No additional neuroprotection provided by barbiturate-induced burst suppression under mild hypothermic conditions in rats subjected to reversible focal ischemia

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Object. Mild-to-moderate hypothermia is increasingly used for neuroprotection in humans. However, it is unknown whether administration of barbiturate medications in burst-suppressive doses—the gold standard of neuroprotection during neurovascular procedures—provides an additional protective effect under hypothermic conditions. The authors conducted the present study to answer this question.

Methods. Thirty-two Sprague–Dawley rats were subjected to 90 minutes of middle cerebral artery occlusion and randomly assigned to one of four treatment groups: 1) normothermic controls; 2) methohexital treatment (burst suppression); 3) induction of mild hypothermia (33°C); and 4) induction of mild hypothermia plus methohexital treatment (burst suppression). Local cerebral blood flow was continuously monitored using bilateral laser Doppler flowmetry and electroencephalography. Functional deficits were quantified and recorded during daily neurological examinations. Infarct volumes were assessed histologically after 7 days. Methohexital treatment, mild hypothermia, and mild hypothermia plus methohexital treatment reduced infarct volumes by 32%, 71%, and 66%, respectively, compared with normothermic controls. Furthermore, mild hypothermia therapy provided the best functional outcome, which was not improved by additional barbiturate therapy.

Conclusions. The results of this study indicate that barbiturate-induced burst suppression is not required to achieve maximum neuroprotection under mild hypothermic conditions. The magnitude of protection afforded by barbiturates alone appears to be modest compared with that provided by mild hypothermia.

KEY WORDS • barbiturate • burst suppression • cerebral blood flow • cerebral ischemia • hypothermia • neuroprotection • rat
unknown whether barbiturate medications provide additional neuroprotection under hypothermic conditions. It has been shown that additional administration of barbiturates leads to a further reduction in the CMRO2 and the cerebral metabolic rate of glucose; however, it has not yet been confirmed that these additional reductions result in additional neuroprotection.

We conducted this study to investigate whether administration of barbiturates in burst-suppressive doses increases the protective efficacy of induced mild hypothermia. Continuous bilateral LD flowmetry was used to evaluate the influence of both types of treatment on CBF.

Materials and Methods

A total of 34 male Sprague–Dawley rats (250–300 g body weight) were used for this study. The animals were cared for before and at all stages during the experiment in compliance with applicable institutional guidelines and regulations of the government of Bavaria.

Animal Preparation and Monitoring

Food was withheld from the rats overnight before surgery, although they were allowed free access to water. Before the surgical procedures, the animals received subcutaneous injections of atropine (0.5 mg/kg) and anesthesia was induced using a 4% halothane mixture. The animals underwent oral intubation and mechanical ventilation with 0.8% halothane in a mixture of 70% N2O and 30% O2 to maintain normal arterial blood gas levels. Temporal muscle and rectal probes were used to monitor body temperature throughout the experiment. A thermostatically regulated, feedback-controlled heating lamp and pad were used to maintain temporal muscle and rectal temperatures at the desired level. The tail artery was cannulated for continuous measurement of arterial blood pressure and heart rate, as well as for blood sampling. The left femoral vein was catheterized for administration of fluids and drugs. Serum glucose was measured before and after ischemia; arterial blood gas, hemoglobin, and hematocrit values were repeatedly measured before, during, and after induction of ischemia.

Laser Doppler Flowmetry and Electroencephalography

A two-channel LD flowmeter was used for continuous monitoring of the CBF of each hemisphere in the area of the cerebral cortex that is supplied by the MCA. To allow placement of the LD flowmeter probe, bilateral burr holes with diameters of 1 mm were drilled 5 mm lateral and 1 mm posterior to the bregma, taking care not to injure the dura mater. The animals were placed supine with the head fixed firmly in a stereotactic frame. A rectangularly bent LD flowmeter probe was positioned in each burr hole by using a micromanipulator. Local cortical blood flow was continuously measured (2-Hz sampling rate) from 1 hour before onset of ischemia until 90 minutes after reperfusion.

For continuous EEG recordings, silver electrodes were connected to both LD flowmeter probes and a reference electrode was placed at the jaw bone. The bandpass was set at 0.15 to 0.45 Hz and the amplitude at 1.2 mm/50 V.

Occlusion of the MCA

All rats were subjected to 90 minutes of MCA occlusion, which was performed by inserting a silicone-coated No. 4-0 nylon monofilament via the external carotid artery, as previously described. In brief, the filament was gently advanced until LD flowmetry revealed a sharp decrease in the ipsilateral CBF to approximately 20% of baseline, indicating adequate MCA occlusion. Two animals were excluded from the study and replaced because LD flowmetry revealed a sharp decrease in contralateral CBF shortly after insertion of the filament, indicating SAH. The presence of SAH was confirmed at autopsy. Reperfusion was achieved by withdrawing the filament into the external carotid artery after 90 minutes.

Drug Administration and Treatment Groups

The rats were randomly assigned to one of four treatment groups, with eight rats in each group.

Normothermic Controls. Anesthesia was maintained in these animals by using halothane. Rectal and temporal muscle temperatures were kept at normothermic levels (37°C). Each animal received an isovolumetric infusion of 0.9% saline (3 ml/kg/hr) beginning 30 minutes before induction of ischemia and continuing until 15 minutes after reperfusion.

Methohexital Treatment (Burst Suppression). In this group halothane administration was discontinued 30 minutes before ischemia was induced. Sodium methohexital infusion was started at a dose of 1 to 1.5 mg/kg/min until an EEG burst-suppression pattern was reached. Burst suppression was maintained by an infusion rate of 0.4 to 0.6 mg/kg/min. Before induction of ischemia, an interval of 15 minutes was allowed to elapse for physiological stabilization and conversion of the anesthetic agent from halothane to metho-
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Methohexital. Methohexital administration was discontinued 15 minutes after reperfusion and the anesthetic agent was switched back to halothane. Body temperature was kept at 37°C throughout the experiment.

**Mild Hypothermia.** Anesthesia was maintained using halothane. Each animal received an isovolumetric infusion of 0.9% saline (3 ml/kg/hr) beginning 30 minutes before ischemia and continuing until 15 minutes after reperfusion. Whole-body hypothermia was induced using ice packs until rectal and temporal muscle temperatures of 33°C were reached and maintained before induction of ischemia. Gradual rewarming was initiated 30 minutes after reperfusion.

**Mild Hypothermia Plus Methohexital Treatment (Burst Suppression).** As described earlier, the anesthetic agent was switched from halothane to methohexital titrated to maintain burst suppression for 30 minutes before ischemia induction. In addition, whole-body hypothermia (33°C) was induced and maintained 30 minutes before ischemia induction. Administration of methohexital was discontinued 15 minutes after reperfusion and the anesthetic agent was switched back to halothane. Gradual rewarming was started 30 minutes after reperfusion. A study flow diagram is presented in Fig. 1.

**Quantification of Ischemic Damage**

Neurological deficits and infarct volume were assessed by a colleague who was blinded to the animals’ treatment. Postoperatively, each animal’s neurological function was evaluated daily using a six-point grading scale: 0, no spontaneous activity; 1, spontaneous circling; 2, circling if pulled by the tail; 3, lowered resistance to lateral push without circling; 4, contralateral forelimb flexion when tail was lifted; and 5, no apparent neurological deficit. Rectal temperature was measured 2 hours after reperfusion and daily thereafter to rule out postischemic hyperthermia. In addition, each animal’s body weight was measured daily.

Seven days after the animals had been subjected to transient cerebral ischemia, anesthesia was again induced in each rat and the rat was perfused transcardially with isotonic heparinized saline, followed by paraformaldehyde for tissue fixation. The brain was removed, embedded in paraffin, and cut into 4-µm-thick coronal sections at 400-µm intervals. The brain slices were stained with hematoxylin and eosin. Twenty-four slices from each brain, which together contained the entire infarct, were used and the infarct area on each slice was planimetrically determined. The infarct volume (IV) expressed in cubic millimeters was calculated to be the sum of the infarct areas on each slice (In) multiplied by the distance (0.4 mm) between the successive slices (IV = 0.4[I₁ + I₂ + ... + I₂₄]). To correct for brain size or edema, infarct volumes are presented as percentage values of the total volume of the contralateral hemisphere.

**Statistical Analysis**

Statistical analysis was performed with the aid of statistical software. Physiological data for each time point and total infarct volumes were analyzed using one-way ANOVA, LD and EEG data were analyzed using two-way ANOVA for repeated measures, and neurological function scores were analyzed using Kruskal-Wallis ANOVA on ranks for each of the 7 postoperative days. When multiple comparisons were indicated, the Dunnett test or Student-Newman-Keuls test for neurological function scores was applied. Differences were considered significant if the probability value was less than 0.05. Results are presented as the mean ± standard deviation.

**Sources of Supplies and Equipment**

The Sprague-Dawley rats were obtained from Charles River Laboratory (Sulzfeld, Germany). The LD flowmeter (model MBF3D) was purchased from Moor Instruments Ltd. (Devon, UK) and the EEG equipment (model 7109) from Nihon Kohden Kogyo, Ltd. (Tokyo, Japan). Sodium methohexital (Brevimytal) was acquired from Lilly Deutschland GmbH (Giessen, Germany). The LD flowmeter (model MBF3D) was purchased from Moor Instruments Ltd. (Devon, UK) and BioScan, Inc. (Washington, DC), and statistical analysis was performed using SigmaStat 2.0 software, which was manufactured by Jandel Scientific, part of SPSS, Inc. (Chicago, IL).

**Results**

**Physiological Parameters**

There were no statistically significant differences among experimental groups with regard to pre-, intra-, or postischemic arterial blood gas, mean arterial blood pressure, hematocrit, and blood glucose values. In the animals in which hypothermia was induced and methohexital given, there was a nonsignificant trend toward a lower mean arterial blood pressure and a decreased heart rate during hypothermia and burst suppression compared with the trend in normothermic control animals. Posts ischemic hyperthermia, which has been reported to occur in the intraluminal thread model, was not observed in our study.

**Measurements of LD Flowmetry**

Baseline ICBF values were measured 30 minutes before MCA occlusion—that is, under normothermic conditions and before methohexital was administered. The dynamic changes in ipsilateral and contralateral ICBF are presented in Fig. 2.

In normothermic controls, MCA occlusion resulted in an immediate reduction of ICBF to 20 to 30% of baseline in the territory supplied by the ipsilateral artery, whereas contralateral blood flow remained unchanged throughout the experiment. After reperfusion, a short period of postischemic hyperemia was followed by a decrease of ipsilateral ICBF to approximately 75% of baseline. Delayed hypoperfusion persisted until the end of the 1.5-hour postischemic observation period.

In normothermic animals, administration of methohexital significantly reduced ipsilateral and contralateral ICBF to approximately 75% of baseline within the first few minutes. A further decrease to approximately 70% of baseline was observed when burst suppression was reached. Occlusion of the MCA resulted in an immediate reduction in ipsilateral ICBF to approximately 20% of baseline, whereas contralateral blood flow remained at approximately 70% of baseline. After reperfusion, a prolonged period of hyperperfusion was followed by a decrease in the ipsilateral ICBF to approximately 75% of baseline. Delayed hypoperfusion persisted until the end of the 1.5-hour postischemic observation period. Contralateral flow recovered slowly to 90% of baseline after discontinuation of the methohexital infusion.

In the hypothermic vehicle-treated group, ipsilateral and contralateral ICBFs decreased to approximately 80% of baseline during cooling. Occlusion of the MCA resulted in an immediate reduction in ipsilateral ICBF to approximately 25% of baseline. After reperfusion, a short period of hyperperfusion was followed by a decrease in ipsilateral ICBF to approximately 75% of baseline. Delayed hyperperfusion persisted until the end of the 1.5-hour posts ischemic observation period. Contralateral ICBF recovered to baseline during rewarming.

In animals treated with methohexital and hypothermia, ipsilateral and contralateral ICBF decreased to approximately 50% of baseline during cooling and barbiturate-induced
burst suppression. Occlusion of the MCA resulted in an immediate further reduction in ipsilateral ICBF to approximately 20% of baseline. After reperfusion, a prolonged period of hyperperfusion was followed by a decrease in ipsilateral ICBF to approximately 60% of baseline. The subsequent hypoperfusion persisted until the end of the 1.5-hour postischemic observation period. Contralateral ICBF gradually recovered to 90% of baseline during rewarming and after discontinuation of the methohexital infusion.

Electroencephalography Results

In normothermic controls, MCA occlusion was followed by a rapid ipsilateral slowing of EEG signals and decrease in EEG amplitude to approximately 50% of baseline, with an increase in relative 6 activity of the ipsilateral hemisphere. Slowing of EEG signals persisted in the ipsilateral hemisphere throughout the experiment. After reperfusion, ipsilateral EEG amplitude recovered to 60 to 70% of baseline.

In normothermic methohexital-treated animals, a burst-suppression pattern was reached approximately 15 minutes after onset of methohexital infusion. After reperfusion and discontinuation of the methohexital infusion, EEG amplitudes recorded on the ipsi- and contralateral sides recovered to approximately 60% and 70% of baseline, respectively.

In hypothermic vehicle-treated animals, EEG amplitudes recorded on the ipsi- and contralateral sides decreased to 80% during cooling. Immediately after MCA occlusion, the ipsilateral EEG amplitude decreased to approximately 40% of baseline. After reperfusion and rewarming, the ipsilateral EEG amplitude recovered to approximately 80% of baseline, whereas the contralateral EEG amplitude recovered to preischemic baseline.

In animals treated with methohexital and hypothermia, the ipsi- and contralateral EEG amplitudes decreased dur-
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pared with normothermic methohexital-treated animals. §p
difference did not reach statistical significance. *p
icits than hypothermic methohexital-treated animals; however, the
ty. Hypothermic vehicle-treated animals had less neurological def-
postoperative Days 1, 3, 5, and 7 are presented for the sake of clar-
tensive activity. Although the animals were examined daily, only
0, no spontaneous circling; 1, spontaneous circling; 2, circling if pulled by the tail; 3, lowered resistance to lateral push; 4,
imals: 5, no apparent deficit; 4, contralateral forelimb flexion; 3, lowered resistance to lateral push; 2, circling if pulled by the tail; 1, spontaneous circling; 0, no spontaneous activity. Although the animals were examined daily, only
rological deficits (Fig. 3).

Fig. 3. Scatterplot demonstrating the courses of neurological recovery over 7 days in rats that suffered focal cerebral ischemia. Each symbol represents the individual neurological score of a single animal. Neurological scores: 5, no apparent deficit; 4, contralateral hemisphere in normothermic vehicle-treated controls. These volumes were also significantly (p < 0.05) smaller compared with normothermic methohexital-treated animals. The reduction in total infarct volume accomplished by methohexital therapy under normothermic conditions (32% reduction compared with normothermic vehicle-treated controls) failed to reach statistical significance (Fig. 5).

Infarct Volume

The total infarct volume was 19.1 ± 8.3% of the contralateral hemisphere in normothermic vehicle-treated controls. Total infarct volume was 13 ± 5.9% in normothermic methohexital-treated animals, 5.6 ± 2.4% in hypothermic vehicle-treated animals, and 6.4 ± 4.3% in hypothermic methohexital-treated animals. Total infarct volumes were significantly (p < 0.05) smaller in hypothermic vehicle-treated animals (71% reduction) and in hypothermic methohexital-treated animals (66% reduction) compared with normothermic vehicle-treated controls. These volumes were also significantly (p < 0.05) smaller compared with normothermic methohexital-treated animals. The reduction in total infarct volume accomplished by methohexital therapy under normothermic conditions (32% reduction compared with normothermic vehicle-treated controls) failed to reach statistical significance (Fig. 5).

When infarct volume was determined separately for cortical and subcortical brain tissue, all treatment strategies were found to be significantly (p < 0.05) effective in limiting cortical infarct volume compared with normothermic vehicle-treated controls. The average cortical infarct volume was 9.9 ± 4.4% in normothermic vehicle-treated controls, 5.6 ± 3% (43% reduction) in normothermic methohexital-treated animals, 0.5 ± 1.2% (95% reduction) in hypothermic vehicle-treated animals, and

Fig. 4. Graph showing weight gain in animals over a 7-day period following focal cerebral ischemia. Values are given in percentages of the animals’ preischemic body weights (mean ± SD) for eight animals in each group. Animals in all treatment groups had significantly better weight gains than normothermic vehicle-treated controls. In accordance with neurological recovery, hypothermic vehicle-treated animals regained their body weight most rapidly, although significant differences among treatment groups were not observed. *p < 0.05 compared with normothermic vehicle-treated controls for each day.

Functional Outcome and Weight Gain

Except for the two animals that were excluded because they had SAH, there were no additional deaths. Normothermic animals that received methohexital had significantly (p < 0.05) fewer neurological deficits from postoperative Day 3 to Day 7, whereas hypothermic animals that received vehicle or methohexital had significantly (p < 0.05) fewer neurological deficits from postoperative Day 1 to Day 7, compared with normothermic vehicle-treated controls. Hypothermic vehicle-treated animals and hypothermic methohexital-treated animals displayed fewer neurological deficits than normothermic methohexital-treated animals. This difference reached statistical significance on postoperative Day 5. In hypothermic vehicle-treated animals, there was a trend toward fewer neurological deficits than those found in hypothermic methohexital-treated animals, although the difference was not statistically significant. At the end of the postoperative observation period, none of the eight normothermic vehicle-treated controls, two of the eight normothermic methohexital-treated animals, five of the eight hypothermic methohexital-treated animals, and six of the eight hypothermic vehicle-treated animals displayed no residual neurological deficits (Fig. 3).

In accordance with their functional recovery, normo-
1.2 ± 2.1% (88% reduction) in hypothermic methohexital-treated animals. Cortical infarct volumes in hypothermic vehicle-treated animals and in hypothermic methohexital-treated animals were significantly smaller compared with both normothermic groups (Fig. 6).

The average subcortical infarct volume was 9.2 ± 2.7% in normothermic vehicle-treated controls, 7.4 ± 1.5% in normothermic methohexital-treated animals, 5.1 ± 2.8% in hypothermic vehicle-treated animals, and 5.2 ± 3.4% in hypothermic methohexital-treated animals. Compared with normothermic vehicle-treated controls, subcortical infarct volumes were significantly (p < 0.05) smaller in hypothermic vehicle-treated animals (45% reduction) and in hypothermic methohexital-treated animals (43% reduction). The reduction in subcortical infarct volume accomplished by methohexital therapy under normothermic conditions (20% reduction) was not statistically significant. Compared with normothermic methohexital-treated animals, subcortical infarct volumes were significantly (p < 0.05) smaller in both hypothermic groups (Fig. 6).

**Discussion**

It can be inferred from the findings of this study that administration of methohexital in burst-suppressive doses provides no additional neuroprotective effect under mild hypothermic conditions in rats subjected to transient MCA occlusion. In accordance with the results of many other studies, our data confirm the superior neuroprotective efficacy of mild-to-moderate hypothermia induction, and also corroborate recent results indicating that barbiturates exert only a modest protective effect.

**Cerebral Blood Flow and Metabolism**

Mild hypothermia- and methohexital-induced burst suppression decreased ICBF to 80% and 70% of baseline, respectively. Hypothermia in combination with methohexital decreased ICBF to 50% of baseline. Rosomoff and Holaday have reported a decrease in CBF by 5% per degree centigrade. Their findings were later confirmed in dogs, monkeys, cats, rabbits, and rats. Administration of barbiturates in burst-suppressive doses has been found to reduce CBF by 30 to 50%. Although we did not currently measure cerebral oxygen or glucose consumption, their inhibition can be assumed. In view of the coupling of CBF and metabolism, and as shown in many other studies, it appears that the effects of barbiturates and hypothermia on cerebrometabolic rates are additive.

Barbiturates decrease blood flow by exerting a direct constrictive effect on cerebral arteries. Barbiturates increase vascular resistance mainly in nonischemic tissue; as a result blood flow may be shifted toward ischemic or previously ischemic tissue by a reversed steal phenomenon. In the present experiments, methohexital-treated animals underwent a prolonged period of postischemic hyperperfusion of the ischemic hemisphere, which may have been attributable to a reversed steal phenomenon. Furthermore, methohexital decreased ICBF levels to 75% of baseline long before burst suppression was attained; this may indicate that vasoconstriction induced by methohexital occurred earlier than depression of the cerebral metabolism, which lowered CBF.

**Morphological Changes and Functional Outcome**

Administration of barbiturates in burst-suppressive doses did not provide additional protection under hypothermic conditions with respect to functional outcome or inhibition of infarction (66% reduction) when compared with hypothermia alone (71% reduction). Mild hypothermia was the most effective therapy leading to the smallest infarct volume, the best functional outcome, and optimum weight gain. This is consistent with findings of numerous studies in which the efficacy of mild and moderate hypothermia was explored in various models of focal and global cerebral ischemia. Administration of methohexital under normothermic conditions resulted in a delayed
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... functional recovery (postoperative Days 3–7) and reduced total infarct volume by 32%. The functional recovery is closely related to the degree of morphological damage. Obviously, more effective treatment strategies are associated with an earlier recovery, whereas less effective therapies are associated with a delay in recovery. Taking into consideration the morphological and functional data, it is most likely that the immediate recovery of the hypothermic methohexital-treated animals was attributable to the protection afforded by hypothermia, whereas the delayed recovery of normothermic methohexital-treated animals could be explained by the merely moderate efficacy of barbiturate treatment.

We used methohexital rather than thiopental (the barbiturate more widely used for protection) because methohexital is shorter acting. In previous experiments we investigated the effects of thiopental in the same model, recognizing that animals could not be weaned from the respirator due to persistent respiratory depression. In the present study, assessment of the animals’ neurological recovery and of the maturation of infarction within 7 days was an important objective to improve the validity of the model. The neuroprotective efficacies of methohexital and thiopental are comparable. In our experiments both drugs attenuated infarction by approximately 30%. Therefore, it is unlikely that thiopental would have conferred additional neuroprotection because of its longer-lasting hypnotic effect. Furthermore, the current magnitude of protection is consistent with data from other recent studies in which thiopental, pentobarbital, or methohexital was used, although it appears modest when compared with corresponding findings of earlier studies. Most earlier laboratory investigations of barbiturate protection predate the contemporary appreciation of the importance of cerebral temperature. There is substantial concern that researchers in earlier studies were unaware of the spontaneous development of cerebral hypothermia in animals in a state of anesthesia. This parameter was usually not monitored or controlled. The most convincing clinical evidence of the efficacy of barbiturate medications has been obtained in patients suffering after ischemic focal brain injury following valvular heart surgery. The work by Nussmeier, et al., was the first randomized study in humans in which an improved outcome after administration of barbiturate medications was demonstrated. Although concern has been expressed regarding the validity of this study, it provided perhaps the best available evidence that barbiturates reduce ischemic brain injury under specific surgical conditions, and it currently stands alone with respect to human data in supporting the use of barbiturates as neuroprotective agents. Consequently, the administration of barbiturate medications has been challenged as the gold standard of brain protection during neurovascular surgery.

Combination of Barbiturate-Induced Burst Suppression and Hypothermia

It has been hypothesized that cerebral metabolism is divided into two compartments: 1) the basal compartment, which maintains cellular integrity and structure and can be suppressed by hypothermia; and 2) the functional component, which is responsible for cellular functions such as neuronal firing, and can be suppressed by barbiturates and other anesthetic agents. Both metabolic assignments are considered to be more or less independent of each other. Therefore, barbiturates and hypothermia may affect the cerebral metabolism in an additive or even synergistic manner. Data published by Steen, et al., indicate that administration of barbiturates causing burst suppression further decreases CMRO2, at 33°C from approximately 75 to 40% of normothermic baseline value. However, the absence of additional neuroprotection by barbiturate administration in our study indicates that decreasing the rate of cerebral metabolism is not as important as commonly assumed. For example, the volatile anesthetic agent sevoflurane provides a substantial degree of metabolic suppression and does not afford more protection than halothane, which only has a modest inhibitory effect on cerebral metabolism. Furthermore, it has been shown that burst suppression is not required to obtain the maximum neuroprotection afforded by barbiturates. Obviously, barbiturates protect the brain by mechanisms that are not restricted to the inhibition of cerebral metabolism. Simeone, et al., studied the effect of pentobarbital and hypothermia (26°C) on the development of ischemic brain edema in rhesus monkeys undergoing transorbital MCA occlusion. On the grounds that both pentobarbital and hypothermia produce similar changes in CBF and CMRO2, but only pentobarbital prevents edema, these researchers postulated that the mode of action of barbiturates in preventing ischemic brain edema is not entirely related to their known effect on blood flow and metabolism. Other protective properties of barbiturates include stabilization of cell membranes, improvement of flow into the ischemic brain tissue by a reversed steal phenomenon, antagonism of oxidative and excitotoxic processes, and, thereby, inhibition of intracellular calcium overload.

Similarly, the concept that protection afforded by hypothermia is attributable mainly to a reduction in the rate of cerebral metabolism has been markedly expanded by the well-documented synergism of many beneficial mechanisms. Multiple mechanisms for hypothermia-induced neuroprotection have been identified, including the following: 1) decreased excitatory transmitter release; 2) decreased generation of free radicals; 3) improvement of ion homeostasis; and 4) reduction of vascular permeability, thereby protecting the blood–brain barrier and preventing edema formation. The deleterious mediating cascades that occur during and after ischemia are already suppressed by mild hypothermia and barbiturates do not provide additional neuroprotection. Moreover, barbiturates produce several deleterious side effects such as cardiorespiratory depression requiring catecholamine support and prolonged ventilation. Catecholamines, however, have been shown to increase cerebral metabolism and aggravate ischemic damage. Other adverse mechanisms are associated with an increased risk of infection attributable to barbiturate-induced immunosuppression and the depression of mental status, which obfuscates neurological evaluation. Furthermore, barbiturates may cause a considerable increase in brain temperature; finally, they may increase the immunosuppressive effect of hypothermia.

Little is known about the combined effects of bar-
biturates and hypothermia under compromised conditions.\textsuperscript{20,30,52} Kim and colleagues\textsuperscript{37} reported that the inhibitory potency of mild hypothermia on the suppression of EEG signals by thiopental in humans is not simply additive, but synergistic. Hågerdal and colleagues\textsuperscript{23} measured high-energy phosphates and lactate in rats subjected to cerebral hypoxia, and found that hypothermia of 27°C offered better protection according to the metabolic criteria than phenobarbital and, at 32°C, administration of phenobarbital did not increase the degree of protection provided by hypothermia alone. These findings are in accordance with the results of the present study, which indicate no additional benefit of barbiturate-induced burst suppression under hypothermic conditions.

In the clinical domain, it is common practice to attempt to augment the neuroprotective potency of hypothermia with intravenously administered anesthetic agents such as barbiturates, an intervention that is viewed as harmless at worst. Nonetheless, there has been no laboratory or clinical evidence to date that supplementing hypothermia with these agents during cerebral ischemia is beneficial.\textsuperscript{34} On the contrary, Lesser, et al.,\textsuperscript{34} reported that thiopental and etomidate offset the inhibitory influence of hypothermia on the release of dopamine in rats subjected to forebrain ischemia. Those authors assume that these cerebral metabolism–reducing agents counteract the beneficial effects of hypothermia by blocking reuptake mechanisms. Because increased extracellular dopamine levels are known to be neurotoxic,\textsuperscript{19} the potentially unfavorable interaction of such agents with hypothermia requires further detailed investigation. If, however, additional neuroprotection is necessary under hypothermic conditions, it must be achieved by other means. In a recent study, we demonstrated that the neuroprotective efficacy of mild hypothermia can be further increased by pharmacological antagonization of excitatory amino acids and free radicals by using clinically available drugs (magnesium and tirilazad).\textsuperscript{56,60}

### Conclusions

To our knowledge this is the first report on the cerebroprotective efficacy of barbiturates in combination with hypothermia. Barbiturates provide cerebral protection under normothermic conditions, but the magnitude of protection is far less than commonly believed. Barbiturates and hypothermia act synergistically on CBF and possibly on the rate of cerebral metabolism, but not with regard to neuroprotection. Considering the lack of efficacy shown by barbiturates in enhancing the protection afforded by hypothermia and in view of their potentially deleterious side effects, we do not recommend administration of barbiturates under hypothermic conditions.

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