A Pilot Study of Dual Treatment With Recombinant Tissue Plasminogen Activator and Uric Acid in Acute Ischemic Stroke

Sergio Amaro, MD; Dolors Soy, PhD; Víctor Obach, MD; Álvaro Cervera, MD, PhD; Anna M. Planas, PhD; Ángel Chamorro, MD, PhD

Background and Purpose—Uric acid (UA) increases the neuroprotective effects of recombinant tissue plasminogen activator (rt-PA) in experimental ischemia. In patients with stroke, increased UA levels have been linked to better stroke recovery, but the clinical safety of dual administration of UA and rt-PA is unknown.

Methods—Using a double-blind design, we assessed the safety of exogenous UA in patients with acute stroke treated with rt-PA. Patients were randomized to an intravenous solution of 500 mL of 5% mannitol/0.1% lithium carbonate (vehicle group, n=8) or 500 or 1000 mg of UA (n=16). Safety end points at day 90, lipid peroxidation (serum malondialdehyde), and serum kinetics of UA were established.

Results—Twenty-four patients with stroke were treated with rt-PA within mean (SD) 133 (35) minutes of clinical onset (admission National Institutes of Health Stroke Scale score mean [SD] 11 [7], age 71 [10.6] years, 71% males). Levels of UA decreased in the vehicle group and increased for approximately 24 hours in the high dose of UA group, which also had lower levels of malondialdehyde at day 5. Mortality (12.5%), symptomatic central nervous system bleeding (0%), and outcome at day 90 were similar in the 3 treatment arms; one patient in the high-dose group had a mild gouty episode.

Conclusions—The administration of UA appears to be safe, decreases lipid peroxidation, and prevents an early fall of UA in serum in patients treated with rt-PA within 3 hours of stroke onset. The clinical efficacy of dual administration of exogenous UA and rt-PA deserves further investigation in a larger acute stroke trial. (Stroke. 2007;38:2173-2175.)

Key Words: acute care • antioxidants • neuroprotection • neuroprotective agents • stroke

Recombinant tissue plasminogen activator (rt-PA) is the only approved therapy for selected patients with acute ischemic stroke, but the fear of bleeding complications make few eligible patients benefit from this therapy.1 Oxidative damage has been related to reperfusion injury in preclinical studies,2 but the role of dual therapy with antioxidants and thrombolytic agents have provided conflicting results in clinical trials.3,4

Uric acid (UA) is a potent natural antioxidant in man,5 and its administration has been advocated for patients with acute stroke.6 Increased levels of serum uric acid were associated with poorer stroke outcome in a recent study,7 but higher levels of UA at stroke admission predicted better outcome in studies that controlled for the effects of confounding factors.8 In experimental ischemia, administration of UA with or without rt-PA reduced the volume of brain infarction and improved neurological function,9,10 and in healthy volunteers, it was safe, increased antioxidant capacity, and decreased oxidative stress.11,12 This study assessed the safety of dual treatment with UA and rt-PA in acute stroke.

Methods

The study is a single center, double-blind, randomized, vehicle-controlled trial of intravenous administration of UA in 24 consecutive patients with acute stroke treated with rt-PA (0.9 mg/kg) within 3 hours of onset. The study was approved by an Institutional Review Board and the Spanish Drug Agency (eudraCT 2004 to 002937-37), and all participants or legal representatives gave written informed consent. Main exclusion criteria were history of gout, renal disease, or intake of drugs that may increase UA levels. The neurological examination was assessed using the National Institutes of Health Stroke Scale (NIHSS) by neurologists certified on its use, and stroke worsening required at least a 4-point change in the NIHSS score.

Patients received rt-PA and were randomized using a computer-generated number sheet to receive 500 mg of UA (n=8), 1 g of UA (n=8), or vehicle alone (n=8) at the end of rt-PA infusion. Vehicle consisted of a 500-mL solution of 5% mannitol and 0.1% lithium carbonate to assure the iso-osmolarity and solubility of the preparation. Trial drug was administered intravenously over 90 minutes and
TABLE 1. Main Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Vehicle Alone (N=8)</th>
<th>500 mg UA (N=8)</th>
<th>1000 mg UA (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years, mean (SD)</td>
<td>70.2 (13)</td>
<td>70.2 (8)</td>
<td>72.9 (12)</td>
</tr>
<tr>
<td>Minutes to rt-PA, mean (SD)</td>
<td>128 (29)</td>
<td>139 (42)</td>
<td>131 (37)</td>
</tr>
<tr>
<td>Minutes to UA or vehicle, mean (SD)</td>
<td>206 (23)</td>
<td>223 (60)</td>
<td>207 (38)</td>
</tr>
<tr>
<td>Male gender, n</td>
<td>8</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>High blood pressure, n</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hypercholesterolemia, n</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Baseline parameters, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score</td>
<td>8.5 (4.8)</td>
<td>9.5 (6.4)</td>
<td>14.2 (8.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>142.5 (33)</td>
<td>153.5 (15)</td>
<td>151.5 (21)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.2 (0.2)</td>
<td>1.0 (0.1)</td>
<td>1.0 (0.2)</td>
</tr>
<tr>
<td>UA, mg/dL</td>
<td>6.8 (2.3)</td>
<td>6.0 (1.7)</td>
<td>5.7 (0.9)</td>
</tr>
<tr>
<td>Malondialdehyde, nmol/L</td>
<td>52.7 (19.3)</td>
<td>55.3 (18.9)</td>
<td>79.1 (54.4)</td>
</tr>
<tr>
<td>Malondialdehyde change at day 5, %</td>
<td>+27.5</td>
<td>+23.4</td>
<td>−32.5</td>
</tr>
</tbody>
</table>

TABLE 2. Outcome Events in the Treatment Arms

<table>
<thead>
<tr>
<th>Outcome Events</th>
<th>Vehicle Alone (N=8)</th>
<th>500 mg UA (N=8)</th>
<th>1000 mg UA (N=8)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular death, n (%)</td>
<td>1 (13)</td>
<td>0</td>
<td>1 (13)</td>
<td>0.58</td>
</tr>
<tr>
<td>Symptomatic central nervous system bleeding, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>. . .</td>
</tr>
<tr>
<td>Improvement at day 7, n (%)</td>
<td>4 (50)</td>
<td>6 (75)</td>
<td>4 (50)</td>
<td>0.50</td>
</tr>
<tr>
<td>NIHSS score at day 90, mean (SD)</td>
<td>2 (2.8)</td>
<td>1.3 (1.5)</td>
<td>5.2 (7.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Modified Rankin scale 0 to 1 at 3 months, n (%)</td>
<td>1 (13)</td>
<td>4 (50)</td>
<td>3 (38)</td>
<td>0.26</td>
</tr>
<tr>
<td>Acute arthritis, n (%)</td>
<td>0</td>
<td>0</td>
<td>1 (13)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

it was prepared according to Good Manufacturing and Clinical Practices. The primary safety end point was the rate of gout attack. The premature termination of the study was anticipated if 2 patients experienced a severe gout attack that required aggressive antiinflammatory therapy.

The kinetics of UA were assessed using a Dax analyzer (Bayer-Technichon, Terrytown, N.J.) with an interassay coefficient of variation lower than 3.5%. Data were analyzed by noncompartmental techniques and the elimination rate constant (Ke) was determined from the slope of the terminal elimination phase of the curve of UA concentrations against time. The investigators were blind to the levels of UA until the end of the study. Lithium concentration was analyzed at the end of the infusion and plasma malondialdehyde, a marker of lipid peroxidation, was measured by high-performance liquid chromatography at baseline and at days 2 and 5.

Statistics
Pair Student t test and χ² test were used as appropriate, and serial changes in serum levels of UA and NIHSS score were assessed using repeated-measures analysis of variance with Scheffe correction. Significance was at the P<0.05 level.

Results

Patients Characteristics
There were no significant differences in baseline characteristics among the 3 treatment groups (Table 1). rt-PA was initiated within mean (SD) 133 (35) minutes of stroke onset, and UA/vehicle was initiated within 212 (42) minutes.

Safety and Clinical Outcome
One patient (admission UA, 11.0 mg/dL; peak UA, 16.1 mg/dL) experienced mild acute arthritis within 24 hours after the infusion of 1 g of UA that rapidly resolved with antiinflammatory drugs. Mortality (12.5%) and symptomatic intracerebral hemorrhage (0%) did not differ among the 3 treatment arms (Table 2). Deaths were attributed to recurrent stroke, in one patient allocated vehicle and malignant infarction and cancer in 2 patients allocated 1 g of UA. Serial changes in NIHSS score and rate of favorable outcome at day 90 did not differ among the 3 treatment groups as shown in Table 2.

Pharmacokinetics of Uric Acid
Uric acid showed a maximal decrease 6 to 7 hours after the onset of stroke in patients allocated vehicle as shown in the Figure. Contrarily, patients treated with 500 mg of UA did not show this decrement of UA levels, and those treated with 1 g showed an increment of UA that remained above baseline levels for approximately 24 hours (elimination half-life of 44
come.15 All participants received a vehicle that contained no antioxidant treatments. The study also showed lower lipid peroxidation (0%) were not higher than in open-label studies of rt-PA use in acute stroke.13

Malondialdehyde
At day 5, patients allocated the high-dose of UA showed a decrement of malondialdehyde levels, whereas patients allocated the low dose or vehicle showed an increment (~32.5%, 23.4%, and 27.5%, respectively; P<0.003).

Discussion
In this pilot study, we did not find any serious adverse events related to the administration of UA in patients receiving rt-PA. Only one patient experienced a mild and transient arthritic bout that completely resolved with antiinflammatory therapy. The rates of death (12.5%) or intracerebral hemorrhage (0%) were not higher than in open-label studies of rt-PA use in acute stroke.13

A very early assessment of the levels of UA allowed the identification of a rapid reduction of UA after stroke only in untreated patients, which was maximal 6 hours after the onset of symptoms. The study also showed lower lipid peroxidation at follow up in patients allocated the high-dose of UA. These findings accord with acute stroke studies describing a progressive decline of intracellular and extracellular antioxidants such as superoxide dismutase, carotenoids, or vitamin E.14 A fall of antioxidant vitamins in plasma has also been associated with increased oxidative stress and worse stroke outcome.15 All participants received a vehicle that contained mannitol and lithium, but we disregard any significant contribution of these agents to the clinical results given the very low doses that were administered. The study was not powered to evaluate whether dual therapy with UA and rt-PA improved the clinical outcome at follow up.10 Yet, the early consumption of UA observed in untreated patients, the effect on lipid peroxidation, and the lack of serious adverse effects support additional clinical assessment of UA administration in acute stroke. The low cost of UA is an additional bonus for a larger trial because even a mild clinical benefit would be cost-effective.

Acknowledgments
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Disclosures
None.

References
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