Tolerability of the Low-Affinity, Use-Dependent NMDA Antagonist AR-R15896AR in Stroke Patients
A Dose-Ranging Study
Kennedy R. Lees, MD, FRCP; Alexander G. Dyker, MD, MRCP; Anil Sharma, FRCP; Gary A. Ford, MD, FRCP; Mark E. Ardron, FRCP; Donald G. Grosset, MD, FRCP

Background and Purpose—AR-R15896AR is a use-dependent, low-affinity blocker of the NMDA ion channel with neuroprotective effects in animal models of focal cerebral ischemia. This study aimed to establish the highest safe and tolerated loading and maintenance dosing regimen of AR-R15896AR in acute ischemic stroke patients and to determine the associated plasma concentrations of AR-R15896AR.

Methods—This was a 4-part, multicenter, randomized, double-blind, placebo-controlled study in 175 patients (mean age, 69 years) within 24 hours of acute stroke symptom recognition. Ascending 60-minute intravenous infusion loading doses of AR-R15896AR were initially examined (100, 150, 200, 250, or 300 mg or placebo in 3:1 randomization, n=36 treated); in part 2, 250, 275, or 300 mg was compared with placebo (n=33). In part 3, a 250-mg loading dose was followed by 9 maintenance doses of 60, 75, 90, 105, or 120 mg every 8 hours versus placebo in 3:1 randomization (n=59); subsequently, in part 4, maintenance doses of 90, 105, and 120 mg after the 250-mg loading dose were directly randomized against placebo (n=42). Safety, tolerability, and pharmacokinetics were the primary end points; NIHSS at 1 week and Barthel and modified Rankin scores at 1 month were also recorded, but the study was neither designed nor powered to assess efficacy.

Results—Rates for mortality and serious adverse events (SAE) were similar in active and placebo groups (9% mortality and 23% SAE for all active combined versus 11% mortality and 33% SAE for placebo). Adverse events associated with AR-R15896AR were dizziness, vomiting, nausea, stupor, and some agitation/hallucination. Withdrawal from treatment occurred only in response to loading doses with AR-R15896AR: placebo, 3 of 46 (7%); 250 mg, 11 of 89 (12%); 275 mg, 1 of 8 (12.5%); and 300 mg, 3 of 15 (20%). No significant difference in outcome was observed between groups. Plasma concentrations of AR-R15896AR were 1524±536 ng/mL at the end of the 250-mg loading infusion and were 1847±478 ng/mL at steady state after the 9 maintenance doses of 120 mg.

Conclusions—The maximum tolerated loading infusion of AR-R15896AR in this study was 250 mg over a period of 1 hour. Subsequent maintenance infusions of 120 mg every 8 hours were well tolerated. With these doses, putative neuroprotective concentrations of 1240 ng/mL are attained by the loading dose and are satisfactorily maintained thereafter. The loading dose may be improved further by adjustment on an individual patient basis, but tolerability issues remain. (Stroke. 2001;32:466-472.)

Key Words: N-methyl-D-aspartate ■ neuroprotection ■ stroke, acute ■ treatment outcome

Survival and functional recovery after acute ischemic stroke can be improved by care within a specialist stroke unit.1 The early use of aspirin confers a small benefit to the majority of patients.2 In a small minority of patients who can be treated very rapidly, thrombolysis with alteplase improves the chance of recovery.3-4 A wealth of experimental evidence from animal models of stroke suggests that neuroprotection with glutamate antagonists, ion channel blockers, or anti-inflammatory strategies can reduce infarct size.5,6 The attraction of these strategies is that they may be suitable for almost universal use and that cerebral imaging before treatment may be unnecessary; to date, however, clinical trials with neuroprotection have been unsuccessful.7-9 There are many potential reasons for this failure, but poor tolerability and/or inadequate dosing may be contributory factors.8,10

The competitive glutamate antagonist selfotel showed neuroprotective effects in the rat model of middle cerebral artery occlusion at plasma concentrations of ≈40 μg/mL. The highest

Received July 10, 2000; final revision received September 25, 2000; accepted October 13, 2000.
From the University Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow, Scotland (K.R.L., A.G.D.); University Hospital, Aintree, Liverpool, England (A.S.); the Departments of Pharmacological Sciences and Medicine, University of Newcastle Upon Tyne (England) (G.A.F.); Leicester Royal Infirmary, Leicester, England (M.E.A.); and the Institute of Neurological Sciences, Southern General Hospital, Glasgow, Scotland (D.G.G.).
Correspondence to Prof Kennedy R. Lees, University Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow G11 6NT, UK. E-mail k.r.lees@clinmed.gla.ac.uk
© 2001 American Heart Association, Inc.
Stroke is available at http://www.strokeaha.org

466
tolerated plasma concentrations in stroke patients were 21 μg/mL, and even these were associated with marked sedative or psychotomimetic effects.\textsuperscript{11} Phase III trials with selfotel were abandoned when an increase in early mortality rates was noted, which may have been related to the central nervous system adverse effects.\textsuperscript{8,12} With the noncompetitive N-methyl-D-aspartate (NMDA) antagonist aptiganel, plasma concentrations that could be tolerated in human stroke ranged from 8 to 12 ng/mL; the minimum putative neuroprotective concentration from the rat middle cerebral artery occlusion (MCAO) model was 10 ng/mL.\textsuperscript{13–15} AR-R15896AR is a low-affinity, use-dependent NMDA channel blocker with affinity for the α-1 receptor.

Preclinical studies with AR-R15896AR have demonstrated neuroprotective activity in animal models, including models of global and focal cerebral ischemia.\textsuperscript{16–20} In the MCAO model in the spontaneously hypertensive rat, animals were given intraperitoneal doses at various times relative to the occlusion (2 hours of focal ischemia by unilateral carotid plus MCA occlusion), with the second and third doses 4 and 12 hours, respectively, after the first dose. There was a significant reduction in cortical infarct volume in actively treated rats (12 mg/kg given as 3 separate doses) when the first dose was administered at periods ranging from 30 minutes before to 30 minutes after MCA occlusion ($P<0.001$). The neuroprotection was smaller when the first dose was given 1 hour after occlusion and absent in the 2-hour postocclusion group. AR-R15896AR (15 mg/kg IV, then 25 mg/kg per day SC for 7 days) was also active in reducing cortical infarct size in the monofilament model of MCAO (2 hours of ischemia).\textsuperscript{18} In another model of “excitotoxic” lesion in which malonic acid is injected directly into the rat striatum, AR-R15896AR (either 9 mg/kg SC or 200 nmol intrastriatal) significantly reduced the striatal lesion volume. In the cat MCAO model (90 minutes of ischemia), infarct volume (MRI T2W imaging) was reduced by 80% after infusion of AR-R15896AR (175 μg·kg$^{-1}$·min$^{-1}$ for 15 minutes) commenced at 30 minutes after the onset of ischemia.\textsuperscript{20} Neuroprotection was observed at 1240 ng/mL, recorded at the end of 15 minutes of dosing during a 90-minute period of ischemia in the cat, and in the rats in the monofilament model experiment given doses that led to concentrations of 2682 ng/mL after 7 days of dosing.

Studies in normal volunteers had found loading doses of up to 160 mg in the young and 120 mg in the elderly to be generally well tolerated, and 8-hour maintenance doses of 70 mg and 60 mg, respectively, to be acceptable. With the latter multiple-dose regimen, average steady-state plasma concentrations of 860 ng/mL were achieved. The most common adverse event was dizziness, but blurred vision was also reported at the highest dose in young volunteers.

The purpose of this study was to establish the highest safe and tolerated loading and maintenance dosing regimen of AR-R15896AR in acute ischemic stroke patients and to determine the plasma concentrations of AR-R15896AR with which these were associated.

**Subjects and Methods**

**Study Design**

This was a multicenter, double-blind, placebo-controlled trial with central randomization and an interactive voice response system. The study received favorable review from local research ethics committees. Written informed consent, witnessed verbal consent, or written relatives’ assent was obtained for each participant, in accordance with institutional and national good clinical practice guidelines and with the Declaration of Helsinki. The study was designed to have 4 parts. The first 2 parts examined the optimal loading dose of AR-R15896AR and the second 2 parts then explored the addition of maintenance doses to the selected loading dose. The first and third parts of the study involved dose escalation in small numbers of subjects; in contrast, the second and fourth parts compared a selection of doses from the preceding part in a randomized fashion. Thus, a series of increasing loading doses were explored in part 1; then, a selection of these was compared in part 2. For parts 3 and 4 of this study, the loading dose was fixed for all subjects receiving active drug. After adding gradually increasing maintenance doses in part 3, the final part of the study compared 3 of the maintenance doses. The increments for dose progression in parts 1 and 3 were prespecified in the protocol, and the decision to move to the next dose was taken jointly between the principal investigator and sponsor after review of acute tolerability data from at least 4 patients (3 randomized to active drug and 1 to placebo). No external data review committee was involved. Randomization was continued for each dose group during the safety assessment on the planned number of patients, giving further safety data at that dose and maintaining recruitment momentum at the study centers.

**Part 1: Loading Dose Escalation**

Within this part, doses used were 100, 150, 200, 250, or 300 mg of AR-R15896AR administered to a minimum of 3 subjects at each dose, or 1 placebo. The drug was infused intravenously into a peripheral vein over a 60-minute period within 24 hours of stroke onset. Progression to the next dose group only took place when the previous dose had been shown to be safe and tolerated.

**Part 2: Randomization to 1 of 3 Selected Loading Doses or Placebo**

In this part of the study, 36 patients were to be randomized into 4 groups of 9 subjects, receiving placebo or 250, 275, or 300 mg of AR-R15896AR administered intravenously over a period of 60 minutes. These doses were chosen on the basis of the preliminary safety and tolerability data from part 1.

**Part 3: Fixed Loading Dose With Maintenance Dose Escalation**

The fixed loading dose used in this part of the study (250 mg administered intravenously over a period of 1 hour) was chosen on the basis of the preliminary safety and tolerability data from part 2 and was followed by 9 maintenance infusions administered over a period of 15 minutes each at 8-hour intervals. Patients were studied in groups of at least 4 (3 active and 1 placebo), with the first group receiving 60 mg every 8 hours. The dose for subsequent groups was increased by 15-mg increments up to a maximum of 120 mg. Progression to the next dose group only took place when the previous dose had been shown to be safe and tolerated.

**Part 4: Randomization to 1 of 3 Selected Loading and Maintenance Dosing Regimens or to Placebo**

On the basis of preliminary assessment of the safety and tolerability data from part 3, 36 patients were to be randomized among 4 groups of 9 patients. The 4 treatments compared were as follows: (1) placebo loading and placebo maintenance doses; (2) 250-mg loading dose plus 9×90-mg maintenance doses; (3) 250-mg loading dose plus 9×105-mg maintenance doses; or (4) 250-mg loading dose plus 9×120-mg maintenance doses.

**Patients**

Previously independent (modified Rankin score 0 or 1) patients with a clinical diagnosis of acute ischemic stroke in any territory within the last 24 hours were considered eligible. Reduced consciousness,
seizure at the onset of stroke, known clinically significant liver or kidney failure, alcohol or substance abuse, or other significant life-threatening conditions were exclusion criteria. Patients were also excluded if they had pathology other than cerebral infarction on the admission CT or MRI scan, if they had participated in a trial of an investigational drug, or if they had fully recovered from the stroke before treatment was assigned. For parts 3 and 4 of the study, patients had to weigh $\geq 55$ kg. Patients were treated within stroke units and received aspirin routinely for ischemic stroke. Patients eligible for thrombolysis were not considered for this trial.

Randomization
Randomization to all dose groups was provided by a computerized telephone service operated by S-Cubed Clinical, Nottingham, UK. An appropriate dose instruction sheet giving precise details of how to prepare and administer the intravenous infusion was issued by fax to the investigator, in response to the randomizing call. By providing patient kits that contained ampoules of active drug and placebo with sufficient volume to cover the likely range of doses to be used, almost any combination of doses could be studied at short notice without the need to resupply centers and without unblinding the investigator.

For assessment of preliminary safety data for each patient in parts 1 and 2, the investigator completed a brief questionnaire 24 hours after the loading dose infusion and returned this by fax to the sponsor. A similar questionnaire was completed after the last maintenance infusion for patients in parts 3 and 4.

Outcome Measures
A CT or MRI brain scan was performed within 72 hours of stroke recognition to confirm the diagnosis. Vital signs were recorded on admission and at intervals throughout the dosing period. A 12-lead ECG was carried out before and toward the end of the loading and maintenance dose infusions. Blood samples for clinical chemistry and hematology were collected on admission and after 1, 3, 7, and 28 days. All adverse events were recorded to 4 weeks. NIH stroke scale Index and modified Rankin Scale scores were recorded after 1 and 4 weeks; these assessments were collected only for descriptive purposes.

Blood samples were collected at all centers to establish peak and trough concentrations for the loading doses and first, second, and eighth maintenance infusions; additional samples were collected to establish the full profile at a single center (Western Infirmary, Glasgow). Plasma concentrations of AR-R15896AR (free base) were determined by a previously validated method, for which the limit of quantification was 10 ng/mL. Standard compartmental and noncompartmental analyses were conducted with the use of WinNonlinPro version 1.5 (Scientific Consulting Inc). Study sites were monitored regularly for data verification and compliance with the protocol. Study blinding was maintained until evaluability of data from all patients had been established. Decisions on dose escalation and the choice of doses for the randomized phases were based on blinded data.

Results
The study commenced in July 1996 and was completed 14 months later, with 5 active centers. One hundred seventy-five patients were enrolled, of whom 174 were randomized. Four patients were discontinued before receiving any treatment and 42 patients were discontinued from treatment, 18 on account of adverse events. Figure 1 shows a flow chart of patient disposition. Demography was similar overall between the active and placebo groups, though with small numbers some of the subgroups showed imbalances in potential prognostic factors. Mean age was 69 years in both groups, with weight 73.7 and 73.2 kg, respectively; 65% and 66%, respectively, were male; there were 9 primary intracerebral hemorrhages (7%) in the active group and 1 (2%) in the placebo group. One patient had a brain tumor on CT scan and 2 had the diagnosis of stroke excluded ultimately. The mean baseline NIHSS score was 8.6 for AR-R15896AR and 9.0 for placebo (range, 1 to 28 for each).
Tolerability and Safety

Adverse effects associated with the loading dose were dizziness, vomiting, nausea, and stupor (Table 1). These were similar to the effects that had been witnessed in volunteers. The dose-response relation appeared shallow, that is, the incidence was similar across a range of doses. Patients withdrew from treatment only at doses 250 mg in parts 1 and 2 of the study, however: 1 of 8 at 275 mg (12.5%) and 3 of 15 at 300 mg (20%). A loading dose of 250 mg was selected for the remainder of the study. All subsequent withdrawals from treatment occurred before maintenance infusions commenced (ie, 3 of 29 after placebo loading infusion [10.3%] and 11 of 72 after a 250-mg loading infusion [15.3%]), and there appeared to be little relationship between the frequency of subsequent adverse events and the maintenance dose (Table 2). Psychotomimetic effects were uncommon during the maintenance infusions: For example, hallucinations and confusion together were seen in 6% of actively treated versus 2% of placebo-treated patients. The overall incidence of adverse events is shown in Table 3.

There was no difference in survival among actively treated versus placebo-treated patients: 5 of 46 patients receiving placebo died (11%) versus 11 of 124 receiving AR-R15896AR (9%). Forty-two patients (24.7%) had 70 serious adverse events. The percentage of patients with a serious adverse event during the whole study was lower in patients receiving active treatment (27 of 124, 21.8%) than in patients receiving placebo treatment (15 of 46, 32.6%; P<0.001). Eighteen patients (10.6%) prematurely discontinued the study because of adverse events, with a higher proportion discontinuing active treatment (15 of 124, 12.1%) than placebo (3 of 46, 6.5%; P<0.001). The most common symptoms leading to discontinuation of AR-R15896AR in parts 1 and 2 were nausea, vomiting, and dizziness, whereas in parts 3 and 4 the most common adverse events leading to discontinuation were dizziness, hallucination, or agitation. All of the 6 patients who had treatment discontinued because of adverse events in parts 3 and 4 had received the loading dose only. There were no consistent clinically relevant trends in laboratory tests of hematology and clinical chemistry related to treatment within the study (Table 4).

Vital Signs

There was no evidence of effects of AR-R15896AR on the ECG. Systolic blood pressure gradually decreased in the placebo

---

TABLE 1. Dose Relation of Adverse Events During Study Drug Treatment in Parts 1 and 2 (Loading Dose Only)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo n=17</th>
<th>100 mg n=3</th>
<th>150 mg n=7</th>
<th>200 mg n=4</th>
<th>250 mg n=15</th>
<th>275 mg n=8</th>
<th>300 mg n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech disorder</td>
<td>1 (7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsions</td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
<td>2 (13%)</td>
<td></td>
<td>1 (7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
<td></td>
<td></td>
<td>1 (13%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>2 (13%)</td>
<td>2 (25%)</td>
<td>2 (13%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1 (14%)</td>
<td></td>
<td></td>
<td>1 (7%)</td>
<td>2 (25%)</td>
<td>2 (13%)</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td>2 (29%)</td>
<td>2 (50%)</td>
<td>2 (13%)</td>
<td>2 (25%)</td>
<td>2 (13%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (12%)</td>
<td></td>
<td></td>
<td></td>
<td>1 (14%)</td>
<td>2 (13%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Stupor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (13%)</td>
<td></td>
</tr>
<tr>
<td>Visual disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

TABLE 2. Dose Relation of Adverse Events During Study Drug Treatment in Parts 3 and 4 (Loading+Maintenance Doses)

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo n=29</th>
<th>60 mg n=6</th>
<th>75 mg n=4</th>
<th>90 mg n=19</th>
<th>105 mg n=16</th>
<th>120 mg n=27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>1 (17%)</td>
<td>2 (50%)</td>
<td>7 (37%)</td>
<td>7 (44%)</td>
<td>9 (33%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7 (24%)</td>
<td></td>
<td>6 (32%)</td>
<td>2 (13%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Stupor</td>
<td>1 (17%)</td>
<td>2 (11%)</td>
<td>2 (13%)</td>
<td>2 (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggressive reaction</td>
<td>1 (17%)</td>
<td></td>
<td></td>
<td>1 (17%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>2 (7%)</td>
<td>1 (25%)</td>
<td>2 (11%)</td>
<td>1 (6%)</td>
<td>3 (11%)</td>
<td></td>
</tr>
<tr>
<td>Hallucination</td>
<td>1 (3%)</td>
<td></td>
<td>1 (5%)</td>
<td>1 (6%)</td>
<td>3 (11%)</td>
<td></td>
</tr>
<tr>
<td>Visual disorders</td>
<td>2 (7%)</td>
<td>1 (25%)</td>
<td>2 (11%)</td>
<td>4 (25%)</td>
<td>4 (15%)</td>
<td></td>
</tr>
</tbody>
</table>
group over the period of observation, whereas in the actively treated groups it showed a small rise, with a mean increase of 13 mm Hg 1 hour after the 250-mg loading dose infusion.

**Stroke Outcome**

The proportions of patients achieving good outcome, as defined by 1-month Barthel score 95 to 100, 1-month modified Rankin scale of 2 to 4, or NIHSS 0 to 1 were 42%, 39%, and 25%, respectively, for AR-R15896AR versus 22%, 23%, and 12% with placebo. Moderate outcome, defined as Barthel score 60 to 90, modified Rankin scale 2 to 3, or NIHSS 2 to 8 was achieved in 24%, 20%, and 45% of patients with AR-R15896AR and 12%, 8%, and 23%, respectively, after placebo. There was no statistically significant difference between placebo and active groups with regard to any outcome.

**Pharmacokinetics**

All patients provided samples at the end of the loading dose infusion in parts 1 and 2, and all patients in parts 3 and 4 provided samples before and at the end of maintenance doses 1, 2, and 8. In addition, extensive sampling was available from 5 patients with loading dose infusions and 7 patients with loading and maintenance infusions.

The plasma concentration at the end of the loading dose infusion increased with dose, ranging from 702 ± 217 ng/mL (mean Cmax ± SD) at 100 mg up to 1922 ± 888 ng/mL at the highest dose of 300 mg. At the end of the infusion, AR-R15896AR concentration declined biexponentially, with a terminal half-life of 14.8 ± 0.6 hours at the highest dose. Clearance and volume of distribution at steady state did not appear to change with infusion rate, with top dose values of 0.113 ± 0.015 L · h⁻¹ · kg⁻¹ and 2.30 ± 0.42 L/kg, respectively. The maximum plasma concentration at steady state after a single loading dose infusion of 250 mg and 8 subsequent maintenance dose infusions increased with dose, ranging from 1146 ± 391 ng/mL at 60 mg TID up to 2298 ± 722 ng/mL at 120 mg TID. The average steady-state concentration increased with dose, up to 1847 ± 478 ng/mL (range, 1370 to 3180 ng/mL) at 120 mg TID. The plasma concentration–time data for the 250-mg loading dose infusion and 120 mg TID maintenance dose infusion are displayed in Figure 2.

**Discussion**

The aim of this study was to establish the highest safe and tolerated loading and maintenance dosing regimen of AR-R15896AR in acute ischemic stroke patients. The highest dose regimen studied, of 250 mg over a period of 1 hour followed by maintenance infusions of 120 mg every 8 hours, was generally well tolerated. At this dose, there was relatively stable or mildly increased blood pressure and heart rate; there were no consistent clinically relevant changes or trends in ECG, body temperature, or any laboratory variable; and only 4 of 27 (15% of patients) discontinued treatment with

---

**TABLE 3. Summary of All Adverse Events Occurring With Frequency of ≥5% in Either Treatment Group (From Parts 1 Through 4 Irrespective of Dose)**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo n=46</th>
<th>AR-R15896AR n=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>7%</td>
<td>29%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9%</td>
<td>15%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Headache</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Stupor</td>
<td>0%</td>
<td>6%</td>
</tr>
<tr>
<td>Agitation</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>2%</td>
<td>6%</td>
</tr>
</tbody>
</table>

**TABLE 4. Neurological Outcome at 1 Week (NIHSS) and Functional Outcome at 1 Month (Barthel Index and Modified Rankin Score)**

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>NIHSS Favorable Outcome</th>
<th>Barthel Index Favorable Outcome</th>
<th>Modified Rankin Scale Favorable Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n (%)</td>
<td>n</td>
</tr>
<tr>
<td>Placebo</td>
<td>16</td>
<td>6 (38%)</td>
<td>16</td>
</tr>
<tr>
<td>100 mg</td>
<td>3</td>
<td>2 (67%)</td>
<td>3</td>
</tr>
<tr>
<td>150 mg</td>
<td>7</td>
<td>3 (43%)</td>
<td>7</td>
</tr>
<tr>
<td>200 mg</td>
<td>3</td>
<td>0 (0%)</td>
<td>3</td>
</tr>
<tr>
<td>250 mg</td>
<td>14</td>
<td>4 (29%)</td>
<td>11</td>
</tr>
<tr>
<td>275 mg</td>
<td>8</td>
<td>1 (13%)</td>
<td>8</td>
</tr>
<tr>
<td>300 mg</td>
<td>12</td>
<td>1 (8%)</td>
<td>12</td>
</tr>
<tr>
<td>Placebo</td>
<td>27</td>
<td>6 (22%)</td>
<td>25</td>
</tr>
<tr>
<td>60 mg</td>
<td>6</td>
<td>0 (0%)</td>
<td>5</td>
</tr>
<tr>
<td>75 mg</td>
<td>3</td>
<td>1 (33%)</td>
<td>2</td>
</tr>
<tr>
<td>90 mg</td>
<td>15</td>
<td>4 (27%)</td>
<td>14</td>
</tr>
<tr>
<td>105 mg</td>
<td>10</td>
<td>3 (30%)</td>
<td>10</td>
</tr>
<tr>
<td>120 mg</td>
<td>25</td>
<td>6 (24%)</td>
<td>24</td>
</tr>
</tbody>
</table>

Favorable outcome was defined as NIHSS 0 to 1, Barthel Index 95 to 100, or Modified Rankin Scale 0 to 1; none of the differences between treatment groups was significant.
AR-R15896AR because of adverse events compared with 3 of 29 with placebo (10%). Serious adverse events were no more common with active treatment than with placebo treatment, and mortality rates were similar between the two groups. Nevertheless, AR-R15896AR was clearly associated with adverse events, particularly dizziness, vomiting, nausea, stupor, and some agitation/hallucinations. These effects are typical for other NMDA antagonists and represented dose-limiting symptoms.26

In the light of these adverse events, the pharmacokinetic analysis is crucial. No patients withdrew from treatment because of adverse events related to the maintenance doses, and plasma concentrations at the highest of the maintenance doses (120 mg TID) were in excess of those associated with neuroprotection in the cat model of focal cerebral ischemia. Direct extrapolation from animal models to human stroke is compromised in patients with stroke. At this stage, there is no experience of using potent antiemetic drugs in combination with AR-R15896AR, though this is a potential approach. The other central nervous system adverse effects that were observed did not require active management during this phase II trial but may respond to coadministration with a benzodiazepine, as has been demonstrated with ketamine in clinical use28,29 and with aptiganel in animals (unpublished observation). Benzodiazepines may, however, reduce consciousness and exacerbate any risk of aspiration.

When the therapeutic index of a neuroprotective compound is narrow, as in the case of the NMDA antagonists, it is essential to explore the dose-response relation systematically. The trial design that was used here is novel and appears to have satisfied its objective. It is necessary to explore a range of doses in a small number of subjects, starting with one that is believed to be well tolerated. The high incidence of spontaneous adverse events in patients with acute stroke can lead to difficulty in interpreting the results of dose escalation studies in small numbers of subjects. For this reason, it is necessary to explore any apparent dose-response relation, further using a randomized design before drawing conclusions about the optimal dose for further study. The randomized comparison of loading doses in this study suggested that 250 mg was the optimal choice. Although the true withdrawal rate was underestimated by part 2 when experience in parts 3 and 4 is considered, the incidence of adverse events was also higher at 275 mg than at 250 mg. Exploratory analyses during the study suggested that adjustment of dose according to patient weight may reduce variability in response further but were not finalized in time to be incorporated into the protocol for parts 3 and 4.

Rapid administration of drug to attain neuroprotective concentrations within the brain is the primary aim. Having achieved this aim, it is presently considered desirable to maintain these concentrations for a period of several days, though the optimal duration is not yet known.30 Although suitable maintenance doses can be estimated from pharmacokinetic considerations, the possibility of cumulative effects of the drug or conversely, tolerance to the drug, exists. It is therefore necessary to explore maintenance doses by using a similar dose escalation design, with randomization to confirm the findings. Again, the design has efficiently established the dose-tolerability relation for maintenance therapy.

It is of note that inclusion of a placebo group is essential in trials such as this. With the dose-escalation design, it became apparent that higher doses were associated with adverse effects, and these were being communicated to future patients during the consent procedures. Without a placebo group, interpretation of symptoms described by subsequent patients would have been confounded because there was evidence of a trend toward increasing adverse events in the placebo group in the later stages of the trial, with 10% of patients finding the placebo loading dose intolerable in parts 3 and 4 versus none of 17 in parts 1 and 2.

This trial could have been conducted in 4 separate stages, with analysis of the results from each stage before proceeding to the next. Instead, the decision to continue randomization while analysis was being performed allowed the momentum to be maintained at each of the recruiting centers at the
expense of including a few more patients than were consid-
ered essential but with substantial savings in time and overall
cost. The data from the additional patients contributed to the
overall analysis.

A phase II dose-ranging study such as this cannot be
expected to test efficacy. The long time window to inclusion
and the short duration of follow-up, plus the inevitable
imbalance in stroke severity among the small subgroups,
confound any interpretation of the outcome measures. This
has been a feature of previous phase II trials with other
neuroprotective compounds such as lube luluzole and
GV150526. In the former case, phase III trials failed to
confirm the apparent efficacy demonstrated in phase II, and in
the latter case, phase III trials have failed to confirm the
apparent adverse outcome that had initially been observed.7,9,31,32

In summary, the maximum tolerated loading infusion of
AR-R15896AR appears to be 250 mg over a period of 1 hour.
Subsequent maintenance infusions of 120 mg every 8 hours
are well tolerated. With these doses, putative neuroprotective
concentrations are just attained by the loading dose and are
satisfactorily maintained thereafter. This loading dose is not
optimal, however, and could be further improved by adjust-
ment on an individual patient basis. Even so, tolerability
issues remain, and further development of the compound for
stroke would depend not only on demonstration of efficacy
but on measures to limit the symptomatic side effects of
treatment and their potential for adversely influencing
income.

Acknowledgments

The study was sponsored and all drug supplies were provided by
AstraZeneca (formerly Astra Charnwood). The support of Drs
Frances Willett, John Hutchison, Andrew Dean, and Henrik Linder
and their colleagues at various stages was much appreciated. The
support of Drs

References

1. Stroke Unit Trialists’ Collaboration. Collaborative systematic review of
the randomised trials of organised inpatient (stroke unit) care after stroke.
2. CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: ran-
domised placebo-controlled trial of early aspirin use in 20,000 patients
3. National Institute of Neurological Disorders and Stroke rt-PA Stroke
Study Group. Tissue plasminogen activator for acute ischemic stroke.
4. Lees KR. ECASS-II: intravenous alteplase in acute ischaemic stroke.
5. McCulloch J. Excitatory amino acid antagonists and their potential for
351:1447–1448.
7. Diener HC, for the European and Australasian Lubeluzole Ischaemic Stroke
Study Group. Multinational randomised controlled trial of lube luluzole in
Norris J, for the ASSIST Investigators. Selfotel in acute ischemic stroke:
possible neurotoxic effects of an NMDA antagonist. Stroke. 2000;31:
347–352.
Orogogozo J, Whitehead J, for the GAIN International Investigators.
Glycine antagonist gavestinel in neuroprotection (GAIN International) in
10. De Keyser J, Sulte G, Luiten PG. Clinical trials with neuroprotective
drugs in acute ischemic stroke: are we doing the right thing? Trends
11. Steinberg GK, Perera AM, Maier CM, Sun GH, Yoon E, Kunis
DM, Bell TE, Powell M, Kotake A, Giffard R. CGS-19755: correlation of
in vitro neuroprotection, protection against experimental ischemia and
CSF levels in cerebrovascular surgery patients. In: Proceedings of the 5th
International Symposium on Pharmacology of Cerebral Ischemia; July
20–22, 1994; Marburg, Germany. Abstract.
Abstract.
13. Park CK, McBurney RN, Holt WF, Cotter RE, McCulloch J, Kang JK,
Choi CR. LXIII-2: the dose-dependency of the antiischemic efficacy and
of the side effects of a novel NMDA antagonist, CNS1102. J Cereb
14. Mair KW, Grosset DG, Lees KR. Effects of prolonged infusions of the
NMDA antagonist aptiganel hydrochloride (CNS 1102) in normal vol-
15. Dyker AG, Edwards KR, Fayad PB, Hornes JT, Lees KR. A safety and
tolerability study of aptiganel hydrochloride in patients with an acute
Blusser J, Morley P, N-alpha-methyl-D-aspartate- or glutamate-mediated
toxicity in cultured rat cortical neurons is antagonized by FPL 15896AR.
17. Cregan EF, Peeling J, Corbett D, Buchan AM, Saunders J, Auer RN,
Gao M, McCarthy DJ, Eissman MS, Campbell TM, Murray RJ, Stagnitto ML,
Palmer GC. [(S)-alpha-phenyl-2-pyridine-ethanamine dihydrochloride], a
low affinity uncompetitive N-methyl-D-aspartic acid antagonist, is effective
in rodent models of global and focal ischemia. J Pharmacol Exp
Simmons R, Gendron P, McCarthy DJ, Palmer GC. Efficacy of AR-R15896AR
in the rat monofilament model of transient middle cerebral artery occlusion.
AR, a low affinity, use-dependent NMDA antagonist, is neuroprotective
20. Sutherland GR, Perron JT, Kozlowski P, McCarthy DJ. AR-R15896AR
reduces cerebral infarction volumes after focal ischemia in cats. Neuro-
Measurements of acute cerebral infarction: a clinical examination scale.
EC, Grotta J, Marler J. Improved reliability of the NIH stroke scale used
23. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index.
24. Rankin J. Cerebral vascular accidents in patients over the age of 60, II:
J. Interobserver agreement for the assessment of handicap in stroke
26. Mair KW, Lees KR. Clinical experience with excitatory amino acid
27. Stroke Therapy Academic Industry Roundtable (STAIR). Recommenda-
tions for standards regarding preclinical neuroprotective and restorative
28. Erdmann W, Salt PJ, Agoston S, Langrehr D. Antagonism of the cardio-
vascular effects of ketamine by diazepam in volunteers. Anesthesiology.
29. Cartwright PD, Pingel SM. Midazolam and diazepam in ketamine anaes-
30. Dyker AG, Lees KR. Duration of neuroprotective treatment for ischemic
31. Diener HC, Hacke W, Hennerici M, Radburg J, Hantson L, De Keyser J,
Lubeluzole in acute ischemic stroke: a double-blind, placebo-controlled
Tolerability of the Low-Affinity, Use-Dependent NMDA Antagonist AR-R15896AR in Stroke Patients: A Dose-Ranging Study
Kennedy R. Lees, Alexander G. Dyker, Anil Sharma, Gary A. Ford, Mark E. Ardron and Donald G. Grosset

Stroke. 2001;32:466-472
doi: 10.1161/01.STR.32.2.466

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/2/466

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/