Remacemide Hydrochloride
A Double-Blind, Placebo-Controlled, Safety and Tolerability Study in Patients With Acute Ischemic Stroke

A.G. Dyker, MD, MRCP; K.R. Lees, MD, FRCP

Background and Purpose—Remacemide hydrochloride and its principal active desglycinyl metabolite are low-affinity noncompetitive N-methyl-D-aspartate (NMDA)-receptor channel blockers. Remacemide hydrochloride has demonstrated neuroprotection in animal models of hypoxia and ischemic stroke. This study assessed the safety, tolerability, and pharmacokinetics of ascending doses of remacemide hydrochloride in patients with recent onset (within 12 hours) ischemic stroke.

Methods—This was a placebo-controlled, dose escalating, parallel group study. Groups of 8 patients (6 active, 2 placebo) were planned to receive twice-daily treatment, with 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 600 mg remacemide hydrochloride given as 2 intravenous infusions followed by 6 days’ oral treatment. Patients who were unable to swallow discontinued study medication but continued to be monitored for safety; these patients were replaced. A CT or MRI scan was performed within 48 hours of admission to establish the cause of focal neurological deficit. Patients with ischemic stroke continued in the study. Patients with other causes of focal neurological deficit were withdrawn and replaced. Because the frequency of dysphagia after stroke in the first dose group (100 mg BID) was higher than had been anticipated, the protocol was amended so that subsequent dose groups received 6 intravenous infusions (2 doses per day for 3 days). Neurological and functional outcome data were collected, but the study was not powered to demonstrate drug efficacy. Patient safety was assessed by clinical observation, laboratory tests, and ECGs, while tolerability was assessed by recording adverse events. Blood sampling was included to determine plasma concentrations of remacemide and the desglycinyl metabolite at fixed points during the dosing period.

Results—The most common adverse events considered by the investigator to be possibly treatment related were related to the central nervous system (CNS), and these events appeared to increase with dose. Four patients were withdrawn from the study because of CNS-related events: 1 in the placebo group, 1 in the 500 mg BID group, and 2 in the 600 mg BID group. Infusion site reactions and gastrointestinal upset were also reported and considered to be treatment related. One patient in the placebo group and 4 patients in the 600 mg BID dose group experienced vomiting, whereas this event was not reported by patients in the other dose groups.

Conclusions—On the evidence of this study, the maximum well-tolerated dose for remacemide hydrochloride in acute stroke is 400 mg BID. Doses of 200 mg BID or higher attained the putative neuroprotective plasma concentrations of remacemide predicted from animal models (250 to 600 ng/mL). The expected gradual accumulation of active metabolite might suggest that optimal neuroprotective concentrations are unlikely to be achieved within the early hours of treatment at this dose. However, plasma concentrations do not directly reflect brain concentrations, because studies in rats show that remacemide and the desglycinyl metabolite rapidly reach comparable brain concentrations within 1 hour, despite a lower plasma concentration of the metabolite. (Stroke. 1999;30:1796-1801.)

Key Words: glutamates • N-methyl-D-aspartate • neuroprotection • remacemide

Remacemide hydrochloride has been shown to be neuroprotective in rat cortical neuron cultures exposed to NMDA in vitro. Rats treated with remacemide hydrochloride after reperfusion in the 4-vessel occlusion model had demonstrably smaller infarctions affecting the CA1 and CA3 subregions of the hippocampus (Astra, unpublished data, 1995). Improvements in pathological findings were matched by improvements in functional outcome (assessed by ability to complete a T maze). Similar results have been obtained in canine models of global ischemia and in focal MCA occlusion models in rats (Astra, unpublished data, 1995).

Studies in cats confirm neuroprotection during a focal ischemic insult. Infusion of remacemide hydrochloride before permanent occlusion of the middle cerebral artery reduced the
development of infarction in the cortex, but the area of dense ischemia within the caudate nucleus was resistant to neuroprotection. The plasma concentrations required for neuroprotection vary according to the animal model used, as summarized in Table 1.

In toxicological studies of remacemide, there were indications of altered neurological and motor function in rats and emesis and occasional seizures in dogs. The incidence of toxic effects appears to be dose related and, in dogs, more prevalent and severe during the first week of dosing. Findings in rodents indicate phenobarbital-type induction of some hepatic drug-metabolizing enzymes, but the doses used in humans would be unlikely to cause hepatic induction. Remacemide is not carcinogenic or teratogenic and appears to have no potential for genotoxicity (Astra, unpublished data, 1995).

Hypertensive responses were noted in animal experiments, but effects were mild and species dependent. Intravenous doses of 1 and 3 mg/kg were without cardiovascular effects in anesthetized and conscious dogs, whereas 10 and 30 mg/kg resulted in increased arterial pressure and heart rate in conscious dogs and increased arterial pressure and decreased heart rate, myocardial contractility, and cardiac output in anesthetized dogs.

The clinical pharmacology of remacemide hydrochloride, following oral administration, has been investigated in >400 healthy volunteers after single (up to 500 mg) and multiple doses (up to 800 mg/d). The most commonly reported adverse events were mild central nervous system (CNS) disorders such as dizziness, headache, mood changes, general fatigue, and somnolence or gastrointestinal symptoms such as abdominal pain, dyspepsia, nausea, and vomiting.

Intravenous single doses (1 to 300 mg) of remacemide hydrochloride have been given to 19 healthy volunteers. The pattern of adverse events was similar to that seen with oral dosing. Events were mild, and the 300 mg dose was well tolerated.

In volunteers, orally administered remacemide hydrochloride has good bioavailability with approximately 30% to 40% first-pass metabolism. It is eliminated with a half-life ($t_{1/2}$) of 3 to 4 hours. The desglycinyl metabolite is eliminated more slowly ($t_{1/2}$ of 12 to 18 hours).

The purpose of this study was to assess the safety, tolerability, and pharmacokinetics of ascending doses of remacemide hydrochloride in patients with acute ischemic stroke. Neurological and functional outcome data were collected, but the study was not powered to demonstrate drug efficacy.

### Subjects and Methods

A sequential escalating dose group design was used to permit a blinded assessment of safety and tolerability at each dose before progression to the next dose. Patients were randomized to receive remacemide hydrochloride or placebo in a 3:1 ratio in groups of 8.

Approval was gained from the local ethics committee. Patients gave written, witnessed informed consent whenever possible. If

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**Table 1. Plasma Concentrations of Remacemide and the Desglycinyl Metabolite Required for Neuroprotection in Animal Models**

<table>
<thead>
<tr>
<th>Model</th>
<th>Dose Needed for Protection, mg/kg</th>
<th>Route</th>
<th>Plasma Total Remacemide $C_{\text{max}}$, ng/mL</th>
<th>Plasma Total Desglycinyl Metabolite $C_{\text{max}}$, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat 4 vessel occlusion</td>
<td>20</td>
<td>IP</td>
<td>243*</td>
<td>254*</td>
</tr>
<tr>
<td>Dog global ischemia</td>
<td>7.5 at reflow</td>
<td>IV</td>
<td>3405†</td>
<td>158†</td>
</tr>
<tr>
<td>Cat focal ischemia</td>
<td>25</td>
<td>IV infusion, 90 min</td>
<td>6120‡</td>
<td>633‡</td>
</tr>
<tr>
<td>Human (for comparison)</td>
<td>400 mg total</td>
<td>IV infusion, 15 min</td>
<td>2428</td>
<td>370</td>
</tr>
</tbody>
</table>

*This value was calculated by assuming IP was similar to SC and extrapolating from mean $C_{\text{max}}$ value at 100 mg/kg.
†Extrapolated from a $C_{\text{max}}$ of 4540 (remacemide) and 210 (desglycinyl metabolite) obtained after an IV infusion of 10 mg/kg.
‡Measured values.

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**Figure 1. Study design.**

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infusion

ECG

lab safety

CN Scale

PK

BP/pulse every 30 min during infusion

0 24 48 72 96 2 4

(time hours) (weeks)
TABLE 2.  Patient Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Placebo BID</th>
<th>100 mg BID</th>
<th>200 mg BID</th>
<th>300 mg BID</th>
<th>400 mg BID</th>
<th>500 mg BID</th>
<th>600 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>18</td>
<td>10</td>
<td>6</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>66.6</td>
<td>66.7</td>
<td>65.7</td>
<td>68.4</td>
<td>67.3</td>
<td>67.2</td>
<td>70.4</td>
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<tr>
<td>Range</td>
<td>49–84</td>
<td>46–83</td>
<td>45–84</td>
<td>41–82</td>
<td>46–81</td>
<td>60–80</td>
<td>55–81</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Median 4-week Barthel Index score</td>
<td>18</td>
<td>12.5</td>
<td>10.5</td>
<td>20</td>
<td>20</td>
<td>15.5</td>
<td>19</td>
</tr>
<tr>
<td>Median Canadian Neurological Scale score</td>
<td>Entry</td>
<td>8</td>
<td>7.5</td>
<td>8.75</td>
<td>8.5</td>
<td>9.5</td>
<td>5.75</td>
</tr>
<tr>
<td></td>
<td>1 mo</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>11.25</td>
<td>11.5</td>
<td>8.5</td>
</tr>
<tr>
<td>White</td>
<td>18</td>
<td>10</td>
<td>6</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

Patients who died during the course of the study were regarded as Barthel Index score 0 and Canadian Neurological Scale score 0.

Patients were unable to write, independent witnessed verbal consent was accepted from the patient. If the patient was unable to give consent verbally, written informed assent was accepted from the next of kin or other close family member.

Acute ischemic middle cerebral artery stroke patients aged 40 to 85 years, without major concurrent neurological or other disease, who were admitted to hospital within 12 hours of the event were entered into the study. A negative pregnancy test was required before premenopausal females were allowed to enter the study.

Preclinical data suggested that remacemide hydrochloride may cause GI upset; thus, patients with peptic ulcer disease were excluded, together with patients on regular nonsteroidal anti-inflammatory drugs or steroids. No information on possible interactions with warfarin was available at the time the study was performed; because warfarin has both a narrow therapeutic index and the potential for serious consequences in inappropriate dosages, it was disallowed in the study. Patients with symptoms suggestive of other significant neurological disease or other active and clinically significant systemic disease were also excluded.

CT scanning before recruitment was not mandatory, because NMDA antagonists may be neuroprotective in patients with intracerebral hemorrhage. Patients found to have intracerebral hemorrhage were replaced but carried on with study medication, and full safety data were collected. Patients had study medication discontinued if CT scanning demonstrated any of the following: abscess, subarachnoid hemorrhage, or tumor.

The original protocol included 3 dose levels (100, 200, and 300 mg BID) to be studied sequentially, with each patient receiving 2 intravenous infusions followed by 6 days of oral treatment. Because the frequency of dysphagia in the first dose group (100 mg BID) was higher than anticipated, the protocol was amended so that subsequent dose groups received just 6 intravenous doses (2 doses per day for 3 days).

Intravenous infusions in the 100 and 200 mg BID dose groups were given over 2 hours. Because no tolerability problems were observed, the period of administration of the first dose was reduced from 2 hours to 30 minutes to optimize early brain penetration of drug. This change was made when half of the patients in the 300 mg BID group had completed treatment. Because 300 mg BID was well tolerated, the protocol was amended to permit doses up to 600 mg BID. Due to some local irritation at the injection site at the lower doses, the volume of dilution of the test treatment was increased from 50 to 250 mL for the 400 mg BID dose group and for subsequent dose groups.

Initial screening included clinical examination, Canadian Neurological Scale, vital signs, urinalysis, ECG and blood samples for hematology, clinical chemistry, and pharmacokinetic control.

Blood and urine were taken for analysis at presentation, 24 hours after the start of drug administration, and at 7–2 days. Routine biochemistry and hematology tests and urinalysis were carried out by standard laboratory methods. Adverse events were documented as they occurred during initial hospital care and were specifically elicited from the patients at 2 weeks and 4 weeks after study entry.

Blood pressure and pulse recordings were made using Marquette semiautomatic oscillometric monitoring equipment (Marquette Electronics Inc) and repeated at frequent intervals during drug dosing, as summarized in Figure 1.

Blood samples (10 mL) were taken from an in situ intravenous cannula from the non-infusion arm, collected in a heparinized tube, centrifuged (3000 rpm for 10 minutes), and the plasma transferred to a polypropylene tube and frozen immediately. Blood was taken for pharmacokinetic analysis at time 0, hourly for the first 4 hours, and thereafter at 8, 12, 16, and 24 hours. Sampling was repeated at the end of each infusion and before the final infusion.

Plasma drug concentrations were assessed utilizing solid phase extraction o-phthalaldehyde derivatization followed by HPLC separation and fluorescence detection. Plasma was analyzed for remacemide and its main desglycinyl metabolite. The calibration range of the method was 10 to 500 ng/mL for both analyses. Results from samples containing >500 ng/mL, were determined after sample dilution in control human plasma to produce a result within the calibration range of the method.

Functional outcome was assessed at the 4-week follow-up, using the Barthel functional scale. Neurological outcome was assessed by the Canadian Neurological Scale with assessments made at baseline, 60 hours, 2 weeks, and 4 weeks. Because this study was not powered to demonstrate efficacy, descriptive statistics were used in the analysis of functional and neurological outcome and adverse events.

Results

Sixty-one patients (36 men 25 women), all white, were recruited to the study. Forty-three patients received remacemide hydrochloride and 18 received placebo. The mean age of subjects was 67.3 years (range 41 to 84 years); there were no significant demographic differences between the dosing cohorts. Demographic data are presented in Table 2.

There were 13 deaths during the study (4 placebo, 9 remacemide hydrochloride). With the exception of 3 patients who were found to have brain tumors, all deaths were attributable to stroke or complications arising from it. The number of deaths in each dose group is summarized in Figure 2.
A total of 18 patients (6 placebo, 12 remacemide hydrochloride) were withdrawn from the study before completing treatment. The reasons for withdrawal are shown in Table 3.

Five patients were withdrawn from the first dose group, after receiving intravenous infusions, because of their inability to swallow oral medication; 4 of these patients (2 placebo; 2 remacemide hydrochloride) died during the follow-up period. The protocol was amended after this dose group had completed, to allow for exclusively intravenous dosing. Three patients were withdrawn, as prescribed in the protocol, due to confirmed presence of, or suspicion of, a brain tumor; these 3 died during the follow-up period. Two patients died during treatment, and 5 patients were withdrawn because of adverse events. One patient was withdrawn when transferred to another hospital for surgery for hemorrhagic stroke, 1 because of suspected Munchausen syndrome (nonneurological state), and 1 because of a misunderstanding regarding the patient’s eligibility to continue in the study.

An additional 4 patients completed treatment but died during the follow-up period.

No changes in vital signs (heart rate, blood pressure) and no excess of ECG abnormalities were noted in patients who received remacemide hydrochloride compared with those who received placebo (Figure 3).

The most common treatment-attributed adverse events were CNS related. Infusion site reactions and gastrointestinal upset, particularly nausea and vomiting, were also reported. CNS and gastrointestinal events were most frequent in the group receiving 600 mg BID. CNS events increased in frequency during later infusions in the 500 and 600 mg BID groups (Figures 4 and 5), consistent with accumulation of either remacemide (Figure 6) or its active metabolite (Figure 7). Common treatment-related adverse events are summarized in Table 4.

There was no increase in the frequency of abnormal laboratory reports in patients treated with remacemide hydrochloride compared with placebo-treated patients.

Mean (2-hour) remacemide and desglycinyl metabolite plasma concentration data indicated accumulation of the metabolite but not of parent drug during the course of repeated infusions at the higher doses. Accumulation of the desglycinyl metabolite is not unexpected based on its known

![Figure 2](image2.png)

**Figure 2.** Mortality at 4 weeks in patients receiving remacemide hydrochloride or placebo. There was no increase in mortality at higher doses of remacemide hydrochloride.

**Figure 3.** Blood pressure in patients receiving remacemide hydrochloride or placebo. Remacemide hydrochloride had no effect on systolic or diastolic blood pressure.

### Table 3. Patients Withdrawn From Study Before Treatment Completion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment</th>
<th>Doses Received</th>
<th>Reason for Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Placebo</td>
<td>2 IV</td>
<td>Unable to swallow</td>
</tr>
<tr>
<td>4A</td>
<td>Placebo</td>
<td>2 IV</td>
<td>Unable to swallow</td>
</tr>
<tr>
<td>6</td>
<td>Placebo</td>
<td>2 IV+5 oral</td>
<td>Brain tumor</td>
</tr>
<tr>
<td>6A</td>
<td>Placebo</td>
<td>1 IV</td>
<td>Unable to swallow</td>
</tr>
<tr>
<td>24</td>
<td>Placebo</td>
<td>4 IV</td>
<td>Deterioration in consciousness level; died 4 days after stroke</td>
</tr>
<tr>
<td>38</td>
<td>Placebo</td>
<td>5 IV</td>
<td>Intolerance to treatment (confused; asked to withdraw)</td>
</tr>
<tr>
<td>1</td>
<td>100 mg BID</td>
<td>2 IV</td>
<td>Unable to swallow</td>
</tr>
<tr>
<td>1B</td>
<td>100 mg BID</td>
<td>2 IV</td>
<td>Unable to swallow</td>
</tr>
<tr>
<td>2</td>
<td>100 mg BID</td>
<td>2 IV+4 oral</td>
<td>Brain tumor</td>
</tr>
<tr>
<td>7</td>
<td>100 mg BID</td>
<td>2 IV+1 oral</td>
<td>Brain tumor</td>
</tr>
<tr>
<td>11</td>
<td>200 mg BID</td>
<td>4 IV</td>
<td>Intolerance to treatment (infusion site reaction)</td>
</tr>
<tr>
<td>16</td>
<td>200 mg BID</td>
<td>2 IV</td>
<td>Died 1 day after stroke</td>
</tr>
<tr>
<td>19</td>
<td>300 mg BID</td>
<td>1 IV</td>
<td>Diagnosed nonneurological state</td>
</tr>
<tr>
<td>21</td>
<td>300 mg BID</td>
<td>1 IV</td>
<td>Withdrawn in error (intracranial hemorrhage)</td>
</tr>
<tr>
<td>37</td>
<td>500 mg BID</td>
<td>5 IV</td>
<td>Intolerance to treatment (hyperreflexia and agitation)</td>
</tr>
<tr>
<td>43</td>
<td>600 mg BID</td>
<td>2 IV</td>
<td>Transferred to another hospital for hemorrhagic stroke surgery</td>
</tr>
<tr>
<td>43A</td>
<td>600 mg BID</td>
<td>4 IV</td>
<td>Intolerance to treatment (hallucinations, nausea, and vomiting)</td>
</tr>
<tr>
<td>44</td>
<td>600 mg BID</td>
<td>2 IV</td>
<td>Intolerance to treatment (light-headed, sleepy, and vomiting)</td>
</tr>
</tbody>
</table>
half-life. This suggests that the desglycinyl metabolite may be responsible for the onset of CNS and gastrointestinal effects after repeated infusions of remacemide (Figure 5).

There was no significant difference in neurological or functional outcome between the remacemide hydrochloride– and placebo-treated groups.

**Discussion**

Doses of ≥200 mg BID attained the putative neuroprotective plasma concentrations of remacemide predicted from animal models (250 to 600 ng/mL). At a dose of 500 mg BID, concentrations above these target levels were attained with an acceptable tolerability profile in 5 of 6 patients (1 patient was withdrawn because of agitation and hyperreflexia). At a dose of 600 mg BID, 2 of 7 patients discontinued the study drug because of adverse events (hallucinations, nausea, and vomiting in one individual and somnolence, nausea, and vomiting in another).

Side effects, particularly hallucinations, agitation, and vomiting, were reported at the higher doses during the later infusions. These findings suggest that remacemide or active metabolite is accumulating over time at higher doses. The desglycinyl metabolite accumulated during the course of repeated infusions consistent with the known half-life of the drug. Whether the side effects would preclude therapeutic administration of remacemide is difficult to assess in the absence of phase 3 efficacy data. Clearly, if treatment was moderately effective in improving neurological and clinical outcome, unpleasant but temporary side effects would be acceptable. An analogous example is the use of radiotherapy and chemotherapy in the treatment of cancer, in which short-term side effects are often unpleasant but considered acceptable because of the poor prognosis of the untreated condition.

The cardiovascular profile at the putatively effective neuroprotective doses is neutral, with neither hypertensive nor hypotensive effects. Hypotensive effects of nimodipine were associated with poor clinical outcome in a placebo-controlled study in patients with stroke, and hypertensive effects have been described in patients administered aptiganel, although the results of a phase 3 clinical trial are still awaited. A neutral cardiovascular profile is currently thought to be beneficial to any drug being considered as a therapy for use in acute stroke.

It is clear that in both animal models of stroke and humans, the effects of cerebral ischemia are manifest on the cerebral metabolism rapidly, within a timescale measured in minutes or hours. Any form of potential neuroprotective treatment should therefore be given by the most rapidly effective route. In practice, this means intravenously. In an ideal scenario, neuroprotective plasma and CNS levels of drug would be

**Figure 4.** Incidence of CNS adverse events (AE) in patients receiving remacemide hydrochloride or placebo. There was an increase in reported events at higher doses.

**Figure 5.** Number of patients reporting CNS side effects after repeated doses of remacemide hydrochloride. Frequency of side effects was increased in after repeated dosing at higher doses consistent with accumulation of drug or active metabolite.

**Figure 6.** Remacemide plasma concentrations: comparison of concentrations of parent drug after second and sixth infusions (2 hours). There was no accumulation of parent drug at higher doses.

**Figure 7.** Desglycinyl metabolite plasma concentrations: comparison of concentrations of metabolite after second and sixth infusions (trough level). An increase in desglycinyl metabolite was observed in the higher-dose groups that was associated with an increase in adverse CNS events.
attained immediately. This is widely recognized and is supported by the results of the recent thrombolysis trials (NINDS, ECASS, MAST, and MAST-I)\textsuperscript{13–16} and by meta-analysis of nimodipine trial results. The most conclusive evidence of neuroprotective effect from the cat focal ischemia model was obtained by pretreatment with remacemide hydrochloride.\textsuperscript{3} On the evidence of this study, the maximum well-tolerated dose for remacemide hydrochloride in acute stroke is 400 mg BID. The expected gradual accumulation of active metabolite might suggest that optimal neuroprotective concentrations are unlikely to be achieved within the early hours of treatment at this dose. However, plasma concentrations do not directly reflect brain concentrations because studies in rats show that remacemide and the desglycinyl metabolite rapidly reach comparable brain concentrations within 1 hour, despite a lower plasma concentration of the metabolite (George Smith, PhD, Astra Charnwood, personal communication, 1998).

**Acknowledgments**

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**References**

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