Neuroprotection of the Brain During Cardiopulmonary Bypass
A Randomized Trial of Remacemide During Coronary Artery Bypass in 171 Patients

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Background and Purpose—Neuropsychological impairment may follow coronary artery bypass surgery as a result of peroperative cerebral microembolism. The hypothesis that remacemide, an NMDA receptor antagonist, would provide protection against such ischemic damage has been tested in a randomized trial.

Methods—One hundred seventy-one patients undergoing coronary artery bypass surgery by a single cardiothoracic surgical team were randomized to receive remacemide (up to 150 mg every 6 hours) or placebo from 4 days before to 5 days after their bypass procedure. Peroperative monitoring included an estimate of the number of microembolic events detected by transcranial Doppler ultrasonography of the middle cerebral artery. A battery of 9 neuropsychological tests was administered before and 8 weeks after surgery.

Results—The proportion of patients showing a decline in performance of 1 SD or more in 2 or more tests was reduced in the treated group (9% versus 12%), but this was not statistically significant. On the other hand, overall postoperative change (reflecting learning ability in addition to reduced deficits) was more favorable in the remacemide group, which demonstrated significantly greater improvement in a global z score ($P=0.028$) and changes in 3 individual tests ($P<0.05$). The 2 patient groups were well matched, including for the burden of microembolic events.

Conclusions—This is the first study to show statistically significant drug-based neuroprotection during cardiac surgery. In addition to offering improvement in cerebral outcome for such at-risk patients, it supports the hypothesis that drugs acting on the excitotoxic mechanism of ischemic cerebral damage can be effective in humans. (Stroke. 1998; 29:2357-2362.)

Key Words: bypass surgery ■ neuroprotective agents ■ neuropsychological tests ■ ultrasonography, Doppler

In experimental animal models it is possible to investigate the mechanism of cell loss due to cerebral ischemia and devise strategies of neuroprotection. Most fruitful to date, at least in the animal models, has been the hypothesis that maturation of infarction involves the release of excessive amounts of glutamate with an increase in intracellular calcium levels via NMDA and AMPA receptor–mediated channels. In the cat, NMDA receptor antagonists reduce the volume of infarction produced by middle cerebral artery occlusion by 50%. The treatment effect is greatest if the drug is administered before ischemia is induced. Very large clinical trials are needed to investigate whether such success is mirrored in stroke patients, principally because of the heterogeneity of both the pathology and natural history of stroke cases. It is therefore useful to seek other clinical situations in which cerebral ischemia has predictable consequences and perhaps in which the ideal circumstance of pretreatment is possible. For some years we and others have been investigating the evidence that cerebral ischemia occurs during cardiopulmonary bypass surgery (CPB), occasionally owing to hemodynamic crises but usually to microembolism. The deleterious change in performance of a battery of cognitive tests detected postoperatively proved to be related to the number of microembolic events recorded peroperatively by transcranial Doppler ultrasonography and to be reduced by strategies to prevent such events by the addition of extra arterial line filters or by the replacement of bubble by membrane oxygenators. We therefore piloted this "model" in 1991 and in 1992 planned a prospective, double-blind, randomized trial of an NMDA receptor antagonist.

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Remacemide [1(±)-2-amino-N-(methyl-1,2-diphenylethyl)-acetamide] hydrochloride was part of a screening program for novel antiepileptic drugs. It was chosen for clinical trial because it had been found to inhibit convulsions induced by NMDA and reduce cerebral damage in animal models of focal ischemia, properties shared with dizocilpine (MK-801). Its modest NMDA antagonism is apparently due to an active desglycinated metabolite. Maximal neuroprotection occurred in the animal studies when the drug was administered before the onset of cerebral ischemia.

We planned to test remacemide in a consecutive series of 180 patients undergoing coronary artery bypass surgery (CABS), using repeated cognitive assessments as the end point indicative of the effects of ischemia. We hypothesized that neuroprotection would be revealed by a reduction in the number of patients achieving a predefined threshold of impairment. As an ancillary end point, we hypothesized that a neuroprotectant would be associated with an overall net improvement (or arguably, more favorable net change) in scores, reflecting relative preservation of learning ability and relative reduction of deficits in the group receiving the active drug. This strategy has been developed independently by Jonas et al and has recently been set out in some detail.8

Subjects and Methods

We considered all patients (except females with childbearing potential) aged between 18 and 75 years who were referred to a single cardiothoracic surgical team for elective, primary coronary revascularization. Patients were excluded from the study for the following reasons: (1) a history of neurological (including previous transient ischemic attacks, stroke, seizures, and “blackouts”), psychiatric, gastrointestinal (specifically, peptic ulceration and hemorrhage), hepatic, renal, or hematological disorder; (2) evidence within the previous 2 years of drug abuse (prescribed or nonprescribed) or alcohol abuse (>14 U/week for women and >21 U/week for men, with a unit defined as 1 glass of wine or 1 measure of spirits or one-half pint of beer); (3) regular use of nonsteroidal inflammatory agents (except acetylsalicylic acid), antiepileptics, antidepressants, nimo-dipine, or H1-type antihistamines; and (4) emergency cases and repeat procedures.

During the period of the study, the surgical team carried out approximately 400 such procedures. Patients not recruited were mostly emergency cases or reoperations. Some 20 patients declined the invitation to participate.

The study was conducted in accordance with the provisions of the Declaration of Helsinki (amended in 1989) and with the approval of the University College London Hospital Ethical Review Committee.

Patients were randomly assigned to receive either remacemide (every 6 hours by mouth) or placebo for 4 days before and 5 days after surgery. Volunteers for the study were randomized by pre-packed drug packs held by the hospital pharmacy. Following randomization but before taking any study medication, patients underwent preoperative neuropsychological assessment (1 week before surgery). On the first day of drug administration, patients on active treatment received 25, 50, 100, and 150 mg remacemide in successive doses and thereafter received 150 mg 4 times per day. The last dose given preoperatively was taken on the morning of surgery and the next 24 hours later. Anesthesia was induced with 2 to 5 mg/kg thiopentone sodium, 1 to 10 µg/kg fentanyl and/or 10 to 15 µg/kg alfentanil and 0.1 mg/kg pancuronium, and maintained with nitrous oxide in oxygen (FiO2, 0.3 to 0.5), lorazepam, and incremental doses of pancuronium and an opiate.

Standard physiological monitoring—ECG, arterial pressure, central venous pressure, nasopharyngeal temperature, FiO2, etCO2, airway pressure, SaO2, and urine output—was used throughout the procedure.

To assess whether the treated and placebo groups were subjected to similar embolic loads and ischemic stress, left middle cerebral artery blood flow velocity and microembolic events were measured with transcranial Doppler ultrasonography (TC2000, Eden Medical Electronics). The MCA was insonated via the left temporal window at a depth of 42 to 58 mm with a lightweight 2-Mhz “improved monitoring” probe mounted in a fixation harness.

Microembolic events, which were associated with a characteristic “chirping” sound and spectral pattern, were counted “off-line” by a single observer who reviewed the video unaware of patient randomization. An embolic signal was defined as a signal ≥3 dB above background toward the probe. On occasions when short bursts of overlapping or continuous microembolic signals (typically 200 to 2000 ms in duration) were observed, their number was estimated by dividing the duration of the burst (in milliseconds) by 25 (approximately twice the fast Fourier transform time of 12 ms). The microembolic event counts were divided into (1) the period between aortic cannulation and the onset of CPB, (2) the period during CPB, in 15-minute epochs, and (3) the period between the termination of CPB and aortic decanulation. It was not possible to distinguish bubbles from particulate emboli with this equipment.

CPB was established with a flatbed membrane oxygenator (model 5400, Bard) with a Harvey cardiotomy reservoir/filter and 2 or 3 low-pressure cardiotomy suckers.

Moderate hypothermia (32°C) was used during CPB. Pump flow was adjusted to achieve 2.4 L·min−1·m−2 at 37°C and 1.8 L·min−1·m−2 at 32°C. Mean arterial pressure (MAP) was maintained between 50 and 60 mm Hg. Alpha-stat acid-base management (ie, no temperature correction) was used throughout.

The cross-clamp fibrillation technique for myocardial protection was used in all cases. Distal coronary anastomoses were fashioned with the proximal aorta cross-clamped and the heart in electrically induced fibrillation. Proximal (aorto-saphenous) anastomoses were made with the aorta unclamped and the heart beating.

All patients were routinely reviewed in the Cardiothoracic Surgery Outpatient Clinic 8 weeks after surgery. This time was selected as being sufficiently distant from surgery to produce stable results unconfounded by acute aspects of surgery and anesthesia. In addition to a physical examination and routine investigations, patients underwent a further neuropsychological evaluation, and the results of this assessment form the end point for the study. Retesting in the first few days after surgery reveals a higher prevalence of disturbance, but this is a period when some patients are still on narcotic medication for pain and may have other metabolic disturbance, and the results are difficult to interpret. Those at 2 months are stable and compare well with those at 1 year.

End-Point Assessment

Patients underwent a battery of neuropsychological tests10–12 1 week before surgery (before commencing study medication) and 8 weeks after surgery. The Vocabulary and Picture Completion subtests of the Wechsler Adult Intelligence Scale—Revised, the National Adult Reading Test, and the Spielberger Trait Anxiety Inventory were only administered preoperatively; all other tests (Table 1) were administered at each neuropsychological evaluation. The individual tests were chosen because of our previous experience with their sensitivity3 and their acceptance in the literature, including the results of consensus methodological conferences.13 Where available, parallel forms were administered to limit the effects of learning between the 2 time points, although it was expected that some learning would occur. Indeed, as stated, it was hypothesized that learning would be more obvious in the presence of a neuroprotectant drug and blunted or absent due to peroperative ischemia in its absence.

Deficit

The definition of neuropsychological deficits in the field of cardiac surgery has been the subject of much discussion. We have previously published a conventional definition and have applied it in this study.14 A standard deviation (SD) unit for each test is computed from all the preoperative scores. A deficit occurs in a test when a patient’s postoperative score has dropped by ≥1 SD from their
preoperative score. For the deficit to be significant it must occur in 2 or more tests. When a test had a number of subtest scores, at least 1 subtest had to have a significant deterioration for that test to be considered to be in deficit. Subtest scores did not contribute independently to the measure of deficit; thus, when >1 subtest showed a significant deterioration, the neuropsychological test still yielded only 1 deficit score. This conventional definition has been widely applied in research on neuropsychological changes following cardiac surgery. From our previous studies, neuropsychological deficit so defined following CABS occurs in approximately one third of a patient's sample size of 180 (90 in each group) was calculated to be adequate to detect a 20% or more reduction in conventionally defined deficits in remacemide-treated patients.

Because of increasing improvements in cardiac surgery and greater attention to the potential effects on the brain, the incidence of deficits has been falling.13 Consequently, deficit analysis has become increasingly insensitive. It was therefore proposed that as an ancillary end point, the overall postoperative change (reflecting both potential preserved learning ability coupled with potential deterioration on the tests) would also be analyzed. Consequently, each subject's test score on each occasion was converted into a standard score using the SD of the preoperative group performance of all patients in the study. From these standard scores a difference score was calculated for each subject by subtracting the postoperative score from the preoperative standard score to reflect the relative change in performance from before to after the surgery. If improved performance in any test was reflected by a lower score (eg, in timed tasks), the directional data were reversed so that all improvements gave rise to positive differences. Because of the potential for all neuropsychological tests to show learning with repetition, it was hypothesized that if any neuroprotective effect was to be discerned in the remacemide group, it would show as greater improvement in scores, owing to a combination of greater learning and less deficit.

Results

Two hundred consenting patients were randomized from a consecutive series over a 2-year period from 1992 to 1994. Before randomization, 29 patients were excluded on the basis of abnormal laboratory baseline values,10 withdrawal of consent,6 the discovery of a history of disallowed medication or gastrointestinal disorder,3 or delay or difficulty in completing preoperative assessments.6 The remaining 171 patients were operated on according to protocol, with 87 receiving remacemide and 84 placebo. The groups were well matched in terms of age, height, weight, duration of CPB, and duration of surgery (Table 2).

Twelve patients were lost to study follow-up before the 8-week assessment because of death or adverse event (4 in each group), delay in surgery that interrupted medication (1 in the active group, 2 in placebo), and refusal to participate in the assessment (1 in placebo). There were 3 deaths. One patient on active treatment had a fatal stroke, and another died of a gastrointestinal hemorrhage. Neither death was considered attributable to either remacemide or study participation. One patient in the placebo group suffered a fatal myocardial infarction. The most common reported side effects are shown in Table 3, with an excess of dizziness, drowsiness, and ataxia attributable to remacemide.

Biochemical, hematologic, and clotting screen data both before and after surgery showed no differences attributable to the use of remacemide. Perioperative nasopharyngeal temperatures and pump flow rates and perioperative and postoperative blood pressures and pulse rates showed no differences between groups. The ECG monitoring revealed that most patients remained in sinus rhythm, again with no difference between groups.

### TABLE 1. Neuropsychological Tests Administered Preoperatively and Postoperatively

<table>
<thead>
<tr>
<th>Test</th>
<th>Administration</th>
<th>Preoperative</th>
<th>8 Weeks</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey Auditory Verbal Learning Test</td>
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<tr>
<td>Non-Verbal Recognition Memory</td>
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<tr>
<td>Trailmaking A</td>
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<tr>
<td>Trailmaking B</td>
<td></td>
<td></td>
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<tr>
<td>WAIS Block Design Test</td>
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<tr>
<td>Tapping Test</td>
<td></td>
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<tr>
<td>LetterCancellation</td>
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<tr>
<td>Symbol Digit Replacement</td>
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<tr>
<td>Choice Reaction Time</td>
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<td></td>
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<tr>
<td>Displaced Reaction Time</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Beck Depression Inventory</td>
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<tr>
<td>Spielberger State Anxiety Inventory</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Spielberger Trait Anxiety Inventory</td>
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<td></td>
</tr>
<tr>
<td>WAIS Vocabulary Subtest</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>WAIS Picture Completion Subtest</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Adult Reading Test</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

WAIS indicates Wechsler Adult Intelligence Scale.

### TABLE 2. Baseline Patient Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Remacemide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (M/F)</td>
<td>87 (78/9)</td>
<td>84 (72/12)</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.5±0.9</td>
<td>59.4±0.9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171.9±0.9</td>
<td>171.3±0.9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80.2±1.5</td>
<td>79.8±1.4</td>
</tr>
<tr>
<td>Surgery time, min</td>
<td>193±5 (n=84)†</td>
<td>191±5 (n=79)*</td>
</tr>
<tr>
<td>Bypass time, min</td>
<td>81±3 (n=84)†</td>
<td>80±3 (n=79)*</td>
</tr>
</tbody>
</table>

Data are mean±SEM, with ranges in brackets. Data incomplete in 5 cases and 3 cases.

### TABLE 3. Side Effects During Treatment

<table>
<thead>
<tr>
<th>Problem</th>
<th>Remacemide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Ataxia</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>
Plasma levels of remacemide and its desglycine metabolite just before the 6 PM dose on the day of admission were 232 ± 69 ng/mL and 102 ± 4 ore restarting oral medication, the comparable levels were 28.6 ± 6 61 ng/mL and 35.8 ± 3 29 ng/mL. Just before the 6 PM dose on the fifth postoperative, day the levels were 172 ± 6 114 ng/mL and 76.9 ± 4 44.7 ng/mL, respectively.

The TCD recordings yielded a measure of cerebral blood flow velocity every 15 minutes, from 15 minutes before the start of bypass to 15 minutes after the end of bypass. There were no significant differences between the treatment groups.

There was also no difference in the number of microembolic events recorded during bypass (for remacemide: mean 244, median 146; for placebo: mean 267, median 198; Mann Whitney, $P=0.16$).

The normality of the distributions of each of the neuropsychological tests was examined by means of the Kolmogorov-Smirnov goodness-of-fit test. Six of the tests were found not to be normally distributed. Square root transformations rendered the Displaced Reaction Time Test, Trail-Making Test A, Trail-Making Test B, and the Block Design Test to a normal distribution. Natural log rendered the Symbol Digit Test normal. It was not possible to render the Choice Reaction Time Test to a normal distribution. The data for this test are presented below, but caution must be used in interpreting the findings because of the nature of the distribution.

No preoperative differences were found between the 2 groups on any of the neuropsychological tests (Table 4). Using the

### Table 4. MEANS, SDs, and t-Tests of the Raw Preoperative Test Scores

<table>
<thead>
<tr>
<th>Test</th>
<th>Remacemide</th>
<th>Placebo</th>
<th>$t$</th>
<th>$P$ (2-Tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block Design</td>
<td>9.27 (2.46)</td>
<td>9.47 (2.83)</td>
<td>-0.50</td>
<td>0.617</td>
</tr>
<tr>
<td>Choice Reaction</td>
<td>0.62 (0.22)</td>
<td>0.61 (0.14)</td>
<td>0.92</td>
<td>0.360</td>
</tr>
<tr>
<td>Displaced Reaction</td>
<td>0.86 (0.35)</td>
<td>0.86 (0.35)</td>
<td>0.02</td>
<td>0.986</td>
</tr>
<tr>
<td>Letter Cancel</td>
<td>93.73 (18.93)</td>
<td>96.83 (25.91)</td>
<td>-0.87</td>
<td>0.386</td>
</tr>
<tr>
<td>Nonverbal Memory</td>
<td>332.61 (39.39)</td>
<td>332.18 (26.20)</td>
<td>0.08</td>
<td>0.935</td>
</tr>
<tr>
<td>Rey</td>
<td>54.94 (13.01)</td>
<td>56.27 (11.54)</td>
<td>-0.68</td>
<td>0.495</td>
</tr>
<tr>
<td>Symbol Digit</td>
<td>177.55 (43.82)</td>
<td>177.71 (54.81)</td>
<td>-0.02</td>
<td>0.984</td>
</tr>
<tr>
<td>Tapping</td>
<td>60.00 (11.85)</td>
<td>62.09 (10.13)</td>
<td>-1.19</td>
<td>0.235</td>
</tr>
<tr>
<td>Trails A</td>
<td>40.57 (13.39)</td>
<td>39.83 (14.12)</td>
<td>0.34</td>
<td>0.736</td>
</tr>
<tr>
<td>Trails B</td>
<td>91.42 (35.47)</td>
<td>88.87 (36.96)</td>
<td>0.45</td>
<td>0.656</td>
</tr>
<tr>
<td>New Adult Reading Test</td>
<td>29.72 (9.68)</td>
<td>30.94 (10.02)</td>
<td>-0.62</td>
<td>0.535</td>
</tr>
<tr>
<td>WAS Vocabulary Subtest</td>
<td>47.38 (12.45)</td>
<td>49.65 (12.23)</td>
<td>-1.19</td>
<td>0.234</td>
</tr>
<tr>
<td>WAS Picture Completion Subtest</td>
<td>16.33 (2.67)</td>
<td>16.17 (2.83)</td>
<td>-0.88</td>
<td>0.378</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>7.34 (5.15)</td>
<td>7.51 (5.14)</td>
<td>-0.21</td>
<td>0.833</td>
</tr>
<tr>
<td>Spielberger Trait Anxiety Inventory</td>
<td>38.00 (9.59)</td>
<td>38.61 (8.39)</td>
<td>-0.44</td>
<td>0.660</td>
</tr>
<tr>
<td>Spielberger State Anxiety Inventory</td>
<td>36.52 (10.59)</td>
<td>38.33 (8.94)</td>
<td>-1.20</td>
<td>0.233</td>
</tr>
</tbody>
</table>

Values in parentheses are SDs. WAIS indicates Wechsler Adult Intelligence Scale.

### Table 5. Mean Difference z Scores for Each Test

<table>
<thead>
<tr>
<th>Test</th>
<th>Remacemide Group</th>
<th>Control Group</th>
<th>$t$</th>
<th>$P$ (2-Tailed)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block Design</td>
<td>.2104 (81)</td>
<td>.2093 (76)</td>
<td>0.01</td>
<td>1.0</td>
</tr>
<tr>
<td>Choice Reaction</td>
<td>.1296 (80)</td>
<td>-0.249 (76)</td>
<td>1.17</td>
<td>0.24</td>
</tr>
<tr>
<td>Displaced Reaction</td>
<td>.0473 (79)</td>
<td>.0913 (76)</td>
<td>-0.3</td>
<td>0.76</td>
</tr>
<tr>
<td>Letter Cancellation</td>
<td>-.1909 (81)</td>
<td>-.1673 (76)</td>
<td>-0.17</td>
<td>0.86</td>
</tr>
<tr>
<td>Nonverbal Memory</td>
<td>.2981 (81)</td>
<td>.0016 (76)</td>
<td>1.98</td>
<td>0.048</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test</td>
<td>.1606 (81)</td>
<td>.1252 (76)</td>
<td>0.29</td>
<td>0.76</td>
</tr>
<tr>
<td>Symbol Digit</td>
<td>.3183 (80)</td>
<td>.2329 (76)</td>
<td>0.85</td>
<td>0.4</td>
</tr>
<tr>
<td>Tapping</td>
<td>.4359 (80)</td>
<td>.1939 (75)</td>
<td>2.25</td>
<td>0.026</td>
</tr>
<tr>
<td>Trails A</td>
<td>.4809 (81)</td>
<td>.3417 (76)</td>
<td>1.28</td>
<td>0.20</td>
</tr>
<tr>
<td>Trails B</td>
<td>.3911 (81)</td>
<td>.1662 (76)</td>
<td>2.31</td>
<td>0.022</td>
</tr>
<tr>
<td>Total z score†</td>
<td>2.3235 (78)</td>
<td>1.2190 (75)</td>
<td>2.22</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Values in parentheses indicate numbers of patients. *This score was calculated with the Choice Reaction Time Test performance included. When analyzed with this test excluded, the difference between the 2 groups remained significant ($P=0.036$).
conventional definition of deficit outlined above, 7 patients in
the remacemide group (9%) and 9 in the placebo group (12%)
had deficits on 2 or more tests at follow-up, a 33% but
nonsignificant reduction (Fisher’s exact test, \( P=0.6 \)).

The results of comparisons of the difference in \( \pm \) score
performance of the 2 groups indicated that all but 2 of the
tests showed more favorable mean change in the remacemide
group. Where appropriate, transformed scores were used in
the analysis.

The remacemide group (Table 5) showed significantly
greater improvement in performance on the composite mea-
ure of neuropsychological performance (total \( z \) score; 
\( P=0.028 \)). Further analysis of the individual subtests indicated
that in 3 of the neuropsychological tests the remaca-
emide group showed significantly superior performance over
the control group (Table 5). In these cases the results suggest
both a better preservation of learning and fewer or less-severe
deficits in the remacemide group.

Discussion
The number of patients showing a neuropsychological deficit
in this study was very low and below that estimated for the
purposes of calculating sample size. The reasons for this
change may lie in the continued improvements in surgical
techniques surrounding such issues as minimal manipulation
of the aorta and complete de-airing of the ventricle. There
were no obvious nonsurgical factors that may have accounted
for this low incidence. Although a greater proportion of
patients with deficits was found in the control group (12% versus 9%), this difference was not significant. This method
of handling the data is, however, considered to be insensitive,
because it applies a conventional but arbitrary cut-off and
ignores any improvements in performance.\(^6\)

We have argued elsewhere\(^1\) that studies of interventions in
cardiac surgery designed to improve outcome that include 2
or more patient groups should use all the data by comparing
the change in performance between the 2 groups. This not
only enables an examination to be made of each of the tests,
as some may be more sensitive to change than others, but,
crucially, also allows the potential effects of learning to be
considered. Although the number of subjects recruited was
for a binary analysis, it would be expected to be adequate for
an analysis that uses all the data.

As a planned ancillary analysis in this study, therefore, we
analyzed the change scores once they had been standardized
to the preoperative SD. This technique enables the overall test
performance to be calculated from the cumulative change
scores. The findings indicated that the overall change in
neuropsychological performance from before to after surgery
was superior in the remacemide group. Significantly greater
improvement was found in 3 of the 9 neuropsychological
tests. In these cases the results suggest both a better preser-
vation of learning and fewer or less-severe deficits in the
remacemide group.

Improvements with repetition in neuropsychological tests
are frequently reported as constituting an unwanted phenom-
non, and tests are either designed to prevent this phenomena
from occurring\(^1\) or corrections are made to account for such
practice effects.\(^10\) In other contexts,\(^13\) the ability to learn or
demonstrate so-called practice effects has been considered a
reflection of improved capacity in individuals impaired in
such ability before intervention. In the context of this study,
postoperative (postinsult) learning, as indirectly adduced
from the \( z \) score changes after preoperative (preinsult) prim-
ing, was greater in patients who received the neuroprotective
agent. Learning is a sensitive measure of cognition, and the
increased capacity for learning in the remacemide group may
therefore be considered a reflection of the protection ac-
corded the nervous system by this agent during bypass. The
anticipated improvement in scores due to learning is thus
interrupted and blunted by the ischemic insult but preserved
by an effective neuroprotectant.

The plasma levels achieved during this study are very similar
to those seen with antiepileptic use of remacemide but lower
than those found during intravenous infusion in animal models
of neuroprotection, which may therefore have limited efficacy.

Consequently, we believe this to be the first report of
statistically significant pharmacological neuroprotection in
this clinical context. Grieço et al\(^8\) recently reported a pilot
study using GM1 ganglioside in 18 patients undergoing
bypass surgery, with 11 patients on placebo. No statistically
significant differences were detectable, and a sample size of
150 was estimated to be needed to confirm or reject a
nonstatistically significant treatment benefit. They, too, fa-
vored a strategy of calculating change scores for all tests to
incorporate both potential improvement in performance
through preservation of learning as well as potential deterio-
rations in performance as a result of the procedure. The
approach reported here and that of Grieço et al\(^8\) differed in
their calculation of change scores, although both expressed
change scores on the basis of preoperative SDs.

To date, only preliminary reports of studies of neuropro-
tective agents in acute stroke have appeared, although many
are ongoing. The excitotoxic hypothesis of neuronal damage
in cerebral ischemia is supported by our data and the trends in
some of these stroke studies. For example, post hoc analysis
of patients under the age of 70, with only mild or moderate
strokes and treated with lubeluzole, shows a benefit in both
mortality and the chances of attaining independence as
judged by a Barthel Index score.\(^15\) Lubeluzole inhibits glu-
tamine rise and glutamine-stimulated rises in cyclic guanosine
monophosphate– and nitric oxide–related neuro-
toxicity.\(^16\) As suggested in the introduction and supported by
the results of this study, the circumstances of CPB appear to
offer a practical test bed for putative neuroprotective agents.
The pathophysiology of massive focal infarction in an em-
bolic stroke and the more diffuse microembolic damage
combined with disordered blood flow during CABS are
clearly different, so it could not be assumed that efficacy in
one context was transferable to the other without a trial in
stroke patients.

Finally, the effect of remacemide in this context highlights
the possibility of further reducing the morbidity of CABS.
The side-effect profile suggested some central nervous sys-
tem influences, but these were minor and transient and were
never a reason for stopping trial medication. There was no
evidence that remacemide had adverse effects on the surgical
procedure. The use of membrane rather than bubble oxygen-
tors and other changes in surgical anesthetic and perfusion practice, including the choice of filters, has already been associated with a decline in the incidence of neuropsychological sequelae. This study suggests neuroprotective drugs that operate through the excitotoxic pathway may further protect patients undergoing this common procedure.

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References

Neuroprotection of the Brain During Cardiopulmonary Bypass: A Randomized Trial of Remacemide During Coronary Artery Bypass in 171 Patients


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