Tolerability and Pharmacokinetics of the Nitrone NXY-059 in Patients With Acute Stroke

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Background and Purpose—Increased free radical formation contributes to the damage caused to the brain by acute ischemia. NXY-059 is a nitrone-based free radical trapping agent in development for acute stroke. NXY-059 has neuroprotective efficacy when given 5 hours after onset of transient focal ischemia in the rat.

Methods—This was a randomized, double-blind, placebo-controlled, parallel group, multicenter study that evaluated the safety and tolerability of 2 NXY-059 dosing regimens compared with placebo within 24 hours of acute stroke. NXY-059 was administered as either 250 mg over 1 hour followed by 85 mg/h for 71 hours or 500 mg over 1 hour followed by 170 mg/h for 71 hours; plasma concentrations were monitored. Neurological and functional outcomes were recorded up to 30 days.

Results—One hundred fifty patients were recruited, of whom 147 received study treatments and completed assessments (50 placebo, 48 lower-dose NXY-059, 49 higher-dose NXY-059). Mean (±SD) age was 68 (±10) years, and baseline National Institutes of Health Stroke Scale score was 7.9 (±6.2). Serious adverse events occurred in 16%, 23%, and 16% of patients, respectively, with deaths in 0%, 10%, and 4%, largely following the proportions with primary intracerebral hemorrhage (6%, 16%, and 8%). Hyperglycemia, headache, and fever were common but not related to treatment. The mean unbound steady state NXY-059 plasma concentrations were 25 and 45 μmol/L, respectively. Population pharmacokinetic analysis estimated clearance to be 4.6 L/h.

Conclusions—NXY-059 was well tolerated in patients with an acute stroke. The testing of higher doses in future trials may be justified. (Stroke. 2001;32:675-680.)

Key Words free radicals • neuroprotection • pharmacokinetics • safety

Although thrombolysis with alteplase improves outcome in patients treated within 3 hours of ischemic stroke onset,1 as few as 1% of patients are presently eligible for such treatment.2,3 There is a substantial unmet need for a neuroprotectant that is safe in hemorrhagic as well as ischemic stroke and that will be effective when initiated later after stroke onset. Trials with a number of drugs acting on the glutamate cascade have been unsuccessful,4–7 perhaps because they fail to protect white matter.8,9 Other mechanisms have been less extensively investigated in humans.10–14

Free radicals are generated during brain ischemia and are implicated in the pathological events that lead to brain damage. NXY-059 is a nitroprone-based free radical trapping agent in development for use in patients with an acute stroke. In rats, NXY-059 protects the brain even when initiated as late as 5 hours after onset of transient focal ischemia15 or 4 hours after permanent middle cerebral artery occlusion.16 Beneficial effects have been demonstrated both early and late, whether assessed by infarct volume measured histologically or by functional testing. Neuroprotection has been confirmed in more than one species, including primates,17 and validated in independent laboratories. These data have been presented at major stroke conferences. Thus, the preclinical evidence for the effectiveness of NXY-059 complies with the recommendations of the Stroke Therapy Academic Industry Roundtable (STAIR) Group.18

In humans, NXY-059 was well tolerated by young healthy male volunteers and by elderly male and female volunteers for periods of up to 72 hours.19 The mean total steady state plasma concentration in the elderly after 72 hours of treatment was 60 μmol/L, and the estimated unbound concentration was 37 μmol/L (infusion rate, 1.1 to 1.5 mg/kg per hour).
Elimination of NXY-059 occurs almost exclusively via the renal route, with approximately 90% excreted unchanged.

To guide the choice of dose for future efficacy trials, in the present study we sought primarily to evaluate the safety and tolerability of NXY-059 in patients with acute stroke; pharmacokinetics were also assessed.

**Subjects and Methods**

**Study Design**
This was a multicenter, double-blind, placebo-controlled trial with central randomization in which an interactive voice response system (Clinphone) was used. It was intended to randomize 150 patients and distribute them equally between placebo, lower-dose NXY-059, and higher-dose NXY-059, with stratification on age and stroke severity to maintain balance in prognostic variables within the treatment groups (Figure 1).

**Patients**
Patients with a clinical diagnosis of acute stroke, whether ischemic or hemorrhagic, within the last 24 hours were considered eligible. Preliminary preclinical data suggest that there may be some benefit of NXY-059, justifying inclusion of patients in whom hemorrhagic stroke had not yet been excluded.20 Stroke symptoms had to be present for at least 1 hour and still be present at the start of treatment, with a measurable deficit on the National Institutes of Health Stroke Scale (NIHSS).21,22 Reduced level of consciousness or evidence of cerebral herniation, known severe hepatic disorder and known or estimated creatinine clearance of 50 to 59 mL/min were not excluded, and other significant life-threatening condition were included, if the initial CT scan suggested that the presenting symptoms were not due to a qualifying ischemic or hemorrhagic stroke, if the patient experienced an intolerable adverse drug reaction, if creatinine clearance fell to <50 mL/min, if a concomitant illness developed or a concomitant illness developed or if the patient had been incorrectly included, if the patient had pathology other than cerebral infarction on any admission imaging tests, if they had participated in a trial of an investigational drug or thrombolytic agent since admission to the hospital, or if they had been started on antihypertensive therapy after stroke onset. In addition, patients were withdrawn from study treatment if they had been incorrectly included, if the initial CT scan suggested that the presenting symptoms were not due to a qualifying ischemic or hemorrhagic stroke, if the patient experienced an intolerable adverse drug reaction, if creatinine clearance fell to <50 mL/min, if a concomitant illness developed or required treatment that would interfere with the trial, or if the patient asked to be withdrawn. Patients who withdrew from continued treatment were encouraged to complete follow-up assessments.

**Study Treatments**
Before randomization, the creatinine clearance was calculated according to the formula of Cockcroft and Gault,23 and patients with an estimated creatinine clearance <50 mL/min were excluded because no data were available on safety, tolerability, or pharmacokinetics at this level of renal function and because NXY-059 is believed to be cleared by urinary excretion.19,24

Study treatment was given as a continuous intravenous infusion for 72 hours, including a 1-hour loading dose (Figure 1). A clear, phosphate-buffered, nonviscous solution was used as placebo. All study treatments were prepared for infusion by dilution in a 500-mL bag of 0.9% sodium chloride solution. Infusion rates for active treatment were 85 and 170 mg/h, with 1-hour loading infusions of 250 and 500 mg, respectively. Patients with creatinine clearance values of 50 to 59 mL/min had a 50% reduction in flow rate.

The infusion rates were chosen on the basis of results of volunteer studies and aimed to attain NXY-059 unbound concentrations >40 μmol/L in a majority of the patients in the higher-dose group, since this exposure was estimated for the dose shown to be neuroprotective when initiated 5 hours after onset of ischemia in a rat stroke model.

**Outcome Measures**
A CT or MRI brain scan was performed within 72 hours of stroke onset to confirm the diagnosis. Vital signs were recorded on admission and at intervals throughout the dosing period. A 12-lead ECG was obtained at admission, 24 to 30 hours after start of treatment, and 4 to 7 days after end of infusion (7 to 10 days after stroke). Blood samples for clinical chemistry and hematology were collected on admission and after 1 hour and 1, 2, 3, and 7 to 10 days. All adverse events were recorded within the first 7 to 10 days and were followed up until day 30. NIHSS score was recorded on admission and after 7 to 10 and 30 days.21,22 Barthel Index was recorded after 7 to 10 and 30 days;22 these assessments were collected for descriptive purposes only (Figure 1).

Blood samples were collected at baseline and at 0.5, 1, 24, and 72 hours after start of treatment for analysis of NXY-059 concentration; up to 4 additional samples after the end of the infusion were collected at 8 centers. Plasma concentrations of NXY-059 were determined by high-performance liquid chromatography at a central laboratory. The limit of quantification was 0.05 μmol/L, with a coefficient of variation of <6.5% in the concentration range 0.365 to 139 μmol/L for plasma samples. Free concentrations of NXY-059 were determined by use of ultrafiltration. Analyses were conducted to charac-
terize population pharmacokinetic parameters of NXY-059 in patients with acute stroke (partly presented here) and to detect any influence of different covariates (including sex, age, creatinine clearance, body weight, body mass index, and center) on the pharmacokinetic parameters (to be published).

Study sites were monitored regularly for data verification and compliance with the protocol. Study blinding was maintained until we had established whether data from all patients were suitable for evaluation.

### Statistical Methods

The analysis of safety was based on all patients who received study drug and had any postrandomization safety data available. All adverse events were analyzed, whether or not they were considered typical complications of stroke. The evaluation of clinical adverse events, including deaths, and laboratory adverse events used statistical tests and estimation procedures as descriptive indicators of treatment group differences.

The analysis of efficacy was based on all patients who received study drug and had any postrandomization safety data available. The efficacy of the 2 doses of NXY-059 and placebo was compared by constructing odds ratios and 95% CIs for different definitions of adverse events, including deaths, and laboratory adverse events used statistical tests and estimation procedures as descriptive indicators of treatment group differences.

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The study commenced in October 1998 and was completed 6 months later, with 15 active centers recruiting between 3 and 33 patients each. One hundred fifty patients were enrolled and randomized (Figure 1), but 3 patients were discontinued before receiving any treatment, and 1 patient in the higher-dose NXY-059 group lacked any follow-up on the efficacy assessments. Figure 2 shows a flowchart of patient disposition. The mean (±SD) age of the patients was 68 (±10) years (range, 37 to 89 years); 60% were male, with a mean weight of 76 (±16) kg (range, 38 to 136 kg) and a mean baseline NIHSS score of 7.9 (±6.2). A prior stroke had occurred in 33 patients (22%). Three patients (2%) were described as functionally dependent before the present stroke, 2 in the higher-dose and 1 in the lower-dose NXY-059 groups. Treatment began at a mean of 15 hours after symptom onset in all treatment groups, and only 10 patients were treated within the first 6 hours. The infusion rate was reduced by 50% in 12 patients (24.5%) in the higher-dose group and 12 patients (25.0%) in the lower-dose group because of a creatinine clearance value of 50 to 99 mL/min.

There were no marked differences in demography between the groups, although, compared with the overall average, baseline NIHSS score was slightly higher in the higher-dose NXY-059 group (8.6±6.4) and slightly lower in the lower-dose group (7.3±5.4). Eight of 50 patients (16%) in the lower-dose group had hemorrhagic stroke compared with 4 of 49 (8%) in the higher-dose group and 3 of 51 (6%) in the placebo group.

### Results

The study commenced in October 1998 and was completed 6 months later, with 15 active centers recruiting between 3 and 33 patients each. One hundred fifty patients were enrolled and randomized (Figure 1), but 3 patients were discontinued before receiving any treatment, and 1 patient in the higher-dose NXY-059 group lacked any follow-up on the efficacy assessments. Figure 2 shows a flowchart of patient disposition. The mean (±SD) age of the patients was 68 (±10) years (range, 37 to 89 years); 60% were male, with a mean weight of 76 (±16) kg (range, 38 to 136 kg) and a mean baseline NIHSS score of 7.9 (±6.2). A prior stroke had occurred in 33 patients (22%). Three patients (2%) were described as functionally dependent before the present stroke, 2 in the higher-dose and 1 in the lower-dose NXY-059 groups. Treatment began at a mean of 15 hours after symptom onset in all treatment groups, and only 10 patients were treated within the first 6 hours. The infusion rate was reduced by 50% in 12 patients (24.5%) in the higher-dose group and 12 patients (25.0%) in the lower-dose group because of a creatinine clearance value of 50 to 99 mL/min.

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### Safety and Tolerability

Treatment was stopped early in 14% of the placebo group and in 17% and 16%, respectively, of the 85-mg/h and 170-mg/h NXY-059 groups. There was no increase in the overall incidence of adverse events during treatment in the NXY-059 groups compared with the placebo group (Table 1). Within the lower-dose NXY-059 group, there were more serious adverse events but fewer adverse events overall than in the other groups.

The most common adverse events present during treatment are shown in Table 2. Hyperglycemia, headache, and fever

### TABLE 2. Adverse Events With Incidence >5% in Any of the Treatment Groups

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>NXY-059 170 mg/h (n=49)</th>
<th>NXY-059 85 mg/h (n=48)</th>
<th>Placebo (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10 (20%)</td>
<td>4 (8%)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Fever</td>
<td>11 (22%)</td>
<td>6 (13%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>11 (22%)</td>
<td>4 (8%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (6%)</td>
<td>5 (10%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Renal function abnormal</td>
<td>6 (12%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>APTT increase</td>
<td>5 (10%)</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (4%)</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (2%)</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

APTT indicates activated partial thromboplastin time.
were common, but the incidences were similar between all groups. None of these events was clearly related to treatment. Reports of abnormal renal function were slightly more frequent in the higher-dose group but were exclusively due to elevations in urinary $\alpha_1$-microglobulin. This is a selective measure of tubular function but is susceptible to substantial interindividual and intraindividual variability in the presence of comorbidity and concomitant medications. No effects on urinary $\alpha_1$-microglobulin could be detected in group level comparisons. Other laboratory tests of hematology or clinical chemistry showed no consistent clinically relevant trend related to treatment group allocation within the study.

Serious adverse events are summarized in Tables 1 and 3. The incidences of these events were equal in the 170-mg/h NXY-059 and placebo groups but were slightly higher in the 85-mg/h NXY-059 group. The imbalance in serious adverse events was mainly due to a higher incidence of cerebral conditions in the lower-dose (85-mg/h) NXY-059 group. Three of the serious adverse event reports in the lower-dose group were due to progressive symptoms of primary intracerebral hemorrhage.

Two patients within the higher-dose group and 5 within the lower-dose group died, giving an overall mortality rate of <5% (Table 1). There was a statistically significant difference in mortality between the lower-dose NXY-059 group and the placebo group ($P=0.025$; Fisher’s exact test, 2-tailed) but not in the overall comparison between the NXY-059 groups and the placebo group ($P=0.096$; Fisher’s exact test, 2-tailed). With 2 exceptions, all of the deaths occurred in patients who had either extensive middle cerebral artery infarctions or hemorrhagic stroke. The exceptions were a patient with cerebellar and brain stem infarction suggesting basilar artery thrombosis and a patient with atrial fibrillation who developed sudden loss of consciousness 11 hours after completing study treatment uneventfully; recurrent stroke was diagnosed by the investigator, and a repeated CT scan showed infarct expansion and mass effect.

Vital Signs

There was no evidence for an effect of NXY-059 on blood pressure, heart rate, or ECG parameters. Within the NXY-059 treatment groups there was an average increase in body temperature of 0.15°C compared with a decrease of 0.08°C in the placebo group. The number of patients with a temperature $>38^\circ$C during the treatment period was 2, 5, and 2 in the higher-dose, lower-dose, and placebo groups, respectively.

Stroke Outcome

The median improvement on the NIHSS was 3 points in all groups. There was no statistically significant difference between placebo and active groups with regard to outcome on the Barthel Index, and there was no difference in proportions of patients achieving an NIHSS score $\leq$1 or an improvement of $\geq$4 points. The distribution of Barthel Index scores at final rating is shown in Table 4.

Pharmacokinetics

The mean unbound steady state plasma concentration of NXY-059 in the higher-dose group was approximately 45 $\mu$mol/L; in the lower-dose group it was 25 $\mu$mol/L (Figures 3 and 4). The fraction unbound ranged from 0.51 to 0.71, and the mean was equal in the 2 NXY-059 groups (0.61, 0.62).

From the population pharmacokinetic analysis, it was concluded that clearance was 4.6 L/h and the volume of the central compartment was 7.2 L. The population model predicted that NXY-059 clearance increased by 1.5%/mL per

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TABLE 3. Serious Adverse Event Reports,* Grouped by Main Body System and Time of Occurrence

<table>
<thead>
<tr>
<th>SAE Reports†</th>
<th>NXY-059 170 mg/h (n=49)</th>
<th>NXY-059 85 mg/h (n=48)</th>
<th>Placebo (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Day 4–30</td>
<td>Treatment</td>
</tr>
<tr>
<td>Cerebral conditions</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Cardiovascular conditions</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Respiratory conditions</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other conditions</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>5 (10%)</td>
<td>3 (6%)</td>
<td>5 (10%)</td>
</tr>
</tbody>
</table>

*Each report could include $>1$ serious adverse event (SAE), and each patient could have $>1$ SAE report.
†Main diagnosis grouped by clinical conditions.

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TABLE 4. Distribution of Outcome According to Barthel Index Scores Among Patients Completing the Trial

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Barthel Index Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good 95–100</td>
</tr>
<tr>
<td>Placebo (n=50)</td>
<td>58</td>
</tr>
<tr>
<td>NXY-059 85 mg/h (n=48)</td>
<td>52</td>
</tr>
<tr>
<td>NXY-059 170 mg/h (n=48)</td>
<td>44</td>
</tr>
</tbody>
</table>

There was no statistically significant difference between placebo and active groups.
minute of creatinine clearance, and the volume of the central compartment increased by 1.8%/kg body wt. No other effect of sex, age, body mass index, or center was detected.

**Discussion**

The primary aim of the present study was to establish the safety and tolerability of administering the nitrone-based free radical trapping agent NXY-059 to acute stroke patients. The treatment was well tolerated, with a general pattern of adverse events that was similar among the 3 groups, and there was no unusual adverse event that would be considered uncommon in stroke. Moreover, no adverse event that was clearly related to treatment could be identified. A rise in temperature was primarily seen in patients with hemorrhagic stroke in both treatment groups, and the imbalance in patients with hemorrhagic stroke confounded the comparison between treatment groups. No clinically significant rise in body temperature could thus be attributed to treatment with NXY-059. Fever is common in stroke, and the overall incidence found here (17%) is identical to the rate in the placebo group of another similar trial. Serious adverse events and mortality were more common in the lower-dose NXY-059 group; however, the lack of a dose-related effect and the higher number of patients with hemorrhagic stroke in this group suggest that imbalance in the distribution of such patients among groups was the main cause of these differences in outcome. Imbalances in mortality and functional outcome are likely to occur in a study of this size because of chance distributions in prognostic factors that affect stroke outcome. Future phase II studies should seek to identify hemorrhage before randomization.

The study was not designed to investigate the efficacy of NXY-059 and would have had insufficient power even if the treatment window had been shorter and follow-up duration longer. There was no significant difference in outcome between the 3 groups.
Population pharmacokinetic analysis was possible and concluded that the population value for clearance in stroke patients was 4.6 L/h. This is somewhat higher than had been reported in healthy elderly subjects, in whom the value is 4.1 L/h. The mean steady state unbound plasma concentration was 45 μmol/L in the higher-dose NYX-059 group. Even though the plasma concentrations achieved in this study compare favorably with those required for neuroprotection in reperfusion animal models of ischemic stroke (8 to 40 μmol/L), higher concentrations have recently been found to be required in models of permanent ischemia.

In conclusion, NYX-059 was well tolerated in patients with an acute stroke, and no concern was raised by the safety evaluation. There were no effects of clinical relevance on laboratory parameters or vital signs. Efficacy cannot be assessed from a study of this size and design. The clearance of NYX-059 in stroke patients is somewhat higher than has been reported in healthy elderly subjects. On the basis of the safety information and plasma concentration data, there appears to be scope and justification for considering higher doses in future trials.

Appendix

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References

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