Failure of the competitive N-methyl-D-aspartate antagonist Selfotel (CGS 19755) in the treatment of severe head injury: results of two Phase III clinical trials

**Gabrielle F. Morris, M.D., Ross Bullock, M.D., Ph.D., Sharon Bowers Marshall, B.S.N., Anthony Marvarou, Ph.D., Andrew Maas, M.D., the Selfotel Investigators, and Lawrence F. Marshall, M.D.**

Division of Neurological Surgery, University of California, San Diego, California; Division of Neurosurgery, Medical College of Virginia, Richmond, Virginia; Division of Neurosurgery, University Hospital, Rotterdam, The Netherlands; and Ciba Geigy Pharmaceuticals, Basel, Switzerland and Summit, New Jersey

**Object.** Excessive activity of excitatory amino acids released after head trauma has been demonstrated to contribute to progressive injury in animal models and human studies. Several pharmacological agents that act as antagonists to the glutamate receptor have shown promise in limiting this progression. The efficacy of the N-methyl-D-aspartate receptor antagonist Selfotel (CGS 19755) was evaluated in two parallel studies of severely head injured patients, defined as patients with postresuscitation Glasgow Coma Scale scores of 4 to 8.

**Methods.** A total of 693 patients were prospectively enrolled in two multicenter double-blind studies. Comparison between the treatment groups showed no significant difference with regard to demographic data, previous incidence of hypotension, and severity of injury. As the study progressed, the Safety and Monitoring Committee became concerned about possible increased deaths and serious brain-related adverse events in the treatment arm of the two head injury trials, as well as deaths in the two stroke trials being monitored concurrently. The Selfotel trials were stopped prematurely because of this concern and because an interim efficacy analysis indicated that the likelihood of demonstrating success with the agent if the studies had been completed was almost nil.

**Conclusions.** Subsequently, more complete data analysis revealed no statistically significant difference in mortality rates in all cases between the two treatment groups in the head injury trials. In this report the authors examine the studies in detail and discuss the potential application of the data to future trial designs.

**Key Words • severe head injury • clinical trial design • N-methyl-D-aspartate • Selfotel • glutamate receptor antagonist • excitatory amino acid**

**OVER the last 15 years, it has been demonstrated that excessive quantities of excitatory neurotransmitters, especially glutamate, develop after neurotrauma. This “agonist surge” contributes to the destruction of neurons due to stimulation of receptor-mediated calcium influx. This phenomenon of “excitotoxicity” has become a major focus of neuroscience research in academic centers and the pharmaceutical industry.**

A neuroprotective effect has been seen most clearly in pharmacological antagonists to the N-methyl-D-aspartate (NMDA) receptor, although it has also been seen in other types of glutamate receptors, and with presynaptic blockade of glutamate release. These dramatic findings in models of both neurotrauma and focal cerebral ischemia have generated impetus within the pharmaceutical industry to develop glutamate antagonists for clinical use.

More recently it has been shown conclusively, in both animal models of neurotrauma and in head-injured humans, that glutamate is massively increased in extracellular fluid for periods ranging from minutes to several days in a substantial number of patients. Subsequent reports have demonstrated dramatic improvements in histological, behavioral, and biochemical outcome measures after the administration of a variety of glutamate antagonist drugs in various animal models of neurotrauma.

Of the three types of postsynaptic glutamate receptors (AMPA [a-aminoo-3-hydroxy-5-methyl-4-isoxazole propionate]/kainate, metabotropic, and NMDA), the NMDA receptor has been the most extensively studied. At least five widely different NMDA antagonists have been evaluated in humans and four of these have now been evaluated in patients with neurotrauma. At this time we are not aware of any drugs directed against the AMPA/kainate and metabotropic receptor sites that are safe for use in humans.

Experimental agents acting as NMDA antagonists may be broadly classified into three major groups: competitive glutamate antagonists, noncompetitive antagonists (ion channel blockers), and subsite selective coagonist blockers. Trials of several of these compounds in head-injured humans are presently in progress.
The compound developed by Ciba Geigy, Selfotel (CGS 19755), is a competitive glutamate antagonist and is the NMDA antagonist for which the largest human experience has now been accumulated. Nearly 1600 patients in four clinical trials have received this compound as supplemental therapy for stroke and severe head injury. Results of these clinical trials have only been reported in abstract form.

In this paper we report the combined results of two parallel phase III international efficacy trials of Selfotel that were conducted in patients with severe traumatic brain injury.

Clinical Material and Methods

Patient Population

Two separate trials in which nearly identical protocols were used were conducted simultaneously in the United States and Israel (the domestic study) and in Europe, Canada, Australia, and Argentina (the international study). Data were prospectively collected in these multicenter, randomized double-blind, two-armed, between-patient-matched trials to determine the efficacy and safety of Selfotel compared with placebo. Ninety-nine medical centers participated in these trials. All centers had an established commitment and dedication to the care of severely head injured patients. The protocol required strict adherence to maintenance of cerebral perfusion pressure (CPP) above 60 mm Hg if possible, and treatment of sustained elevation of intracranial pressure (ICP) at levels greater than 20 mm Hg. For inclusion in the trials, patients needed to demonstrate a postresuscitation Glasgow Coma Scale (GCS) score of 4 to 8 and at least one reactive pupil. Furthermore, an abnormal computerized tomography (CT) scan demonstrating intracranial injury was required, consistent with the Traumatic Coma Data Bank (TCDB) modified CT classifications II to VI. The ages of the patients ranged from 15 to 79 years.

Trial Design and Rationale

The trial design was based on data collected from preclinical efficacy trials, two clinical safety and tolerability trials, the clinical pharmacological profile of Selfotel, and on the assessment of plasma and cerebrospinal fluid pharmacokinetic profiles in neurosurgical patients following treatment with Selfotel. A target sample size of 920 patients for both trials was selected based on the results of the phase II clinical trials with this drug. The primary end point was the demonstration of a 10% improvement in the dichotomized Glasgow Outcome Scale (GOS) score (treatment compared with placebo), with 80% power. Thus, the primary outcome measures were the 6-month GOS scores supported by the Disability Rating Scale scores. Additional secondary variables that were prospectively identified as potential outcome measures included the effect of the drug on ICP and CPP during the 1st week of hospitalization, and the 3-month GOS and Disability Rating Scale scores.

The Safety and Monitoring Committee was authorized to stop the trial if a significant difference (p < 0.05) in mortality rates was observed between the Selfotel and the placebo groups during the course of the trial.

Statistical Analysis

Data were prospectively collected in these multicenter, randomized double-blind, two-armed, between-patient-matched trials. A standard double-blind format was used for drug randomization and administration.

Informed consent for each patient was obtained before enrollment in these studies in accordance with national laws and local regulations. The ethics committee or review board at each institution provided written approval of these protocols before any patients were recruited.

Study Performance and Test Drug Administration

Protocol 011 was the international arm of the trial and included 52 centers in Europe, Argentina, Australia, and Canada. Protocol 008 was performed concurrently at 43 centers in the United States and four in Israel. Patients were screened for potential randomization as soon as possible after injury and hospital admission so that dose administration could occur no later than 8 hours from the time of injury and within 4 to 6 hours of hospitalization (protocols 011 and 008, respectively). A standard double-blind format was used for drug randomization and administration.

Patients with severe closed head injury were treated with placebo or an intravenous infusion of 5 mg/kg of Selfotel once a day for 4 days. The trial drug and placebo were supplied in identical ampules, assuring that the treating physicians, the investigator’s site personnel, and the Ciba Geigy personnel involved in monitoring the conduct of the trial remained blinded to the trial drug codes. The blinding remained intact throughout the duration of the study. Data collection began as close to the time of injury as possible and continued during the first 14 days of hospitalization with serial follow-up examinations at 1, 3, and 6 months postinjury.

Data Collection

To ensure adequate standardization, all treatment centers used identical case report forms for each patient. Patient confidentiality was maintained throughout the study. Data were collected locally at the treating center and entered centrally at Ciba Geigy in conjunction with the trial’s coordinating centers: The University of California at San Diego for the international arm of the study and the American Brain Injury Consortium at Virginia Commonwealth University for the domestic arm. Required neuroimaging included the patient’s initial postinjury CT scan and at least one additional scan. This additional scan was either the patient’s worst one or the one that demonstrated a deterioration in the patient’s CT classification of injury.

Clinical Treatment

All patients received the full range of standard therapy for the management of severe head injury as outlined in a detailed protocol, which was identical for the two arms of the trial. Particular emphasis was placed on the prevention and treatment of secondary insults, because the adverse effects of hypotension and hypoxia were well recognized by the time patient enrollment began. The goals included avoidance of intracranial hypertension and maintenance of adequate CPP (> 60 mm Hg). All concomitant therapies and medications were recorded for each patient.

Institutional Review Board and Informed Consent

Informed consent for each patient was obtained before enrollment in these studies in accordance with national laws and local regulations. The ethics committee or review board at each institution provided written approval of these protocols before any patients were recruited.
Failure of Selfotel in treatment of head injury: phase III trial

TABLE 1
Patient demographics on enrolment in the Selfotel trial for treatment of severe head injury*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Selfotel (339 patients)</th>
<th>Placebo (354 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>260 (77)</td>
<td>277 (78)</td>
</tr>
<tr>
<td>female</td>
<td>79 (23)</td>
<td>77 (22)</td>
</tr>
<tr>
<td>age (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=25</td>
<td>142 (42)</td>
<td>158 (45)</td>
</tr>
<tr>
<td>26-50</td>
<td>158 (47)</td>
<td>159 (45)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>39 (12)</td>
<td>37 (10)</td>
</tr>
<tr>
<td>mean ± SD</td>
<td>32.1 ± 13.0</td>
<td>31.1 ± 13.2</td>
</tr>
<tr>
<td>range</td>
<td>15-79</td>
<td>15-79</td>
</tr>
<tr>
<td>GCS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>6.1 ± 1.2</td>
<td>6.1 ± 1.3</td>
</tr>
<tr>
<td>range</td>
<td>4-9</td>
<td>3-8</td>
</tr>
<tr>
<td>best motor score at entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = none</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>2 = extension</td>
<td>49 (14)</td>
<td>58 (16)</td>
</tr>
<tr>
<td>3 = abnormal flexion</td>
<td>79 (23)</td>
<td>66 (19)</td>
</tr>
<tr>
<td>4 = withdrawal</td>
<td>105 (31)</td>
<td>115 (32)</td>
</tr>
<tr>
<td>5 = localizes</td>
<td>105 (31)</td>
<td>113 (32)</td>
</tr>
<tr>
<td>6 = obey commands</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>pupils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>both reactive</td>
<td>250 (74)</td>
<td>260 (73)</td>
</tr>
<tr>
<td>1 nonreactive</td>
<td>26 (8)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>both nonreactive</td>
<td>18 (5)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>predisposing secondary insults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>shock</td>
<td>43 (13)</td>
<td>43 (12)</td>
</tr>
<tr>
<td>hypoxia</td>
<td>37 (11)</td>
<td>27 (8)</td>
</tr>
<tr>
<td>cardiac arrest</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>severe disability, persistent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vegetative state</td>
<td></td>
<td></td>
</tr>
<tr>
<td>death</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in parentheses represent percentages. Abbreviation: SD = standard deviation.

provide an adequate number of patients, data obtained from all centers were combined under these two protocols (011 and 008). Comparison of the treatment groups was performed based on demographics, baseline clinical characteristics, and extensive subgroup analysis.

Results
The trials were stopped prematurely on December 4, 1995 at the request of the Safety and Monitoring Committee because of concern about the number of deaths and serious brain-related adverse events in two contemporaneous stroke trials and in both of the head injury trials. Although this decision was based primarily on data available to the Committee in August 1995, the trends continued to be unfavorable for Selfotel, and therefore it was believed appropriate in the overwhelming majority of patients. In 81% of the patients the CPP did not fall below 60 mm Hg during any 2 consecutive hours. There was also no significant difference in the percentage of time in which patients’ ICPs exceeded 20 mm Hg between the placebo and Selfotel groups (placebo = 23%, Selfotel = 20.6%).

At the time of trial cessation, a total of 693 patients were enrolled, 427 from the international and 266 from the domestic arm. The groups were similar demographically when analyzed for gender, age, weight, initial GCS score, entry motor response, and initial pupillary reactivity, as detailed in Table 1. Similarly, hypotension was seen before dose administration in 43 patients from each treatment regimen, and three patients had predisposing cardio-pulmonary arrest (two had received Selfotel and one was in the placebo group). Thirty-seven of the patients who received Selfotel had an episode of hypoxia prior to randomization, as did 27 of the patients who received placebo (p > 0.1, chi-square analysis).

A favorable outcome was defined as a “good” or “moderate” score on the GOS. At 6 months, favorable outcomes were achieved in 185 (55%) of the 338 patients who had received Selfotel and in 204 (58%) of the 352 patients in the placebo group (p > 0.25, chi-square analysis). In all there were 142 deaths, 74 in the Selfotel and 68 in the placebo group (p > 0.25, chi-square analysis). Patient outcomes are displayed in Table 2.

Protocol adherence was excellent within the trials. Interventions for mass lesions and elevated ICP were appropriate in the overwhelming majority of patients. In 81% of the patients the CPP did not fall below 60 mm Hg during any 2 consecutive hours. There was also no significant difference in the percentage of time in which patients’ ICPs exceeded 20 mm Hg between the placebo and Selfotel groups (placebo = 23%, Selfotel = 20.6%).

Table 3 displays data from the initial postinjury CT scan, demonstrating that the treatment groups were very similar initially. Subarachnoid hemorrhage (SAH) was seen on initial CT scans in 61% and 60% of the drug and placebo groups, respectively.

Subgroup Evaluation
Table 4 shows the outcome in patients from the international arm of the present trial who underwent operation for mass lesions. Patients with surgically treated epidural hematomas (EDHs) demonstrated a mortality rate of 12% (two patients) when treated with Selfotel and 7% (two patients) when given placebo. In patients with surgically treated subdural hematomas (SDHs) the mortality rate
to these head-injured patients, but that possibility cannot
cant evidence that administration of the drug was harmful
effect on outcome. There was also no statistically signifi-
to patients with severe head injury confers no beneficial

taxial stroke trials. Because this was an intent-to-treat
was approximately sevenfold greater than that used in the
were found to be drug related, even though the dose used
was related to central nervous system events, usually in-
tracranial hypertension. Hypothermia appeared more fre-
quent in patients receiving Selfotel (55 compared with
Concurrent to these trials in which Selfotel was used to
treat severe head injury, there were two parallel trials eval-
uating the efficacy of the same drug in the management of
stroke. The significant excess mortality rate in the Selfotel
group in the stroke trials contributed heavily to the deci-
sion to halt the severe head injury trials. In the head-

These trials have shown that administration of Selfotel
to patients with severe head injury confers no beneficial
effect on outcome. There was also no statistically signifi-
cant evidence that administration of the drug was harmful
to these head-injured patients, but that possibility cannot

be entirely excluded on the basis of these two trials. Be-
cause the trials were not completed, it is also impossible
to conclude unequivocally that a possible beneficial effect
would not have been seen from the compound. A futility
analysis performed at the time the trials were stopped
indicated that the likelihood of demonstrating a beneficial ef-
fect, if the trials had been completed, would be extremely
low (<5%).

The decision to stop the head injury trials was based in
part on combined data from two stroke trials, which in-
dicated a significantly increased risk of serious adverse
brain-related events as well as excessive mortality rates in
the patients receiving Selfotel in the stroke trials. Al-
though the appropriateness of combining the data from
stroke and head injury trials can certainly be debated, at
the time that the decision was made by the Safety and
Monitoring Committee, mortality trends in the head injury
trials, as well as severe adverse brain-related events, were
also unfavorable. Ultimately, however, as more patients
were accrued in the head injury trials, these differences
lessened and did not reach significance.

A decision to stop a trial, or trials, is a serious one. In
these instances, there was clearly legitimate concern about
the safety of the drug at the time the decision was made
and there are still concerns that there may have been an
adverse effect of the compound, particularly in the stroke
trials. Moreover, given the cost of these trials, which for
900 patients is approximately 20 million dollars, futility
analyses are an appropriate means to determine whether
such a large expenditure should continue. We clearly
would like such trials to continue until completion if there
is no unacceptable risk involved, because of the increased
understanding of the disease process that is an inevitable
byproduct of such trials. However, the sponsor’s primary
interest is to determine whether the agent is efficacious.

Patients were stratified by severity of injury or the pre-
ence of secondary ischemic events. No trends toward ben-
efit were seen in the Selfotel groups. Post-hoc subgroup
analyses also failed to demonstrate populations that bene-
fited from the drug.

The control and Selfotel-treated groups were surpris-
ingly well matched for severity of injury, secondary ad-
verse events, pattern of injury, age, and the frequency of
SAH. In the international arm of the study, there was a
greater frequency of EDH in the placebo group (28 com-
pared with 13 patients).

Several hypotheses may be advanced to explain the
apparent lack of effect of the drug. Previous studies in an-

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Selfotel (338 patients)</th>
<th>Placebo (354 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCDB modified CT classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I = diffuse injury, NVP</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>II = diffuse injury</td>
<td>135 (40)</td>
<td>146 (41)</td>
</tr>
<tr>
<td>III = diffuse injury w/ swelling</td>
<td>86 (25)</td>
<td>81 (23)</td>
</tr>
<tr>
<td>IV = diffuse injury w/ shift</td>
<td>15 (4)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>V = evacuated mass lesion</td>
<td>84 (25)</td>
<td>88 (25)</td>
</tr>
<tr>
<td>VI = nonevacuated mass lesion</td>
<td>16 (5)</td>
<td>20 (6)</td>
</tr>
<tr>
<td>traumatic subarachnoid hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>207 (61)</td>
<td>211 (60)</td>
</tr>
<tr>
<td>no</td>
<td>131 (39)</td>
<td>143 (40)</td>
</tr>
<tr>
<td>mass lesion type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDH</td>
<td>52 (15)</td>
<td>52 (15)</td>
</tr>
<tr>
<td>SDH</td>
<td>119 (35)</td>
<td>133 (38)</td>
</tr>
<tr>
<td>intraparenchymal hematoma</td>
<td>132 (39)</td>
<td>129 (36)</td>
</tr>
</tbody>
</table>

1* Numbers in parentheses represent percentages. Data unavailable in one
2  S elfotel-treated patient. No statistical difference was seen in CT scan find-
3 ings between the groups (chi-square analysis, p > 0.25). Abbreviation:
4  NVP = no visible pathology.

**TABLE 3**

Pretreatment CT scan data obtained in 692
head-injured patients*

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Favorable Death</th>
<th>Favorable Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDH</td>
<td>42% (13)</td>
<td>39% (12)</td>
</tr>
<tr>
<td>EDH</td>
<td>64% (11)</td>
<td>12% (2)</td>
</tr>
<tr>
<td>parenchymal contusions</td>
<td>19% (3)</td>
<td>38% (6)</td>
</tr>
</tbody>
</table>

* Lesion data only available for patients enrolled in the international arm of
the trial.

**TABLE 4**

Subgroup analysis of the effect of lesion type and treatment on outcome in patients with a pretreatment CT scan classification of V*

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...mal models have shown that following diffuse brain injury without secondary ischemic complications (fluid-percussion injury) a brief and transient 10-minute surge of glutamate is detected.\textsuperscript{2,24} In contrast, in animals with SDHs, the magnitude of release is five times higher and persists for many hours.\textsuperscript{25,16} In animals with secondary ischemic insults superimposed on impact injury, the release of glutamate into extracellular fluid is even more marked.\textsuperscript{13,30} Similarly, recent microdialysis studies performed at several different centers have shown that the level of glutamate measured in extracellular fluid in patients with severe head injury is within the normal range found in those with no or minimal brain damage on CT scanning (TCDB Categories I and II).\textsuperscript{18} In contrast, glutamate measured adjacent to focal cerebral contusions, or within the hemisphere from which an SDH has been removed, may be 50 times higher (60–100 μmol/L in dialysates).\textsuperscript{4,6} In patients who experienced secondary ischemic events, glutamate release was likewise shown to be markedly increased, and this increase was shown to be sustained for several days.\textsuperscript{4,20} It is thus surprising that no beneficial effect was shown in those subgroups of patients with intracranial hematomas and secondary ischemic insults.

Selfotel is a competitive glutamate antagonist. Thus, its binding to the receptor site must occur in competition with glutamate that is present in the extracellular fluid. Although this compound has a high receptor affinity, it is likely that the concentrations of Selfotel that reached appropriate locations within the brain were too small to block the massive increase in local glutamate concentrations that have been recently demonstrated in humans with brain injury.\textsuperscript{21,27} Moreover, because Selfotel could only be given after injury, when the glutamate content was already high at the receptor site, it would be unlikely that the drug would displace glutamate from the NMDA receptor. Thus, we hypothesize that, although this compound may achieve sufficient brain penetration to bind the receptor in the presence of normal physiological concentrations of glutamate (1–2 μmol/L), Selfotel is unable to influence receptor-mediated events adequately in the presence of the much higher glutamate concentration observed in severe human head injury, which often persists for several days.\textsuperscript{4,6,27}

We also speculate that the penetration of this nonlipophilic compound into areas of injured brain may be impeded by poor passage across the blood-brain barrier and by reduced cerebral blood flow in precisely those areas in which the drug is most needed. During preclinical and early phase I development of Selfotel, a full appreciation of its pharmacokinetics in the brain was not obtained because of the difficulty in obtaining a drug assay methodology with sufficient sensitivity to detect the compound in the extracellular fluid. Although brain pharmacokinetic studies were attempted both in animal models and in humans undergoing cerebrovascular surgery, detailed measurements of the Selfotel concentration in the extracellular fluid were never obtained.

A third possible explanation for the lack of effect of this compound in these clinical trials may have been its racemic nature. Selfotel consists of a 50% mixture of the active and inactive isomers of the compound 4-phosphono-methyl-2-piperidine-carboxylic acid.

Finally, it is possible that the prolonged administration of agents producing NMDA receptor blockade may itself be deleterious because of interference with neural transmission.\textsuperscript{21}

In a previous small phase II study,\textsuperscript{3} an apparent ICP lowering effect was shown for Selfotel. In a second study in which 108 patients were enrolled, 53 patients who received Selfotel demonstrated an ICP profile over the 4 days of measurement that indicated an apparent ICP-lowering effect for the compound. No ICP-lowering trend was, however, seen in this study.

Hypothermia was seen more frequently in the Selfotel group; an observation in keeping with reports of other NMDA receptor antagonists in animals.

Subgroup Analysis

In patients with EDHs and SDHs who underwent surgery, the results, as reported here, are extraordinarily good, particularly in the placebo group, in which mortality rates of 26% in those with SDH and 7% in those with EDH were observed. Even if one takes into account the fact that patients with fixed and nonreactive pupils or a motor score of 1 were excluded from the present trial, the outcome in these patients in the placebo group is in striking contrast with those reported in previous studies of severe head injuries.\textsuperscript{4} This illustrates one difficulty with clinical trials; it is doubtful that any agent could show a beneficial therapeutic effect compared with the results in this group, in which 60% of the surgically treated SDHs had a favorable outcome. Designers of future clinical trials will need to take into account what appears to be a significant improvement over the years in the management of patients with mass lesions, particularly extraaxial mass lesions, when compared with the previous reported experience.

An alternative hypothesis is that outcome was worse in the Selfotel groups because of an adverse effect of the drug. Such a hypothesis cannot be rejected on the basis of data available from this trial. However, it seems more likely, given the relatively favorable results of the Selfotel-treated EDH and SDH groups compared with historical controls,\textsuperscript{17} that the difference is due to chance.

Implications for the Future

These studies, although not taken to completion, provide strong evidence that Selfotel exerts no positive influence on the course of clinical events following severe traumatic brain injury. These trials do not indicate whether

<table>
<thead>
<tr>
<th>TABLE 5</th>
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<tbody>
<tr>
<td>Overall incidence of adverse experiences in 693 patients enrolled in the Selfotel trial for severe head injury</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>total no. w/ adverse events</td>
</tr>
<tr>
<td>intracranial hypertension</td>
</tr>
<tr>
<td>anemia</td>
</tr>
<tr>
<td>pneumonia</td>
</tr>
<tr>
<td>hypotension</td>
</tr>
<tr>
<td>hypokalemia</td>
</tr>
<tr>
<td>hypertension</td>
</tr>
<tr>
<td>hypothermia</td>
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<tr>
<td>agitation</td>
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glutamate antagonists in general, and competitive NMDA antagonists in particular, are ineffective or harmful in this clinical context. The factors that have caused Selfotel to fail in human trials for the treatment of traumatic brain injury and stroke, in contrast to its favorable record in animal studies, may include: failure to achieve adequate brain concentration of the compound postinjury, failure to deliver the compound to the receptor site early enough after injury, and, possibly, the racemic nature of the compound. In the future, microdialysis techniques would be useful in measuring drug levels within the brain in earlier phases of clinical trials.

Conclusions

Selfotel, given in four doses of 5 mg/kg each, 24 hours apart, did not demonstrate a satisfactory risk/benefit ratio in severe head trauma. Because this compound is competitive with glutamate at the receptor and glutamate levels are elevated (up to 50-fold or more) in certain patients after severe head injury, the compound may not influence events at the receptor site.

Acknowledgments

The authors express their sincere gratitude to all of the study participants and the Principal Investigators whose hard work made this report possible. The authors also thank Göran Karlsson, Ph.D., and Herbert Faleck, D.O.

Appendix A

Principal investigators and centers ranked by number of patients enrolled for Protocol 008, the domestic arm of the study (United States and Israel).

R. Bullock, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia; L. Levi, Ramah Medical Center, Haifa, Israel; J. P. Muizelaar, Wayne State University, Detroit, Michigan; A. Parent, University of Mississippi Medical Center, Jackson, Mississippi; J. Burgess, Fairfax Hospital, Alexandria, Virginia; T. Harrington, Barrow Neurological Institute, Phoenix, Arizona; S. Powers, University of Louisville, Louisville, Kentucky; S. Knoller, Chaim Sheba Medical Center, Tel Hashomer, Israel; J. H. Stewart, Medical College of Wisconsin, Milwaukee, Wisconsin; S. Constantini, Hadassah Hospital, Ein Karem, Jerusalem, Israel; M. Turner, Methodist Hospital, Indianapolis, Indiana; A. J. Popp, Albany Medical College, Albany, New York; R. M. Chesnut, San Francisco General Hospital, San Francisco, California; D. Herr, Washington Hospital Center, Washington, District of Columbia; J. Falk, Orlando Regional Medical Center, Orlando, Florida; P. Hitchon, University of Iowa Hospital, Iowa City, Iowa; L. F. Marshall, University of California, San Diego Medical Center, San Diego, California; J. Nichols, Centura St. Anthony’s Hospital Central, Denver, Colorado; J. Runge, Carolina Medical Center, Charlotte, North Carolina; D. Scholten, Butterworth Hospital, Grand Rapids, Michigan; S. Glazer, Bowman Gray School of Medicine, Winston-Salem, North Carolina; G. Rockswold, Medical University of Minnesota, Minneapolis, Minnesota; A. Mahmood, Henry Ford Hospital, Detroit, Michigan; J. Wilberger, Allegheny General Hospital, Pittsburgh, Pennsylvania; R. Schmidt, University of Utah Hospital, Salt Lake City, Utah; C. Wrobel, Kern Medical Center, Bakersfield, California; F. Boop, University of Arkansas, Little Rock, Arizona; H. Kaufman, West Virginia University Hospital, Morgantown, West Virginia; B. Bailey, Medical University of South Carolina, Charleston, South Carolina; W. Faillace, University of Florida, Jacksonville, Florida; W. Ganz, St. Paul-Ramsey Medical Center, Rapid City, South Dakota; J. Weaver, University of Massachusetts Medical Center, Worcester, Massachusetts; R. Martz, Sacred Heart, Spokane, Washington; E. Reichenthal, Soroka Medical Center, Beer-sheba, Israel; M. McCarthy, Miami Valley Hospital, Dayton, Ohio; G. Gulda, Medical Research Institute of Delaware, Newark, Delaware; K. Foley, University of Tennessee, Memphis, Tennessee; W. Rosenberg, University of Cincinnati, Cincinnati, Ohio; G. Steinberg, Stanford Medical Center, Stanford, California; A. B. Young, University of Kentucky Chandler Medical Center, Lexington, Kentucky; Doron, Tel Aviv Medical Center, Tel Aviv, Israel; E. Downing, Neurological Institute of Savannah, Savannah, Georgia; F. Aldrich, University of Maryland Hospital, Baltimore, Maryland; R. M. Flannery, Medical College of Georgia, Augusta, Georgia; C. Gordon, Spine Care Associates of Tyler, Tyler, Texas; L. Leibrock, University of Nebraska Medical Center, Omaha, Nebraska; J. Hormes, Kennestone Hospital, Marietta, Georgia.

Principal investigators and centers ranked by number of patients enrolled for Protocol 011, the international arm of the study (Europe, Canada, Australia, and Argentina).

F. C. Murillo, Hospital Virgen del Rocio, Sevilla, Spain; A. I. R. Maas, University Hospital Rotterdam, Rotterdam, The Netherlands; J. Sahuquillo, Hospital Valle de Hebron, Barcelona, Spain; B. Alliez, Hôpital Nord, Mâlines, France; R. D. P. Llorente, Hospital “12 de Octubre,” Madrid, Spain; F. M. Artru, Hôpital Pierre Wertheimer, Lyon, France; F. Servadei, Ospedale Bufalini, Cesena, Italy; J. Compton, Nepean Hospital, Penrith, Australia; L. Atkinson, Princess Alexandra Hospital, Woolloongabba, Australia; R. Fontana, Ospedale Niguarda de Granada, Milano, Italy; N. Stocchetti, Ospedale Riuniti Parma, Parma, Italy; J. Largarrigue, Hôpital de Rangueil, Toulouse, France; G. Berry, Royal Brisbane Hospital, Herston, Australia; A. Bricolo, Ospedale Civile Maggiore, Verona, Italy; S. Beretta, Ospedale S. Raffaele, Milano, Italy; K. Reddy, Hamilton Civic Hospital, Hamilton, Canada; J. Laidlaw, Alfred Hospital, Prahan, Australia; M. Fearnside, Westmead Hospital, Sydney, Australia; C. Plots, U. Z. Gastrojiise, Leuven, Belgium; J. Fenwick, Vancouver Hospital and Health Science Centre, Vancouver, Canada; J. J. Rouby, Hôpital Pitie-Salpetriere, Paris, France; A. Unterberg, Universität-Klinik Rudolf-Virchow, Berlin, Germany; F. P. Grisoli, Hôpital de la Timone, Marseilles, France; T. Bookallil, The John Hunter Hospital, New Lambton, Australia; F. Bucheit, Hôpital de Hautepierre, Strasbourg, France; Y. Guegan, Hôpital Pontchaillou, Rennes, France; J. D. Born, Hôpital de la Citadelle, Liege, Belgium; A. Brawanski, Neurochirurgische Universität-Klinik, Regensburg, Germany; M. S. Garrote, Hospital de Emergencias, Rosario, Argentina; C. Koch-Jensen, Aalborg Sygehus Syd, Aalborg, Denmark; J. Meixensburger, Neurochirurgische Universitat, Wurzburg, Germany; P. Schmiedek, Klinikum Mannheim, Mannheim, Germany; N. Jones, Royal Adelaide Hospital, Adelaide, Australia; M. L. Schwartz, Sunnybrook Health Sciences Centre, Toronto, Canada; D. Ceraso, Hospital Fernandez, Buenos Aires, Argentina; J. Compton, Liverpool Hospital, Penrith, Australia; F. Gjerris, Rigshospitalet, Copenhagen, Denmark; D. Grimaud, Hôpital St. Roch, Nice, France; T. Grumme, Zentralklinikum, Augsburg, Germany; F. F. Madsen, Hvidovre Hospital, Hvidovre, Denmark; D. Malloy, Halifax Professional Center, Halifax, Nova Scotia, Canada; H. J. Reulen, Klinikum Grosshadern, University of Munich, Germany; M. R. Gaab, Neurochirurgische Universitäts-Klinik, Regensburg, Germany; G. F. Morris, et al.

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Address reprint requests to: Ross Bullock, M.D., Ph.D., Division of Neurosurgery, Medical College of Virginia, P.O. Box 980631, Richmond, Virginia 23298–0631.