Neuropsychiatric Complications after Cardiopulmonary Bypass: Cerebral Protection by a Barbiturate

Nancy A. Nussmeier, M.D.* Carolee Arlund, R.N.† and Stephen Slogoff, M.D.‡

The authors prospectively investigated the ability of thiopental to decrease neuropsychiatric complications as a consequence of open-ventricle operations requiring cardiopulmonary bypass. Eighty-nine randomly assigned patients received sufficient thiopental to maintain electroencephalographic silence throughout the period from before atrial cannulation to termination of bypass. These patients received an average of 39.5 mg/kg of thiopental, while 93 control patients received only fentanyl. On the first postoperative day, five thiopental (5.6%) and eight control (8.6%) patients exhibited clinical neuropsychiatric abnormalities. By the tenth postoperative day, all neuropsychiatric dysfunction had resolved in the thiopental group but persisted in seven (7.5%) control patients (P < 0.025). The incidence of complications was significantly related to calcification of replaced valves, aortic valve replacement, advanced age, and prolonged bypass, but not to low blood pressure during perfusion. The authors believe their data are consistent with embolism as the most important cause of sensory-motor neurologic dysfunction following cardiopulmonary bypass. The data also provide evidence that thiopental in sufficient dosage can reduce the clinical consequences of these events. This is the first demonstration of cerebral protection by a barbiturate in humans. (Key words: Anesthesia: cardiac. Anesthetics, intravenous: thiopental. Brain: protection; stroke. Surgery: cardiac.)

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Our data suggested cerebral protection by thiopental, but the incidence of neuropsychiatric complications in treated and control groups was not significantly different. We extended this study using a more rigorous design, which included only patients at highest risk (open ventricle), and increased the dose and duration of thiopental administration. These new data indicate that thiopental reduces the clinical expression of cerebral emboli associated with cardiopulmonary bypass. We believe this model provides the first demonstration in humans of the ability of thiopental to mitigate the consequences of focal cerebral ischemia.

Methods

PATIENT SELECTION

The study was approved by the institutional committee for human experimentation, and all patients consented to participation. Any adult patient not previously operated on for heart disease and scheduled for an elective procedure requiring opening of a cardiac chamber (valve replacement or repair, ventricular aneurysm resection, or closure of septal defect) was eligible for study. On the day before operation, a neuropsychiatric evaluation was performed by one investigator (NN). Neurologic evaluation included: 1) strength of all upper- and lower-extremity motor groups; 2) sharp–dull perception in all spinal-nerve distributions; 3) motor and sensory function of the cranial nerves II–XII; 4) activity of spinal and plantar reflexes; and 5) cerebellar function by finger-to-nose and heel-to-toe movements, gait, and station. Psychiatric evaluation included: 1) assessment of orientation; 2) clearly inappropriate affect or clearly atypical behavior, such as hostility or withdrawal; 3) grossly abnormal ideation, including hallucinations or delusions; and 4) memory, both recent and remote. Patients with any abnormalities at this examination or with history of cerebrovascular or other neurologic disease were excluded.

At the preoperative interview and again on the fifth postoperative day, the two-part Trail Making Test, a psychometric exercise highly sensitive to the presence of organic brain disease10 was administered in the hope of detecting subclinical decrements in cerebral function. As in our previous study,4 large decrements in test performance were found in patients with postoperative clinical dysfunction. However, large decrements were also found in 27% of patients without clinical abnormality. These were equally distributed between thiopental and control groups.

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* Assistant Professor of Anesthesiology. Present address: Department of Anesthesiology, University of California, San Francisco, 513 Parnassus, Room S-436, San Francisco, California 94143.
† Research Associate in Anesthesiology.
‡ Clinical Professor of Anesthesiology.

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Address reprint requests and correspondence to Dr. Slogoff: Cardiovascular Anesthesia, Texas Heart Institute, P. O. Box 20269, Houston, Texas 77225.
and were unrelated to variables subsequently found to be significantly associated with clinical dysfunction. Because this test lacked sufficient specificity to detect subclinical focal brain damage in this complex setting, these data will not be presented.

PERIOPERATIVE MANAGEMENT

Our previous study identified age greater than 59 yr and female sex as significantly related to postoperative neuropsychiatric dysfunction. Patients suitable for study were, therefore, allocated to control or thiopental groups according to a computer-generated, random-allocation scheme designed to balance the groups for sex and age. Preanesthetic medication for all patients consisted of diazepam 100 μg/kg, orally, and morphine 100 μg/kg plus scopolamine 100–200 μg, intramuscularly, 1 h prior to anesthesia. Bifrontal EEG calibrated at 5 μV/mm, seven-lead ECG, direct arterial blood pressure, and nasopharyngeal temperature were monitored. Induction of anesthesia for all patients was achieved by intravenous administration of diazepam 200 μg/kg, fentanyl 15 μg/kg, and pancuronium 150 μg/kg. When necessary to control hypertension, enfurane in oxygen was also administered by inhalation. Approximately 10 min prior to cannulation of the aorta, thiopental was first administered to patients in the thiopental group in 50–100 mg increments until the electroencephalogram became isoelectric. Thiopental was then administered by continuous infusion beginning at a rate of 500 μg · kg⁻¹ · min⁻¹. The rate of infusion was adjusted to maintain a burst suppression pattern with more than 60 s between bursts throughout the period of cannulation, CPB, and weaning from bypass. Thiopental administration ceased when CPB was discontinued. Patients in the control group received additional fentanyl 20–40 μg/kg at the beginning of CPB and received no thiopental at any time. After CPB, no anesthetic drug other than enfurane was administered and this only to control hypertension. Patients who suffered hypotension, defined as a systolic blood pressure of less than 80 mmHg for more than 5 min, at any time during operation except for the period of CPB, were excluded from study. Three patients were excluded for this reason, and none suffered neuropsychiatric dysfunction after operation.

Bubble oxygenators of several types were used (Travenol, Rygg, Harvey, Cobe, and Bentley), all with a 40-μ depth filter in the cardiectomy return. Arterial filters were not used. Oxygenators were primed with 20 ml/kg of 5% dextrose in lactated Ringer’s solution to which heparin, 2000 U/L, was added. Heparin, 300 U/kg, was administered before cannulation. During CPB, flow varied between 40 and 60 ml · kg⁻¹ · min⁻¹ as determined by venous return. Mean arterial pressure ranged between 40–90 mmHg, with hematocrit varying from 18% to 29%. Nasopharyngeal temperature was maintained greater than 34°C by heat exchanger. No patient in the control group had absent or acutely depressed EEG activity during any period during operation.

All operations were performed through a median sternotomy. A cannula was placed in the right superior pulmonary vein for venting air and blood during bypass. Before termination of CPB, air was aspirated by needle from the left ventricle and by continuous suction from the proximal aorta. CPB was not discontinued until adequate cardiac function had been established. One patient who required intra-aortic balloon counterpulsation to wean from bypass, and three additional patients who were returned to bypass for additional operative procedures after initial weaning, were excluded. One of these four, a control patient, died intraoperatively; none of the survivors suffered neuropsychiatric dysfunction.

POSTOPERATIVE NEUROPSYCHIATRIC EVALUATION

On the first postoperative day, a limited neuropsychiatric evaluation was performed by one investigator (CA), who was not aware of the anesthetic drugs administered. Examination included movement-against-resistance of all extremities in response to command; biceps, knee, and plantar reflexes; orientation as to person, time, and place; and grossly abnormal behavior or ideation. All positive findings were confirmed by a second investigator. The presence of deviant personality characteristics was confirmed by a family member. On the fifth postoperative day, the entire preoperative neuropsychiatric examination was repeated. To avoid false-positive diagnoses from persistent drug effects or peripheral neuropathies, a neurologic abnormality was considered present only when at least two complementary motor, sensory, or reflex abnormalities were found (e.g., weakness of an arm with sensory loss on the same side). To eliminate "ICU psychosis," a psychiatric abnormality was considered present only if its onset was less than 24 h after emergence from anesthesia. In tabulations, abnormalities were considered transient if they were absent on the tenth postoperative day and persistent if still present, even though improving, on that day.

Statistical analysis was performed in two stages. First, comparison of independent patient and perioperative categorical variables were examined by chi-square corrected for continuity or by Fisher’s Exact test when appropriate; continuous variables were examined by Student’s t test or one-way analysis of variance. Then, those factors that were significantly related to the appearance of postoperative neuropsychiatric dysfunction or showed a trend toward statistical significance (P < 0.10) were entered into a stepwise discriminant function analysis using forward selection with backward elimination. Continuous variables are reported as mean ± SD.
Results

The demographic characteristics of the 89 patients randomly assigned to the thiopental group were not different from the 95 patients in the control group (table 1). Neuropsychiatric dysfunction was present within 24 h of emergence from anesthesia in 13 patients, five (5.6%) in the thiopental group, and eight (8.6%) in the control group (table 2). In the thiopental group, one patient had hemiparesis with disorientation, and four had psychiatric without neurologic abnormalities. These psychiatric abnormalities consisted of two or more of the following: disorientation, memory loss, belligerence, excessive lethargy, hallucinations, or delusions. In the control group, two patients had only psychiatric abnormalities, which consisted of excessive lethargy with hallucinations in one and hostility with paranoid delusions in the other; two had hemiparesis; two had hemiparesis with psychiatric abnormalities; one had homonymous hemianopsia; and one had dysarthria with other signs of cerebellar dysfunction.

By the tenth postoperative day, all neuropsychiatric abnormalities disappeared in the thiopental group, whereas abnormalities persisted in seven of the eight patients in the control group (P < 0.025) (table 2). Transient neuropsychiatric abnormalities actually disappeared by the fifth postoperative day.

Neuropsychiatric abnormalities were significantly more likely in patients who were older (≥60 yr), required aortic valve replacement, or had calcified mitral or aortic valves, and in those requiring longer periods of bypass (table 3). Postoperative clinical dysfunction was not related to sex, lowest perfusion flow rate measured during any 5-min period, or low perfusion pressure expressed as TM<sup>-60</sup>, an index of both degree and duration of low perfusion pressure. TM<sup>-60</sup> is the sum of the products calculated by multiplying 5 min by the difference between 50 mmHg and the observed perfusion pressure when less than 50 mmHg over any 5-min period. It is expressed as mmHg·min. These data are reported as group means and as percentage of patients exceeding 100 and 200 mmHg·min (table 3). Incidences and means listed in table 3 were not significantly different between the thiopental and control groups (table 1). Discriminant analysis comparing those patients with persistent neuropsychiatric dysfunction only to the remaining 175 patients confirmed the relationships for all contributory and noncontributory factors listed previously but now found the most powerful predictor of outcome to be assignment to thiopental or control group.

Because psychiatric abnormalities diagnosed on the first postoperative day could be attributed to residual anesthetic or metabolic effects as well as embolic events, the two treatment groups were also compared without patients in whom psychiatric dysfunction but not neurologic deficits occurred. Thus, excluding patients with psychiatric deficits only, on the first postoperative day, one of 89 thiopental patients versus six of 93 control patients awoke with new sensory–motor dysfunction. At ten days after operation, deficits persisted in all six control patients, while the one thiopental patient had returned to normal (P < 0.03). Discriminant analysis comparing patients with neurologic dysfunction only and persistent neurologic dysfunction only to those without confirmed the significant roles in outcome of age ≥ 60 yr, prolonged duration of CPB, aortic valve replacement, valvular calcification, and thiopental treatment. For the six patients with psychiatric dysfunction only, significant factors in early post-

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**Table 1. Patient and Perioperative Characteristics for the Two Treatment Groups**

<table>
<thead>
<tr>
<th></th>
<th>Thiopental Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>89</td>
<td>93</td>
</tr>
<tr>
<td>Males (%)</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57 ± 14</td>
<td>55 ± 15</td>
</tr>
<tr>
<td>Age ≥ 60 yr (%)</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 ± 14</td>
<td>75 ± 16</td>
</tr>
<tr>
<td>Perioperative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>Aortic valve replacement (min)</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>Valvular calcification (%)</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>Lowest flow on CPB (ml kg⁻¹ min⁻¹)</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Hypotension during CPB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TM&lt;sub&gt;-50&lt;/sub&gt;</td>
<td>186 ± 155</td>
<td>159 ± 146</td>
</tr>
<tr>
<td>TM&lt;sub&gt;-50&lt;/sub&gt; ≥ 100 mmHg min (% patients)*</td>
<td>73</td>
<td>56</td>
</tr>
<tr>
<td>TM&lt;sub&gt;-50&lt;/sub&gt; ≥ 200 mmHg min (% patients)*</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Thiopental dose (mg/kg)</td>
<td>39.5 ± 8.4</td>
<td></td>
</tr>
</tbody>
</table>

* See “Results” for definition of TM<sup>-50</sup>

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**Table 2. Transient and Persistent Neuropsychiatric Dysfunction in Thiopental and Control Groups**

<table>
<thead>
<tr>
<th></th>
<th>All Complications*</th>
<th>Persistent at 10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thiopental</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Thiopental</td>
<td>Control</td>
</tr>
<tr>
<td>Patients with dysfunction</td>
<td>5 (5.6%)</td>
<td>8 (8.6%)</td>
</tr>
<tr>
<td>Neurologic only</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric only</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Both</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

* Includes transient and persistent deficits elicited in the examination on the first postoperative day.
† Difference significant at P < 0.025.
TABLE 3. Contributory and Noncontributory Factors in Clinical Neuropsychiatric Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Clinically Abnormal</th>
<th>Clinically Normal</th>
<th>( F^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>13</td>
<td>169</td>
<td>—</td>
</tr>
<tr>
<td>Contributory factors†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>replacement (%)</td>
<td>85</td>
<td>45</td>
<td>8.0</td>
</tr>
<tr>
<td>Valvular calcifications (%)</td>
<td>69</td>
<td>33</td>
<td>7.5</td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>71 ± 19</td>
<td>50 ± 19</td>
<td>4.9</td>
</tr>
<tr>
<td>Age ≥ 60 yrs (%)</td>
<td>77</td>
<td>46</td>
<td>4.6</td>
</tr>
<tr>
<td>Noncontributory factors†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>69</td>
<td>68</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Lowest flow on CPB (ml·kg(^{-1})·min(^{-1}))</td>
<td>43 ± 11</td>
<td>45 ± 12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hypotension during CPB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TM(^{&lt;10}) mmHg·min</td>
<td>169 ± 126</td>
<td>173 ± 153</td>
<td>&lt;1</td>
</tr>
<tr>
<td>TM(^{&gt;100}) mmHg min (% patients)</td>
<td>62</td>
<td>64</td>
<td>&lt;1</td>
</tr>
<tr>
<td>TM(^{&gt;200}) mmHg min (% patients)</td>
<td>38</td>
<td>38</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

* \( F \) value generated by stepwise discriminant function analysis; ranked from highest contribution to group discrimination to no contribution (\( F < 1 \)).
† Based on a \( P \) value < 0.05 for univariate analysis.

Operative outcome were advanced age, duration of CPB, aortic valve replacement, and valvular calcifications.

One thiopental and three control patients who were clinically normal 24 h after operation subsequently suffered neuropsychiatric complications. Hemiplegia and loss of consciousness occurred on the fifth postoperative day in one patient 12 h after the onset of atrial fibrillation. He died shortly thereafter. Dysphasia, confusion, and amnesia appeared on the fourth postoperative day in another patient who developed new atrial fibrillation. Aphasia and confusion occurred suddenly on the third postoperative day in the third patient, while the fourth patient developed confusion and lethargy on the third postoperative day, both without apparent cause. Data from these patients were excluded from Table 2 because onset of symptoms was temporally unrelated to CPB. The three survivors were still dysfunctional, although improving, on the tenth postoperative day.

On weaning from bypass, thiopental patients required single or multiple doses of drugs to increase myocardial contractility more frequently than control patients (Table 4). In addition, the time from induction of anesthesia until the patient could respond to a command and the time to extubation were significantly prolonged in the thiopental group (Table 4), most of whom received 2.5–3 g of thiopental during operation.

**Discussion**

In dogs and primates, large doses of thiopental or pentobarbital decrease the neurologic deficit and mortality from cerebral infarction induced by interruption of the middle cerebral artery.\(^\text{6-9}\) Lesser morbidity and mortality were associated with a measurable reduction in the mass of infarcted brain tissue and were attributed to drug-induced reduction of oxygen uptake in the area of "relative vulnerability" surrounding the infarct.\(^\text{6,9}\) This protective effect can be demonstrated only when the barbiturate is administered before, during, or very shortly after the ischemic event.\(^\text{12,13}\) The maximum protective effect occurs at doses that abolish cortical electrical activity.\(^\text{14,15}\) Clinical trials of brain protection by barbiturates in humans have been limited to drug administration following massive head trauma or global ischemia.\(^\text{16-19}\) All such human trials failed to demonstrate any beneficial effect or were seriously handicapped by lack of appropriate control groups.

Our initial study\(^4\) of barbiturate protection using the CPB model assumed that most neuropsychiatric sequelae resulted from emboli or hypotension occurring in the period between cannulation of the heart and aorta and cessation of bypass.\(^\text{1-5}\) In that study, patients with hypotension during other periods of operation were excluded, and all thiopental (15 mg/kg) was administered during the prebypass period. Although neuropsychiatric abnormalities were less frequent in patients who received thiopental, the incidence was not significantly different from the control group. Complications were more frequent in older patients and after operations with open ventricles but were unrelated to the degree or duration of low perfusion pressure. The postoperative neurologic deficits observed suggested focal brain lesions of embolic origin.

The present study was an extension of the previous one, using a more rigorous design. Only patients having operations requiring an open ventricle were included be-

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TABLE 4. Effects of Thiopental on Weaning from Bypass and Postoperative Awakening

<table>
<thead>
<tr>
<th></th>
<th>Thiopental Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%) requiring Calcium*</td>
<td>61</td>
<td>40</td>
</tr>
<tr>
<td>Ephetedrine*</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Epinephrine*</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Digoxin*</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Inotropic infusion</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Time to respond* (h)</td>
<td>10.9 ± 4.1</td>
<td>8.4 ± 4.1</td>
</tr>
<tr>
<td>Time to extubation* (h)</td>
<td>19.0 ± 7.7</td>
<td>14.0 ± 5.0</td>
</tr>
</tbody>
</table>

* Differences significant at \( P < 0.05 \).
cause the risk of neuropsychiatric dysfunction was two to
three times greater than in patients undergoing coronary
artery bypass.4 Second, the dose and duration of thio-
pental administration was increased, so that near-maximal
EEG suppression was maintained throughout the period
during which ischemia might occur. By contrast, in our
earlier study, thiopental effects were continuously waning
during the vulnerable period and may have been absent
at the end of bypass, the period most likely to be associated
with embolization of air or particulate matter. The thio-
pental dose required to achieve this level and duration of
EEG suppression (39.5 ± 8.4 mg/kg) was almost three
times the dose in the earlier study. We believe the higher
doses permitted this demonstration of significant cerebral
protection by thiopental compared with fentanyl, a drug
with minimal effect on cerebral oxygen uptake.26 The
suggestion of a beneficial effect of thiopental in our earlier
report, coupled with our current data using three times
the barbiturate dose used in that study, provides a dose-
response relationship that strengthens the validity of our
conclusion.

The overall incidence of neuropsychiatric complica-
tions in this study was one-fourth the incidence observed
in the open-ventricle group of our previous study (7.1%
vs. 28.9%), and the lower incidence occurred in both con-
trol and thiopental groups. In part, this lower incidence is
attributable to exclusion of all patients with any pre-
operative neurologic abnormality or history of abnor-
mality, a screening not done in the earlier study. More
importantly, however, we believe the reduction resulted
from heightened awareness by operating surgeons of the
risk of emboli based on our first report and their more
conscientious elimination of air and particulate matter
from the left heart before terminating bypass.1 The pres-
cent study confirmed previous observations on the lack of
relationship between low perfusion pressure and neuro-
psychiatric complications14,21,25 and the positive relation-
ship between duration of bypass and incidence of compi-
lcations.25 The significantly greater frequency of com-
plications following aortic valve replacement and in
patients with valvular calcifications supports the view that
emboli are the major cause of this complication. Com-
puterized tomography performed coincidentally in six of
seven patients with persistent dysfunction supported the
diagnosis of fresh focal infarction compatible with embo-
lization.

Cerebral protection with thiopental was not entirely
benign. Although thiopental exerts a negative inotropic
action,24 it is widely and safely used in patients with heart
disease.25 All patients in the thiopental group were suc-
 cessfully weaned from CPB but required more frequent
inotropic support than the control group. In addition,
the large doses led to longer sleeping times, delayed tra-
cheal extubation, and obviously increased sedation during
the first three postoperative days. Other drugs with lesser
cardiac effects and duration of action may be as effective
as thiopental. Cerebral protection has been demonstrated
by other CNS depressants in animals25,26 and by some
calcium entry blockers as well.26 The side effects of thio-
pental protection, while not prohibitive, suggest an ex-
amination of these other agents under the same clinical
circumstances.

Hypothermia has been induced during CPB in an at-
temt to protect the brain during perfusion and prevent
postoperative neuropsychiatric sequelae by reducing cere-
bral oxygen consumption.25 Hypothermia, however, is
induced after initiation of bypass and of necessity reversed
prior to the first attempt at weaning, a period during
which embolization from the heart is least likely because
the heart is excluded from the circulation. During periods
of highest risk, aortic cannulation and weaning, nor-
mothermia is usually present. Although thiopental ad-
ministration ceased on discontinuation of CPB, thiopental
effect was still maximal at the end of bypass and persisted
to some degree into the postbypass period because of the
high total dose given. We do not believe hypothermia can
provide cerebral protection during these vulnerable pe-
riods in the fashion of thiopental.

We demonstrated that patients pretreated with thio-
pental had a significantly lower incidence of persistent
neuropsychiatric complications (none; 95% confidence
limits: 0–3.4%) than those who did not receive the drug
(7.5%; 95% confidence limits: 3.1–15.1%). Because the
overall incidence of sequelae was similar in the thiopental
and control groups, barbiturate therapy did not appear
to decrease the frequency of embolization but rather did
appear to reduce its clinical expression, presumably by
decreasing the size of the resulting infarction. This is pre-
cisely the same phenomenon seen in animal models of
barbiturate protection. Because neurologic complications
are not rare after open-ventricle operations, we believe
this therapeutic modality is now indicated for patients un-
dertaking valve replacements, resection of ventricular
aneurysms, and other operations requiring opening of
the ventricle. However, other drugs equally effective in
producing EEG suppression without the hemodynamic
consequences and persistence of thiopental should be
sought. We believe that focal cerebral ischemia associated
with CPB is appropriate for investigation of new agents
for cerebral protection in humans.

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are acknowledged.

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