

Effects of Propofol on Cerebral Hemodynamics and Metabolism in Patients with Brain Trauma

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The authors determined the effect of propofol on cerebral blood flow, intracranial pressure, and cerebral arteriovenous oxygen content difference in severely brain-injured patients during orthopedic treatment of fractures of the extremities. The Glasgow Coma Scale score was 6 or 7 at the time of the study. Data were collected in the operating room before and during (5 and 15 min) administration of propofol (2 mg/kg iv bolus immediately followed by a 150 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ infusion) before surgical stimulation. Propofol was infused during 41.4 ± 7.3 min. After operation, the last set of measurements was made 15 min after propofol was stopped. The study was performed on 10 adults (age range, 15–40 yr) whose lungs were mechanically ventilated (air/O₂) and who were sedated (phenoperidine, 1 mg/h), and was conducted using a radial artery cannula; a 7.5-Fr, thermodilution, flow-directed, pulmonary artery catheter; an intraventricular catheter; and a catheter in the jugular venous bulb. The ¹³³xenon intra-internal carotid artery injection technique was used to determine regional cerebral blood flow (rCBF). Anesthetic blood concentration of propofol (3–5 $\mu\text{g}/\text{ml}$) was associated with decreases in cerebral perfusion pressure (CPP; from 82 ± 14 to 59 ± 7 mmHg; $P < 0.001$), rCBF (from 35 ± 6 to 26 ± 5 ml · 100 g⁻¹ · min⁻¹; $P < 0.01$), and intracranial pressure (ICP; from 11.3 ± 2.6 to 9.2 ± 2.5 mmHg; $P < 0.001$). Cerebrovascular resistance and cerebral arteriovenous oxygen content difference were unchanged. After propofol was stopped (at a blood propofol concentration theoretically corresponding to recovery from anesthesia), rCBF and ICP returned to preinduction values without any rebound. It was concluded that propofol reduces ICP but may lower CPP because of its effects on mean arterial pressure. Propofol appears to exert no consistent effect on cerebral vascular resistance and does not alter cerebral arteriovenous oxygen content difference. (Key words: Anesthesia; neurosurgery. Anesthetics: intravenous; propofol. Brain: blood flow; intracranial pressure; head injury.)

THE PHARMACOKINETIC profile of propofol solubilized in a soybean emulsion suggests its suitability as an infusion for either maintenance of anesthesia or sedation.¹ Indeed, propofol has proven to be a satisfactory agent for total iv anesthesia^{2,3} or sedation of critically ill patients.^{4,5} Because

there have been only a few studies on the effects of propofol on cerebral hemodynamics and metabolism in patients with^{6–8} or without intracranial pathology,^{9,10} we investigated its effects as the sole anesthetic agent on cerebral blood flow, intracranial pressure, and cerebral oxygen extraction in patients with severe brain trauma.

Materials and Methods

After approval by our local Committee on Human Research, informed consent was obtained from members of the patients' families. The study was performed on 10 patients with closed-head injury requiring orthopedic treatment of fractures of the extremities within the first week after admission to the neurosurgical intensive care unit (ICU) (table 1). The mean age of the patients was 28 yr, and the mean weight was 58.8 kg (range, 50–70 kg). On admission, the patients' neurological status was assessed using the Glasgow Coma Scale. All patients had a score of six or less. They were initially managed with tracheal intubation, controlled hyperventilation, sedation (thiopental and/or phenoperidine; see table 1), and hemodynamic monitoring. Heart rate (HR) was obtained *via* precordial electrodes. A radial artery cannula allowed arterial blood pressure measurement and blood sampling. A 7.5-Fr, thermodilution, flow-directed, pulmonary artery catheter enabled right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) to be measured. Cardiac output was determined in triplicate with iced injectate. Blood temperature in the pulmonary artery was obtained from the thermistor of the flow-directed pulmonary artery catheter. The following derived, systemic, hemodynamic values were calculated in the usual manner:¹¹ mean arterial blood pressure (MAP), cardiac index (CI), stroke index (SI), and systemic vascular resistance index (SVRI). Intracranial pressure (ICP) was monitored using an intraventricular catheter after computerized tomography (CT) of the brain.

At the time of the study, the Glasgow Coma Scale score was in the range of 6–7 (table 1). Ventilation with air and oxygen was adjusted to a PaCO₂ of 30–35 mmHg and a PaO₂ of 100–150 mmHg. Thiopental had been stopped at least 12 hours earlier. Sedation was maintained with phenoperidine (1 mg/h). The tip of a polyethylene catheter was positioned in an internal jugular vein to obtain jugular venous bulb pressure (Jug P) and blood samples. Blood gas tensions, pH, HCO₃⁻, hemoglobin, and he-

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TABLE 1. Patient Conditions

Patient	Age (yr)	GCS Score at the Time of the Study	Intracranial Pathology	Associated Injuries	Initial Treatment Duration (days)	Missed Fracture	Delay Following Admission for Treatment of the Missed Fracture (days)
1	31	6	Intraparenchymal hemorrhages, diffuse brain swelling	None	Thiopental 4	Olecranon fracture	6
2	24	7	Temporoparietal hemorrhagic contusion; cerebral edema	Abdominal injury (splenic laceration)	Thiopental 2 Phenoperidine 4	Radial fracture	4
3	40	6	Temporal hemorrhagic contusion; brain displacement	Pelvic fractures; kidney contusion	Thiopental 2	Metacarpal fracture	4
4	19	6	Acute intracerebral hemorrhage; cerebral edema	Rib fractures; pneumothorax; hemothorax; femoral fracture	Thiopental 4 Phenoperidine 5	Lateral malleolus fracture	5
5	35	7	Cerebral edema; split ventricles	Tibial fracture; femoral fracture	Thiopental 2	Metatarsal and tarsal fractures	3
6	24	6	Diffuse brain damage; split ventricles	Abdominal injury (splenic trauma); femoral fracture	Thiopental 4 Phenoperidine 6	Radial fracture	6
7	32	7	Fronto-temporal contusion; brain swelling; brain displacement	Rib fractures; pneumothorax; abdominal injury (splenic)	Thiopental 5 Phenoperidine 6	Bimalleolar fracture	6
8	15	6	Temporal contusion; midline shift	None	Phenoperidine 3	Metacarpal fracture	3
9	25	6	Frontotemporal cerebral infarction; cerebral edema	Facial fracture; rib fractures; hemothorax	Thiopental 3	Medial malleolus fracture	4
10	35	7	Cortical contusion; mass effect	Lumbar spine fracture; kidney laceration; acetabular fracture; mandibular fracture	Thiopental 2 Phenoperidine 4	Metatarsal fracture	4

moglobin saturation were measured in arterial and jugular venous blood. Cerebral perfusion pressure (CPP) was calculated as MAP-ICP. On the morning of the study (8–9 A.M.), another small polyethylene catheter was inserted *via* the common carotid artery to the internal carotid artery contralateral to the lesion (if any; see table 1). The correct position of the catheter in the internal carotid artery was verified by angiography. The ¹³³xenon intra-arterial injection technique was used to determine hemispheric regional cerebral blood flow (rCBF). A bolus of 1 mCi of ¹³³xenon dissolved in 1 ml of sterile saline solution was quickly injected into the internal carotid artery (injection time, 1–2 s).

The washout of radioactivity was measured by a portable detector (Mo 141, Mecaserto) placed over the ipsilateral temporoparietal area of the skull. Collimation was provided by a cylindrical lead tube and a 1" × 1" sodium iodide crystal. The portable detector used gave a circular (20 mm in diameter) field of view of the crystal and had a collimator depth of 52 mm. The detector, which had a single photomultiplier tube, was connected to a rate

meter equipped with a linear writing potentiometer. The rCBF was calculated from the slope of the logarithmically displayed first 2 min of the clearance curve¹² according to the following equation:

$$rCBF = 100 \cdot \lambda \cdot 0.693 \cdot T_{1/2}^{-1}$$

where $T_{1/2}$ is the time required for peak activity to return to 1/2 peak activity and λ is the average blood-to-tissue partition coefficient. The coefficients of tracer distribution between blood and tissues were calculated for hematocrits equal to 50. For other hematocrits, it has been proposed for rare gases (in view of their particular affinity for hemoglobin) that correction coefficients be used.¹³ For ¹³³xenon, this correction coefficient is given by the following formula:

$$C_H = 0.755 / (H/100 + 0.487 [1 - H/100])$$

where H = hematocrit. Then $\lambda = (0.87) \times C_H$. Cerebrovascular resistance (CVR) was calculated as CPP/rCBF. The oxygen extraction ratio (OER) was calculated as follows:

$$\text{OER} = ([a - \text{jug v}] \text{O}_2) / \text{arterial content of O}_2$$

where $([a - \text{jug v}] \text{O}_2) =$ arteriojugular venous oxygen content difference.

In the afternoon (2–3 P.M.), data were collected four times in the operating room in the absence of surgical stimulation. The first set of measurements was made just before propofol administration. Anesthesia was then induced with iv propofol (2 mg/kg; injection time, 20 s), followed immediately by a continuous infusion of propofol ($150 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). The second and third sets of measurements were made 5 and 15 min, respectively, after induction. The patient then underwent surgery, and propofol was stopped after the operation. The last set of measurements was made 15 min after propofol was discontinued. Before each new recording, we checked to be sure that background radioactivity was below 20 disintegrations per second. Injected activity (1 mCi of $^{133}\text{xenon}$) was adequate to obtain data even in relatively low-flow patients despite surrounding background noise. Moreover, only the first 2 min after injection were taken into account for study of the $^{133}\text{xenon}$ clearance curve. In the 10 patients, activity during these 2 min was always greater than that of background noise as checked before injection.

Arterial blood samples were obtained at each recorded point for measurements of propofol concentrations. Samples were placed in tubes containing potassium oxalate and stored at 4°C prior to analysis. Whole blood propofol concentrations were measured after extraction into cyclohexane by a high-pressure liquid chromatographic

method using fluorescence detection.¹⁴ The limit of assay sensitivity was approximately 2 ng/ml, and the coefficient of variation over the concentration range measured was approximately 8%.

The data, presented as mean \pm SD, were analyzed by analysis of variance (ANOVA) for repeated measurements. After a significant F statistic ($P < 0.05$), Scheffé's method was used to localize the differences. $P < 0.05$ was considered to be significant. Correlations between specific variables (e.g., MAP, CPP, ICP, and rCBF) were tested for significance using a linear regression method.

Results

Data are summarized in table 2. Propofol was infused during 41.4 ± 7.3 min. The infusion technique resulted in a stable blood concentration of propofol in the range of 3–5 $\mu\text{g}/\text{ml}$. The decrease in MAP (-24.7% at 5 min during infusion and -25.8% at 15 min during infusion) was associated with decreases in CI (-10.2% and -15.3% , respectively) and SVRI (-15.6% and -12.1% , respectively). Mean rCBF for the group decreased by 25.7% during decreased CPP (-25.6% at 5 min during infusion and -28% at 15 min during infusion). The same pattern was found for individual values of rCBF (fig. 1). There was a linear relationship between MAP and rCBF, with a correlation coefficient of 0.40 ($P < 0.05$). Intracranial pressure decreased (fig. 2), and CVR was unchanged. In fact, CVR increased by 2–91% in six patients and decreased by 4–28% in four patients (fig. 3). In one patient,

TABLE 2. Systemic and Cerebral Hemodynamic and Metabolic Values

	Before Propofol	During Propofol		15 min after Stopping Propofol	ANOVA P value
		5 min	15 min		
HR (beats/min)	100 \pm 13	104 \pm 14* \S	100 \pm 13	96 \pm 13* \S	<0.001
MAP (mmHg)	93 \pm 13	70 \pm 7 \ddagger	69 \pm 8 \ddagger	82 \pm 10 \ddagger	<0.001
RAP (mmHg)	3.4 \pm 1.3	2.2 \pm 1.7*	1.6 \pm 2.0 \ddagger	3.0 \pm 1.9	<0.001
PCWP (mmHg)	5.9 \pm 1.6	3.7 \pm 1.3 \ddagger	3.3 \pm 1.8 \ddagger	5.2 \pm 1.5	<0.001
CI ($\text{l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$)	4.12 \pm 0.48	3.70 \pm 0.56*	3.49 \pm 0.45 \ddagger	4.01 \pm 0.48	<0.001
SI ($\text{ml} \cdot \text{beat}^{-1} \cdot \text{m}^{-2}$)	42 \pm 9	36 \pm 8 \ddagger	36 \pm 8 \ddagger	43 \pm 9	<0.001
SVRI ($\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^2$)	1,798 \pm 410	1,517 \pm 364*	1,581 \pm 354	1,621 \pm 349	<0.01
CPP (mmHg)	82 \pm 14	61 \pm 9 \ddagger	59 \pm 7 \ddagger	71 \pm 11*	<0.001
ICP (mmHg)	11.3 \pm 2.6	9.2 \pm 2.5 \ddagger	9.5 \pm 2.4 \ddagger	10.9 \pm 2.0 \S	<0.001
rCBF ($\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$)	35 \pm 6	26 \pm 5 \ddagger	26 \pm 5 \ddagger	35 \pm 10 \S	<0.001
CVR ($\text{mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g} \cdot \text{min}$)	2.43 \pm 0.75	2.46 \pm 0.58	2.35 \pm 0.69	2.14 \pm 0.54	NS
(a-jug v)O ₂ (ml O ₂ /dl)	4.58 \pm 0.45	4.38 \pm 0.73	4.27 \pm 0.63	4.62 \pm 0.90	NS
OER (%)	29.5 \pm 7.8	30.6 \pm 6.9	31.8 \pm 8.2	31.7 \pm 9.6	NS
Blood propofol conc. ($\mu\text{g}/\text{ml}$)	0	4.2 \pm 0.7	4.3 \pm 0.6	0.7 \pm 0.2	
PaCO ₂ (mmHg)	33 \pm 2	33 \pm 1	33 \pm 1	33 \pm 2	NS
Blood temperature ($^\circ\text{C}$)	37.5 \pm 0.3	37.3 \pm 0.4	37.3 \pm 0.3	37.2 \pm 0.3	NS

HR = heart rate; MAP = mean arterial blood pressure; RAP = right atrial pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; SI = stroke index; SVRI = systemic vascular resistance index; CPP = cerebral perfusion pressure; ICP = intracranial pressure; rCBF = mean regional cerebral blood flow; CVR = cerebral vascular resistance; (a-jug v) O₂ = arterio-jugular venous difference in oxygen

content; OER = cerebral oxygen extraction ratio.

Data (mean \pm SD) were collected in ten patients with brain trauma before, during, and after propofol administration; when compared with before propofol values: * $P < 0.05$; $\ddagger P < 0.01$; $\ddagger P < 0.001$; when compared with values at 15 min during propofol administration: $\S P < 0.05$; || $P < 0.01$; || $P < 0.001$.

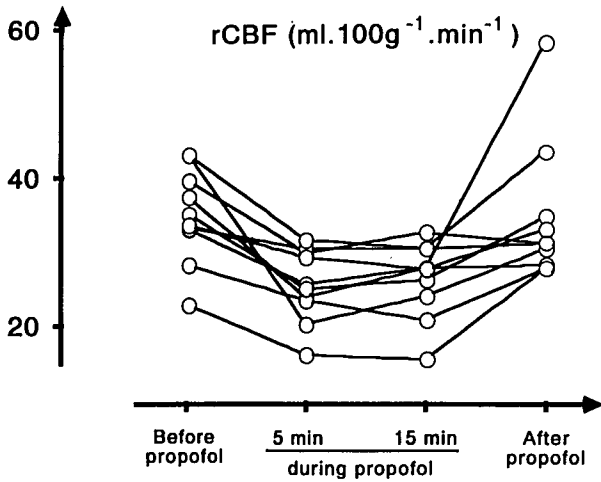


FIG. 1. Individual effect of propofol administration on cerebral blood flow (rCBF) in ten patients with brain trauma.

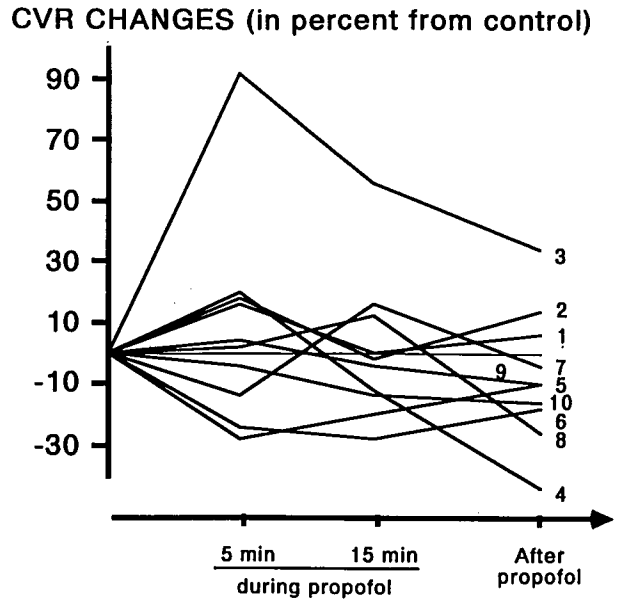


FIG. 3. Individual changes in cerebrovascular resistance (CVR) during propofol administration in ten patients with brain trauma.

CPP decreased to just below the minimum safe level of 50 mmHg (fig. 4) due to a decrease in arterial blood pressure. Because the lowest level of CPP (47 mmHg) was accompanied by decreased ICP (from 12 to 9 mmHg) and reversed by increased MAP following surgical stimulation, no treatment was instituted. Finally, propofol did not alter cerebral arteriovenous oxygen content difference.

Fifteen minutes after propofol was stopped, blood propofol concentration was less than 1 $\mu\text{g}/\text{ml}$. Cerebral perfusion pressure remained less than pre-propofol values, but rCBF was unchanged in comparison with pre-propofol values.

Discussion

In the present study, the infusion rate of 150 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, which is triple the MIR ED_{50} (minimal infusion rate that would suppress movement in response

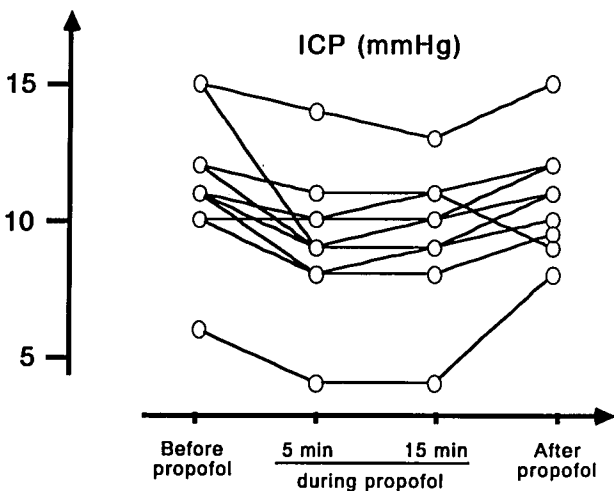


FIG. 2. Individual effect of propofol administration on intracranial pressure (ICP) in ten patients with brain trauma.

to the initial surgical incision in 50% of patients) of propofol,¹⁵ achieved a blood concentration ensuring a near-pharmacologic steady state and a stable depth of anesthesia.^{16,**} Consequently, our results are not relevant for use of propofol as a sedative drug in the ICU when less propofol ($1\text{--}3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and a lower blood propofol concentration ($2\text{--}3 \mu\text{g}/\text{ml}$) would be used.^{17,18} The blood propofol concentration of $0.7 \pm 0.2 \mu\text{g}/\text{ml}$ measured 15 min after propofol was stopped correlates with those in awakening, healthy volunteers¹⁷ or in ICU patients.¹⁸

Our results for the systemic hemodynamic effects of propofol are in agreement with previous studies^{19,20}: decrease in MAP related to a decrease in CI or a decrease in SVR; decrease in preload resulting in decreased SI; and slight increase in HR despite decreased MAP.

Our rCBF results obtained before propofol was administered are approximately 30% lower than those in awake normal subjects. This low basal rCBF may be explained by the comatose state.²¹ High doses of fentanyl and sufentanil (and probably alfentanil) decrease the frequency of the electroencephalogram, depress the cerebral metabolic rate, and decrease cerebral blood flow.^{††,22,23} Therefore, the opioid used (phenoperidine) may have accounted for the low "baseline" rCBF. The presence of cerebral vasospasm in these patients was excluded by angiography following catheterization of the internal carotid artery. The role of hypothermia and hypocapnia may be

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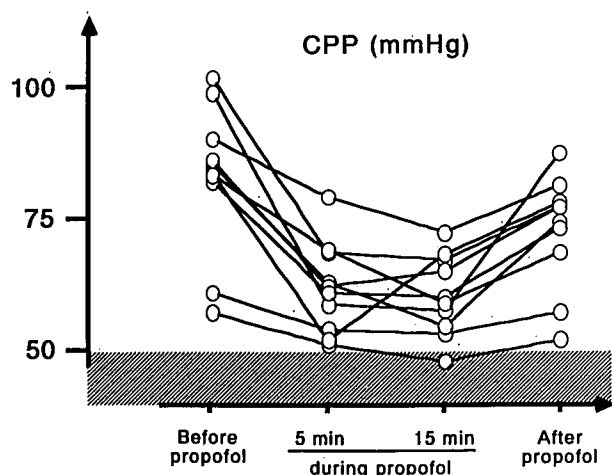


FIG. 4. Individual effect of propofol administration on cerebral perfusion pressure (CPP) in ten patients with brain trauma.

excluded because they were only moderately altered. Finally, the ^{133}Xe intra-arterial injection technique may have been a factor. Clearance of the isotope was monitored by a single collimated scintillation detector measuring the cerebral blood flow of gray matter in the temporo-parietal region. Although such detected changes in radioactivity are considered representative of mean hemispheric blood flow in milliliters per 100 g of brain per minute,²⁴ it is possible that the counting of radioactivity from brain tissue in the peripheral field of our single detector was less efficient than that of multiple collimated scintillation detectors. Hence, inasmuch as arterial carbon dioxide tension, blood temperature, and the position of the detector on the skull remained unchanged throughout the procedure, the changes in rCBF can be accurately compared.

In our series, rCBF decreased during propofol infusion and reduced CPP. The decrease of the latter resulted from a decrease in arterial pressure and not from an increase in intracranial pressure. The possibility of low perfused regions cannot be excluded with the method used (single detector). Although it has been reported that a decrease in cerebral perfusion pressure to the generally accepted safe lower limit of 50 mmHg was well tolerated in terms of flow-metabolism coupling and intracranial pressure,²⁵ we feel that in patients such as ours, propofol should be used by rapid iv infusion rather than iv bolus for induction and in reduced doses for maintenance to avoid peaks in blood concentration resulting in major decreases in arterial blood pressure and cerebral perfusion pressure.

Messeter *et al.* examined the effects of induced barbiturate coma on cerebral hemodynamics and metabolism in comatose and severely brain-injured patients (Glasgow Coma Scale score, 3–7).²⁶ Hemispheric cerebral blood flow was determined after iv administration of ^{133}Xe xenon

using two extracranial detectors. In patients with preserved CO_2 response, thiopental treatment caused decreases in cerebral blood flow and intracranial pressure (reaching normal range). In patients with impaired CO_2 response, the cerebral blood flow response to thiopental was inconsistent and intracranial pressure decreased but never below 20 mmHg. In both types of patients, the decrease in mean arterial blood pressure was moderate (from 105 to 88 mmHg).

More recently, the same investigators²⁷ obtained more precise data in 19 brain-injured patients. In patients with preserved vasoreactivity, thiopental administration was accompanied by decreases in cerebral blood flow (from $38 \pm 4 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ to $23 \pm 3 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$; $P < 0.005$), intracranial pressure (from $23 \pm 3 \text{ mmHg}$ to $18 \pm 2 \text{ mmHg}$; $P < 0.05$), and mean arterial blood pressure (from $99 \pm 3 \text{ mmHg}$ to $87 \pm 4 \text{ mmHg}$; $P < 0.01$). Since cerebral vascular resistance increased (from $2.2 \pm 0.2 \text{ mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g} \cdot \text{min}$ to $3.7 \pm 0.8 \text{ mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g} \cdot \text{min}$; $P < 0.05$), the decrease in cerebral blood flow was not due to decreased mean arterial blood pressure. Cerebral arteriovenous oxygen content difference was unaffected by thiopental so that the calculated cerebral metabolic rate for oxygen decreased. In patients with impaired vasoreactivity, a small decrease in cerebral blood flow (-12% ; $P < 0.02$) was recorded, reflecting the decrease in cerebral perfusion pressure since no increase in cerebral vascular resistance occurred. Intracranial pressure, cerebral arteriovenous oxygen content difference, and cerebral metabolic rate for oxygen were unaffected. In conclusion, the results clearly demonstrate the ability of thiopental to reduce cerebral blood flow, cerebral metabolic rate, and intracranial pressure in a way that is not entirely dependent on CPP.

It is therefore questionable whether propofol can reduce intracranial pressure independent of its effects on CPP in head-injured patients. In 10 severely brain-injured patients,²⁸ administration of $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of propofol (without a loading dose) led to a progressive decrease in extradural pressure from 15 to 5 mmHg at the fourth hour of infusion, with a slight decrease in CPP. In another study of patients undergoing intracranial surgery for tumor resection, aneurysm clipping, trigeminal neuralgia, or cerebrospinal fluid (CSF) fistula,⁶ CSF pressure was measured during propofol anesthesia (1.5 mg/kg over 30 s followed by $100 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). The authors used a spinal needle placed in the lumbar subarachnoid space and assumed that this procedure would reflect intracranial pressure in their selected patients without obstruction of the CSF pathway between the lateral ventricles and the lumbar cisterna. Cerebral perfusion pressure decreased from 85 ± 2.3 to $76 \pm 3.1 \text{ mmHg}$ (mean \pm SEM; calculated as $\text{MAP} - \text{CSF pressure}$) and CSF pressure decreased from 11.9 ± 1.4 to $7.5 \pm 1 \text{ mmHg}$. More recently, the same investigators (using the same anesthetic protocol)

demonstrated that the higher the control CSF pressure is, the greater the subsequent decrease in CSF pressure.⁸ During intubation, CSF pressure increased above baseline values in patients with initially normal CSF pressure (8 ± 1 mmHg) but not in patients with initially high CSF pressure (18 ± 2 mmHg).

Fifteen minutes after discontinuance of propofol (at a blood-propofol concentration theoretically corresponding to recovery from anesthesia in patients without intracranial pathology), cerebral blood flow and intracranial pressure returned to preinduction values without any rebound.

It may be concluded that propofol reduces intracranial pressure in patients with severe brain trauma and intracranial pressure equal to or less than 15 mmHg but may decrease CPP because of its effects on mean arterial pressure. Propofol exerts no consistent effect on cerebral vascular resistance and does not alter cerebral arteriovenous oxygen content difference. Administration of less propofol by continuous infusion, both for induction and maintenance of anesthesia and for better control of left ventricular filling pressures, may minimize hemodynamic changes and maintain CPP above the safe lower limit of 50 mmHg.

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