Safety and Tolerability Study of Aptiganel Hydrochloride in Patients With an Acute Ischemic Stroke

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Background and Purpose—Aptiganel (CNS 1102) is a selective, noncompetitive antagonist that acts on the ion channel associated with the \(N\)-methyl-\(D\)-aspartate (NMDA) receptor and is neuroprotective in experimental focal cerebral ischemia models at a plasma concentration of 10 ng/mL. In human volunteers, dose-limiting effects of aptiganel are blood pressure increases and central nervous system (CNS) excitation or depression. This study assessed the safety and tolerability of non–weight-adjusted doses of aptiganel in patients with acute ischemic stroke.

Methods—This was a double-blind, randomized, placebo-controlled multicenter study in patients presenting within 24 hours of acute ischemic stroke. Ascending single intravenous bolus doses of aptiganel (3, 4.5, 6, and 7.5 mg) were assessed in 21 patients with a 3:1 active drug:placebo randomization schedule. In 15 subsequent patients, selected bolus doses were followed by constant intravenous infusion for 6 to 12 hours (6 mg plus 1 mg/h, \(n = 10\); then 4.5 mg plus 0.75 mg/h, \(n = 15\)) in a 4:1 randomization schedule. Prospectively collected pharmacokinetic data guided selection of infusion rates. Neurological and functional status were recorded at entry and after 1 week, although the study was not designed to test efficacy.

Results—Forty-six patients were randomized from 4 centers (3 in the United States and 1 in the United Kingdom): 36 received aptiganel HCl, and 10 were given placebo. Hypertension and CNS events were commonly reported after a bolus dose of 7.5 mg and after a 6-mg bolus followed by an infusion of 1 mg/h. The lower regimen of 4.5-mg bolus followed by infusion of 0.75 mg/h achieved plasma aptiganel concentrations of \(\geq 10\) ng/mL and was well tolerated by patients but still raised systolic blood pressure by \(\sim 30\) mm Hg over baseline.

Conclusions—A 4.5-mg intravenous bolus of aptiganel HCl followed by infusion of 0.75 mg/h for 12 hours is a tolerable dose that can produce plasma drug concentrations shown to be neuroprotective in animal models. However, increases in systolic blood pressure and an excess of CNS effects were both observed at this dose. (Stroke. 1999;30:2038-2042.)

Key Words: aptiganel ■ stroke, acute ■ neuroprotection ■ glutamate antagonists ■ NMDA antagonists

Neuronal damage after stroke is aggravated by accumulation of neurotoxic excitatory amino acids.\(^1\) Aptiganel [\(N\)-(1-naphthyl)-\(N\)-(3-ethyl phenyl)-\(N\)-methyl guanidine hydrochloride (CNS 1102)] is a selective noncompetitive antagonist within the ion-channel pore of the \(N\)-methyl-\(D\)-aspartate (NMDA) receptor. In vitro studies show it to be a high-affinity antagonist that is neuroprotective in cultures of brain cells exposed to toxic concentrations of the excitatory amino acid glutamate.

Aptiganel reduced cerebral infarct volume by 66%, measured histologically and by diffusion-weighted MRI scanning, after permanent occlusion of the middle cerebral artery (MCA) in rats.\(^2\) The plasma concentration associated with the minimum neuroprotective intravenous dose of 250 \(\mu\)g/kg is 10 ng/mL (E.R. Gamzu, verbal communication, 1998). Similar results were obtained in other permanent and reperfusion models of rat brain ischemia. The neuroprotection achieved within these animal models was comparable to other neuroprotective compounds currently undergoing development.\(^3,4\)

Aptiganel has been given as a 15-minute bolus to 21 healthy male volunteers within a double-blind ascending-dose study. Dose-dependent central nervous system (CNS) effects and increases in systolic blood pressure were reported at doses \(> 30\) \(\mu\)g/kg.\(^5\) More prolonged infusions did not increase the total dose that could be tolerated by normal volunteers.

Stroke patients appear to tolerate aptiganel better than healthy volunteers. Up to 110 \(\mu\)g/kg produced minimal neurological or hemodynamic effects in stroke patients.\(^6\) The present study aimed to determine the maximally tolerated bolus dose of aptiganel and to define an appropriate infusion to maintain plasma levels at steady state.
Patients and Methods

Study Design

This was a multicenter, double-blind, randomized, placebo-controlled safety and tolerability study of ascending doses of aptiganel in 2 phases. The first phase (part A) consisted of single ascending doses and the second (part B) of a bolus dose followed by an extended infusion.

Ethical approval was gained locally. Patients gave written, witnessed informed consent. If the patient was unable to give consent, written informed assent was accepted from the next of kin or other close family member. The design for the first part of the study was one of dose escalation in increments of 1.5 mg (starting dose >3 mg) until a maximally tolerated or an unsafe level was reached. A dose would be considered unsafe if 50% of the patients experienced a >30 mm Hg rise in systolic blood pressure that was maintained for ≥1 hour.

Eligibility Criteria

Patients with acute neurological deficit consistent with a diagnosis of carotid artery territory stroke were considered eligible, according to the following criteria: acute neurological deficit of at least 1-hour duration but ≤24 hours; males or nonfertile females; 21 years of age or older; weight 50 to 150 kg inclusive; baseline NIH Stroke Scale score ≥4 to 20; and pretreatment CT scan consistent with diagnosis of ischemic stroke. Patients with any of the following conditions were excluded from the study: coma or stupor (unable to localize pain); malignant hypertension; significant hypotension (blood pressure <90/50 mm Hg); any other unstable medical condition; or involvement in any other investigational drug study within the previous 3 months.

Trial Medication

In part A of the study, patients received drug or placebo (3:1 randomization by telephone) diluted to 10 mL with normal saline and administered over 2 to 5 minutes by intravenous injection. Doses of aptiganel were not adjusted for patient weight, because previous work suggested this would be unnecessary.

In part B, 2 bolus doses selected from the first phase were followed by a 6-hour infusion (extended to 12 hours if judged by the attending physician to be well tolerated). Patients were randomized in a ratio of 4:1 active drug:placebo. Rates of infusion in part B were based on pharmacokinetic data derived from part A and previous studies. The first group of patients received a 6-mg bolus dose followed by 1 mg/h. Additional assessment at this dose was abandoned due to the high frequency of intolerable side effects. Subsequent patients received a 4.5-mg bolus followed by 0.75 mg/h.

Outcome Measures

Tolerability and vital signs were closely monitored for 24 hours. Adverse events were documented contemporaneously. No formal statistical analysis was performed on the adverse event data, and descriptive statistics were used to compare outcome data. Blood and urine were taken for analysis at presentation, 24 hours after start of drug administration, and at 7±2 days. Pharmacokinetic samples were drawn from an indwelling forearm cannula contralateral to the drug infusion at frequent intervals up to 12 hours after bolus injection. The investigators summarized the tolerability and vital sign data and provided their assessment of treatment “acceptability” by facsimile transmission to the coordinating center 24 hours after dosing.

The study was not designed to test efficacy, but preliminary outcome data were collected (NIH Stroke Scale,7 Scandinavian Stroke Scale, and Barthel Index). NIH and Scandinavian Stroke Scale assessments were made at screening, 24 hours after bolus dosing, and at 7±2 days. Functional Barthel Index score was assessed on day 2, although the questionable value of such early assessment is acknowledged.

Laboratory Methods

Plasma was stored at −20°C until pharmacokinetic analysis by high-performance liquid chromatography with ultraviolet detection, validated in the range of 1.25 to 100 ng/mL. Intra-assay coefficients of variation ranged from 1.0% to 2.5%, with interassay coefficients of variation <4%.

Results

Four clinical sites participated in the study: 3 in the United States and 1 in the United Kingdom. Forty-six patients were admitted to the study; 36 received aptiganel, and 10 were given placebo.

Part A

Twenty-one patients were recruited to this part of the study: 16 received aptiganel and 5 placebo, with ≥4 patients evaluated in each group before dose escalation. Nine men and
12 women were recruited; mean age was 62 years [range 28 to 84 years]; weight was 77 kg [range 51 to 124 kg]. One patient receiving placebo died of a recurrent stroke on day 21 after treatment. The other 2 patients who died received active treatment at the 6-mg dose. One patient suffered a second stroke after pacemaker insertion. He died of respiratory failure after an episode of pneumonia 25 days after entering the study. A second patient died after going into respiratory arrest subsequent to experiencing a large hemispheric cerebral infarction.

CNS effects were reported equally frequently among the placebo and 3-, 4.5-, and 6-mg dose groups. CNS effects were both more frequent and more severe in the 7.5-mg dose group; of these 6 patients, marked sedation occurred in 1, hallucinations occurred in a second, and 3 became confused.

Systolic blood pressure rose in a dose-dependent manner with active treatment but fell with placebo. One of 3 patients at the 3-mg dose had a 35-mm Hg rise in blood pressure. One of 3 patients at the 4.5-mg dose exhibited a 64-mm Hg rise in systolic blood pressure at 2.5 hours. Two of 3 patients at the 6-mg dose had rises in systolic pressure of 44 and 38 mm Hg, respectively. In the highest-dose group (7.5 mg), systolic blood pressure rose in 3 of 6 patients by 49, 60, and 62 mm Hg. The rise in systolic blood pressure and severe CNS adverse effects within the 7.5-mg dose group precluded continued evaluation of this dose in part B of the study.

Plasma aptiganel concentrations above the putative neuroprotective level were attained with doses of 4.5 mg or greater. Plasma concentrations did not correlate with patient weight.

Part B

Twenty-five patients (9 men, 16 women; mean age 72 years [range 43 to 86 years]; weight 78 kg [range 43 to 126 kg]) were recruited to part B of the study. Twenty received drug, and 5 were given placebo. Eight patients received a 6-mg bolus followed by an infusion of 1 mg/h for a maximum of 12 hours. The actual duration of the infusion was at the discretion of the investigator on the basis of the observed effects. Because the 6-mg bolus plus 1-mg/h dose was poorly tolerated, 4.5 mg followed by 0.75 mg/h was subsequently administered to 12 patients. There were no deaths during the follow-up period of part B of the study.

Six patients had their trial medication discontinued prematurely owing to hypertension or intolerance (5 from the 6-mg plus 1-mg/h group and 1 from the 4.5-mg plus 0.75-mg/h group; Table 1). CNS effects were severe and frequent at the 6-mg plus 1-mg/h dose, with 6 of 8 patients suffering profound sedation. Three of 8 patients were treated for systolic blood pressure rises to >210 mm Hg. Only 1 patient in the 4.5-mg plus 0.75-mg dose group developed severe sedation with agitation and hallucinations, but symptoms were prolonged, lasting 4 days. CNS adverse events remained more common in this group than after placebo (Table 2).

The average rise in systolic blood pressure with aptiganel 4.5 mg plus 0.75 mg/h was 30 mm Hg (Figure 1). Four of the 12 patients recruited to this group were administered antihypertensive treatment, with subsequent dramatic reductions in blood pressure. The response was even more marked when compared with the expected blood pressure fall in placebo patients. Aptiganel had no effect on hematology, urinalysis, or biochemistry tests or on the electrocardiograms.

Plasma aptiganel concentrations achieved by both doses exceeded putative neuroprotective levels (Figure 2) and were similar for the 2 dose groups (P=0.35 by ANOVA). Infusions were more frequently discontinued before 12 hours in the 6-mg plus 1-mg/h group. Plasma pharmacokinetics remained linear, and clearance was unaffected by the duration of infusion. Patient weight did not influence concentrations achieved. There was no correlation between plasma levels achieved and the severity of side effects reported. The C_{max} ranged widely, from 10 to 21 ng/mL, in those patients who did not receive the full 12 hours of infusion. Pharmacokinetics are summarized in Table 3.

There was no significant difference between placebo and actively treated groups in terms of the final NIH Stroke Scale, Scandinavian Stroke Scale, or Barthel Index scores. Patients treated with bolus plus infusion had poorer NIH Stroke Scale scores at admission than patients who received placebo.
Discussion

In a population of stroke patients, a non–weight-adjusted dose of aptiganel 4.5 mg followed by an infusion of 0.75 mg/h achieves and maintains plasma levels thought to be neuroprotective in animals (>10 ng/mL). This dosing schedule is reasonably tolerated but causes a mean rise in systolic blood pressure of 30 mm Hg. Although sedation occurred at this dose in only 1 of 12 subjects, this instance was delayed, prolonged, and severe. The blood pressure rises responded promptly to antihypertensive treatment. There was no correlation between the time after stroke at which treatment was commenced and the severity of blood pressure effects. Higher-dose infusions of 6 mg plus 1 mg/h were associated with dramatic increases in blood pressure and frequent reporting of intolerable CNS side effects.

Hemodynamic changes may influence stroke outcome. At the time of cerebral ischemia, cerebral autoregulation is deranged. Thus, changes in blood pressure could directly produce changes in local cerebral perfusion, particularly in penumbral areas. Reductions in blood pressure, ie, those induced by treatment that may be given to counteract the effects of aptiganel, could potentially reduce the local cerebral perfusion of the ischemic area. Although moderate rises in blood pressure may be beneficial because they increase blood flow, dramatic increases such as those obtained with higher doses of aptiganel could potentially lead to reperfusion injury or hemorrhagic transformation of infarction.

In healthy volunteers with aptiganel-induced increases in blood pressure, MCA velocity was increased, but no change in total cerebral blood flow was detected by Doppler ultrasonography.9

Treatment that lowers blood pressure in the acute stroke phase has been repeatedly demonstrated to worsen clinical outcome. This was reported in the INWEST trial of intravenous and oral nimodipine therapy in patients with acute stroke10 and also in a study of the neuroprotective ion-channel–blocker lifarizine.11 As yet, the clinical effects of a moderate increase in blood pressure or of correcting drug-induced rises in blood pressure are uncertain.

In conclusion, the 4.5-mg plus 0.75-mg/h dosing regimen was associated with both excess CNS effects and a hypertensive effect compared with placebo. Additional evaluation of the efficacy of the 4.5-mg plus 0.75-mg/h schedule within a phase III clinical efficacy study is justified, but hemodynamic and CNS effects should continue to be addressed carefully.

TABLE 3. Summary of Clinical Pharmacokinetics

<table>
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<th>Dose Group, mg</th>
<th>Cmax, ng/mL</th>
<th>Clearance, mL/min</th>
<th>Vdss, L</th>
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<td>3</td>
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<td>371</td>
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<td>0.6</td>
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<td>53</td>
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<td>367</td>
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<tr>
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<td>101</td>
<td>34</td>
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</tr>
<tr>
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<td>13.5</td>
<td>1557</td>
<td>480</td>
<td>4</td>
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<tr>
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<td>493</td>
<td>112</td>
<td></td>
</tr>
<tr>
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<td>16.3</td>
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<td>1224</td>
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<tr>
<td>SEM</td>
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<td>208</td>
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</table>

Vdss indicates volume of distribution at steady state.

Figure 2. Plasma aptiganel concentration (mean, SEM) in patients administered a 6-mg loading dose of aptiganel HCl followed by constant infusion of 1 mg/h for 12 hours or a 4.5-mg loading dose followed by 0.75 mg/h for 12 hours.

Acknowledgments

This work was supported by Cambridge NeuroScience Inc (CNSI), Cambridge, Mass. The authors are grateful to Dr Elkan Gamzu and Dr Laima Mathews of CNSI for assistance with manuscript review. The contribution of study coordinators and coinvestigators at each of the clinical sites is gratefully acknowledged.

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Stroke. 1999;30:2038-2042
doi: 10.1161/01.STR.30.10.2038

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