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Consequences of Electroencephalographic-suppressive Doses of Propofol in Conjunction with Deep Hypothermic Circulatory Arrest

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Background: Some patients who undergo cerebral aneurysm surgery require cardiopulmonary bypass and deep hypothermic circulatory arrest. During bypass, these patients often are given large doses of a supplemental anesthetic agent in the hope that additional cerebral protection will be provided. Pharmacologic brain protection, however, has been associated with undesirable side effects. These side effects were evaluated in patients who received large doses of propofol.

Methods: Thirteen neurosurgical patients underwent cardiopulmonary bypass and deep hypothermic circulatory arrest to facilitate clip application to a giant or otherwise high-risk cerebral aneurysm. Electroencephalographic burst suppression was established before bypass with an infusion of propofol, and the infusion was continued until the end of surgery. Hemodynamic and echocardiographic measurements were made before and during the prebypass propofol infusion and again after bypass. Emergence time also was determined.

Results: Prebypass propofol at $243 \pm 57 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ decreased vascular resistance from 34 ± 8 to 27 ± 8 units without changing heart rate, arterial or filling pressures, cardiac index, stroke volume, or ejection fraction. Propofol blood concentration was $8 \pm 2 \mu\text{g}/\text{ml}$. Myocardial wall motion appeared hyperdynamic at the end of cardiopulmonary bypass, and all patients were weaned therefrom without inotropic support. After bypass, vascular resistance decreased further, and cardiovascular performance was improved compared to baseline

values. Nine of the 13 patients emerged from anesthesia and were able to follow commands at 3.1 ± 1.4 h. Three others had strokes and a fourth had cerebral swelling.

Conclusions: Propofol infused at a rate sufficient to suppress the electroencephalogram does not depress the heart or excessively prolong emergence from anesthesia after cardiopulmonary bypass and deep hypothermic circulatory arrest. (Key words: Anesthesia: emergence; neurosurgical. Anesthetic, intravenous: propofol; thiopental. Brain, pharmacologic protection: side effects. Heart: cardiac performance; ejection fraction. Surgery, cardiac: cardiopulmonary bypass; deep hypothermic circulatory arrest. Surgery, neurosurgery: cerebral aneurysm.)

WHEN adult surgical patients undergo cardiopulmonary bypass and deep hypothermic circulatory arrest, they are often given a large dose of a supplemental anesthetic agent with the intention of further depressing cerebral metabolic rate and presumably conveying additional cerebral protection. Although the presumption is controversial, the practice has become widespread.^{1,2} Barbiturates, etomidate, and propofol are all used intraoperatively for that purpose, because any one can be administered in a dose sufficiently large to induce an isoelectric electroencephalogram (EEG). However, in cardiac surgical patients, large doses of thiopental impede separation from cardiopulmonary bypass and delay emergence from anesthesia.³⁻⁵ The relative frequency and severity of these unwanted side effects have not been evaluated for other drugs used ostensibly to protect the brain during cardiopulmonary bypass and deep hypothermic circulatory arrest. The current investigation examines propofol in that setting.

Methods

Thirteen neurosurgical patients gave informed consent to participate in a study approved by the institution. Thorough neurologic and cardiovascular examinations were conducted before surgery on all patients. They then un-

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derwent anesthesia, cardiopulmonary bypass, and deep hypothermic circulatory arrest to have clips applied to a giant or otherwise high-risk cerebral aneurysm.

Anesthesia was induced with intravenous 50 $\mu\text{g}/\text{kg}$ midazolam, 50 $\mu\text{g}/\text{kg}$ fentanyl, and 5 mg/kg thiopental. Vecuronium (0.2 mg/kg), lidocaine (100 mg), and esmolol (0–100 mg) were given before tracheal intubation. Isoflurane (0.5–1%) in nitrous oxide and oxygen (2:1) was administered, and ventilation controlled to maintain Pa_{CO_2} at approximately 30 mmHg throughout the procedure.

Standard cardiovascular hemodynamic monitoring was employed using a radial artery catheter, a thermodilution pulmonary artery catheter, and electrocardiography. In addition, a 5-MHz phased-array ultrasonic transducer probe was passed into the esophagus and positioned so that two-dimensional left ventricular short-axis echocardiographic images could be obtained at the level of the papillary muscles. These images were continuously displayed in real time and videotaped for off-line analysis by a cardiologist ignorant to the circumstances of the study. End-systolic and end-diastolic images were then measured with a planimeter to ascertain left ventricular internal cross-sectional areas. End-systole was identified by cavity size, and end-diastole from the timing of the electrocardiogram. Only frames taken during expiration were chosen, and cross-sectional areas were determined from the average of ten separate heart beats. Ejection fraction was calculated as left ventricular end-diastolic area minus left ventricular end-systolic area, divided by left ventricular end-diastolic area. Ejection fraction was multiplied by 100 to be expressed as a percentage. Although preload- and afterload-dependent,⁶ this area-based ejection fraction provides a quantitative assessment of left ventricular performance.^{7,8}

Body temperature was monitored with thermocouple sensors (Mon-a-Therm, Mallinckrodt, St. Louis, MO). One was embedded 3 cm into the parenchyma of the cerebral cortex at the operative site after the dura mater had been reflected, another was positioned against a tympanic membrane, and others were placed in the nasopharynx and esophagus. Pulmonary artery temperature was also monitored from the thermistor at the catheter tip. Raw EEG signals were obtained from scalp electrodes, placed at C3-P3 and C4-P4. These unprocessed analog signals were continuously displayed in real-time 2-s sweeps on a Neurotrac system (Moberg Medical, Ambler, PA). When anesthesia be-

came stable, the displayed EEG signal was maximized to serve as the baseline.

The surgical procedure began with aneurysmal exposure. After intraoperative confirmation that safe clip application required an arrested circulation, cardiopulmonary bypass was established. A 19-French femoral artery cannula and a long 21-French femoral venous right atrial cannula were used in conjunction with centrifugal bypass pumps and a membrane oxygenator. Heparinization, a bloodless prime, and a flow rate of $2.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ were employed. Hypothermia was induced by passing the perfusate through a refrigerated water bath heat exchanger initially set at 8°C. When three of the monitored body temperatures decreased below 18°C,⁹ the circulation was arrested and the patient was allowed to exsanguinate into the bypass reservoir to further collapse the aneurysmal sac. Arterial pressure decreased to almost zero, and the final neurosurgical dissection and clip application were accomplished under these conditions. Cardiopulmonary bypass was then resumed, and the patient was rewarmed to 37°C. Normal sinus rhythm was reestablished before separation from bypass was attempted.

Before initiating cardiopulmonary bypass, each patient received propofol: first as a 1 mg/kg bolus, and then by 100 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ infusion. The dose was increased every few minutes until the EEG displayed a burst suppression pattern with a 1:5 ratio. The propofol infusion was continued at that rate until circulatory arrest, even though the EEG became isoelectric during bypass cooling. When cardiopulmonary bypass was resumed, the propofol infusion was begun again at the rate that provided prebypass normothermic burst suppression. Bypass rewarming proceeded until three monitored temperatures exceeded 36°C. If hypertension developed, fentanyl and/or nitroprusside were administered. After separation from bypass, isoflurane and nitrous oxide were restarted and the propofol infusion was continued as before. At the completion of surgery, all anesthetics were discontinued, and patients were brought to an intensive care unit with their tracheas intubated and their lungs ventilated with oxygen. Emergence from anesthesia was defined as the length of time from the end of surgery until the patient regained the ability to follow simple commands, such as "open your eyes," "squeeze my hand," "wiggle the toes on your right foot," and "take a deep breath."

Hemodynamic and echocardiographic measurements were made and blood samples were obtained at the following times: (1) just before the start of the preby-

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pass propofol infusion, (2) when the propofol infusion rate stabilized and there was a consistent burst-suppression EEG pattern with a 1:5 ratio, and (3) after successful separation from cardiopulmonary bypass. Baseline measurements and those made during propofol administration preceded bypass cannulation, and the final set was not obtained until the cannulae were removed. Whole blood was collected in oxalated tubes and refrigerated overnight at 4°C for the propofol assay. High performance liquid chromatography with a C18 reversed-phase column and fluorescence detection at excitation and emission wavelengths of 276 and 310 nm were used in the analysis.¹⁰ The sensitivity of the assay was 100 ng/ml, and the coefficient of variation ranged between 4% and 6%.

Results are expressed as mean \pm SD. Statistical comparisons were performed by repeated-measures analysis of variance, and specific differences isolated with a Bonferroni correction. $P < 0.05$ was considered significant.

Results

All patients completed the study protocol, and data were collected from 6 women and 7 men. Their mean age was 50 ± 16 yr (range 15–67 yr). All were classified ASA physical status 2 or 3. Four had experienced a prior subarachnoid hemorrhage, and seven came to surgery with a significant preoperative neurologic deficit. No patient was found to have more than minor cardiac dysfunction, but five were hypertensive and three had electrocardiographic evidence of left ventricular hypertrophy. All preoperative echocardiograms were normal.

Table 1 displays propofol infusion rates, blood concentrations, temperature, blood gas values, hematocrit readings, and hemodynamic parameters. Propofol caused an initial brief decrease in arterial pressure of about 10%. Within 20 min, at a propofol infusion rate of between 200 and $300 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, burst suppression with a 1:5 ratio was achieved. At that time, vascular resistance was decreased, but heart rate, arterial and filling pressures, cardiac output, stroke volume, and ejection fraction were unchanged from baseline values.

Cardiopulmonary bypass was initiated 2–3 h after surgical incision and long after anesthesia had become stable. With hypothermia, the EEG became isoelectric, but the established propofol infusion rate was main-

Table 1. Propofol Infusion Rates and Blood Concentrations, Temperature, Blood Gases, and Hemodynamic Data

	Baseline	Propofol Infusion	
		Before Bypass	After Bypass
Propofol infusion rate ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	0	$243 \pm 57^*$	$230 \pm 51^*$
Propofol blood concentration ($\mu\text{g}/\text{ml}$)	0	$8 \pm 2^*$	$7 \pm 2^*$
Brain temperature ($^{\circ}\text{C}$)	34 ± 1	34 ± 1	$36 \pm 1^*$
Pa_{CO_2} (mm Hg)	31 ± 3	30 ± 3	28 ± 3
Heart rate (beats/min)	54 ± 8	58 ± 8	$73 \pm 9^*$
Arterial pressure (mmHg)	82 ± 8	77 ± 8	$76 \pm 8^*$
CVP (mmHg)	9 ± 4	9 ± 4	10 ± 4
PAD pressure (mmHg)	13 ± 4	13 ± 5	14 ± 4
Cardiac index ($\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$)	2.6 ± 0.6	2.7 ± 0.5	$3.5 \pm 0.8^*$
Stroke volume ($\text{ml} \cdot \text{b}^{-1} \cdot \text{m}^{-2}$)	43 ± 9	46 ± 8	$49 \pm 8^*$
Vascular resistance (units)	34 ± 8	$27 \pm 8^*$	$20 \pm 7^*$
Hematocrit (%)	33 ± 4	32 ± 4	$24 \pm 3^*$
Ejection fraction (%)	50 ± 10	52 ± 11	$58 \pm 9^*$

CVP = central venous pressure; PAD = pulmonary artery diastolic; Baseline = during anesthesia and surgery, just before the start of propofol infusion.

* Significantly different from baseline measurement, $P < 0.05$.

tained until the circulation was arrested. Cooling to 17°C took 27 ± 6 min, and circulatory arrest lasted 28 ± 15 min. With bypass and the propofol infusion reestablished, rewarming to 37°C was accomplished in 63 ± 11 min. Total bypass time was 132 ± 35 min. Before bypass was terminated, echocardiographic myocardial wall motion appeared hyperdynamic in every patient. All patients were separated easily from bypass without the need for inotropic support or vasoactive infusions. Postbypass cardiovascular measurements made 10–15 min later, revealed anemia and an additional 35% decrease in vascular resistance. Nevertheless, patients were normotensive with adequate filling pressures; and heart rate, cardiac output, stroke volume, and ejection fraction were all increased compared to baseline.

Surgery lasted 8.5 ± 1.1 h and anesthesia 9.4 ± 1.1 h. Patients received $60 \pm 16 \mu\text{g}/\text{kg}$ of fentanyl and a total propofol dose of 3.6 ± 1.4 g for a mean infusion rate of $206 \pm 43 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. After an average postoperative time of 3.1 ± 1.4 h, nine patients could follow simple commands and their endotracheal tubes were removed. Three others remained somnolent for several days and were diagnosed as having sustained an intraoperative stroke. Another was lethargic for 2 days (computerized axial tomography revealed cere-

bral edema) but made a complete recovery. Two of the patients who had strokes died of neurologic sequelae. Two other patients did not fully recover to their preoperative neurologic states. The rest did well. No intraoperative or early postoperative adverse cardiovascular events occurred in any patient, and those patients with poor neurologic outcomes exhibited the same hemodynamic data as those who did well.

Discussion

This study was originally designed as a randomized trial comparing the adverse cardiovascular consequences experienced by neurosurgical patients who received large doses of either thiopental or propofol during cardiopulmonary bypass and deep hypothermic circulatory arrest. However, soon after the study's inception, it became apparent that patients who received propofol emerged from anesthesia much sooner; thus, both the use of thiopental and randomization were abandoned. What follows is a comparison of two groups studied consecutively: data from the patients who received propofol are presented in this article and data from the thiopental group have already been published.¹¹

The current data indicate that an infusion of propofol, at a rate sufficient to suppress the EEG, can be administered before, during, and after cardiopulmonary bypass without depressing ventricular function or impeding separation from bypass. The only important hemodynamic effect noted was a decreased vascular resistance. The relative lack of cardiovascular depression from the propofol infusion is credible because only patients with normal cardiac function were studied, no one received a large bolus injection, and patients were already anesthetized when the propofol infusion began; *i.e.*, anesthetized patients tend to be better hydrated and more vasodilated than the typical apprehensive or uncomfortable patient awaiting induction of anesthesia.

This same anesthetic state prevailed when patients from the previously published report¹¹ received comparable EEG-suppressive doses of thiopental. However, the thiopental-treated patients responded somewhat differently during the infusion; stroke volume decreased and heart rate increased. These hemodynamic effects were not clinically important, but they demonstrate that drugs that cause major depression of cerebral metabolic activity may or may not adversely affect

Table 2. Hemodynamic Responses to Doses of Thiopental or Propofol Sufficient to Induce Burst Suppression on the EEG

	Thiopental (n = 24)	Propofol (n = 13)
Heart rate (beats/min)	11 ± 6	4 ± 7*
Arterial pressure (mmHg)	-1 ± 5	-5 ± 8
CVP (mmHg)	0 ± 2	0 ± 2
PAD pressure (mmHg)	0 ± 2	0 ± 3
Cardiac index (L · min ⁻¹ · m ⁻²)	0.0 ± 0.5	0.1 ± 0.3
Stroke volume (ml · b ⁻¹ · m ⁻²)	-5 ± 4	3 ± 5*
Vascular resistance (units)	0 ± 4	-7 ± 2*
Ejection fraction (%)	-2 ± 2	2 ± 3*

CVP = central venous pressure; PAD = pulmonary artery diastolic.

Intraoperative prebypass measurements were made at baseline and again during burst suppression. Changes in the variables are listed and compared by an unpaired *t* test.

* Response to the two drugs was significantly different (*P* < 0.01).

cardiovascular parameters. The drug-induced hemodynamic alterations are compared in table 2, and it appears that thiopental induces somewhat more myocardial dysfunction than does propofol. Nevertheless, the thiopental-treated patients were separated from bypass as easily as their propofol-treated counterparts, and emergence time was the only clinically relevant difference between them. Moreover, these data are taken from two consecutively studied groups, and error may be introduced when current and historical data are compared.

The current results indicate that patients with giant or otherwise high-risk cerebral aneurysms can receive large doses of propofol before, during, and after cardiopulmonary bypass and deep hypothermic circulatory arrest and can still emerge from anesthesia without undue delay. These data contrast with those from our previous study in which thiopental-induced EEG suppression resulted in prolonged postoperative somnolence.¹¹ Emergence time was not reported in that publication, but the data were recorded and are now presented. The demographic data from that study and the current study are similar, and patients were subjected to the same surgical procedures and anesthetic management. Nevertheless, in 16 of 24 patients who received thiopental for cerebral metabolic suppression and did not experience a new neurologic deficit at surgery, emergence and extubation occurred 11.4 ± 2.8 h after the end of surgery. That emergence time significantly exceeded that which occurred after propofol EEG suppression in the current study.

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parisons in mind, it might seem appropriate to conclude that propofol is superior to thiopental for inducing pharmacologic suppression of cerebral metabolic activity during circulatory arrest. Such a conclusion misses the point. Cerebral protection is the goal in these cases; and because neurologic outcome was not significantly different in our two study groups, we cannot advocate propofol as the better choice. Only thiopental has been demonstrated to possess human cerebral protective properties.³ Like thiopental, propofol decreases neuronal activity, cerebral metabolic rate, and cerebral blood flow in a dose-related fashion,¹² and there is laboratory evidence indicating that propofol may also preserve neuronal function in the face of ischemia.¹³⁻¹⁴ However, contradictory data also exist,¹⁵ and the efficacy of propofol in attenuating the effects of human cerebral ischemia is still to be tested.¹² Until then, the extensive literature supporting barbiturate brain protection cannot be ignored.

Only hypothermia unequivocally enhances human tolerance for cerebral ischemia,¹⁶ and supplemental pharmacologic cerebral metabolic suppression during deep hypothermia may well be superfluous. Nevertheless, this study demonstrates that an EEG-suppressive dose of propofol does not depress cardiovascular performance or excessively prolong emergence from anesthesia when administered in conjunction with deep hypothermic circulatory arrest.

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