Minocycline to Improve Neurologic Outcome in Stroke (MINOS)
A Dose-Finding Study

Susan C. Fagan, PharmD; Jennifer L. Waller, PhD; Fenwick T. Nichols, MD; David J. Edwards, PharmD; L. Creed Pettigrew, MD; Wayne M. Clark, MD; Christiana E. Hall, MD; Jeffrey A. Switzer, DO; Adviey Ergul, MD, PhD; David C. Hess, MD

Background and Purpose—Minocycline is a promising anti-inflammatory and protease inhibitor that is effective in multiple preclinical stroke models. We conducted an early phase trial of intravenous minocycline in acute ischemic stroke.

Methods—Following an open-label, dose-escalation design, minocycline was administered intravenously within 6 hours of stroke symptom onset in preset dose tiers of 3, 4.5, 6, or 10 mg/kg daily over 72 hours. Minocycline concentrations for pharmacokinetic analysis were measured in a subset of patients. Subjects were followed for 90 days.

Results—Sixty patients were enrolled, 41 at the highest dose tier of 10 mg/kg. Overall age (65±13.7 years), race (83% white), and sex (47% female) were consistent across the doses. The mean baseline National Institutes of Health Stroke Scale score was 8.5±5.8 and 60% received tissue plasminogen activator. Minocycline infusion was well tolerated with only 1 dose limiting toxicity at the 10-mg/kg dose. No severe hemorrhages occurred in tissue plasminogen activator-treated patients. Pharmacokinetic analysis (n=22) revealed a half-life of approximately 24 hours and linearity of parameters over doses.

Conclusions—Minocycline is safe and well tolerated up to doses of 10 mg/kg intravenously alone and in combination with tissue plasminogen activator. The half-life of minocycline is approximately 24 hours, allowing every 24-hour dosing. Minocycline may be an ideal agent to use with tissue plasminogen activator. (Stroke. 2010;41:2283-2287.)

Key Words: dose-finding ■ ischemic stroke ■ minocycline ■ neuroprotection ■ pharmacokinetics

Minocycline is a broad-spectrum neuroprotective agent with multiple proposed mechanisms of action in a wide variety of injury models.1–5 In addition to being an anti-inflammatory agent, minocycline has been shown to be anti-apoptotic6 and an inhibitor of both polyadenosine diphosphate ribose polymerase-1 and the matrix metalloproteinases.7,8 Particularly intriguing is the potential for minocycline to be vascular-protective and reduce the harmful bleeding effects of tissue plasminogen activator (tPA).9,10

Considering minocycline as a repurposed drug with a known safety profile, we evaluated its safety, tolerability, and pharmacokinetics in a dose-escalation trial in patients with acute ischemic stroke.

Materials and Methods
This study was an open-label, dose-escalation trial and was approved by the Institutional Review Boards of the Medical College of Georgia, University of Kentucky, and the Oregon Health Sciences University and the Food and Drug Administration (see Investigational New Drug 77 796; ClinicalTrials.gov identifier NCT0063039) before initiation. All patients or their representative were required to give informed consent before participation. Inclusion criteria were: (1) >18 years of age; (2) acute onset focal neurological deficit consistent with acute ischemic stroke or CT scan consistent with acute cerebral ischemia; (3) onset of symptoms <6 hours; and (4) measurable neurological deficit (National Institutes of Health Stroke Scale score >1). The exclusion criteria were: (1) allergy to tetracycline antibiotics; (2) pregnancy or suspected pregnancy (pregnancy test were done on women of childbearing potential); (3) hepatic and/or renal insufficiency (liver function tests >3× upper limit of normal; creatinine >2 mg/dL); (4) thrombocytopenia (platelet count <75 000/mm3); (5) history of intolerance to minocycline; (6) dizziness at the time of stroke or in the past month (by self-report); (7) aphasia likely to interfere with patient’s ability to report adverse effects; (8) previous functional disability (modified Rankin Scale score >1); (9) stuporous or comatose; (10) presence of another serious illness likely to confound the study; (11) unlikely to be available for 90-day follow-up; (12) severe stroke (National Institutes of Health Stroke Scale score >22); and (13) undergoing an interventional neuroradiological intervention in first 12 hours. Patients were allowed to have

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2283
received tPA because no negative effect on in vitro clot lysis was detected over a wide range of concentrations.\textsuperscript{9}

**Drug Administration**

All patients received an intravenous loading dose of minocycline (MINOCIN; Wyeth, Tokyo, Japan) followed by maintenance doses of half the daily dose every 12 hours for a total of 6 doses. Four dose tiers were planned (3, 4.5, 6, and 10 mg/kg daily) and weight-based doses were capped at 270, 315, 420, and 700 mg daily for each of the 4 tiers. Each dose was reconstituted in 250 mL of lactated Ringer solution and infused over 1 hour.

**Pharmacokinetics**

In eligible patients enrolled at the Medical College of Georgia, blood samples were drawn for quantification of minocycline serum concentrations. Blood (5 mL) was collected at the end of the initial infusion and at 1, 6, 12, 24, 48, and 72 hours after the last dose. Samples were analyzed using high-performance liquid chromatography, as previously reported.\textsuperscript{11,12} Pharmacokinetic parameters were calculated using standard compartmental analysis.

**Safety Assessment**

Investigators closely monitored each patient for evidence of study drug intolerance, particularly focusing on dizziness, gastrointestinal complaints, and infusion reactions. All adverse events were immediately reported to the Safety Officer (F.T.N.) for a decision whether to discontinue the study medication and/or reduce the dose. In addition, daily laboratory tests for assessment of complete blood count and serum chemistries were drawn. The Internal Safety Committee reviewed each patient and met weekly. A Data Safety Monitoring Board was appointed by the National Institutes of Health Committee reviewed each patient and met weekly. A Data Safety

**Dose-Finding Strategy**

A modified continual reassessment method (CRM) design\textsuperscript{13,14} was used to determine the maximum tolerated dose of minocycline. Monitoring of the CRM was performed using software designed by John Cook at MD Anderson (http://biostatistics.mdanderson.org/SoftwareDownload) called CRM based on a Windows platform.

**Results**

Between April 2008 and November 2009, 60 patients were enrolled. Table 1 gives the demographic and baseline characteristics of the 60 patients enrolled in the study overall and by dose tier. At 90 days, 50\% had excellent outcome as determined by a modified Rankin Scale score of 0 or 1 with no difference between the dose tiers (Table 1). There were 5 individuals who died during the time of the study; only 1 was considered as potentially being related to the administration of minocycline and the cause of death was reported as a direct result of the admission infarction. This was the only dose-limiting toxicity recorded in the study. Of the other 2 deaths occurring within hospitalization, the cause of death was listed as malignant brain edema from the qualifying infarction. For the 2 deaths occurring between discharge and 90 days, the cause of death was listed as gastric cancer (presumed) and medical complications or condition due to worsening congestive heart failure.

The only dose-limiting toxicity occurred in an 88-year-old man who had an National Institutes of Health Stroke Scale score of 22 before enrollment and developed elevated hepatic enzymes 1 day before his death and after 3 doses of...
minocycline. There was no explanation for the elevated enzymes other than the minocycline and the impending death. The death was thought to be due to malignant cerebral edema, but the elevation in hepatic enzymes was thought to be “possibly” due to the minocycline. The reversibility of the laboratory abnormality could not be determined due to the patient’s death.

Table 2 gives the descriptive statistics for adverse events occurring within hospitalization overall and by dose tier. The most common types of adverse events that occurred during hospitalization were central nervous system and cardiovascular events. Central nervous system events included altered mental status, depression, fatigue, insomnia, labile emotions, lightheadedness, malignant brain edema, agitation, and insomnia. Cardiovascular-related events included chest pain, heart palpitations, hypotension, bradycardia, tachycardia, and worsening hypertension. There were no recurrent strokes occurring within hospitalization. Other adverse events that were reported most frequently by patients included pain and edema. Gastrointestinal disturbances were reported in 12 patients and infection-related adverse events within hospitalization were minimal (n/H110053 overall). Infusion-related adverse events were uncommon with no phlebitis seen. Pulmonary adverse events included shortness of breath and chest pain, fluid overload, atelectasis (×2), small left pneumothorax, mild pulmonary edema, and bilateral pulmonary crackles.

Table 2. In-Hospital Adverse Events Overall (N=132) and by Dose

<table>
<thead>
<tr>
<th>AE Category</th>
<th>Specific AE</th>
<th>Overall (n=132)</th>
<th>3 mg/kg (n=23)</th>
<th>4.5 mg/kg (n=5)</th>
<th>6 mg/kg (n=5)</th>
<th>10 mg/kg (n=99)</th>
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<tbody>
<tr>
<td>Mortality</td>
<td>In-hospital</td>
<td>3 (2.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>CNS</td>
<td>Dizziness</td>
<td>3 (2.3)</td>
<td>2 (8.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic</td>
<td>3 (2.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Transformation</td>
<td>Neurological worsening†</td>
<td>5 (3.8)</td>
<td>0 (0.0)</td>
<td>1 (20.0)</td>
<td>0 (0.0)</td>
<td>4 (4.0)</td>
</tr>
<tr>
<td></td>
<td>Other CNS</td>
<td>8 (6.1)</td>
<td>3 (13.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (5.1)</td>
</tr>
<tr>
<td>GI</td>
<td>Nausea/vomiting/diarrhea</td>
<td>12 (9.1)</td>
<td>3 (13.0)</td>
<td>1 (20.0)</td>
<td>0 (0.0)</td>
<td>8 (8.1)</td>
</tr>
<tr>
<td>Skin</td>
<td>Skin reactions</td>
<td>4 (3.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (4.0)</td>
</tr>
<tr>
<td></td>
<td>Phlebitis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>Infusion reactions</td>
<td>UTI</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td>2 (1.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (2.0)</td>
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<tr>
<td>Cardiovascular</td>
<td>MI</td>
<td>0 (0.0)</td>
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<tr>
<td></td>
<td>CHF</td>
<td>0 (0.0)</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>Atrial Fibrillation</td>
<td>3 (2.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td></td>
<td>Stroke or TIA</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>Other CV events</td>
<td></td>
<td>16 (12.1)</td>
<td>3 (13.0)</td>
<td>1 (20.0)</td>
<td>2 (40.0)</td>
<td>10 (10.1)</td>
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<tr>
<td>Renal insufficiency‡</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>Thrombocytopenia§</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Elevated liver enzymes§</td>
<td></td>
<td>4 (3.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (4.0)</td>
</tr>
<tr>
<td>Reduced platelet count§</td>
<td></td>
<td>4 (3.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (20.0)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Other laboratory values</td>
<td></td>
<td>8 (6.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (20.0)</td>
<td>7 (7.0)</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>13 (9.8)</td>
<td>2 (8.7)</td>
<td>0 (0.0)</td>
<td>1 (20.0)</td>
<td>10 (10.1)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td>8 (6.1)</td>
<td>1 (4.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>7 (7.0)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>24 (18.2)</td>
<td>2 (8.7)</td>
<td>2 (40.0)</td>
<td>0 (0.0)</td>
<td>20 (20.0)</td>
</tr>
</tbody>
</table>

*As graded by investigator.
†Greater than 4-point increase in National Institutes of Health Stroke Scale.
‡Serum creatinine >2 μg/mL.
§Platelets <100 000.
||From baseline.
CNS indicates central nervous system; GI, gastrointestinal; UTI, urinary tract infection; MI, myocardial infarction; CHF, chronic heart failure; TIA, transient ischemic attack; CV, cardiovascular.

Pharmacokinetics
Pharmacokinetic parameters are summarized in Table 3. In the Figure, the average concentration time curves for the 3- and 10-mg/kg doses are shown. In summary, the half-life and peak concentrations were linear over the doses studied and the half-life averaged near 24 hours.
Discussion
This is the first report of the safety and pharmacokinetics of escalating doses of intravenous minocycline in patients with acute ischemic stroke. All of the 3 deaths occurring during hospitalization were attributed to the patient’s underlying illness and included 2 cases of malignant cerebral edema and 1 infarct extension. Despite the fact that 68% of the 60 subjects enrolled received the highest dose of 10 mg/kg, most adverse effects reported were mild, self-limiting, and unrelated to dose. All were reversible and none were dose-limiting, except for the 1 case mentioned in which the patient died due to the effects of the stroke. It was reassuring that even at the highest dose, no cases of thrombophlebitis were reported. Mild to moderate burning at the infusion site was reported in 12 patients, but careful assessment did not reveal any inflammation or tissue destruction. Dizziness was not reported in any of the patients studied.

In this early-phase dose-finding trial, the modified CRM failed to identify the maximum tolerated dose of intravenous minocycline in acute ischemic stroke. The CRM was developed for use in the treatment of neoplastic diseases in which the acute toxicities are particularly sinister and common. Minocycline, however, is an antibiotic with an admirable safety profile and decades of use in a wide range of patient populations. High-dose intravenous minocycline has not been studied in humans and it was necessary to perform this investigation to demonstrate tolerability with concentrations in the serum that were shown to be robustly neuroprotective in animal models of stroke.3 In fact, the average peak concentrations were >13 μg/mL at all doses studied beyond 3 mg/kg. Even in the 3-mg/kg dose, peak concentrations in all but 2 patients exceeded that shown to be neuroprotective in rodents treated with 3 mg/kg of intravenous minocycline.2 There were 2 patients in whom the peak concentrations did not exceed 3 μg/mL, but both patients exceeded 100 kg in body weight and their actual dose, given the capped dose at 270 mg, was much <3 mg/kg. The half-life of near 24 hours in the stroke population is similar to that previously reported in elderly patients17 and will allow once-daily dosing in future trials. Another pertinent pharmacokinetic finding in this study was the linearity of the parameters over the doses studied and the high variability in volume of distribution, consistent with the high mean and SD of body weight in these patients. Despite the wide variation in peak concentrations, the admirable safety profile suggests a wide therapeutic index for this drug in stroke.

A recent trial of minocycline in patients with amyotrophic lateral sclerosis revealed a worse outcome in the group treated for 9 months, leading the authors to question the

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cmax (First)</th>
<th>Cmax (Last)</th>
<th>Half-Life, Hours</th>
<th>V, L</th>
<th>V, L/kg</th>
<th>AUC (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0 mg/kg</td>
<td>4.91 (2.26)</td>
<td>5.03 (2.01)</td>
<td>23.8 (1.9)</td>
<td>62.8 (32.4)</td>
<td>0.57 (0.19)</td>
<td>96.2 (43.7)</td>
</tr>
<tr>
<td>4.5 mg/kg</td>
<td>14.97 (4.06)</td>
<td>11.08 (2.65)</td>
<td>26.7 (10.8)</td>
<td>20.3 (4.0)</td>
<td>0.30 (0.08)</td>
<td>154.3 (34.2)</td>
</tr>
<tr>
<td>6.0 mg/kg*</td>
<td>14.32</td>
<td>17.21</td>
<td>21.6</td>
<td>28.9</td>
<td>0.34</td>
<td>223.3</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>17.93 (7.99)</td>
<td>23.65 (10.24)</td>
<td>26.9 (6.2)</td>
<td>44.1 (20.7)</td>
<td>0.57 (0.24)</td>
<td>347.7 (113)</td>
</tr>
</tbody>
</table>

*Only one patient at 6 mg/kg enrolled in pharmacokinetic substudy. Cmax indicates maximum drug concentration; V, volume of distribution; AUC (24), area under the curve at 24 hours.

Figure. Average minocycline serum concentrations over time in the 3- and 10-mg/kg dose group (n=12). Only patients with complete data out to 48 hours were included. Peak concentrations after the last dose declined in a log-linear manner with a half-life of approximately 24 hours.
The wisdom of continuing to pursue minocycline as a neuroprotective compound. In the case of acute neuroprotection, however, in which dosing is limited to several days after the injury, we feel strongly that minocycline remains very promising. Even when the drug was administered orally for 5 days after acute ischemic stroke, significantly better stroke outcome was reported. An oral dose would achieve serum concentrations similar to those of a 3-mg/kg intravenous dose in most patients given that minocycline has 100% bioavailability and rapid absorption.

Minocycline holds special promise as an adjunctive therapy to tPA in stroke. It has no negative effect on the fibrinolytic effect of tPA and reduces the incidence and impact of reperfusion hemorrhage in experimental models. More than 60% of our patients also received tPA and we had no cases of severe intracerebral hemorrhage (Safe Implementation of Thrombolysis in Stroke-Monitoring STudy or European Cooperative Acute Stroke Study II criteria). The effects of minocycline on the inhibition of matrix metalloproteinases may explain this perceived benefit. The vascular protective effect of minocycline in acute ischemic stroke deserves further study.

Intravenous minocycline, at doses between 3 and 10 mg/kg daily for 3 days, is safe and achieves concentrations in the serum that have been shown to be neuroprotective in experimental stroke. A large efficacy trial, with once-daily dosing, should be conducted.

Acknowledgments
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S.C.F. received grant support from and is a consultant to Pfizer, Inc, a consultant to Ferrer, and received grant support from the VA Merit Review, National Institute of Neurological Disorders and Stroke (RO1 NS063965). L.C.P. is a consultant for Genesis Biopharma and received grant support from the VA Merit Review. C.E.H. received grant support from Actelion and the National Institute of Neurological Disorders and Stroke and is a REACH cofounder. A.E. received grant support from the VA Merit Review and is an American Heart Association Established Investigator (EA0740002N), National Institutes of Health (RO1DK704385). D.C.H. is a speaker for Genentech and Boehringer Ingelheim, a consultant for Ferrer, and co-founder of REACH, CALL, Inc.

References
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1 Program in Clinical and Experimental Therapeutics, College of Pharmacy, University of Georgia, 2 Departments of Neurology, 3 Physiology and 4 Biostatistics, Medical College of Georgia, Augusta, Ga; 5 Department of Neurology, University of Kentucky, Lexington, Ky; 6 Department of Neurology, Oregon Health and Sciences University, Portland, Ore; 7 Department of Neurology, University of Texas, Southwestern, Dallas, Texas; 8 Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, MI.

Abstract

MINOS 試験：ミノサイクリンにより脳卒中後の神経学的転帰を改善させる臨床試験 — 用量設定試験

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Stroke 2010; 41: 2283-2287

<table>
<thead>
<tr>
<th>用量</th>
<th>Cmax（初回）</th>
<th>Cmax（最終）</th>
<th>半減期（時間）</th>
<th>V（L）</th>
<th>V（L/kg）</th>
<th>AUC（24）</th>
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<tbody>
<tr>
<td>3.0 mg/kg</td>
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</tbody>
</table>

* 薬物動態解析を行った 6 mg/kg 群の患者は 1 例のみであった。

Cmax：最高血中濃度, V：分布容積, AUC (24)：24 時間曲線下面積。