The Effects of Propofol on Brain Electrical Activity, Neurologic Outcome, and Neuronal Damage Following Incomplete Ischemia in Rats

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This study compares the effects of propofol and fentanyl/N_2O on spontaneous brain electrical activity, neurologic outcome, and neuronal damage due to incomplete cerebral ischemia in rats. Thirty Sprague-Dawley rats were assigned to one of three groups: group 1 (n = 10) received 70% N_2O in O_2 plus fentanyl (bolus 10 $\mu g \cdot kg^{-1}$, infusion 25 $\mu g \cdot kg^{-1} \cdot h^{-1}$); group 2 (n = 10) received 70% N_2 in O_2 and propofol (infusion 0.8–1.2 $mg \cdot kg^{-1} \cdot min^{-1}$) adjusted to maintain EEG burst suppression during ischemia; group 3 (n = 10) was anesthetized with propofol and received 6 $ml \cdot kg^{-1}$ 10% glucose intraperitoneally 15 min before the start of ischemia. Incomplete cerebral ischemia was produced by right common carotid artery occlusion combined with hemorrhagic hypotension (35 mmHg) for 30 min. Arterial blood gases, pH, and rectal temperature were kept constant in all groups. Plasma glucose was lower during ischemia in propofol-anesthetized rats compared to that in fentanyl/N_2O- ($P = 0.009$) and glucose-loaded propofol-treated rats ($P = 0.008$). Neurologic outcome and brain tissue injury were significantly better in propofol-anesthetized compared to fentanyl/N_2O-anesthetized rats ($P < 0.05$). Elevated plasma glucose in propofol-treated rats resulted in similar neurologic outcome and histopathologic injury as seen in propofol-anesthetized rats given no glucose. Recovery of EEG θ–α activity after ischemia was inversely correlated to neurologic deficit (fentanyl/N_2O: r = −0.71; propofol: r = −0.83; $P < 0.01$). These results show that propofol improves neurologic outcome and decreases neuronal damage from incomplete cerebral ischemia when compared to fentanyl/N_2O. This effect is not dependent on plasma glucose. Improved neurologic outcome is indicated by early postischemic EEG recovery. (Key words: Anesthetics, intravenous: propofol; fentanyl. Brain: ischemia. Measurement techniques: electroencephalography; neurologic outcome; histopathology.)

PROPOFOL, a rapidly acting intravenous anesthetic, suppresses brain electrical activity and decreases cerebral oxygen consumption (CMR_{O_2}) and cerebral blood flow.[1,2] Anesthetics that decrease CMR_{O_2} have been shown to decrease neuronal injury during ischemia by decreasing cerebral oxygen demand.[3,4] However, in cats, propofol does not improve neurohistopathologic outcome following incomplete cerebral ischemia.†† In the present study we evaluated the effects of propofol on postischemic EEG, neurologic outcome, and brain histopathology due to incomplete ischemia in rats.

Materials and Methods

These experiments were performed following approval of the Institutional Animal Care Committee. Thirty nonfasted male Sprague-Dawley rats (330–420 g) were anesthetized in a bell jar saturated with isoflurane, and their tracheas intubated and their lungs mechanically ventilated with 1.38% isoflurane inspired and 70% N_2O in O_2. Catheters were inserted into the right femoral artery and both femoral veins for continuous blood pressure measurement, blood sampling, and drug administration. A catheter was inserted into the right jugular vein for blood withdrawal during ischemia. The right common carotid artery was isolated and a loose ligature placed around the vessel for later clamping. Rectal temperature was measured using a Yellow Springs thermistor probe and was held constant at 37° C by servomechanism using an overhead heating lamp. Arterial CO_2 tension (Pa_{CO_2}) was maintained between 35 and 40 mmHg by adjusting ventilation. Arterial pH was maintained normal by bicarbonate infusion. Heart rate (beats per minute), mean arterial pressure (mmHg), arterial oxygen tension (Pa_{O_2}, mmHg), Pa_{CO_2}, pH, and plasma glucose (Yellow Springs Glucose Analyzer) were measured at control, during ischemia, and 20 min after reinfusion of the shed blood during recovery. Vecuronium was continuously infused (0.1 $mg \cdot kg^{-1} \cdot min^{-1}$) to maintain muscle paralysis. At the completion of surgery, isoflurane was removed from the inspiratory gas mixture, and the rats were allowed to equilibrate with 70% N_2O in O_2 for 25 min.

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†† Weir DL, Goodchild CS, Graham DI: Propofol: Effects on indices of cerebral ischemia. Journal of Neurosurgical Anesthesiology 1:284–289, 1989.

Drugs were given according to the following treatment groups. In group 1 (n = 10), 70% N_2O ventilation was maintained. A bolus of fentanyl (10 $\mu g \cdot kg^{-1}$) was given, followed by a continuous infusion of fentanyl (25 $\mu g \cdot kg^{-1} \cdot h^{-1}$). In group 2 (n = 10), 70% N_2O was replaced by 70% N_2, and infusion of propofol (2 $mg \cdot kg \cdot ^{-1} min^{-1}$) was started to achieve EEG burst suppression (electrical silence 3–5 s), which was maintained by adjustment of the propofol dosage. Rats in groups 1 and 2 were allocated on a random basis. Because plasma glucose concentrations were different between group 1 and 2, a third group was studied after finishing the experiments in group 1 and 2. Rats in group 3 (n = 10) received the same propofol treatment as in group 2 and also were given 6 ml·kg^{-1} of 10% glucose intraperitoneally 15 min before the start of ischemia.

Cerebral ischemia was produced in all treatment groups by the combination of right common carotid occlusion and hemorrhagic hypotension to a level of 35 mmHg for 30 min. A range of 1 mmHg was allowed for the target pressure. After 30 min of ischemia, the carotid artery was unclamped; the withdrawn blood slowly reinfused for 10 min; and drug administration was discontinued. The catheters were then removed and the incisions closed. Tracheal extubation occurred following establishment of spontaneous respiration, and the animals were transferred to their cages. The animals were monitored for 15 min following extubation to ensure that there were no respiratory problems.

ELECTROENCEPHALOGRAPHY

Platinum needle electrodes were used for continuous EEG recording from the parietal cortex of both hemispheres with a reference electrode over the nasion. Bandpass was set at 0.15–45 Hz. After amplification (Biosignalverstaerker, *nbn*-electronics), the EEG signals were displayed on an oscillograph and stored on magnetic tape (R-71, TEAC). The EEG power spectra were analyzed after Fourier transformation (epoch length 5.2 s, digitization 100/s). Integrated EEG power was calculated for selected frequency bands: δ 0.15–3.9 Hz, θ 4.0–7.9 Hz, α 8.0–12.9 Hz, and β 13–45 Hz.

NEUROLOGIC OUTCOME

Neurologic outcome scores were evaluated every 24 h for 3 days, starting 24 h after ischemia (table 1). A score of 0 represents no detectable neurologic deficit, and a score of 18 indicates death related to stroke. Stroke related death was scored after a minimum of 3 h following tracheal extubation only if the rat showed progressive signs of stroke impairment. For rats in group 3, not allocated on a random basis, the evaluator was blinded to

TABLE 1. Outcome Score of Postischemic Neurologic Examination

Category	Score	Description
Consciousness	0	Normal
	1	Restless
	2	Lethargic
	3	Stuporous
	4	Seizures
	5	Death
Walking	0	Normal
	1	Paw adduction
	2	Hypomobility
	3	Circling to stroke side
	4	Unable to stand
Rope platform	0	Climbs to platform
	1	Hangs on 5 s and pulls up rear legs
	2	Hangs on 5 s
	3	Hangs on <5 s
	4	No grasp reflex
Rotating screen	0	Grasps to 180° > 5 s
	1	Grasps to 180° < 5 s
	2	Grasps to 90°, not to 180°, falls
	3	Falls from vertical screen
Limb tone	0	Normal
	1	Weak
Pain reflex	0	Normal
	1	Hypoactive

the treatment condition by combining the animals with a separate study.

BRAIN HISTOPATHOLOGY

Those rats surviving the 3-day examination period were anesthetized with isoflurane, and their chests were opened. These rats were killed by transcardial perfusion of 20 ml isotonic saline followed by 20 ml 10% buffered formalin. The brain was removed and stored in formalin for 8 days for subsequent histologic examination. The forebrain was dissected into coronal blocks and imbedded in paraffin, and 7-μm sections were cut and mounted on slides. The slices were stained using hematoxylin and eosin and examined using light microscopy. All specimens were combined with brain tissues from other ongoing ischemia studies. The neuropathologist was blinded to the treatment condition. Neuronal histopathology was evaluated in the coronal section at the level of the caudate nucleus and at the level of the hippocampus formation. The ischemic hemisphere in the caudate section was graded on a six-point scale according to the following markers: 0 = no observable neuronal death; 1 = scattered neuronal death; 2 = small focal infarcts in caudate and cortical areas; 3 = large infarcts involving 50% of the caudate; 4 = infarcts involving at least 50% of the total hemisphere; and 5 = total hemispheric infarction. Brain tissue damage of the hippocampus (CA1, CA2, CA3, and CA4) was graded using a five-point scale according to the following markers: 0 = no damage; 1 = 0–25%; 2 = 26–50%; 3 = 51–75%; and 4 = 76–100% hippocampal injury.

BRAIN TEMPERATURE

Separate experiments were performed to evaluate the effect of propofol and ischemia on brain temperature. Four rats were anesthetized with fentanyl/N_2O and four rats with propofol using identical dosages as in group 1 and group 2, respectively. Surgery was performed as described above. The skull was exposed and a 3-mm hole drilled over the right cerebral hemisphere. A flexible Yellow Springs thermistor probe, 1 mm in diameter, was inserted 3 mm into the brain. Ischemia was produced for 30 min, followed by a 15-min recovery. Rectal temperature was maintained at 37° C using an overhead heat lamp. Brain temperature was measured during baseline anesthesia (time = 0); at 1, 2, 5, 10, 15, 20, and 30 min of ischemia; and after 5, 10, and 15 min of recovery. The rats were then killed.

STATISTICS

Data are reported as mean ± standard error of the mean. According to the study design, statistical analysis was performed separately for groups 1 and 2 (randomized design) and group 3 (nonrandomized design). For groups 1 and 2, nonparametric data including neurologic deficit score and histopathology were analyzed using a Kruskal-Wallis analysis. A Bonferroni correction was made for multiple comparisons. A Spearman rank-order correlation was used to correlate total outcome scores with histopathology. Neurologic outcome was also correlated with EEG parameters measured during recovery. Parametric physiologic data were analyzed using a two-way analysis of variance and Tukey test for *post hoc* comparisons be-

tween groups and treatments. Significance was assumed for $P < 0.05$. An exploratory data analysis was performed on results of group 3. The data of group 3 were tested *versus* group 1 and group 2 using unpaired t tests, and calculated absolute P values are presented instead of significances.

Results

SYSTEMIC PARAMETERS

Before the start of ischemia (baseline), there was no significant difference in physiologic variables between treatment groups (table 2). Pa_{CO_2} and pH were controlled. Plasma glucose increased 50% in group 1 (fentanyl/N_2O) but not in group 2 (propofol) during ischemia. Glucose-loaded propofol-anesthetized rats (group 3) showed an increase in plasma glucose before and during ischemia compared to group 2.

ELECTROENCEPHALOGRAPHY

During isoflurane/N_2O-anesthesia the EEG of both groups was dominated by δ–θ-wave activity superimposed with faster waves (figs. 1 and 2). Withdrawal of isoflurane decreased total power with a shift to faster waves. Low-voltage high-frequency activity seen under N_2O/O_2 ventilation (equilibration) shifted to low-frequency activity following propofol and fentanyl administration (figs. 3 and 4). In group 1, the induction of incomplete cerebral ischemia was followed by a rapid decrease of EEG total power ($-67 \pm 5\%$) with an increase in relative δ activity ($+20 \pm 4\%$) over both hemispheres. Following reperfu-

TABLE 2. Arterial Blood Pressure, Heart Rate, Arterial Blood Gas Tensions, Arterial pH, and Plasma Glucose

	MAP (mmHg)	HR (beats · min⁻¹)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pH	Plasma Glucose (mg · dl⁻¹)
Fentanyl/N_2O (n = 10)						
1.38 Isoflurane + 70% N_2O	85 ± 5*	351 ± 15	145 ± 4	39.4 ± 1.0	7.40 ± 0.01	205 ± 15
70% N_2O; baseline	129 ± 4	366 ± 26	142 ± 5	38.6 ± 1.1	7.43 ± 0.01	181 ± 7
Ischemia 15 min	35 ± 1*	339 ± 19	147 ± 5	38.8 ± 1.2	7.40 ± 0.02	—
Ischemia 30 min	35 ± 1*	347 ± 21	139 ± 6	39.6 ± 1.2	7.39 ± 0.02	285 ± 43*
Recovery 20 min	116 ± 6*	354 ± 19	128 ± 7	41.8 ± 1.3	7.38 ± 0.03	175 ± 36
Propfol (n = 10)						
1.38 Isoflurane + 70% N_2O	77 ± 4*	340 ± 15	151 ± 6	39.1 ± 1.2	7.41 ± 0.02	183 ± 7
70% N_2O; baseline	132 ± 4	359 ± 24	144 ± 4	38.3 ± 0.8	7.43 ± 0.01	172 ± 5
Ischemia 15 min	35 ± 1*	325 ± 14	149 ± 4	39.3 ± 0.8	7.39 ± 0.02	—
Ischemia 30 min	35 ± 1*	335 ± 17	144 ± 5	40.3 ± 0.8	7.40 ± 0.02	138 ± 5†
Recovery 20 min	126 ± 4*	364 ± 11	131 ± 7	38.5 ± 0.9†	7.42 ± 0.01	95 ± 6*·†
Propfol + glucose (n = 10)						
1.38 Isoflurane + 70% N_2O	80 ± 6*	345 ± 18	148 ± 5	39.3 ± 1.1	7.42 ± 0.01	266 ± 22
70% N_2O; baseline	127 ± 6	365 ± 26	147 ± 6	38.2 ± 1.1	7.40 ± 0.02	327 ± 25
Ischemia 15 min	35 ± 1*	340 ± 19	151 ± 5	38.5 ± 0.7	7.39 ± 0.02	—
Ischemia 30 min	35 ± 1*	345 ± 20	147 ± 5	37.9 ± 1.1	7.39 ± 0.02	283 ± 35
Recovery 20 min	121 ± 6*	370 ± 18	141 ± 9	38.0 ± 1.1	7.41 ± 0.02	226 ± 26*

Data are represented as mean ± SEM.

Animals treated with propfol + glucose were not tested for significance *versus* fentanyl/N_2O or propofol-treated animals (see text).

MAP = mean arterial blood pressure; HR = heart rate.

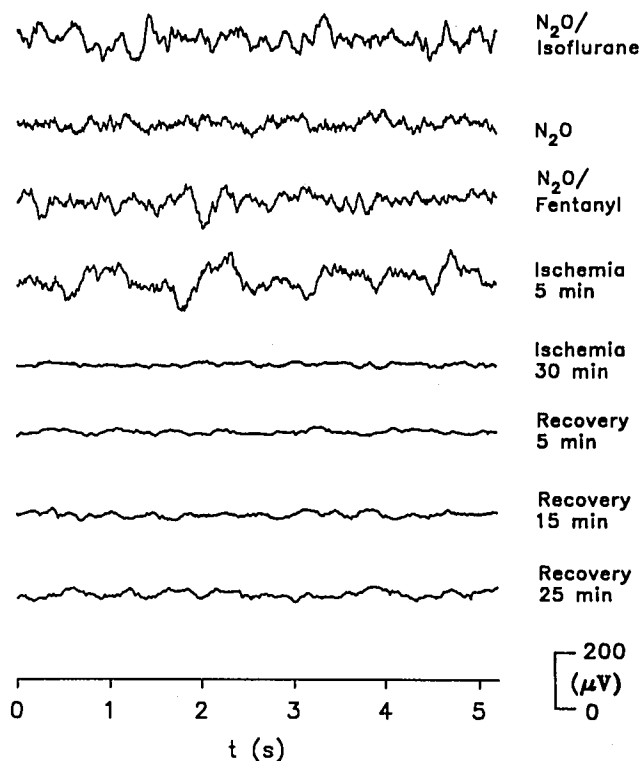* $P < 0.05$ compared to baseline within each group.

† $P < 0.05$ compared to control (fentanyl/N_2O).

FIG. 1. EEG of the right (ischemic) cerebral hemisphere of a rat anesthetized with fentanyl/N₂O. Administration of fentanyl/N₂O was terminated at the end of the ischemic challenge. The recovery EEG was recorded after unclamping the carotid artery and reinfusing previously shed blood.

sion, EEG recovery was observed over the nonischemic hemisphere (δ activity $-20 \pm 3\%$; $\theta-\alpha$ activity $+27 \pm 4\%$) but not over the ischemic side. In group 2, burst suppression was induced and maintained during ischemia by adjusting the propofol dosage to $0.8-1.2$ mg·kg^{-1}·min^{-1}. At the end of recovery, δ-wave activity was decreased ($-19 \pm 3\%$), and $\theta-\alpha$ activity was increased ($38 \pm 4\%$) in both hemispheres. EEG recovery was not analyzed in group 3.

NEUROLOGIC OUTCOME

Neurologic deficit scores following incomplete cerebral ischemia are shown in figure 5. Propofol-anesthetized rats of group 2 had significantly better outcome than did fentanyl/N₂O control rats on each of the 3 days of the evaluation period. Intraischemic plasma glucose was not correlated with total neurologic deficit score ($r = 0.51$; $P > 0.05$). In group 3, neurologic outcome was comparable to that of group 2 ($P = 0.89$). In groups 1 and 2, averaged $\theta-\alpha$ EEG activity of both hemispheres evaluated at the end of the recovery period was inversely correlated to neurologic score on day 3 (group 1: $r = -0.71$; group 2: $r = -0.83$; $P < 0.01$).

HISTOPATHOLOGY

Histopathology scores for each group are shown in figure 6. Fentanyl/N₂O-anesthetized rats had significantly greater ischemic neuronal injury than did propofol-treated rats ($P < 0.05$). Histopathologic injury was similar in groups 2 and 3 ($P = 0.61$). Neuronal injury was seen in both the caudate and hippocampus sections of the ischemic hemisphere. No neuronal cell damage was observed in the contralateral hemisphere in any animal. Histopathology scores showed a significant correlation with the total neurologic score on groups 1 and 2 ($r = 0.83$, $P < 0.01$).

BRAIN TEMPERATURE

Brain temperature before, during, and after ischemia was measured in four rats anesthetized with fentanyl/N₂O and in four rats anesthetized with propofol (table 3). Rectal temperature was maintained at $37°$ C. Before the start of ischemia, brain temperature was $36.8 \pm 0.2°$ C with fentanyl/N₂O and $36.4 \pm 0.3°$ C with propofol. After 30 min of ischemia, brain temperature decreased
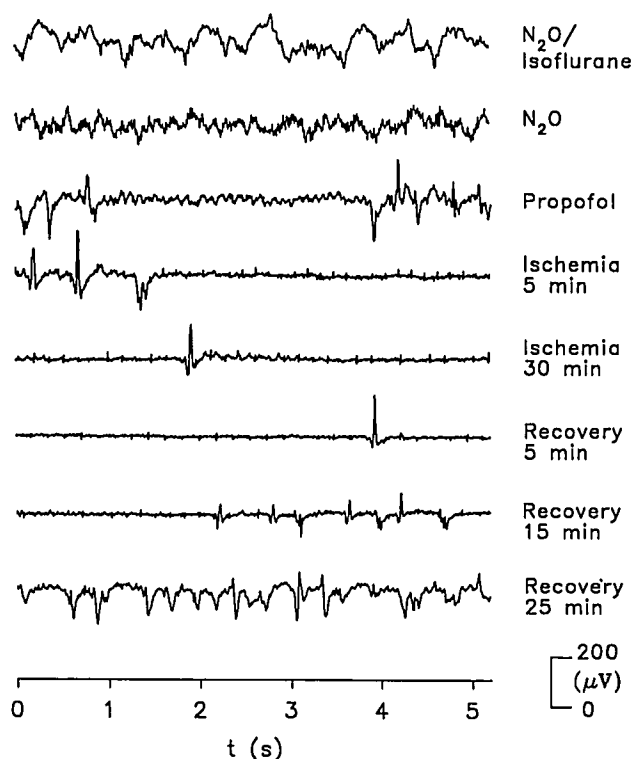

FIG. 2. EEG of the right (ischemic) cerebral hemisphere of a rat anesthetized with propofol. Administration of propofol was terminated at the end of the ischemic challenge. The recovery EEG was recorded after unclamping the carotid artery and reinfusing previously shed blood.
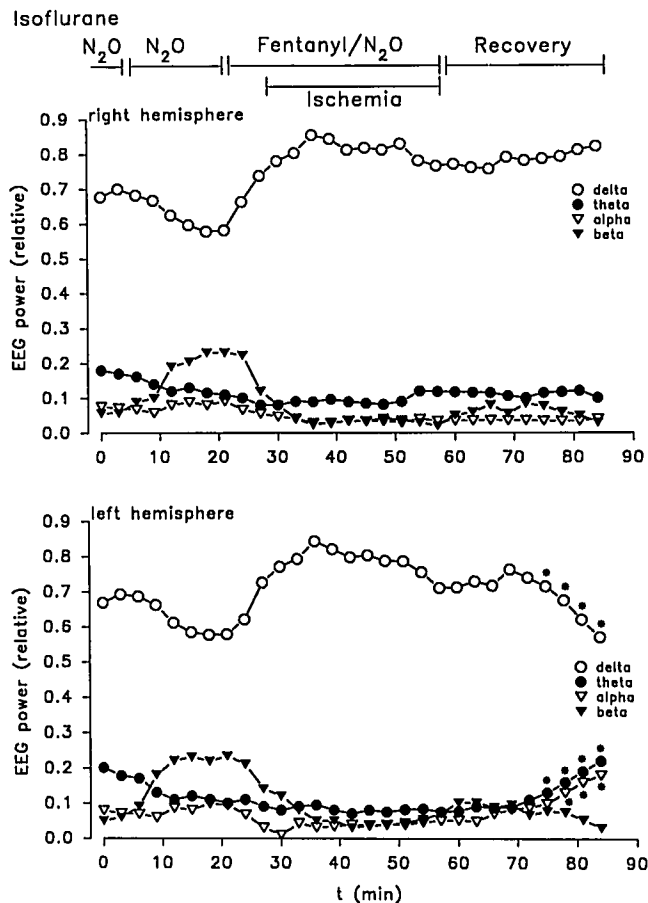
FIG. 3. Normalized relative EEG power in selected frequency bands of ten rats anesthetized with fentanyl/N$_2$O compared to control (δ: 0.15–3.9 Hz; θ: 4.0–7.9 Hz; α: 8.0–12.9 Hz; β: 13.0–45.0 Hz). *Top:* Right (ischemic) hemisphere *versus* frontal reference. *Bottom:* Left hemisphere *versus* frontal reference. At the end of ischemia previously shed blood was reinfused over 10 min (*P < 0.05 vs. contralateral hemisphere).

to 35.8 ± 0.2° C with fentanyl/N$_2$O and 35.5 ± 0.2° C with propofol. Brain temperature increased to 37° C in both groups during recovery.

Discussion

These results show that propofol, given in dosages to maintain EEG burst suppression, significantly improved neurologic outcome and brain histopathology compared to fentanyl/N$_2$O-anesthetized controls. Early EEG recovery was closely correlated to improved neurologic deficit. The difference in outcome was not due to intra- or post-ischemic variations in systemic hemodynamics, blood gas tensions, or pH. Propofol used at dosages to induce EEG burst suppression had a marked effect on plasma glucose, abolishing the increase normally seen during ischemia. Increased plasma glucose has been shown to worsen neu-

rologic outcome and to increase brain tissue damage.[5-7] However, glucose-loaded propofol-anesthetized rats had an outcome from ischemia similar to that of propofol-treated rats given no glucose. This indicates that the brain protective effects of propofol are not dependent on changes in plasma glucose.

Propofol may improve neurologic outcome and neuronal damage by means of its cerebral metabolic depressant effects. Propofol decreases cerebral blood flow and CMR$_{O_2}$ in humans[1,8] and animals[2,9] to a similar degree as reported for thiopental[10,11] and etomidate.[12] In dogs, a propofol infusion that produced EEG burst suppression decreased cerebral blood flow and CMR$_{O_2}$ by more than 50% from baseline values.[2] We chose an infusion dose that produces burst-suppression EEG because this is a standard for evaluating the maximum effect of the drug. It is proposed that anesthetics protect neurons from injury during incomplete ischemia according to their ability to
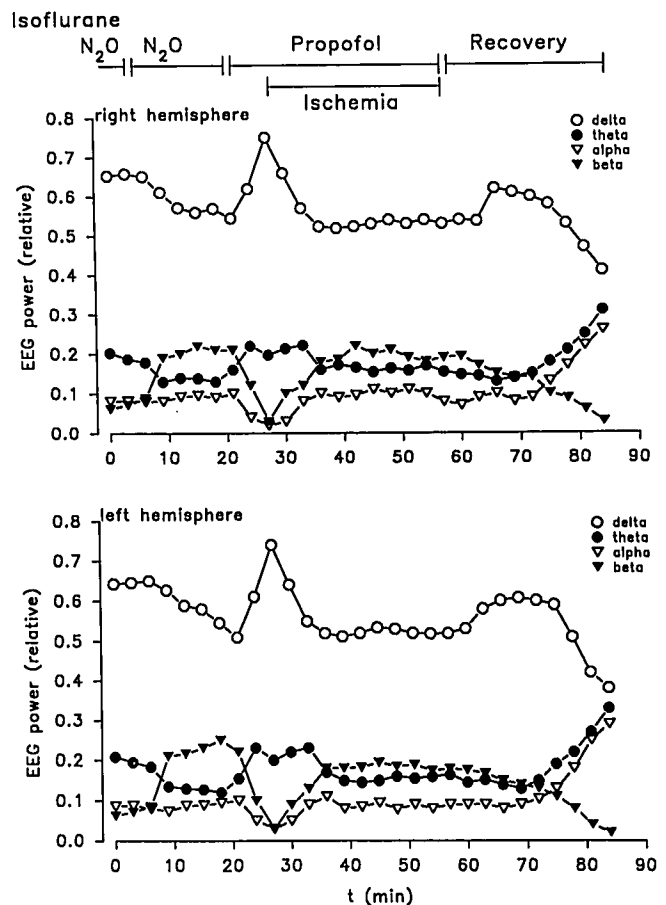

FIG. 4. Normalized relative EEG power in selected frequency bands of ten rats anesthetized with propofol compared to control (δ: 0.15–3.9 Hz; θ: 4.0–7.9 Hz; α: 8.0–12.9 Hz; β: 13.0–45.0 Hz). *Top:* Right (ischemic) hemisphere *versus* frontal reference. *Bottom:* Left hemisphere *versus* frontal reference. At the end of ischemia previously shed blood was reinfused over 10 min.
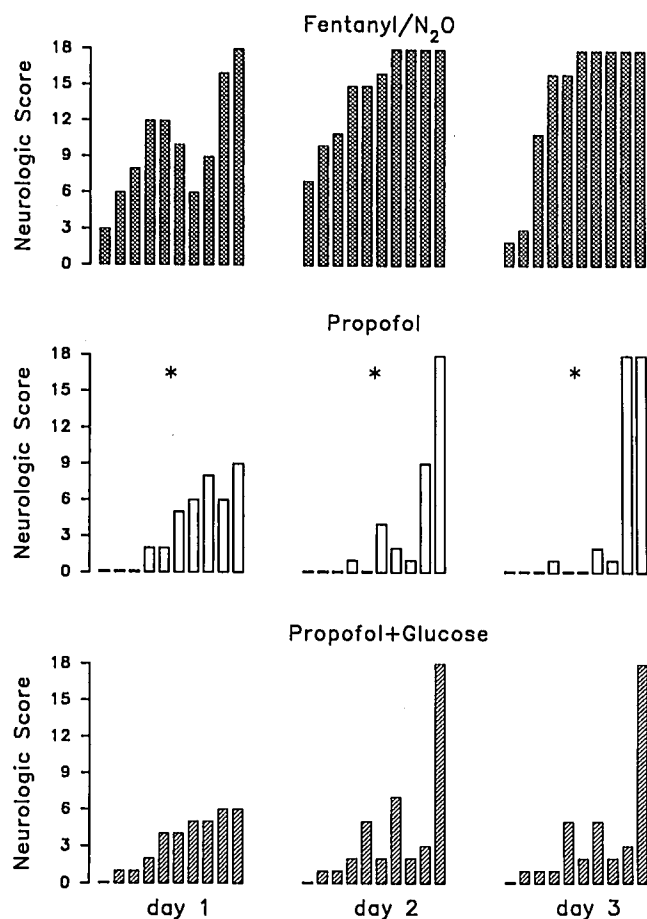
FIG. 5. Individual neurologic deficit score (range 0–18; 0 = normal, 18 = stroke-related death) in rats anesthetized with fentanyl/N_2O (group 1), propofol (group 2), and glucose-loaded propofol (group 3) over the 3-day evaluation period. Group 2 had a better total outcome score than did group 1 (*$P < 0.05$ vs. fentanyl/N_2O). Results of group 3 were not tested for significant differences versus group 1 and 2 (see text).

decrease metabolic demand.[13,14] According to this, we would expect nonmaximum anesthetic doses of propofol to produce less protection from ischemic injury than the dose used here.

In a cat model of ischemic hypotension, Weir *et al.*§ observed that propofol improved postischemic hypoperfusion and recovery of brain tissue pH and extracellular potassium concentration compared to cats anesthetized with 1 MAC halothane. However, neuronal cell death, measured 2 h after the ischemic challenge, was not different between the two groups. One problem in that study was the use of 1 MAC halothane as a control treatment. In previous studies, it has been shown that 1 MAC halothane decreases CMR_{O_2} approximately 30% and improves outcome from incomplete ischemia compared to N_2O.[3] This may have inhibited the ability of Weir *et al.*§ to see an improved outcome with propofol. It is also questionable

whether neuronal cell death measured 2 h after ischemia indicates complete ischemic damage. Pulsinelli *et al.*[15] have reported that neuronal death increases for several days after ischemia. This suggests that the neuronal damage measured by Weir *et al.*§ may not accurately indicate the extent of the ischemic injury. In this study we have seen significant improvement of neurologic as well as histopathologic outcome with propofol compared to fentanyl/N_2O anesthesia. Our ability to see an improved outcome with propofol is probably due in part to the use of fentanyl/N_2O as a control treatment and to the allowance of 3 days for ischemic injury to develop after ischemia.

Busto *et al.*[16] reported that brain and rectal temperature may diverge during forebrain ischemia and that small decreases in brain temperature during ischemia improve outcome from ischemia. Rectal temperature was maintained at 37° C in these experiments throughout the ischemic period, but brain temperature was not measured.
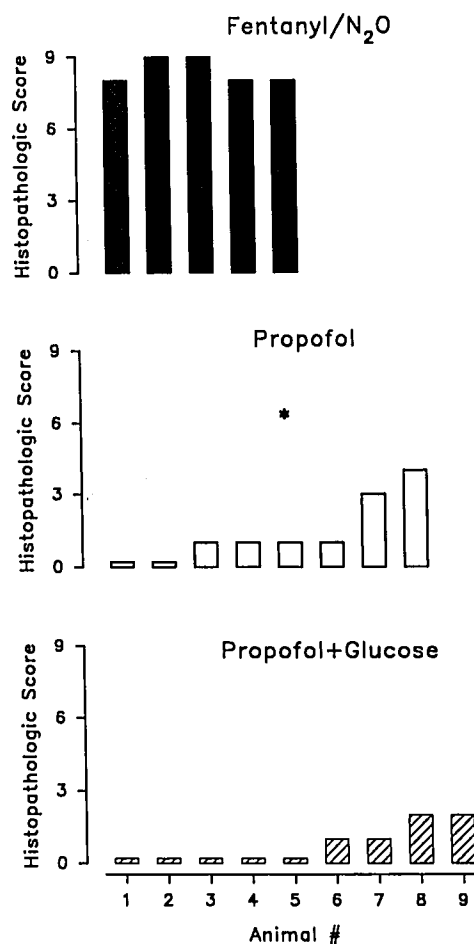

FIG. 6. Individual histopathologic injury score of rats surviving the 3-day evaluation period (group 1: fentanyl/N_2O (n = 5); group 2: propofol (n = 8); group 3: glucose-loaded propofol (n = 9); *$P < 0.05$ vs. fentanyl/N_2O; group 3 was not tested for significant differences vs. groups 1 and 2 [see text]).

TABLE 3. Brain Temperature in Fentanyl/N_2O- and Propofol-anesthetized Rats at Baseline, during Ischemia, and at Recovery

	t (min)	Fentanyl/N_2O (n = 4)	Propofol (n = 4)
Baseline	0	36.8 ± 0.2	36.4 ± 0.3
Ischemia	1	36.7 ± 0.2	36.1 ± 0.2
	2	36.4 ± 0.1	36.0 ± 0.2
	5	36.1 ± 0.1	35.9 ± 0.3
	10	35.9 ± 0.1*	35.8 ± 0.3
	15	35.9 ± 0.1*	35.6 ± 0.2*
	20	35.9 ± 0.2*	35.6 ± 0.2*
	30	35.8 ± 0.2*	35.5 ± 0.2*
Recovery	5	36.8 ± 0.2	36.4 ± 0.2
	10	37.0 ± 0.1	36.9 ± 0.2
	15	37.0 ± 0.1	37.0 ± 0.1

* $P < 0.05$ compared to baseline.

In a separate study we found that brain temperature decreased in both fentanyl/N_2O- and propofol-anesthetized rats. However, there was not a significant difference between groups. This indicates that in future studies it will be important to control head temperature. However, it does not indicate that brain temperature produced a different outcome between fentanyl/N_2O- and propofol-anesthetized rats.

In the present study, postischemic EEG recovery over the ischemic hemisphere predicted neurologic outcome. The value of EEG monitoring for indicating unilateral or global cerebral ischemia has been demonstrated by several authors.[17–19] In the fentanyl/N_2O group, EEG changes following carotid ligation and arterial hypotension indicated the onset of incomplete ischemia.[20] Bilateral improvement of EEG was seen in group 2 but not in group 1 during the recovery period. According to previous studies, impairment of EEG recovery may reflect ischemia-mediated neuronal dysfunction.[20,21] Different pharmacokinetics for propofol and fentanyl[22,23] may have contributed to differences in EEG recovery between the two groups. However, this is questioned by the interhemispheric differences in EEG recovery seen in fentanyl/N_2O-anesthetized rats and by the close correlation of EEG recovery and outcome in both experimental groups. It is concluded that prolonged postischemic EEG depression indicates increased neurologic deficit in this study.

Although we found marked, significant differences between N_2O/fentanyl and propofol-anesthetized rats, generalization of the results may be limited for statistical reasons. The glucose-loaded propofol-anesthetized rats were included in the study on a nonrandom basis after experimentation with the two other groups were completed. Thus, the overall study design changed from a completely randomized to a sequential design. However, evaluation of two of the most important parameters in this study, neurologic and histopathologic scores, were still performed by blinded observers, because animals from the additional group were combined with animals from other ongoing ischemia studies. For this reason, it is unlikely that results were biased by the study design.

In conclusion, our data indicate that propofol, given in doses that produce EEG burst suppression, improves EEG recovery and neurologic outcome and decreases neuronal death after incomplete ischemia compared to fentanyl/N_2O anesthesia. EEG recovery following ischemia predicts neurologic recovery. The cerebral protective effects of propofol cannot be explained by changes in plasma glucose or brain temperature. Propofol may improve ischemic outcome by decreasing neuronal metabolic demand or sympathetic activity.

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