Patients in the acute phase after moderate or severe head injury often exhibit agitation and fluctuations in ventilatory capacity. A variety of sedatives, narcotics, and neuromuscular blocking agents are used to control ventilation and prevent agitation-related intracranial pressure (ICP) spikes in these patients. Sedative regimens in head-injured patients, however, remain non-standardized and largely unproven. In a recently published set of guidelines, no “standards” or “guidelines” could be supported by published data on the use of these agents. Only the following “option” was offered: “Sedation and neuromuscular blockade can be useful in optimizing transport of the head-injured patient. However, both treatments interfere with the neurological examination. In the absence of outcome-based studies, the choice of sedative is left to the physician. Neuromuscular blockade should be employed when sedation alone proves inadequate, and short-acting agents should be used when possible.”

Propofol in the treatment of moderate and severe head injury: a randomized, prospective double-blinded pilot trial


Division of Neurosurgery, University of California Medical Center, Los Angeles, California; University of California–Harbor Medical Center, Torrance, California; Washington Hospital Center, Washington, DC; Highland Hospital, University of California: Davis–East Bay, Oakland, California; University of Alabama Hospital, Birmingham, Alabama; New Jersey Medical School and Hospital, Newark, New Jersey; University Medical Center, Las Vegas, Nevada; University of Southern California–Los Angeles County, Los Angeles, California; Medical Center of Delaware, Newark, Delaware; University of Tennessee Medical Center, Memphis, Tennessee; and Temple University Hospital, Philadelphia, Pennsylvania

Object. Sedation regimens for head-injured patients are quite variable. The short-acting sedative–anesthetic agent propofol is being increasingly used in such patients, yet little is known regarding its safety and efficacy. In this multicenter double-blind trial, a titratable infusion of 2% propofol accompanied by low-dose morphine for analgesia was compared with a regimen of morphine sulfate in intubated head-injured patients. In both groups, other standard measures of controlling intracranial pressure (ICP) were also used.

Methods. Forty-two patients from 11 centers were evaluated to assess both the safety and efficacy of propofol: 23 patients in the propofol group (mean time of propofol usage 95 ± 87 hours) and 19 patients in the morphine group (mean time of morphine usage 70 ± 54 hours). There was a higher incidence of poor prognostic indicators in the propofol group than in the morphine group: patient age older than 55 years (30.4% compared with 10.5%, p < 0.05), initial Glasgow Coma Scale scores of 3 to 5 (39.1% compared with 15.8%, p < 0.05), compressed or absent cisterns on initial computerized tomography scanning (78.3% compared with 57.9%, p < 0.05), early hypotension and/or hypoxia (26.1% compared with 10.5%, p = 0.07). During treatment there was a trend toward greater use of vasoressors in the propofol group. However, the mean daily ICP and cerebral perfusion pressure were generally similar between groups and, on therapy Day 3, ICP was lower in the propofol group compared with the morphine group (p < 0.05). Additionally, there was less use of neuromuscular blocking agents, benzodiazepines, pentobarbital, and cerebrospinal fluid drainage in the propofol group (p < 0.05). At 6 months postinjury, a favorable outcome (good recovery or moderate disability) was observed in 52.1% of patients receiving propofol and in 47.4% receiving morphine; the mortality rates were 17.4% and 21.1%, respectively. Patients who received the highest doses of propofol for the longest duration tended to have the best outcomes. There were no significant differences between groups in terms of adverse events.

Conclusions. Despite a higher incidence of poor prognostic indicators in the propofol group, ICP therapy was less intensive, ICP was lower on therapy Day 3, and long-term outcome was similar to that of the morphine group. These results suggest that a propofol-based sedation and an ICP control regimen is a safe, acceptable, and, possibly, desirable alternative to an opiate-based sedation regimen in intubated head-injured patients.

Key Words: propofol, traumatic brain injury, intracranial hypertension, neuroprotection
Propofol in traumatic brain injury

The short-acting sedative–anesthetic nonanalgesic agent propofol (Diprivan; Zeneca Pharmaceuticals, Wilmington, DE) is being increasingly used in patients in the neurosurgical intensive care unit (ICU), particularly for head-injured patients. However, only a few studies have addressed its efficacy in these patients. Propofol is potentially advantageous in this setting, given its wide dose response, short elimination halflife (24–64 minutes), and neuroprotective effects. Low infusion rates result in light-to-moderate sedation and high rates result in electroencephalographic (EEG) burst suppression similar to that achieved with high-dose pentobarbital. Previously, propofol has been dispensed as a 1% infusion. A new 2% formulation was produced to reduce infusion volumes, and the additive ethylenediamine tetraacetic acid (EDTA) was included to reduce the risk of bacterial colonization of the lipid vehicle. Using this new formulation, a prospective randomized double-blind pilot trial was undertaken to assess the safety and efficacy of a propofol-based sedation regimen compared with a regimen of morphine sulfate in head-injured patients requiring mechanical ventilation. Although the primary study end point was determination of drug safety, the clinical end points included: 1) control of ICP and maintenance of cerebral perfusion pressure (CPP); 2) therapy intensity for ICP control, CPP control, and sedation; 3) 6-month neurolological outcome; and 4) treatment-related adverse events.

Clinical Material and Methods

Ethical Considerations

This protocol was independently reviewed and approved by the institutional review board of each participating institution. The trial was conducted in compliance with the regulations governing informed consent promulgated by the United States Food and Drug Administration (Code of Federal Regulations 21, Parts 50 and 56). Written informed consent for participation was required from the next of kin of each patient. The trial was also designed and monitored in accordance with the procedures of Zeneca Ltd., which include the key elements of good clinical practices as required by regulatory authorities.

Patient Population

Inclusion and Exclusion Criteria. Eligible patients included those who were aged 17 years or older, had sustained a closed or penetrating traumatic brain injury resulting in a postresuscitation Glasgow Coma Scale (GCS) score of 3 to 12, and required mechanical ventilation. Patients were excluded from the efficacy analysis if trial medication therapy was not begun within 96 hours of injury and medications were not administered for a minimum of 12 hours. Other exclusion criteria included a history of hypersensitivity to propofol or its constituents, renal insufficiency, hepatic failure, a known lipid metabolism disorder, spinal cord injury with paraplegia or quadriplegia, participation in another investigational drug trial within 31 days of trial entry, or body weight more than 130 kg.

Group Assignment and Randomization. Patients were stratified by postresuscitation GCS score into four categories (3, 4–5, 6–8, or 9–12) and randomized in a double-blind fashion to either the propofol or morphine sedation regimens. All patients received three simultaneous infusions, A, B, and C. Infusion A was a white emulsion containing either propofol or Intralipid (Pharmacia Upjohn, London, United Kingdom) as placebo. Infusion B was a clear solution composed of either morphine sulfate or normal saline as placebo. Infusion C was a low-dose morphine sulfate infusion for analgesia. For the propofol group patients, Infusion A consisted of propofol (ZD08-59#1 2% [20 mg/ml] with 0.005% EDTA) and Infusion B was normal saline. For morphine group patients, Infusion A was Intralipid and Infusion B was morphine. Given that propofol lacks analgesic effects, both groups also received an initial 2.5-mg bolus of morphine followed by Infusion C of morphine at 1 to 3 mg/hour for at least 48 hours.

Patient Management and Dosing Regimens

All patients were admitted to the ICU after initial stabilization or after craniotomy for evacuation of an intracranial hematoma. Management was in concordance with previously published guidelines for managing patients with severe head injury and included an algorithm for maintaining ICP less than 20 mm Hg and CPP higher than 70 mm Hg. Intracranial pressure therapy was implemented in a stepwise fashion as outlined in Table 1. The mode of ICP monitoring was left to the discretion of the investigator, although use of a ventriculostomy was encouraged. The sedation schedule outlined in Table 2 was used for all patients. As trial drug infusions began, patients were weaned from sedatives, narcotics, and neuromuscular blocking agents. Infusions A and B were initiated simultaneously at Step 1 and were increased as needed for agitation, bucking on the ventilator, abnormal posturing, or ICP levels persisting above 20 mm Hg. Trial Infusions A and B could be increased at a maximum rate of one step every 5 minutes. In patients without physiological evidence of pain (for example, those with tachypnea, tachycardia, or hypertension), administration of low-dose mor-

<table>
<thead>
<tr>
<th>Step</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Controlled ventilation (PaCO₂ 30–35 mm Hg); normothermia (temperature ≤ 37.4°C)</td>
</tr>
<tr>
<td>2</td>
<td>Ventricular CSF drainage: every 5–10 mins until ICP &lt; 20 mm Hg</td>
</tr>
<tr>
<td>3</td>
<td>Increase sedation: increase Infusions A &amp; B per titration schedule</td>
</tr>
<tr>
<td>4</td>
<td>Mannitol: if ICP remains elevated for &gt; 5 mins, administer 25–50 g every 2 hrs as needed to maintain ICP &lt; 20 mm Hg (maximum 250 g/24 hrs &amp; maintain serum osmolality &lt; 310)</td>
</tr>
<tr>
<td>5</td>
<td>High-dose pentobarbital: for intractable intracranial hypertension may be instituted after Infusions A &amp; B have been titrated to max rates &amp; ICP remains ≥ 30 mm Hg w/ CPP &lt; 70 mm Hg or ICP &gt; 40 mm Hg w/ CPP &gt; 70 mm Hg; titrate to achieve burst suppression on EEG</td>
</tr>
</tbody>
</table>

* If systolic blood pressure drops to less than 100 mm Hg or CPP to less than 60 mm Hg, both Infusions A and B should be lowered accordingly. If the blood pressure does not improve, both infusions should be stopped.
Phenytoin (Infusion C) could be stopped after 48 hours. Neurovascular blocking agents could be given at any time even if the patient was not adequately responsive to trial medications. Benzodiazepines could be used after Step 8 had been reached. Mannitol could also be administered if elevated ICP was not responsive to ventricular cerebrospinal fluid (CSF) drainage and to increasing Infusions A and B. Metabolic suppressive therapy, using high-dose pentobarbital, could be introduced for intractable intracranial hypertension only after patients reached maximum rates for Infusions A and B (Table 2). Cerebral perfusion pressure was maintained with the use of intravascular volume expansion and vasopressor therapy.

**Injury Severity Determinants**

Prognostic indicators were documented, including patient age, postresuscitation GCS score, systemic hypotension (systolic blood pressure < 90 mm Hg), hypoxia (arterial oxygen saturation < 60 mm Hg), and abnormal pupillary responses (poorly reactive or an asymmetry of ≥ 2 mm) in the prehospital setting or during the first 24 hours of hospitalization. The first two computerized tomography (CT) scans obtained in each patient were also analyzed for perimesencephalic cistern effacement, diffuse swelling, diffuse swelling with a midline shift greater than 4 mm, diffuse injury with punctate hemorrhages, subarachnoid hemorrhage, evacuated mass lesions, multiple contusions, and gunshot wounds. An Injury Severity Scale score was also calculated for each patient (Table 3).

**Table 2**

<table>
<thead>
<tr>
<th>Infusion Step</th>
<th>Infusion A (µg/kg/min)</th>
<th>Infusion B (µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 initial rate</td>
<td>2 (10)</td>
<td>1 (0.25)</td>
</tr>
<tr>
<td>2</td>
<td>4 (20)</td>
<td>2 (0.50)</td>
</tr>
<tr>
<td>3</td>
<td>6 (30)</td>
<td>2 (0.75)</td>
</tr>
<tr>
<td>4</td>
<td>8 (40)</td>
<td>4 (1.00)</td>
</tr>
<tr>
<td>5</td>
<td>10 (50)</td>
<td>5 (1.25)</td>
</tr>
<tr>
<td>6</td>
<td>12 (60)</td>
<td>6 (1.50)</td>
</tr>
<tr>
<td>7</td>
<td>14 (70)</td>
<td>7 (1.75)</td>
</tr>
<tr>
<td>8 benzodiazepines allowed</td>
<td>16 (80)</td>
<td>8 (2.00)</td>
</tr>
<tr>
<td>9</td>
<td>18 (90)</td>
<td>9 (2.25)</td>
</tr>
<tr>
<td>10</td>
<td>20 (100)</td>
<td>10 (2.50)</td>
</tr>
<tr>
<td>11</td>
<td>22 (110)</td>
<td>11 (2.75)</td>
</tr>
<tr>
<td>12</td>
<td>23 (120)</td>
<td>12 (3.00)</td>
</tr>
<tr>
<td>13</td>
<td>25 (130)</td>
<td>13 (3.25)</td>
</tr>
<tr>
<td>14</td>
<td>27 (140)</td>
<td>14 (3.50)</td>
</tr>
<tr>
<td>15 maximum rate†</td>
<td>29 (150)</td>
<td>15 (3.75)</td>
</tr>
<tr>
<td>16</td>
<td>31 (160)</td>
<td>16 (4.00)</td>
</tr>
<tr>
<td>17</td>
<td>33 (170)</td>
<td>17 (4.25)</td>
</tr>
<tr>
<td>18</td>
<td>35 (180)</td>
<td>18 (4.50)</td>
</tr>
<tr>
<td>19</td>
<td>37 (190)</td>
<td>19 (4.75)</td>
</tr>
<tr>
<td>20</td>
<td>39 (200)</td>
<td>20 (5.00)</td>
</tr>
</tbody>
</table>

* For the propofol group, Infusion A consisted of 2% propofol and Infusion B consisted of normal saline; for the morphine group, Infusion A consisted of 10% Intralipid and Infusion B consisted of morphine sulfate.

Dosages of all trial medications were calculated using patient’s baseline body weight (kg). The rates shown above were calculated only as an example using the weight of a 65-kg adult.

† Infusion B rates are based on a MgSO₄ concentration of 1 mg/ml.

‡ Rates higher than this were allowed only with permission of Zeneca.

**Efficacy Assessment**

Intracranial pressure and CPP measurements were recorded on an hourly basis as previously described. For each patient, baseline ICP and CPP before receiving study drugs, mean daily ICP and CPP, and total number of hours that ICP was greater than 20 mm Hg and CPP was lower than 70 mm Hg were recorded. The frequency of use of mannitol, neuromuscular blocking agents, benzodiazepines, barbiturates, and vasopressors, and the daily volume of CSF drainage were recorded. Neurological outcome was determined at 6 months postinjury by obtaining the Glasgow Outcome Scale (GOS) and Disability Rating Scale (DRS) scores. Favorable outcome was defined as a GOS score of good recovery or moderate disability or a DRS score of no, partial, or moderate disability (DRS score of 0–6).

**Safety Assessment**

Clinical Laboratory Assessments. Multiple blood samples were drawn to measure ionized calcium, total calcium, total magnesium, potassium, sodium, inorganic phosphate, blood urea nitrogen, creatinine, triglyceride, and parathyroid hormone concentration.

Hemodynamics. Systolic, diastolic, and mean arterial blood pressures, heart rate, central venous pressure, cardiac index, and body temperature were recorded immediately before initiation of trial drug therapy, 4 hours after start time, and daily thereafter until 24 hours after administration of trial drugs was discontinued.

Adverse Events. Fatalities, life-threatening events associated with trial drug use, and any other adverse events that were both serious and unexpected were reported. Patients were also evaluated daily for signs or symptoms of sepsis. Criteria included: 1) tachycardia (heart rate > 90 beats/minute); 2) hyperthermia (temperature > 38°C); 3) hypothermia (temperature < 36°C); 4) white blood cell elevation (> 12,000/mm³); 5) white blood cell depression (< 4000/mm³); and 6) positive blood culture(s).

Statistical Considerations and Sample Size

The primary end point of the trial was determination of drug safety. Specifically, the study sought to determine whether ZD0859#1 2% propofol significantly altered ionized calcium, serum total calcium, total magnesium, potassium, sodium, inorganic phosphate, or parathyroid hormone levels when administered for sedation of severely head injured patients. Given this objective, the power analysis was determined on the basis of projected standard deviations (SDs) for changes in ionized calcium. Although the original protocol called for 100 patients, a lower number of patients was deemed sufficient because no clinically significant changes in calcium homeostasis were reported in an earlier Diprivan 1% trial, approved by the Food and Drug Administration in June 1996. Both the 1% and 2% formulations have the same concentration of EDTA (0.005%). For these reasons, this trial was terminated earlier than expected because sufficient safety
data had been acquired. All patients treated with trial drugs, regardless of duration, were included in the safety analyses.

Because this was a multicenter trial, all statistical analyses and results were based on appropriate pooling of data across centers. Between-group analysis of continuous variables was assessed using Student’s t-test or analysis of variance (ANOVA) for comparison of more than two groups. Multiple comparisons were not adjusted for an inflated alpha. Percentage comparisons were performed using a Bernoulli process (binomial distribution). The Mann–Whitney U-test was used to assess differences for nonparametric factors such as median GCS score and median number of CT diagnoses. All variances were expressed as an SD. All differences for which the probability value was less than 0.05 were considered significant.

Results

Enrollment and Patient Exclusions

From September 1, 1995 to August 18, 1996, 70 acutely head injured adults from 11 centers were randomized; however, five were withdrawn before being given trial drugs. Of the remaining 65 patients, a total of 23 patients were not included for evaluation of efficacy of trial drugs for the following reasons. In two patients (one from each treatment group), trial drugs were not administered within 96 hours of injury and, in seven patients, trial drugs were not given for at least 12 hours (four in the propofol group and three in the morphine group). In seven patients in the morphine group varying amounts of 1% propofol were administered before beginning trial medications. Three patients from this group were excluded because they received relatively large amounts of propofol during a period of at least 24 hours. The remaining four patients were included for analysis because they received small sedating amounts of 1% propofol for less than 12 hours, all less than 20 µg/kg/minute and averaging 12.3 µg/kg/minute. Two patients, both in the propofol group, were excluded because only telephone consent was obtained. Also, one patient in the propofol group was excluded because police records and autopsy findings had indicated the patient sustained a primary anoxic injury from strangulation with a resultant common carotid occlusion and multiple cerebral infarctions within 2 days of injury. Of the remaining 50 patients (27 in the propofol regimen and 23 in the morphine regimen), eight patients (four in each treatment group) were lost to follow-up review, leaving 23 patients in the propofol group and 19 in the morphine group with a 6-month follow up. These 42 patients are the focus of this paper.

Patient Characteristics and Predictors of Outcome by Patient Group

The patients’ median ages did not differ significantly but there was a higher proportion of patients older than 55 years in the propofol group (30.4%) compared with the morphine group (10.5%) (p < 0.05). The median postresuscitation GCS score was 7 in the propofol group and 6 in the morphine group; however, the propofol group had a higher proportion of patients with a GCS score of 3 to 5 (39.1% compared with 15.8%, p < 0.05). The GCS score was 8 or less in 22 patients (95.7%) in the propofol group and in 17 (89.5%) in the morphine group. Pupillary abnormalities were documented within the 1st day postinjury with approximately equal frequency. Systemic hypotension and/or hypoxic insults were documented through the 1st day postinjury in six patients (26.1%) receiving propofol and in two patients (10.5%) receiving morphine (p = 0.07). The median number of major CT diagnoses was similar in both groups. However, the propofol group had a higher number of patients with compressed or absent cisterns on initial CT scans (78.3% compared with 57.9%, p < 0.05). The frequency of other CT diagnoses was similar between the two groups (Table 3).

Trial Drug Administration

The average times after injury that trial infusions were initiated in the propofol and morphine groups were 34 ± 21 hours and 38 ± 26 hours, respectively. The mean duration of therapy was 95 ± 87 hours in the propofol group and 70 ± 54 hours in the morphine group (p = 0.26). The average infusion rates for the propofol group were 55 ± 42 µg/kg/minute of propofol and 1.3 ± 0.7 mg/hour of morphine. For the morphine group, combining the titratable and low-dose infusions, the mean morphine infusion rate was 10 ± 6.7 mg/hour.

Intracranial Pressure, CPP, and Therapy Intensity

The modes of ICP monitoring in the propofol group included ventriculostomy in 16 patients and a parenchy-
propofol group (34.4 ± 5.9 mm Hg) and the morphine group (36 ± 4.2 mm Hg) while patients were receiving study drugs (p = 0.32).

**Neurological Outcome**

At 6 months postinjury, a favorable outcome, as assessed using the GOS, was observed in 12 (52.2%) of the propofol patients and in nine (47.4%) of the morphine patients; the mortality rates were 17.4% and 21.1%, respectively (Table 5). If the two patients without ICP monitoring in the propofol group are excluded, the favorable outcome rate is unchanged. Similarly, 14 patients (60.9%) in the propofol group and 11 (57.9%) in the morphine group had favorable outcomes, as assessed using the DRS.

**Adverse Events and Cause of Death**

The number of patients sustaining adverse events resulting in study withdrawal was five (21.7%) in the propofol group and eight (42.1%) in the morphine group. However, only four events (17.4%) in the propofol group and six (31.6%) in the morphine group were considered severe in intensity (Table 6). Uncontrollable intracranial hypertension was the cause of withdrawal in three patients in the propofol group and in five in the morphine group (p = 0.06) and was considered a key factor in three of four deaths in both groups. One patient in the propofol group was withdrawn after 23 hours of trial medications because of hypotension. She was receiving a moderate dose of propofol, averaging 65 µg/kg/minute. She had sustained severe multiple trauma with chest injuries and experienced a hypotensive episode before beginning the study medications. She recovered to a level of moderate disability. Another patient in the propofol group was withdrawn because of low CPP after 29 hours of therapy. He was receiving a relatively low dose of propofol, averaging 28 µg/kg/minute, and also recovered to a level of moderate disability. Pneumonia was documented in five patients (21.7%) in the propofol group and in two (10.5%) in the morphine group (p = 0.13). Sepsis occurred in three patients (13%) in the propofol group and in one (5.3%) in the morphine group (p = 0.2). None of the infections reported were considered directly related to the trial medications.
Propofol in traumatic brain injury

TABLE 5
Outcomes of 42 patients with moderate or severe head injury*

<table>
<thead>
<tr>
<th>6-Mo Outcome</th>
<th>Propofol (23 patients)</th>
<th>Morphine (19 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>good recovery</td>
<td>3 (13%)</td>
<td>5 (26.3%)</td>
</tr>
<tr>
<td>moderate disability</td>
<td>9 (39.1%)</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td>severe disability</td>
<td>5 (21.7%)</td>
<td>6 (31.6%)</td>
</tr>
<tr>
<td>vegetative state</td>
<td>2 (8.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>death</td>
<td>4 (17.4%)</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td>lost to follow up</td>
<td>4 of 27 (14.8%)</td>
<td>4 of 23 (17.4%)</td>
</tr>
</tbody>
</table>

* Outcomes based on GOS.

Regarding the effects of Intralipid administration, only one patient was withdrawn because of hyperlipemia (peak triglyceride level 471 mg/dl, normal range 10–250 mg/dl). This patient from the morphine group had been receiving high doses of trial infusions for 6 days. In the propofol group, seven patients (30.4%) had at least one episode of transient elevation in serum triglycerides. These patients were receiving propofol averaging 64 ± 53 μg/kg/minute for 164 ± 113 hours. They tended to be older with a mean age of 47 years. The patient with elevated triglycerides who received study medications for the shortest time (45 hours) and with the lowest mean dose (19 μg/kg/minute), was also the oldest (75 years). He recovered to a level of moderate disability.

Data Analysis With Inclusion of Patients Lost to Follow Up

When the eight patients lost to follow-up review were included in the prognostic indicator and ICU data analyses, similar differences were seen between the two treatment groups for most analyses. Specifically, the propofol group (27 patients) continued to have a higher incidence of poor prognostic indicators than the morphine group (23 patients): patient age older than 55 years, GCS score of 3 to 5, early hypotension and/or hypoxia (p < 0.05 for all comparisons), and compressed or absent cisterns on CT scan (p = 0.1). Regarding ICP, the difference seen on therapy Day 3 was no longer significant. However, the amount of CSF drainage remained less on therapy Days 2 and 3 in the propofol group (p < 0.01 and p < 0.05, respectively). Use of neuromuscular blocking agents, benzodiazepines, and pentobarbital was also less in the propofol group (p < 0.05 for all comparisons). However, use of mannitol (p < 0.05) and vasopressors (p = 0.06) was less in the morphine group. Regarding adverse events, there were no intergroup differences in incidence of uncontrollable intracranial hypertension, systemic hypotension, low CPP, or infections.

Propofol Subgroup Analysis—Dose Effect

Patients in the propofol group were further categorized, retrospectively, into either high-dose or low-dose subgroups based on the total amount of propofol received, the time to initiation of therapy, and infusion duration. High-dose patients were defined as receiving a total propofol dose of at least 100 mg/kg, beginning propofol within 48 hours of injury, and remaining on infusion for a minimum of 24 hours; low-dose patients did not meet at least one of these criteria. The 10 patients in the high-dose subgroup were compared with 13 patients in the low-dose subgroup and 19 patients in the morphine group (Tables 7 and 8).

Predictors of Outcome. The propofol high-dose subgroup was more severely injured according to the initial GCS score and had a higher incidence of multiple contusions compared with both the low-dose subgroup and the morphine group. There was also a trend toward a higher incidence of abnormal cisterns in the high-dose group compared with the morphine group. The low-dose subgroup, however, consisted of patients who were significantly older than both the high-dose subgroup and the morphine group and had a higher incidence of evacuated subdural hematomas compared with the high-dose subgroup.

Intracranial Pressure and CPP Control. There were no significant differences across the three groups regarding mean daily ICP and CPP values. On therapy Day 2, however, there was a trend toward a higher mean CPP in the high-dose propofol subgroup (81 ± 8 mm Hg) compared with the low-dose (68 ± 19 mm Hg) subgroup and the morphine group (72 ± 12 mm Hg) (p = 0.16, ANOVA). Similarly, on therapy Day 3 there was a trend toward lower ICP in the high-dose (14 ± 5 mm Hg) and low-dose (15 ± 6 mm Hg) subgroups compared with the morphine group (18 ± 4 mm Hg) (p = 0.12, ANOVA).

Therapy Intensity for CPP and ICP Control. Use of CSF drainage was less in both the high-dose and low-dose propofol subgroups on therapy Days 2 and 3 compared with the morphine group (p < 0.01 and p = 0.11, respectively). Additionally, on therapy Day 4, there was a trend of less CSF drainage in the high-dose subgroup compared with the morphine group (p = 0.06). Use of mannitol and neuromuscular blocking agents was greater in the high-dose subgroup and the morphine group, whereas benzodiazepine and pentobarbital use was greatest in the morphine group. In contrast, use of vasoressors was significantly greater in the high-dose subgroup compared with both the low-dose subgroup and the morphine group.

Neurological Outcome. A favorable neurological outcome, as assessed using the GOS and DRS, was achieved in 70% and 80% of patients in the high-dose propofol subgroup, compared with 38.5% and 46.2% in the low-dose subgroup, respectively (p < 0.05 for both GOS and DRS.
discussion

Summary of Study Findings

Despite randomization in this pilot study, the propofol and morphine groups were not evenly matched in prognostic indicators. Specifically, the propofol group had more patients who were older than 55 years of age, had an initial GCS score of 3 to 5, had early hypotension and/or hypoxia and compressed or absent basilar cisterns on the initial CT scan. Even with this preponderance of adverse risk factors, ICP was lower on therapy Day 3, therapy intensity for ICP control was less, and there was a trend for fewer patient withdrawals for intractable intracranial hypertension in the propofol group. Furthermore, 6 months postinjury neurological outcome was similar in the two groups. When the eight patients lost to follow-up review were included in the acute data analysis, the propofol group still had a significantly greater incidence of poor prognostic indicators and a lower therapy intensity, as measured by use of neuromuscular blocking agents, benzodiazepines, pentobarbital, and CSF drainage. However, mannitol and vasopressor use was more frequent in the propofol group.

The subgroup analysis of propofol patients demonstrated that the high-dose subgroup and the morphine group were well matched in terms of age, incidence of hypotension, hypoxia, and abnormal pupils. However, the high-dose propofol patients were more severely injured, as determined by GCS scores, and tended to have more unfavorable CT findings compared with the morphine group. Despite these poor prognostic factors, the high-dose propofol subgroup tended to have better ICP and CPP control and required less CSF drainage and benzodiazepine and pentobarbital therapy. However, vasopressor use was greatest in the high-dose subgroup. Finally, the high-dose propofol subgroup had the highest favorable neurological outcome rate compared with both the low-dose subgroup and the morphine group.

Methodological Problems

The original target number of 100 patients for this trial was not reached because sufficient drug safety data were obtained with fewer patients than expected. The sample size was further reduced by patient exclusions deemed necessary to maintain study validity. Specifically, a minimum of 12 hours on trial drugs and onset of therapy within 96 hours of injury were thought to constitute reasonable, albeit not ideal, windows for inclusion. It would have been preferable to have a longer minimum time on trial drugs and a narrower time window for trial entry. The issue of wide variability in total dose and duration of propofol was addressed by including them in the prognostic indicator and ICU data analysis. Thevariability in treatment regimens across centers is also a methodological issue that is seen frequently in such clinical studies. For example, the fact that ventriculostomies were used in only 16 of 23 patients in the propofol group and in 16 of 19 patients in the morphine group may have created bias in the analysis of therapy intensity for ICP and CPP control. The differences in CSF drainage on therapy Days 2 and 3 remained significant, however, even with a relatively small number of patients with ventriculostomies.

A titratable morphine infusion was used for the “standard therapy” group because opiate-based sedative regi-
Propofol in traumatic brain injury

Propofol is commonly used in intubated head-injured patients. However, it was somewhat surprising that the morphine dose was so high, averaging 10 mg per hour, even though the titration protocol allowed for relatively liberal use of CSF drainage and therapy with mannitol and neuromuscular blocking agents. This fact may attest to the relative ineffectiveness of opiates for achieving sedation and ICP control. Their routine use in head-injured patients is also of questionable wisdom, given that opiate antagonists have been shown in some spinal cord injury models to be neuroprotective. These and other disadvantages of an opiate-based sedation regimen are further discussed later.

Previous Head Injury Studies Using Propofol

Relatively few studies of propofol use for posttraumatic coma have been reported during the last decade. In one of these studies, 10 severely head-injured patients were given a 1% propofol infusion over 24 hours after having been started initially on infusions of morphine (5–10 mg/hour), midazolam (5–10 mg/hour), and vecuronium (0.1 mg/kg/hour). Propofol infusion rates averaged 48 μg/kg/minute, which is similar to the mean rate in the present study. The ICP was unchanged but CPP took an upward trend and was significantly higher at the end of 24 hours. In another 24-hour study, severely head injured patients were randomized to receive either a 1% propofol infusion or a fentanyl infusion; both groups received pancuronium. In the 15 patients randomized to propofol (dose range 17–50 μg/kg/minute), CPP increased significantly from 75 to 93 mm Hg. The ICP remained stable in the low ICP subgroup and decreased in the high ICP subgroup. In the 16 patients receiving fentanyl, ICP also decreased in the high ICP subgroup, but CPP decreased slightly. In a more recent study of intubated moderately and severely head injured patients, nine patients were given a 1% propofol infusion (mean dose 55 μg/kg/minute, range 36–95 μg/kg/minute) and six were sedated with infusions of morphine (range 0–4 mg/hour) and midazolam (range 0–5 mg/hour). Throughout a mean data collection period lasting 40 hours, no differences were observed between groups for blood pressure, ICP, CPP, or outcome. However, propofol was associated with a significant fall in the arteriovenous difference in oxygen at 4 hours after onset of propofol infusion. At 8 hours postinfusion this difference disappeared. The findings from these studies suggest that a propofol-based regimen is safe and as effective as a narcotic-based regimen for sedation and ICP control. It is difficult, however, to draw further conclusions from these reports.

Propofol as a Neuroprotectant

Given the significant disparity in injury severity between the two treatment groups in this study, both acute and long-term outcome data suggest a propofol-based regimen may be superior to an opiate-based regimen in head-injured patients. Several neuroprotective actions of propofol may help explain this favorable effect on neurological recovery. These include potentiation of γ-aminobutyrate (GABAergic) inhibition and inhibition of N-methyl-D-aspartate glutamate receptors and voltage-dependent calcium channels. Propofol is also a potent antioxidant and inhibitor of lipid peroxidation, unlike barbiturate medications.

Similar to barbiturate agents, etomidate, and benzodiazepines, propofol causes cerebral metabolic suppression primarily by potentiating the GABAergic receptor-channel complex. Propofol-induced EEG burst suppression results in a decrease in cerebral blood flow of 38 to 58%, a decrease in the cerebral metabolic rate of oxygen of 22 to 43%, and a decrease in the cerebral metabolic rate of glucose of 36 to 55%. This metabolic depressant effect is thought to be a key factor in enhanced neurological recovery and reduced neuronal damage in experimental ischemia and reperfusion models. The clinical importance of other actions of propofol is unclear. Specifically, the effects on NMDA and calcium channels are uncertain. However, given the role of excitotoxicity and intracellular calcium influx in posttraumatic mitochondrial dysfunction, attenuation of this influx by propofol may be beneficial. The addition of the calcium chelator EDTA to the propofol formulation, albeit in relatively small quantities, may further reduce the harmful effects of calcium. Propofol’s potent free-radical scavenging effects and ability to inhibit lipid peroxidation may also be relevant in the clinical setting by enhancing cell membrane viability.

In the present study, the mean propofol dose was 55 μg/kg/minute. Infusion rates typically resulting in an EEG burst suppression range from 100 to 220 μg/kg/minute. Given that cerebral metabolic measurements...
were not routinely performed in this trial, it is unknown whether significant metabolic suppression was achieved in these patients. Additionally, it is unclear if other neuroprotective mechanisms, including effects on NMDA receptors, calcium channels, and lipid peroxidation are biologically relevant when propofol is administered at these levels. The favorable trends in ICP control and therapy intensity in the propofol group and the high favorable outcome rate in the high-dose propofol subgroup suggest that moderately high doses, even below those needed to induce EEG burst suppression, may enhance neurological recovery.

**Advantages and Disadvantages of Propofol**

In addition to its neuroprotective qualities, there are several other properties that make propofol an attractive sedative for head-injured patients. First, its short elimination half-life of less than an hour facilitates rapid titration to a desired clinical effect and permits frequent neurological assessments. Second, the wide dose response allows it to be used as a sedative or as a metabolic suppressive and neuroprotective agent. In contrast, the short-acting neuroprotectant, etomidate, is not suited for prolonged use because of renal toxicity related to its propylene glycol vehicle and because it suppresses adrenocortical steroid production. Pentobarbital, the metabolic suppressant that is traditionally used, has a half-life of 15 to 48 hours and typically requires a minimum of 48 hours after drug stoppage before patients can be assessed neurologically. Third, propofol reduces ICP as demonstrated in previous reports and as suggested by this study, although this effect has not been consistently shown. In contrast, neither midazolam (Versed) nor the opiates morphine, fentanyl, or sufentanil reliably decrease ICP in severely head injured patients. Fourth, propofol is a potent anticonvulsant and, as shown, patients receiving propofol emerge from sedation more rapidly compared with those receiving benzodiazepines, which may, in turn, shorten mechanical ventilation time and the number of days in the ICU. The similar favorable outcome rate in the two treatment groups and the lower therapy intensity for ICP control, although this effect has not been consistently shown. The new 2% formulation should reduce the lipid load by 50% compared with an equipotent drug dose with the 1% formulation.

Elevated triglyceride levels from the lipid vehicle can occur with prolonged high-dose propofol infusion and are more likely to occur in older patients. This side effect is short lived once the infusion is stopped or diminished. The new 2% formulation should reduce the lipid load by 50% compared with an equipotent drug dose with the 1% formulation. Regarding risk of infection due to the lipid vehicle, the addition of EDTA appears to be safe from an infection standpoint. Although there was a trend toward a higher pneumonia rate in patients in the propofol group, these pneumonias were not attributed to drug administration per se. Further studies confirming the safety of this formulation from an infection standpoint are nearing completion.

Finally, regarding the issue of cost, propofol is clearly more expensive than morphine on a per unit basis. However, as this study confirms, most intubated head-injured patients are not adequately sedated with morphine alone. In contrast, a propofol-based sedation regimen appears to reduce the need for concomitant narcotics and muscle relaxants significantly. Given the lipid vehicle used with propofol, the daily need for lipid nutritional supplements is also decreased. Additionally, as other studies have shown, patients receiving propofol emerge from sedation more rapidly compared with those receiving benzodiazepines, which may, in turn, shorten mechanical ventilation time and the number of days in the ICU. Overall, these factors appear to make a propofol sedation regimen cost-effective; however, further study of this issue is warranted.

**Conclusions**

In this preliminary study, we have demonstrated the potential advantages of a propofol-based sedation and ICP control regimen in intubated head-injured patients. The similar favorable outcome rate in the two treatment groups and the lower therapy intensity for ICP control, despite a preponderance of poor prognostic factors in the propofol group, suggests that a propofol-based regimen with low-dose opiate analgesia is a safe and, possibly, desirable alternative to an opiate-based regimen in head-injured patients. Further studies are clearly needed to define the neuroprotective dose range of propofol in both experimental and human head injury. A randomized phase II trial of early high-dose propofol during the period of acute brain swelling in severely head injured patients is currently being planned, based on the findings of this study and in light of the favorable results of high-dose barbiturate studies performed over a decade ago.
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References


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