin 0-2) was greater in the patients treated with rpro-UK despite presenting a higher number (not significant) of symptomatic intracranial haemorrhages. These data should be replicated in other studies and the Food and Drug Administration (FDA) has not, as yet, accepted its use.

Combined endovenous and arterial thrombolysis

Several studies have evaluated the viability of performing combined endovenous and arterial treatment. This strategy combines the rapid initiation of thrombolysis with endovenous treatment and the probable benefit of a greater degree of recanalization with the arterial procedure in patients in whom endovenous treatment has not been effective. The Emergency Management of Stroke (EMS) trial²⁸ compared combined endovenous and arterial thrombolysis with arterial thrombolysis in the first 3 hours of stroke in patients with a NIHSS greater than 5 and showed that this therapeutic approach is feasible and may provide a higher degree of recanalization versus arterial treatment alone. The IMS I²⁹ and II³⁰ studies evaluated combined treatment with endovenous rt-PA at a dose of 0.6 mg/Kg (15% in bolus) during 30 minutes in patients with stroke of less than 3 hours of evolution and an NIHSS greater than or equal to 10. This initial treatment was followed by arteriography and arterial fibrinolysis in patients presenting arterial occlusion. The arterial treatment should be implemented within 5 hours of the initiation of symptoms. Both studies suggested that

combined endovenous and arterial treatment may provide advantages versus endovenous treatment alone. The IMS III study (www.ims3.org) will assess the efficacy of combined treatment (0.6 mg/Kg endovenous, maximum 60 mg followed by arterial treatment) versus the usual endovenous treatment alone (0.9 mg/Kg, maximum 90 mg)³¹.

Mechanical thrombolysis

Different devices have been implemented with the aim of performing mechanical embolectomy in patients with acute stroke. The best known is the MERCI study³² which included patients with arterial occlusion within the first 8 hours after the onset of symptoms. This device showed an arterial recanalization rate of 48% (primary study objective), but, to date, no randomised clinical trials have evaluated the clinical effect.

Thrombolysis in clinical practice

Since FDA approval of the use of rt-PA in ischaemic stroke of less than 3 hours of evolution in 1996, numerous publications reporting experiences in the routine use of thrombolysis have appeared. In general, the data on functional independence, mortality and the incidence of symptomatic intracranial haemorrhage at 3 months have been similar to those published in the controlled clinical trials.

Although some studies have described a greater mortality in patients treated with rt-PA in centres with little experience (less than 5 thrombolysees per year)³³, the results of the SIST-MOST study did not show significant differences in the frequency of haemorrhagic complications or the neurological state at 3 months among experienced centres or with limited experience in thrombolysis⁶.

However, in the usual clinical practice there may be some situations in which thrombolysis may be indicated and these have not been taken into account in the clinical trials³⁴. The data available in the literature on these not unusual situations in clinical practice are reported below.

Thrombolysis in vertebrobasilar occlusion

Basilar occlusion is associated with a mortality of 80-90%. This fact justifies the empiric administration of arterial thrombolytic drugs with therapeutic windows of 12 and even 24-48 hours. In these patients, the mortality is reduced to 26-46%

and a favourable clinical outcome is observed in 50% of the cases³⁵. The mean percentage of arterial recanalization achieved is 50%. However, endovenous treatment may achieve similar clinical results despite lower percentages of arterial recanalization because it may be much more rapidly administered. Thus, the adequate treatment for vertebrobasilar occlusion remains controversial, especially in cases of less than 3 hours and it is accepted that endovenous treatment may be the first choice in these cases³⁶.

Thrombolysis in the occlusion of the internal carotid artery

Endovenous thrombolysis is less effective in acute occlusion of the internal carotid artery than in the occlusion of intracranial arteries. Linfante et al administered endovenous rt-PA in the first 3 hours after stroke and observed 88% of recanalization in the isolated occlusion of the middle cerebral artery (n = 19) versus 31% on coexistence of occlusion of the ipsilateral internal carotid artery (n = 17)³⁷. These patients may achieve greater benefit from treatment with arterial thrombolysis with or without associated endovenous thrombolysis³⁸. The use of angioplasty with or without associated stenting may also be indicated in this group of patients³⁹.

Arterial dissections

In a review of 30 patients with carotid dissection, the clinical evolution and the appearance of adverse effects was similar to that of the remaining patients without dissection^{40,41}. Although these data do not allow a general conclusion to be drawn, clinical suspicion of carotid dissection would not be a major contraindication for the use of thrombolytic drugs. In carotid occlusion due to arterial dissection, arterial recanalization by the implantation of a stent associated or not with arterial thrombolysis of the middle cerebral artery may be better than the use of endovenous treatment alone⁴².

Stroke related to or presented as an aortic dissection, which is a difficult clinical picture to recognise in the urgent evaluation of a patient with acute stroke is a different situation. Although there are few cases in the literature, endovenous thrombolytic treatment is contraindicated and pericardial effusion and cardiac tamponade have been reported as complications⁴³.

Recent history of major surgery

A history of major surgery within the last 14 days or the use of anticoagulant drugs at the time

of the stroke, are major contraindications for the administration of thrombolytic drugs. However, good results have been reported for arterial thrombolysis in patients with a history of major surgery within the previous 5 days, although 2 out of 3 patients in whom craniectomy had been performed developed intracranial haemorrhage⁴⁴. In view of these preliminary data, arterial thrombolysis may be a therapeutic option in patients with stroke of less than 3 hours and a recent history of major surgery (except in cases of craniectomy) or those receiving anticoagulant treatment.

Endovenous thrombolysis may be considered on the development of haemorrhagic complications in patients who have undergone a minor procedure in a compressible or accessible site.

Use of oral anticoagulant drugs

The use of oral anticoagulant drugs has been considered as a major contraindication for the administration of thrombolytic drugs in clinical trials¹⁻³. However, according to the guidelines of the American Stroke Association⁴⁵ patients receiving treatment with oral anticoagulants may be candidates for thrombolysis if the INR is less than or equal to 1.7.

Thrombolysis in the elderly and in paediatric care

Randomised clinical trials on thrombolysis have habitually excluded patients over the age of 80 years. However, stroke is very prevalent in this population group⁴⁶. Several studies have evaluated the efficacy and the complications of thrombolysis in elderly patients⁴⁷⁻⁵⁰ including our setting⁵¹. All these studies as well as a metaanalysis including a large proportion of these patients in the studies published⁵² have demonstrated that elderly patients do not show a greater rate of intracranial haemorrhages than younger patients, although they do present a higher mortality and dependence at 3 months after the stroke. In the absence of randomised clinical studies it does not currently seem that advanced age in itself should be an absolute contraindication for receiving thrombolysis and age should be considered together with other variables such as the functional situation and the comorbidity of the patient.

Similarly, clinical trials do not include patients under the age of 18 years. However, some patients have been successfully treated in some cases reported in the literature⁵³. It has been estimated that 1.6% of the children with stroke have received thrombolysis in the United States, although the clinical benefit in this group of patients has not been established⁵⁴.

The 2008 guidelines of the European Stroke Organization recommends that rt-PA may be used in patients under the age of 18 years and in older patients of 80 years, although this is outside the current European licence⁵⁵.

Minor symptoms or early improvement in symptoms

Some patients do not receive thrombolysis on presenting mild symptomatology or "being too well to receive treatment". However, up to one fourth of these patients die or cannot be discharged home due to clinical worsening or the persistence of "minor symptoms"⁵⁶. Ten percent of the patients excluded from thrombolysis because of minor symptoms present neurologic deterioration with extension of the infarction during the first 48 hours⁵⁷. Whether these patients should be treated with rt-PA or not is currently a matter of debate.

Epileptic seizures

The presence of epileptic seizures has usually been considered a contraindication for thrombolysis in clinical trials and in daily practice. This is due to the difficulty in differentiating whether the neurological symptoms are due to cerebral ischaemia or are a post critical Todd phenomenon. At present, the new neuroimaging techniques can differentiate patients who present seizures related to acute cerebral ischaemia who may benefit from thrombolysis⁵⁸.

Pregnancy

The use of thrombolytic drugs during pregnancy is worrisome for the potential risk of causing detachment of the placenta and/or loss of the foetus. The placental barrier is not passed by rt-PA and studies in animals have not shown teratogenicity⁵⁹.

In a series of 8 pregnant patients who received fibrinolysis for the treatment of cerebrovascular disease (6 ischaemic strokes and 2 thrombosis of the venous sinuses) two miscarriages not related to the treatment occurred and 7 of the 8 women had good recovery following the stroke⁶⁰. As in all uncommon situations, the data are limited and the balance between risks and benefits should be evaluated in each case.

Conclusions

Endovenous rt-PA is the only treatment which is currently approved for the treatment of acute ischaemic stroke during the first 3 hours. However,

its efficacy and the proportion of patients treated are limited. New imaging techniques and arterial techniques are currently being implemented as tools which may allow lengthening of the therapeutic window to more than 3 hours to allow patients to benefit from recanalization therapies.

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Trombolisis en el ictus isquémico

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El activador tisular del plasminógeno recombinante (rt-PA) endovenoso es el único fármaco actualmente aprobado para el tratamiento del ictus isquémico agudo dentro de las tres primeras horas del inicio de los síntomas. Sin embargo, ello sólo permite tratar un pequeño porcentaje de los pacientes con ictus. Las nuevas técnicas de imagen, especialmente la resonancia magnética, se presentan como una herramienta fundamental para la selección de candidatos a trombolisis más allá de las 3 horas del inicio de los síntomas. Las terapias intraarteriales también jugarán un papel importante en el tratamiento del ictus agudo en el futuro. [Emergencias 2008;20:419-427]

Palabras clave: Trombolisis. Ictus. Rt-PA.