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Comparison of the Effects of Propofol and Pentobarbital on Neurologic Outcome and Cerebral Infarct Size after Temporary Focal Ischemia in the Rat

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Background: **Although propofol is known to have effects on cerebral physiology similar to the barbiturates, a direct comparison of the relative effects of these drugs on outcome from cerebral ischemia has not been performed. The authors postulated that pentobarbital or propofol would yield similar effects on neurologic and histologic outcome from temporary focal ischemia in the rat.**

Methods: **Wistar rats were anesthetized with sufficient doses of pentobarbital (n = 20) or propofol (n = 20) to cause electroencephalographic burst suppression. The middle cerebral artery was then occluded for 75 min. Animals were awakened 4–6 h after onset of reperfusion and allowed to recover for 1 week. Neurologic function and infarct size were then assessed.**

Results: **Relevant physiologic values were similar between groups during ischemia and early reperfusion. No difference between groups was observed for severity of hemiparesis (*P* = 0.10). Total cerebral infarct volumes (median ± quartile deviation) were similar for the two groups (pentobarbital = 190 ± 36 mm^3; propofol = 200 ± 24 mm^3, *P* = 0.35).**

Conclusion: **Neurologic and histologic outcome were similar in pentobarbital or propofol anesthetized rats undergoing temporary focal cerebral ischemia and a 1-week recovery interval. (Key words: Anesthetics, barbiturate: pentobarbital; alkyl phenol: propofol. Animals: rat. Brain: infarction, ischemia: middle cerebral artery.)**

THE cerebral effects of barbiturates and propofol are similar in numerous respects. All cause a dose-dependent reduction in electroencephalographic (EEG) activity, which has been associated with a parallel reduction in cerebral metabolic rate (CMR) and cerebral blood flow (CBF).[1-4] Barbiturates and propofol reduce intracranial pressure (ICP),[5,6] and both have potential free radical scavenging activity.[7-9] The presumed mechanism of hypnotic action is agonism of the gamma-aminobutyric acid (GABA) receptor,[10] although several barbiturates and propofol have been also shown to exhibit antagonism of the excitatory neurotransmitter glutamate.[11,12]

Barbiturates have been carefully examined in the setting of cerebral ischemia. This class of agents has been found to improve outcome from focal but not global ischemic insults in a variety of animal models and clinical studies.[13-17] The mechanistic basis for this barbiturate-induced neuroprotection is not well defined, although pharmacologic properties described previously have been suggested as potential beneficial factors.

Propofol offers similar mechanistic potential in the setting of cerebral ischemia but, in contrast, has undergone only limited investigation. No human trials have been performed, and the few reported laboratory studies have not specifically compared outcome from ischemia in laboratory preparations anesthetized with propofol or with a barbiturate.[18-21] Accordingly, this study was designed to test the hypothesis that rats anesthetized with either propofol or pentobarbital would ex-

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hibit similar neurologic and histologic outcome from temporary focal cerebral ischemia.

Materials and Methods

This study was approved by the Duke University Animal Care and Use Committee. Male Wistar rats (aged 8–10 weeks; Harlan Sprague-Dawley, Indianapolis, IN) were fasted from food but allowed free access to water for 12–18 h before the experiment. Each animal was then anesthetized with 4% halothane in O_2. The trachea was intubated, and the lungs were mechanically ventilated with a delivered gas mixture of 1.0–1.5% halothane in 50% oxygen and balance nitrogen. *Via* skin incision, the tail artery was cannulated for measurement of mean arterial blood pressure (MAP) and sampling of blood. *Via* a cervical skin incision, the left internal jugular vein was cannulated for administration of drugs. Finally, a 22-gauge needle thermistor was percutaneously placed adjacent to the skull. Pericranial temperature was continuously monitored and servoregulated (YSI Model 73A, YSI Co., Inc., Yellow Springs, OH) at 38.0 ± 0.1°C by surface heating or cooling. EEG activity was monitored from active needle electrodes beneath the temporalis muscle bilaterally and a ground lead in the tail. MAP, pericranial temperature, and the EEG were continuously displayed and recorded with a Macintosh computer (Performa 6116CD, Apple Computer Co, Cupertino, CA) using a MacLab 4E analog to digital converter (AD Instrument Pty. Ltd., Castle Hill, Australia).

The animals were then prepared for reversible middle cerebral artery occlusion (MCAO) using a modification of techniques described by others.[22,23] A midline cervical incision was made, and the right common carotid artery and its bifurcation were identified. The external carotid artery was ligated and cut. The internal carotid artery was dissected distally until the origin of the pterygopalatine artery was visualized. One hour was allowed for surgical preparation.

Animals were then randomly assigned to one of two groups. In one group (n = 20), pentobarbital (Nembutal®, 50 mg/ml, Abbott Laboratories, North Chicago, IL) was continuously infused intravenously so as to induce a pattern of EEG burst suppression with an interburst interval of approximately 5–15 s. In the second group (n = 20), propofol (Diprivan®, Zeneca Pharmaceuticals, Wilmington, DE) was infused intravenously to induce a similar pattern of burst suppression. The propofol emulsion contained the bacteriostatic agent 0.005% disodium edetate. In both groups, halothane was discontinued with onset of the respective infusions. An interval of 45 min was allowed to establish the respective anesthetic states.

Ten minutes before ischemia onset, PaO_2, $PaCO_2$, arterial pH, hematocrit, and plasma glucose were measured. All rats then underwent 75 min of MCAO achieved by passing a 0.25-mm diameter silicon-coated nylon monofilament into the distal internal carotid artery *via* the external carotid stump. The filament was passed until a slight resistance was felt (approximately 21–23 mm).

After 75 min of MCAO, the filament was withdrawn. Pentobarbital infusion was discontinued at the time of reperfusion. In contrast, propofol infusion was continued for an additional 2 h beyond the onset of reperfusion. Pilot studies had determined that this regimen would result in similar times to emergence from anesthesia (*i.e.*, recovery of righting reflex) in the two groups. Arterial blood gases and pH measurements were repeated after 45 min of ischemia and at 15 min after reperfusion. The venous catheter was removed on discontinuation of the intravenous agent; the vessel was ligated, and the incision was closed. The arterial catheter was maintained for MAP monitoring for 3–4 h after reperfusion, then removed. The artery was ligated, and the incision was closed.

Rats in both groups were mechanically ventilated until adequate spontaneous ventilation and recovery of the righting reflex were observed (typically 4–5 h after reperfusion). The trachea was then extubated. Pericranial temperature regulation and EEG monitoring were also discontinued at this time. All rats were provided with supplemental oxygen (FiO_2 = 50%) for approximately 12 h and then returned to their cages and given free access to food and water for 7 days.

A neurologic examination, intended to assess severity of hemiparesis, was performed 7 days after ischemia. Each rat was assigned a score of 0–3 where 0 = no deficit, 1 = left forelimb flexion, 2 = decreased resistance to lateral push without circling, and 3 = same behavior as 2, with circling.[24] Neurologic testing was performed by a single observer blinded to group assignment.

After neurologic examination, all animals were weighed and then anesthetized with 4% halothane in O_2. The brains were removed and frozen at −40°C in 2-methylbutane. Using a cryotome, quadruplicate 20-μm thick coronal sections were obtained at 660-μm intervals throughout the rostral–caudal extent of the

infarct. The sections were then dried and stained with hematoxylin and eosin.

Infarct volume was measured by digitally sampling stained sections with a video camera controlled by an image analyzer (M2 Turnkey System, Imaging Research, St. Catharines, Ontario). The image of each section was stored as a $x \times y$ matrix of pixel units. For each tissue section, the pixel units were calibrated to give values as mm^2. The digitized image was then displayed on a video monitor. With the observer blinded to experimental conditions, infarct borders in cortex and subcortex were individually outlined (corpus callosum excluded) using an operator-controlled cursor. The area of infarct (mm^2) was determined automatically by counting pixels contained within the outlined regions of interest. Infarct volumes (mm^3) were computed as running sums of infarct area multiplied by the known interval (*e.g.*, 660 μm) between sections over the extent of the infarct calculated as an orthogonal projection.

Physiologic values were not compared between groups by statistical analysis so as to preserve power for comparison of major dependent variables. Because of outliers in the data, cerebral infarct volumes were compared between the pentobarbital and propofol groups using the nonparametric Mann-Whitney-Wilcoxon test.[25] Confidence bounds for differences between group medians were calculated using the corresponding (Hodges-Lehmann) approach.[25] Reported *P* values and confidence bounds are two-sided and exact (StatXact 3® for Windows, Cytel Software Co., Cambridge, MA). The Mann-Whitney-Wilcoxon test was also used to compare neurologic scores. Infarct volumes and neurologic scores are reported as median ± quartile deviation. For graphical display of the data, a curve relating infarct volume and neurologic score was calculated using locally weighted least squares regression, with a tension of 0.8.[26] Other values (*e.g.*, drug doses) are reported as mean ± SD. Significance was assumed if $P < 0.05$.

Results

The brain from one propofol anesthetized rat (neurologic score = 1) was inadequately preserved for histologic processing. Therefore, data from this animal were excluded from any analysis. Physiologic values for each group are shown in table 1. There were no important differences in any of the variables measured. A modest metabolic acidosis was present in propofol-anesthetized rats during early reperfusion. Pericranial temperature was successfully maintained at 38.0 ± 0.1°C throughout ischemia and until recovery of the righting reflex. Pentobarbital-treated animals recovered the righting reflex within 266 ± 92 min after ischemia compared with 237 ± 51 min in the propofol group.

Table 1. Physiologic Values for the Experimental Groups

	Pentobarbital (n = 20)	Propofol (n = 19)
Body weight (g)	285 ± 22	285 ± 18
10 min pre-ischemia		
MAP (mmHg)	76 ± 14	77 ± 15
Arterial *p*H	7.40 ± 0.02	7.40 ± 0.04
Pa_{CO_2} (mmHg)	38 ± 2	39 ± 2
Pa_{O_2} (mmHg)	137 ± 16	143 ± 32
Glucose (mg/dl)	92 ± 16	106 ± 14
Hematocrit (%)	39 ± 2	40 ± 2
45 min after onset of ischemia		
MAP (mmHg)	86 ± 13	79 ± 11
Arterial *p*H	7.41 ± 0.03	7.36 ± 0.03
Pa_{CO_2} (mmHg)	39 ± 2	40 ± 3
Pa_{O_2} (mmHg)	131 ± 30	132 ± 17
15 min after reperfusion		
MAP (mmHg)	113 ± 19	94 ± 17
Arterial *p*H	7.43 ± 0.03	7.34 ± 0.03
Pa_{CO_2} (mmHg)	38 ± 2	37 ± 3
Pa_{O_2} (mmHg)	140 ± 18	136 ± 19
Body weight day 7 (g)	234 ± 34	231 ± 38

Values are mean ± SD.

A total dose of 135 ± 12 mg/kg of pentobarbital and 291 ± 45 mg/kg of propofol were given to the respective experimental groups. Maintenance of EEG burst suppression required a typical infusion rate of 63 ± 30 $mg \cdot kg^{-1} \cdot h^{-1}$ of pentobarbital and 85 ± 20 $mg \cdot kg^{-1} \cdot h^{-1}$ of propofol, respectively.

Total cerebral infarct volumes (median ± quartile deviation) were 190 ± 36 mm^3 and 200 ± 24 mm^3 for the pentobarbital and propofol groups, respectively (fig. 1). Administration of pentobarbital *versus* propofol did not significantly change the median total infarct volume ($P = 0.35$). The sample size was sufficient to have 95% confidence that the true median difference (propofol–pentobarbital) was between −16 mm^3 and +49 mm^3. Median ± quartile deviation cortical (pentobarbital = 105 ± 21 mm^3; propofol = 119 ± 23 mm^3) and subcortical (pentobarbital = 78 ± 22 mm^3; propofol = 86 ± 13 mm^3) infarct volumes were numerically similar between groups. Median ± quartile deviation neurologic scores were 2 ± 1 and 2 ± 0 for the pentobarbital and propofol groups respectively (fig. 2). Administration of pentobar-

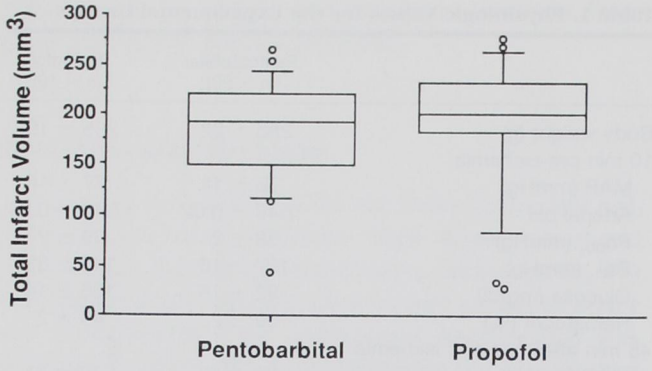

Fig. 1. Total cerebral infarct volume following 75 min of middle cerebral artery occlusion and a 7 day recovery interval in rats anesthetized with either pentobarbital (n = 20) or propofol (n = 19) during the ischemic insult. Box depicts median value and quartile ranges. Whisker bars depict 10th and 90th percentiles. Open circles depict values for individual rats exceeding 10th or 90th percentiles. There was no difference between groups for infarct size (P = 0.35).

bital *versus* propofol did not significantly change the median neurologic score (P = 0.10). The sample size was sufficient to have 95% confidence that the true median difference (propofol-pentobarbital) was between 0 and 1.

Discussion

This study demonstrates that when rats are anesthetized with either pentobarbital or propofol and then subjected to 75 min of MCAO, no significant differences in neurologic or histologic outcome are evident after a 1-week recovery interval.

Three other studies have examined effects of propofol on ischemic outcome.[19-21] Those studies have produced inconsistent conclusions. Ridenour *et al.* subjected propofol or halothane anesthetized rats to a 2-h interval of MCAO followed by 96 h of recovery.[20] Resultant cerebral infarct volumes were similar for the two groups. Because halothane was not viewed as a neuroprotectant, it was concluded that propofol was unlikely to provide potent neuroprotection. Subsequent work directly comparing rats maintained either awake or anesthetized with 1 MAC halothane during transient focal ischemia has shown that halothane causes reduction in cerebral infarct volume when compared with the awake state.[27,28]

Kochs *et al.* also used rats to examine effects of propofol on ischemic outcome.[19] Compared with a nitrous oxide and fentanyl anesthetized control group, propofol anesthetized rats exhibited decreased histologic injury and improved neurologic scores when recovering from a 30-min episode of unilateral carotid occlusion combined with systemic hypotension (hemispheric ischemia). Although the findings of Kochs *et al.* are consistent with our observations, the hemispheric ischemia model remains peculiar in that virtually all anesthetic agents offer improved outcome relative to animals anesthetized with nitrous oxide and fentanyl.[29-33] This suggests that nonspecific mechanisms of neuroprotection are characteristic of the state of anesthesia *per se* during hemispheric ischemia and may involve suppression of adrenergic responses to ischemia.[34] Such factors appear to also be shared by propofol.[19] The extent to which these nonspecific factors apply during temporary MCAO is not known.

Finally, Tsai *et al.* studied rats anesthetized with xylaxine and ketamine, which were then given either saline or propofol intravenously.[21] An insult of permanent MCAO combined with 60 min of bilateral carotid artery

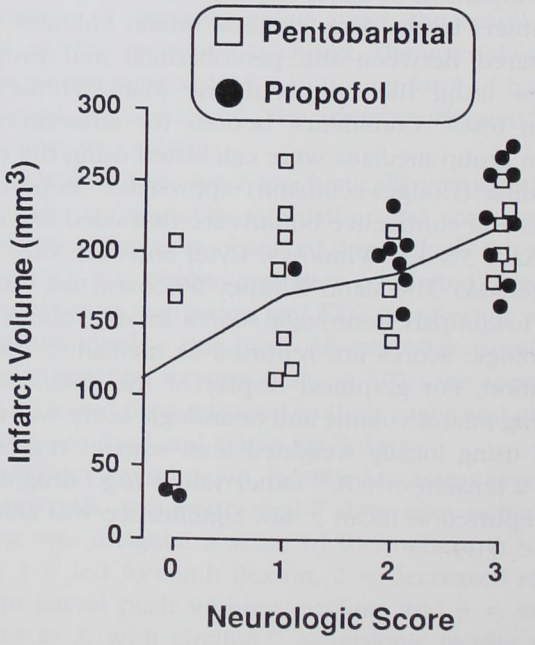

Fig. 2. Seven days after 75 min of intraluminal occlusion of the middle cerebral artery rats were examined for severity of hemiparesis (0 = absent; 3 = severe). Each point depicts values for a single rat as a function of total infarct volume (mm³). Either pentobarbital (n = 20) or propofol (n = 19) were given in doses sufficient to maintain electroencephalographic burst suppression throughout the ischemic interval. There was no statistical difference between groups for either infarct size (P = 0.35) or neurologic score (P = 0.10). A smoothing curve was drawn to emphasize the relationship between infarct volume and neurologic score.

occlusion was used. Cerebral infarct volume, measured after 24 h of recovery, was unaffected by propofol administration. This work poses several methodologic concerns. Head temperature was not controlled during ischemia. Small differences in brain temperature are known to cause major changes in ischemic outcome.[35,36] Therefore such work should be interpreted with caution. Further, ketamine is a known N-methyl-D-aspartate receptor antagonist that may have yielded neuroprotection on which propofol provided no additional advantage. In contrast, it remains plausible that propofol simply does not modulate ischemic outcome.

We chose the experimental design executed in this experiment for several reasons. The fundamental question to be answered was whether outcome from temporary focal ischemia is similar in rats anesthetized with a barbiturate *versus* propofol. Pentobarbital was selected because of previous experience with this barbiturate in a rat MCAO model. Rats anesthetized with pentobarbital in doses sufficient to cause EEG burst suppression exhibited improved histologic outcome relative to awake control rats undergoing MCAO.[37] The end-point of EEG burst suppression was chosen for convenience in the current experiment because doses of pentobarbital and propofol could be adjusted to similar depths of anesthesia. Because pentobarbital has previously been shown to also offer significant protection when given in a dose less than that required to cause EEG burst suppression,[37] it seems appropriate to investigate lower doses of propofol. This may be particularly important for propofol given several reports of adverse consequences of high dosages of this drug.[38-41]

The principal reason for examining effects of propofol on ischemic outcome relates to the potential use of this drug during surgical procedures that pose risk for ischemic cerebral injury. To date, no human studies have examined efficacy of propofol in reducing ischemic brain damage. Doses of propofol that produce EEG burst suppression appear to be hemodynamically tolerated in humans undergoing cardiopulmonary bypass or circulatory arrest procedures.[42,43] More rapid emergence from propofol anesthesia would offer a distinct advantage over available barbiturates. Nevertheless, we believe that sufficient evidence has not yet been provided to support routine substitution of propofol for barbiturates during the perioperative period. Although existing laboratory data indicate that propofol can reduce ischemic brain damage, confirmation in species other than the rat would be of considerable value to confirm efficacy of this compound.

In conclusion, rats anesthetized with either pentobarbital or propofol in doses sufficient to cause EEG burst suppression were found to have similar neurologic and histologic outcomes 1 week after 75 min of reversible MCAO. Although the outcome from ischemia was found to be equivalent for pentobarbital and propofol, this study does not directly establish neuroprotection by propofol because propofol anesthetized rats were not compared with rats undergoing the insult while awake. These results suggest that further research regarding the effect of propofol on ischemic brain damage is warranted.

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