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Thiopental Treatment after Global Brain Ischemia in Pigtailed Monkeys

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The authors investigated the value of high-dose thiopental (TH) therapy after 16-min complete global brain ischemia (GBI) in three groups of pigtailed monkeys, using a neck cuff model of GBI with 96 h intensive care postischemia (PI). *Control group (n18):* Normotension was restored within 2 min PI; paralysis/controlled ventilation was maintained for 48 h PI with 50% N_2O/O_2. *Thiopental loading group (n13):* Control treatment plus TH-loading with 90 mg/kg iv given from 5 to 65 min PI (mean peak TH plasma level 130 μg/ml). *Thiopental anesthesia group (n14):* Control treatment plus TH anesthesia with 90 mg/kg iv given over 12 h PI (sustained TH plasma levels of 25–35 μg/ml and EEG burst suppression). Norepinephrine requirement for blood pressure control PI was greater in the TH groups than in the control group ($P < 0.05$). Lidocaine was needed for control of arrhythmias in the TH loading group. There was no significant difference in mortality or neurologic outcome between the groups. At 96 h PI seven of 11 animals were awake in the control group, compared with seven of 12 and six of 12 in the two TH groups. Neurologic deficit scores (NDS) for the survivors at 96 h PI were 23 ± 6% (mean ± SD) (n10) in the control group, compared with 25 ± 9% (n11) and 26 ± 12% (n10) in the two TH groups (NDS 100% = brain death, 0% = normal). Seizures PI (in 1–2 of each group) were associated with worse neurologic deficits. At 96 h PI, all three groups had developed the same type and distribution of histologic lesions. Thus, the authors were unable to demonstrate any brain-damage-ameliorating effect of TH loading or TH anesthesia after 16 min GBI in pigtailed monkeys. (Key words: Anesthetics, intravenous: thiopental. Brain: ischemia; resuscitation; seizures. Heart: cardiac arrest.)

THE WIDESPREAD BELIEF that 4–5 min of global brain ischemia (GBI) is the maximum the brain can tolerate without suffering permanent damage,[1] has been challenged by new knowledge concerned with the pathophysiology of GBI,[2] by promising trials in animals,[3,4] and by clinical case reports.[5] Events occurring postischemia (PI) may cause further neuronal damage,[6] and these are being approached therapeutically in the hope of improving neurologic outcome. Attention has focused mainly so far on treatment with barbiturates. Barbiturates have been shown to reduce cerebral metabolism, blood flow, and edema.[7–9] Furthermore, certain barbiturates seem to improve the ratio of cerebral blood flow to metabolic demands, not only in hypoxia[10] and focal ischemia,[11] but also after complete GBI.[12] In experimental *focal* ischemia, there is extensive documentation that barbiturate pretreatment (protection) as well as postinsult treatment (resuscitation) is beneficial.[13–16] In spite of these experimental results, controlled studies in clinical focal ischemia documenting such benefits are still lacking. The situation regarding *global* ischemia is controversial. Yatsu *et al.* found methohexithal protection to be beneficial in incomplete GBI (hypoxemia plus hypotension).[17] There also have been promising reports on barbiturate protection[18] as well as resuscitation[19] in complete GBI, but recent studies[20,21] and the one reported here do not support this initial optimism.

The first study of barbiturate treatment *after* GBI was the one by Bleyaert *et al.*[19] They produced 16-min GBI in rhesus monkeys with an inflatable neck cuff, leaving the lungs ventilated and the rest of the body perfused.[22] Using this model, treatment with large doses of thiopental (TH) after ischemia seemed highly beneficial.[19] This triggered worldwide optimism about barbiturate treatment after cardiac arrest. However, this study has caused substantial controversy, and the criticism has focused mainly on the following points: 1) only five animals were used in each of the TH-treated groups; 2) the clinical relevance of a head ischemia model in contrast to total circulatory arrest has been questioned; and 3) questions have been raised about completeness of ischemia.

We recently have tested the neck cuff model of GBI,[23] and we feel confident that the model is useful for evaluating therapies after GBI. In the present study, we investigated the value of high-dose thiopental loading as well as prolonged thiopental anesthesia after 16 min GBI, taking into consideration the above criticism. We decided to use the neck cuff model in the present study in order to repeat as closely as possible the study by Bleyaert *et al.*,[19] which has caused so much controversy and has been a major stimulus for the clinical use of barbiturates after GBI.

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Methods

We used 45 pigtailed monkeys (Macaca Nemestrina) of either sex, weighing 3.4–6.7 kg, uniformly fed, and then fasted overnight before the experiments. The model previously has been described in detail.[22,23] Briefly, the animals were anesthetized with 0.5% halothane in 66% N_2O and O_2, paralyzed with pancuronium, intubated, and ventilated with a Harvard piston ventilator. Five per cent dextrose in 0.45% NaCl was infused iv, 4–5 $ml \cdot kg^{-1} \cdot h^{-1}$. After 48 h PI, 10% dextrose in 0.45% NaCl was used. A sterile cutdown was performed in the groin, and an arterial catheter inserted for blood pressure monitoring and blood sampling. For pressure and cardiac output monitoring, a 5 Fr Swan-Ganz thermodilution catheter was inserted via the femoral vein into the pulmonary artery. For EEG monitoring, bipolar, frontoparietal needle electrodes were used. The ECG (lead 2) also was monitored via needle electrodes. Continuously monitored were ECG, arterial blood pressure, pulmonary artery pressure, EEG, end-tidal CO_2 (Beckman LB 2 infrared analyzer), and rectal temperature. Arterial blood gases, blood glucose, electrolytes, osmolality, and hematocrit were determined immediately pre-ischemia and at frequent intervals PI. During the PI period, blood samples were drawn for determination of TH plasma levels, using high-pressure liquid chromatography. Cardiac output measurements in triplicate were done with the thermodilution method at the same points of time during and after TH infusion. Prior to ischemia, halothane was discontinued for exactly 5 min. The resulting incomplete halothane washout provided a certain depth of anesthesia that was judged to be needed for this type of experiment. Ischemia was produced with a neck cuff, abruptly inflated to a pressure of 1,500 mmHg; the lungs were ventilated through a noncompressible endotracheal tube; and systemic hypotension was maintained with trimetaphan and positive end-expiratory pressure (PEEP) to increase the likelihood of complete ischemia. Ventilation during ischemia was with $F_{I_{O_2}}$ 1.0. All animals were subjected to 16 min of GBI and were divided randomly into three groups.

Control Group (N18)

Control treatment included paralysis with pancuronium and controlled ventilation (IPPV) for 48 h PI. Ventilation was with an $F_{I_{O_2}}$ of 1.0 during ischemia and for the first 2 h PI, thereafter with an $F_{I_{O_2}}$ of 0.5; 50% N_2O was added to provide some analgesia and sedation. Mean arterial pressure (MAP) of 80 mmHg was restored within 2 min PI and was kept thereafter at 100 ± 20 mmHg, using norepinephrine (0.08 mg/ml, 1–3 ml/h) or trimetaphan (5 mg/ml, 0.5–2 ml/h) as needed to correct hypo- or hypertension, respectively. Rectal temperature was kept at 37.5 ± 1° C. The ventilation rate was adjusted to keep Pa_{CO_2} at 25–30 mmHg. Pa_{O_2} was kept above 100 mmHg with the aid of PEEP or increased $F_{I_{O_2}}$ if needed. Fluid balance was controlled carefully by adjusting iv infusions and using furosemide 1 mg iv if needed, to maintain a zero balance. At 48 h PI, residual effects of pancuronium were reversed with atropine 0.15 mg and neostigmine 0.3 mg iv, and the animals were weaned from IPPV and extubated as soon as clnically feasible.

Thiopental Loading Group (N13)

In addition to control treatment, we started a TH infusion at 5 min PI. A dose of 90 mg/kg was given iv (30 mg/kg infused in the first 5 min, the remaining 60 mg/kg infused over 55 min), as previously used by Bleyaert *et al.*[19] To control arrhythmias, lidocaine was started at 5 min PI; an iv volus of 10 mg was followed by an infusion of 1 mg/ml at a rate of 8–16 ml/h. Lidocaine was discontinued at 4 h PI. Blood samples for determination of TH plasma levels were drawn at 10, 20, and 65 min PI, thereafter at 2, 6, 12, and 24 h PI; cardiac output determinations were made preischemia and at the same points of time PI.

Thiopental Anesthesia Group (N14)

In addition to control treatment, a TH infusion was started at 5 min PI. A dose of 90 mg/kg was infused over 12 h as follows: 1 $mg \cdot kg^{-1} \cdot min^{-1}$ from 5–20 min PI, 0.25 $mg \cdot kg^{-1} \cdot min^{-1}$ from 20–65 min PI, and 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ thereafter, until the end of infusion at 12 h PI. Lidocaine was not given. Blood was drawn for TH plasma levels at 20 and 65 min and at 2, 6, 12, and 24 h PI. Cardiac output determinations were made preischemia and at the same points of time PI.

Postischemic Intensive Care

Intensive care was maintained for 96 h PI. This included control of fluid balance, normotension, normothermia, ventilation (Pa_{CO_2} 25–30 mmHg during IPPV), and oxygenation (Pa_{O_2} > 100 mmHg during IPPV and >80 mmHg during spontaneous breathing). Tetracycline was given every 12 h starting at 12 h PI, and phenytoin 10–20 mg iv was given when needed to control seizures but never before 48 h PI. Nursing care included changing of position every 4 h and tracheal suctioning when needed. Monitoring lines were removed between 48 and 72 h PI to allow the animals to move more freely. When possible, the animals were placed in a padded playpen for the last 24–48 h PI to enable better observation of behavior and neurologic deficits. Cautious oral feeding was started after about 60 h PI as feasible.

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TABLE 1. Studies Excluded from Final Analysis

Group	Excluded (n)	Reason for Exclusion
Control	7	2 technical/human errors 2 hypoxemia, pulmonary edema 1 sepsis 1 leg gangrene, severe infection 1 normotension restored too late PI
Thiopental loading	1	1 accidental hypotension (trimetaphan)
Thiopental anesthesia	2	1 incomplete ischemia, (EEG not isoelectric in 20 s) 1 technical/human error

Total 10/45 experiments excluded. Failure rate 22%.

EEG Return PI

The pattern of EEG return PI was recorded continuously. Start of EEG activity with burst suppression was defined as that point of time when there was less than 30 s between bursts. EEG activity was defined as continuous when there were no longer isoelectric periods between the bursts.

Exclusions

Experiments that did not follow protocol were excluded from data analysis, according to predetermined exclusion criteria.[22,23] These criteria include incomplete ischemia, postischemic hypotension or severe hypertension, hypoxemia, hypercapnia, hyperthermia, and sepsis. Ischemia was judged to be incomplete if the EEG was not isoelectric within 20 s after neck cuff inflation, if increasing facial congestion was observed, or if persisting retinal circulation was seen on ophthalmoscopy. Monkeys that died from primary brain death during the observation period in spite of life support according to protocol were included in the final analysis (OPC).

Outcome Evaluation

Final outcome was evaluated by the following three variables:

1) *Overall performance categories (OPC). All* included animals were evaluated clinically and assigned to one of five OPCs. OPC 1 and 2 were good outcome (awake with variable motor deficits), OPC 3 included stupor, OPC 4 vegetative state, and OPC 5 brain death. Animals dying a primary brain death during the observation period were assigned to OPC 5.

2) *Neurologic deficit scores (NDS), quality of survival.* At 6, 12, 24, 48, 72, and 96 h, PI neurologic deficit (ND) scores were determined in per cent.[22] NDS 100% means brain death, and 0% means normal. The NDS is determined from level of consciousness, respiration, cranial nerve function, motor and sensory function, and behavior. All ND scores were obtained by the same two investigators. We gave up having blinded investigators doing this, because the animals were extremely variable in their response to testing; therefore, prolonged presence with the animals was necessary to obtain reliable scores. Only animals surviving 96 h PI were evaluated with this method, making the final NDS an expression of quality of survival in each group.

3) *Histologic examination.* After the final clinical evaluation, the animals were reanesthetized with pentobarbital, and a left-sided thoracotomy was performed. Four per cent buffered paraformaldehyde was infused into the left cardiac ventricle, while the descending aorta was cross-clamped and the right atrium opened; thus the brain was perfused/fixed at the moment of death.[19,22,23] For determining histologic damage (HD) scores, four brains were selected at random from each group. In addition, four brains were selected deliberately from animals with higher than average ND scores (1 + 1 + 2 from the three groups). This enabled us to check if high ND scores (bad clinical outcome) indeed correlated with high HD scores. The same two neuropathologists (GR, JM) blindly examined 18 different brain areas and scored them for edema, ischemic neuronal changes, and infarction.[19,22] Theoretically, the worst possible HD score for each region, both sides combined, was 56, and for the entire brain 1,008.

Statistical Analysis

Laboratory values, ND, and HD scores are reported as mean values ± standard deviations (SD). Analysis of variance was used to compare the mean ND and HD scores between the three groups. The animals were ranked from best to worst, based on ND and HD scores, and the relationship between these two ranking lists was analyzed using Kendall's correlation coefficient. A Fischer Exact test was used to compare OPCs. A chi-square test was used to compare the incidence of polyuria.

Results

Thirty-five experiments followed protocol, 11 in the control group, 12 in the TH loading group, and 12 in the TH anesthesia group. Ten experiments were excluded from final analysis for not adhering to protocol (table 1). The groups were comparable with regard to preischemic variables that may influence neurologic outcome (table 2). In particular, the preischemic blood sugar levels were almost identical in the three groups.

Completeness of Brain Ischemia

The EEG became isoelectric at 8–14 s after neck cuff inflation in all experiments. In addition, persistent facial

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TABLE 2. Preischemic Variables

Group	Pa_{O_2} mmHg	Pa_{CO_2} mmHg	Rectal T °C	Hct %	Blood sugar mg/dl
Control (n = 11)	160 ± 23	28 ± 4	37.5 ± 0.15	39 ± 2	123 ± 17
TH loading (n = 12)	153 ± 10	29 ± 4	37.4 ± 0.2	38 ± 3	120 ± 23
TH anesthesia (n = 12)	154 ± 22	30 ± 3	37.4 ± 0.14	40 ± 4	124 ± 22

Mean ± SD. No significant differences between the groups.

pallor and a bloodless retina were observed throughout the ischemic period.

Reperfusion Pressure PI

The blood pressure was restored to normal (MAP > 80 mmHg) within 2 min PI, and the blood pressure patterns were similar in the three groups (fig. 1). The total dose of norepinephrine needed to restore and maintain normotension was significantly greater in both thiopental groups than in the control group ($P < 0.05$), whereas the difference between the two thiopental groups was not statistically significant. (Control group 170 ± 65 μg, TH loading group 410 ± 100 μg, TH anesthesia group 305 ± 130 μg).

Lidocaine

Lidocaine was used for antiarrhythmic prophylaxis only in the TH loading group. Total doses were 30–40 mg in the first 4 h PI. Occasional single ventricular extrasystoles were seen in this group. Otherwise, no serious arrhythmias were observed in any of the three groups.

Thiopental Plasma Levels (fig. 2)

In the TH loading group TH plasma levels peaked at a mean value of 130 μg/ml at the end of the initial 5 min of TH infusion. In the TH anesthesia group, TH plasma levels remained around 30 μg/ml for 12 h PI.

Cardiac Output (fig. 2)

Cardiac output remained near normal PI in the control group, while a moderate decline to about 85% of control value occurred in the two TH groups. This difference was statistically significant only at 6 h PI ($P < 0.05$). There was no significant difference in cardiac output between the two TH groups.

EEG Recovery

In the control group, EEG started to return with a burst suppression pattern at 45 ± 10 min PI, and continuous EEG activity was observed at 110 ± 53 min PI. In the TH loading group, EEG burst suppression started between 5 and 12 h PI. In the TH anesthesia group, burst suppression started before the end of TH infusion

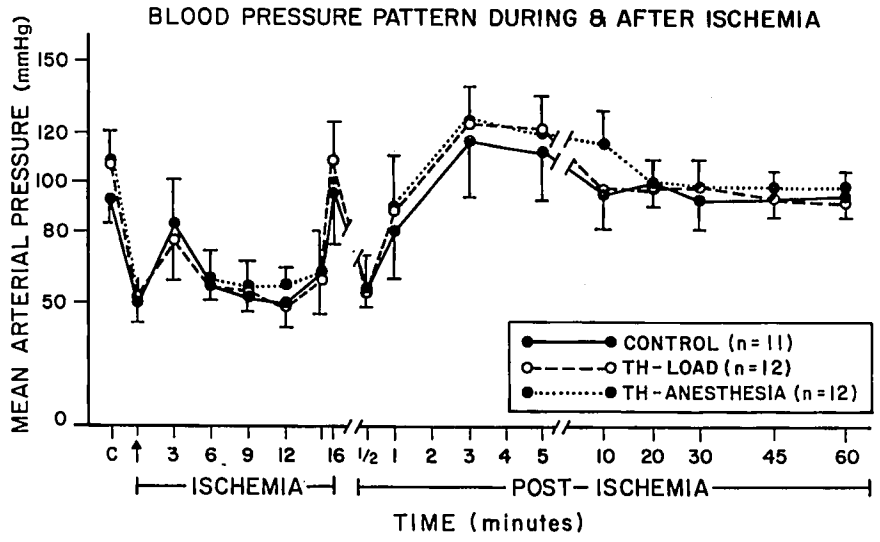

FIG. 1. Mean arterial pressure (MAP) pattern during and after ischemia in the three groups. As always with this model, there is a tendency of MAP rise during the first 3 min of ischemia. At no point in time postischemia was there a significant difference in MAP between the three groups.

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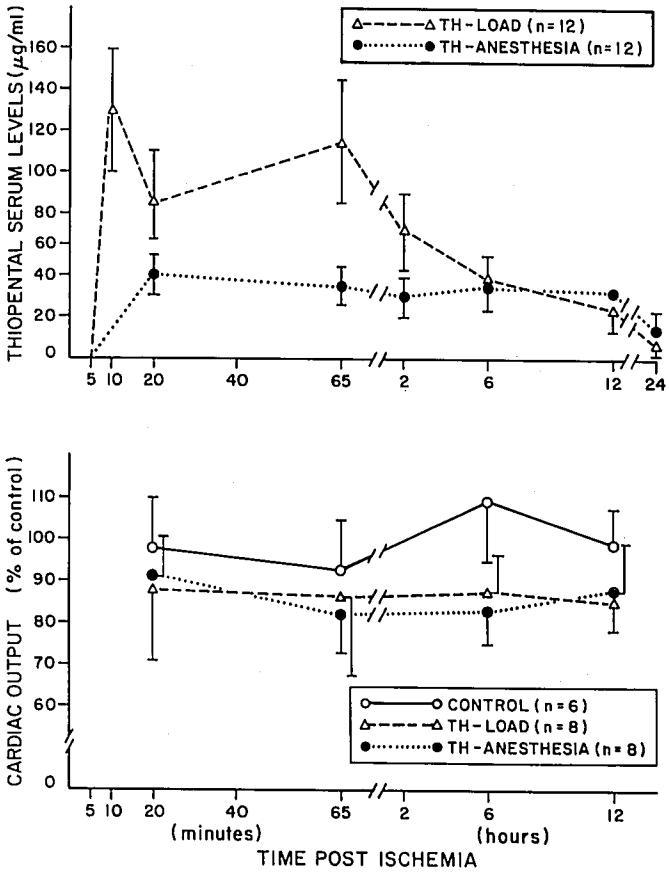

FIG. 2. Thiopental plasma levels (*upper graphs*) of thiopental loading and thiopental anesthesia groups. Cardiac outputs (*bottom graphs*) in per cent of control for all three groups. MAP was controlled at 100 ± 20 mmHg in all three groups with norepinephrine infusion. While cardiac output stayed normal in the control group, a moderate decrease was seen in the thiopental groups. Cardiac output with thiopental was significantly lower than without thiopental only at 6 h PI ($P < 0.05$).

in six of the animals, but in all of these, the EEG activity remained at a burst suppression level until after 12 h PI when the TH infusion ended. Thus, in all animals in this group, the EEG was depressed significantly for at least 12 h PI. Initial EEG recovery with burst suppression and later a moderately active continuous activity was observed also in four animals that later died from brain death at 48–72 h PI (table 3).

TABLE 3. Outcome. Overall Performance Categories (OPC)

Group	Overall Performance Categories				
	1 Awake Near Normal	2 Awake Motor Deficits	3 Stupor	4 Coma Vegetative	5 Coma Brain Death
Control (n = 11)	0	7	3	0	1
TH loading (n = 12)	0	7	3	1	1
TH anesthesia (n = 12)	1	5	3	1	2

The table shows number of monkeys in each outcome category. No significant differences between the groups.

SEIZURES

We did not see seizures clinically or on EEG during the first 48 h PI, when the animals were paralyzed and received 50% N_2O, even without thiopental. Four monkeys had clinically evident seizures between 48 and 72 h PI: one in the control group, one in the TH loading group, and two in the TH anesthesia group. Phenytoin 10–20 mg iv stopped or ameliorated the seizures.

RESPIRATION

The degree of controlled hyperventilation during the first 48 h PI was the same in the three groups, with Pa_{CO_2} values of 25–30 mmHg. At 48–50 h PI, adequate spontaneous breathing was restored in all animals, and they were extubated within 6 h thereafter. Pa_{CO_2} levels during spontaneous breathing remained below 35 mmHg.

POLYURIA

In 14 of the 24 TH-treated animals, a very pronounced polyuria occurred PI, in seven of 12 in the TH loading group and in seven of 12 in the TH anesthesia group, in contrast to two of 11 in the control group ($P < 0.05$). The excessive loss was replaced with 5% dextrose/0.45% NaCl, with 10 mmol/l K^+ added. In all but two animals the polyuria subsided at 50–60 h PI. In the polyuric animals, urine electrolytes were in the following range: Na^+ 55–85 mmol/l, K^+ 5–10 mmol/l. The polyuria was observed also in some animals with normal blood glucose and no glucose in the urine.

OUTCOME

Overall Performance Categories (OPC) (table 3). Judged by overall performance, the outcome was quite similar in the three groups. At 96 h PI, seven of 11 animals were awake (OPC 1 or 2) in the control group compared with seven of 12 and six of 12 in the two TH groups. Four of thirty-five animals were assigned to OPC 5. They developed the clinical picture of primary brain death at 48–72 h PI and died before 96 h PI (no difference between the groups).

Neurologic Deficit Scores (NDS) (Quality of Survival). The survivors of the three groups followed an almost identical pattern of neurologic recovery (fig. 3). During the first 48 h PI, NDS remained high because of neuromuscular blockade, N_2O, and thiopental. Little additional recovery occurred after 72 h PI. There was no significant difference

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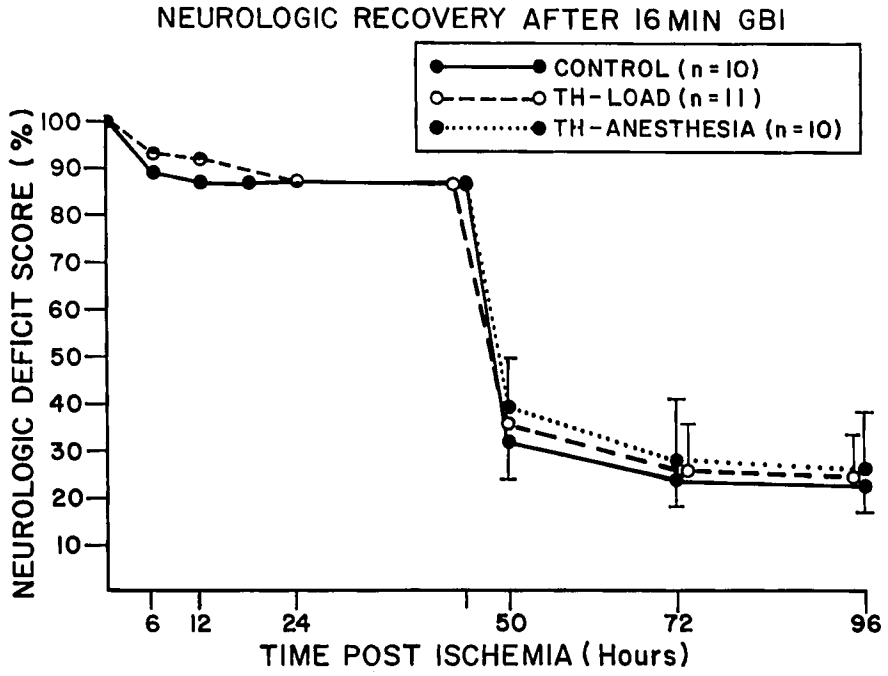

FIG. 3. Neurologic deficit (ND) scores post-ischemia in the three groups. Only the animals surviving 96 hours are included; the final score thus expresses quality of survival in the respective groups. Strictly speaking, ND scores are not truly evaluable until after 48 h PI, when pancuronium is reversed and N_2O discontinued. The final ND scores at 96 h PI were almost identical in the three groups.

in ND scores at 96 h PI between the groups: Control group (n10): 23 ± 6% (range 16–35%); TH loading group (n11): 25 ± 9% (range 17–44%); TH anesthesia group (n10): 26 ± 12% (range 3–48%). The four animals that developed seizures survived for 96 h PI, but with higher ND scores than those without seizures (NDS 35%, 44%, 36%, and 48%). They had the highest ND scores of the survivors in their respective groups.

Histologic Evaluation. Ischemic neuronal changes were predominant in the hippocampus, thalamus, midbrain, and cerebellum, while the neocortex largely was unaffected. The histologic damage scores (HDS) in the three groups were: control group: 35 ± 21 points (n = 4); TH loading group: 63 ± 34 points (n = 4); TH anesthesia group: 36 ± 10 points (n = 4) ($P > 0.05$). The scores support the conclusion that there is no difference in outcome between the groups. However, with the small number of brains examined in this study, the HDS *alone* cannot be reliably used for comparing outcome between the groups. ND scores of 40–50% at 96 h PI correlated with HD scores of 200–250 points; higher HD scores were incompatible with long-term survival. When ranking the outcome from best to worst, based on HDS, this ranking correlated closely with the NDS ranking ($r = 0.70$, $P < 0.001$). When doing this correlation analysis, we included the four brains deliberately picked from animals with high ND scores. This close correlation lends credibility to both methods. Thus, it appears that the HDS method is reliable and can be used alone for evaluating outcome after ischemia if one has the necessary expertise and time.

Discussion

In this study we were unable to detect any benefits from large-dose TH loading or from prolonged TH anesthesia after 16 min GBI. The outcome was almost identical in the three groups regarding overall performance (table 3) and ND scores among the survivors (fig. 3). Furthermore, the TH-treated groups had the same incidence of seizures PI as the control group. The clinical outcome evaluation was supported by the histologic examination.

Two main questions arise when our results are viewed in relation to those of Bleyaert *et al.*[19]: 1) Why were we unable to confirm beneficial effects of TH loading after GBI? 2) Why were none of our pigtailed monkeys completely normal at 96 h PI, as Bleyaert reported for rhesus monkeys with the same therapy?

There is a five-part answer to the first question.

(1a) The answer may lie in the blood pressure patterns immediately PI. In the study by Bleyaert *et al.*, MAP of 80 mmHg was not reached until 10 min PI in the control group, compared with 2 min PI in the TH loading group. In our present study, MAP of 80 mmHg was reached in all groups within 1–2 min PI (fig. 1). Cantu *et al.* found that neurologic outcome improved when normotension was restored quickly, when compared with no blood pressure support after GBI of 10–15 min duration.[24] Miller and Myers showed that hypotension PI impaired functional recovery[3] and caused more extensive neuronal necrosis in the cerebral cortex.[25] In the present study, the neocortex was largely undamaged, possibly because of our prompt restoration of normotension PI. In the study

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by Bleyaert *et al.*, the control group with hypotension during the first 10 min PI had much more cortical damage than the TH-treated animals with normotension quickly restored.

(1b) Bleyaert *et al.* conducted most of their control experiments before the treatment groups were started. It is possible that the TH loading experiments were done by a more expert team, as suggested by better blood pressure control PI. The outcome may be influenced by minor changes in the quality of postischemic care. It is our impression that the outcome of control experiments tend to improve through the years, even with the same model and the same duration of ischemia. This impression also has been expressed by other investigators.[26]

(1c) In Bleyaert's study, the control group was ventilated for only 3–6 h PI, compared with 12–24 h in the TH-treated animals. However, in a recent study, we found no difference in neurologic outcome between groups with such differences in the duration of IPPV PI.[23]

(1d) There were several differences between our study and the one by Bleyaert *et al.* We ventilated the animals with 50% N_2O to provide sedation. However, since our groups were identical in this regard, beneficial treatment effects should not be precluded. We used lidocaine in our TH loading group. Bleyaert used lidocaine just occasionally, apparently because TH loading post-GBI is better tolerated in rhesus monkeys. Lidocaine has antiseizure properties in low doses, it reduces the efflux of potassium from ischemic cells, and brain oxygen consumption may be lowered.[27,28] These are all potentially beneficial effects. However, we detected no tendency toward improved outcome in our lidocaine-treated animals.

(1e) In the present study, preischemic blood glucose levels were highly comparable in the three groups (table 2). It is unclear how this was in Bleyaert's study. It seems well documented that preischemic hyperglycemia makes neurologic outcome worse.[29]

Finally, the two studies used two different subspecies of monkeys. However, it is extremely unlikely that treatment benefits should be detectable only in the rhesus monkey.

The second question was, "Why did we not see any completely normal monkeys after TH loading the way Bleyaert *et al.* did?"

(2a) This discrepancy might be explained by the subspecies difference. In these two studies the histologic damage (HD) scoring was done with the same method by the same two neuropathologists who did not know the treatment. Interestingly, our pigtailed monkeys with ND scores of 20–25% at 96 h PI, had the same HD scores as Bleyaert's best group (TH loading at 5 min PI) with seventh day ND scores of 0%. We speculate that the more aggressive rhesus monkeys tried harder to get up upon testing, whereas the much more docile pigtailed monkeys with the same amount of structural damage did not bother to try. After all, most of our pigtailed monkeys in all three groups were awake at 96 h PI.

(2b) Our shorter observation time PI also may be an important explanation. Miller and Myers claim that neurologic function may improve for up to 30 days after severe GBI in rhesus monkeys.[3] However, 96 hours should be a long enough observation time to detect outcome differences between groups. At 96 h PI, Blayert's best monkeys already were near normal, with NDS < 10%, and there was a significant difference from the control group already at 36 h PI.[19]

Other GBI Studies with Barbiturates

Optimal PI intensive care, including ventilatory support and blood pressure control, is mandatory when studying the effects of barbiturates or other CNS-depressant therapies after GBI. Prolonged brain ischemia may in itself cause hypotension PI,[24] and this may be enhanced with barbiturates. Without proper life support, hypotension, hypoxemia, hypercapnia, and other complications may cause further neurologic damage.[24,25,30] Among studies with barbiturates *after* GBI, only the one by Todd *et al.*[21] and the present study meet these requirements. Todd *et al.* found increased survival rate among cats treated with TH after 12–16 min of ventricular fibrillation, probably because of seizure depression by TH. This observation is important, since it seems to confirm that treatment started postischemia can influence neurologic outcome favorably. However, they could not detect improved neurologic outcome among the survivors in the TH group when compared with surviving control animals. This raises the question of whether TH treatment may increase the number of vegetative survivors. This should become apparent from the results of the ongoing randomized clinical study of TH loading after cardiac arrest.[31] Snyder *et al.* detected no benefits from pentobarbital treatment after asphyxial cardiac arrest in dogs,[32] but they did not meet the necessary requirements for PI intensive care. Pulsinelli *et al.* studied temporary bilateral hemispheric ischemia in the rat, followed by pentobarbital during recirculation.[33] They found worse histologic outcome in the treated animals, but did not control blood pressure and did not support ventilation. Levy and Brierly studied temporary unilateral hemispheric ischemia in gerbils and found pentobarbital treatment to reduce the extent of edema and infarction in the affected hemisphere.[16] However, this study is probably more relevant to the problem of focal ischemia, since only part of the brain was deprived of its blood supply and this produced a clinical picture of stroke in these animals.

To our knowledge, only two well-controlled outcome studies have been done on *protection* (pretreatment) with

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barbiturates in complete GBI. Goldstein *et al.* found pretreatment with pentobarbital to be highly beneficial in dogs, where GBI was produced with vessel ligation.[18] Steen *et al.* were unable to reproduce these results, using the same model.[20] They used N_2O in treatment and control groups, which Goldstein did not. Although N_2O may not be as indifferent as hitherto believed,[34] it is most unlikely that it should offset a beneficial effect of the barbiturate.

Cardiovascular Effects of Thiopental

In pilot studies, we found that TH loading, as used in the present study, was well tolerated by healthy monkeys, but when TH loading was preceded by GBI, five of six animals developed ventricular fibrillation early during TH infusion, even when hypotension was controlled with norepinephrine.[35] However, cardiac arrest could be prevented by lidocaine prophylaxis in addition to vasopressor support. Brain metabolism can be minimized and ICP reduced with TH serum levels of 20–40 μg/ml, which are well tolerated by the cardiovascular system.[35,36] We, therefore, developed a mode of TH administration that provided significant EEG depression for 12 h without serious cardiovascular side effects.[35] This administration was used in our TH anesthesia group in this study. Cardiac output decreased only 15% from control levels, and the same moderate decline also was seen in the TH loading group, while cardiac output remained normal in the control group (fig. 2). This mild reduction in cardiac output is probably of no clinical importance. The difference in norepinephrine requirement between control and TH groups may be important, since norepinephrine can influence cerebral metabolism, particularly if the blood–brain barrier is disrupted.[37]

Seizures

The incidence of seizures PI was the same in control and TH groups. This differs from the observation by Todd *et al.*, who found reduced incidence of seizures in cats treated with TH after 12–16 min of ventricular fibrillation.[21] Seizures were associated, however, with poor neurologic outcome in our study, an observation also made by other investigators who have found seizures PI to be a bad prognostic sign; seizures may cause additional brain damage and increase mortality.[21,38,39] Since even animals in the control group developed seizures late PI, seizure prophylaxis starting early and continued until recovery of consciousness appears therapeutically sound.

Polyuria Postischemia

Polyuria post-ischemia was a big problem in the TH-treated groups. It took a considerable effort to prevent hypovolemia, hypotension, and hemoconcentration. With the high urine sodium concentrations seen (55–85 mmol/l), diabetes insipidus seems an unlikely diagnosis. This problem also was seen with normal blood sugar levels, and we have seen it in several experiments with this model where barbiturates were not used. Thus, it is unlikely that the excessive diuresis is osmotic, caused by sugar or thiopental. We speculate that we may have seen the clinical picture of "salt-wasting syndrome associated with cerebral disease."[40]

Conclusion

The present study does not support the use of barbiturates for brain resuscitation. Thiopental did not reduce mortality, did not reduce the incidence of brain death or seizures, and did not improve the quality of survival after 16 min of GBI in pigtailed monkeys. There is clearly insufficient support at the present time for recommending clinical use of large doses of barbiturate after GBI, as in cardiac arrest. The ongoing clinical trial of thiopental loading after cardiac arrest hopefully will provide more conclusive information.[31]

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