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The Neurologic Effects of Thiopental Therapy Following Experimental Cardiac Arrest in Cats

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To define the utility of high-dose barbiturate therapy following an episode of complete global cerebral ischemia, we investigated the effects of 60 mg/kg of thiopental given to cats five minutes after resuscitation from 12, 14, or 16 min of electrically induced ventricular fibrillation (VF). All aspects of the arrest, resuscitation, with post-arrest care were carefully controlled, with the EEG becoming isoelectric 20–25 s after the onset of VF, a 89–91 per cent rate of successful resuscitation, with an overall mean resuscitation time of 2.5 ± 0.2 (SEM) min. For any given duration of VF, there were no differences (control *vs* thiopental) in any pre- or post-arrest parameters (blood pressure, blood gases, electrolytes, *etc.*) A total of 68 resuscitated cats were entered into various treatment and control groups, and all but one group received 20–24 h of post-resuscitation paralysis, mechanical ventilation, and ICU support before being extubated. Cats received an additional six days of aggressive nursing care, and daily examinations were performed with the assignment of a neurologic deficit score (NDS) between 0 (normal) and 100 (brain dead). Autopsies were performed to determine the cause of death in animals which died before the end of the seven-day observation period.

The early post-arrest period was marked by the occurrence of repetitive, rhythmic bursts of high-frequency electroencephalographic (EEG) activity (? seizures) in 38 per cent of control animals (16/42, all arrest times combined). Ten of these animals died as a result of severe neurologic injuries. By contrast, only 12 per cent of treated cats (3/26) developed similar EEG patterns ($P < 0.05$) and there were no neurologic deaths in the thiopental groups. The differences in the incidence of neurologic deaths (control *vs.* thiopental) was significant ($P < 0.02$). The change in overall mortality did not quite reach significance (36 per cent *vs.* 21 per cent), and treatment had no effect on the incidence of deaths due to cardiovascular causes (*e.g.*, myocardial infarctions).

In spite of the effects on mortality, treatment had no effect on the neurologic function of *survivors* (assessed by NDS). These findings suggest that thiopental improved survival rates by suppressing an unusual post-arrest EEG pattern (? anticonvulsant effect), but had no additional cerebral protective effects. (Key words: Anesthetics, intravenous: thiopental. Brain: anoxia; electroencephalography; ischemia; protection. Complications: arrest, cardiac.)

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IT HAS BEEN SUGGESTED that large doses of barbiturates may improve neurologic outcome following a period of total cerebral ischemia, (*e.g.*, cardiac arrest) even when drug administration is started after resuscitation.[1] The importance of such a finding is obvious, but, unfortunately, the experiments supporting this view remain controversial.[2–4] One reason for disagreement concerns the methods used to produce global brain ischemia in the laboratory. Obviously, the outcome may be altered if the method does not produce *complete* ischemia,[5,6] while techniques utilizing strangulation or requiring extensive surgical manipulations may have little clinical relevance.[7] Attempts to mimic the most common clinical situation, *i.e.*, cardiac arrest produced by ventricular fibrillation (VF), have been fraught with difficulties due to high post-resuscitation mortality rates and/or an inability to standardize events in the ischemic and post-ischemic periods.[8–10] Nevertheless, the clinical relevance of VF makes it a theoretically attractive method for investigating post-resuscitation therapies. With this goal in mind, we developed a model of complete global cerebral ischemia in cats, produced by the electrical induction of VF and followed by cardiopulmonary resuscitation (CPR) and a prolonged period of post-arrest intensive care support. This model was then used to evaluate the effects of high-dose thiopental given after resuscitation.

Materials and Methods

Adult conditioned cats weighing 2–4 kg were allowed water *ad libitum* and fasted overnight. Anesthesia was induced with 4 per cent halothane in oxygen (in a Plexiglas® box), the trachea intubated with a cuffed tube, and mechanical ventilation begun with tidal volumes of 12 ml/kg, a respiratory rate sufficient to maintain Pa_{CO_2} between 30–35 mmHg, and with 2 cmH_2O positive end-expiratory pressure (PEEP). After intubation, animals were paralyzed with intravenous pancuronium bromide, 0.1 mg/kg (and maintained with 0.1-mg/kg increments), and the inspired gas mixture changed to 1 per cent halothane in 70 per cent nitrous oxide and oxygen. Atropine, 0.08 mg/kg, was given intramuscularly and the eyes protected with an antibiotic ointment. Needle electrodes were used for EKG monitoring (lead II), and esophageal temperature was kept at 37°C with servo-controlled heating lamps. The animal was turned into a supine

position, and after infiltration with bupivicaine 0.25 per cent, a small cutdown was performed in the groin. Sterile catheters were placed via femoral vessels into the abdominal aorta and the right atrium, with the position of the right atrial catheter tip confirmed by EKG using a wire placed through the catheter lumen. The catheters were secured and the wound closed and dressed. The electroencephalogram (EEG) was obtained with collodion-secured subcutaneous platinum needles [2 leads: fronto-occipital (F_z-P_z) and biparietal (C_3-C_4)] and recorded on a Beckman Accutrace® machine with one of the EEG channels simultaneously recorded on the main polygraph along with the EKG, arterial pressure (BP), and right atrial pressure (RAP). All EEGs were recorded at a gain of 5 μV/mm, with frequency cutoffs at 1 and 50 Hz. Other monitored variables included expired CO_2 (Beckman LB-2®), inspired oxygen concentration (FI_{O_2}-IL model 406), arterial blood gases, and pH. Arterial samples were drawn intermittently for the determination of hematocrit (Hct), Na^+ and K^+ (flame photometry), osmolality (freezing point depression) and plasma glucose (glucose oxidase). Plasma thiopental levels were measured by gas chromatography (see appendix). The total volume of blood drawn from any cat was limited to 15 ml (over 24 h).

Thirty-five to 45 min after anesthetic induction (timed from the start of halothane inhalation), halothane was discontinued, and the cat ventilated for an additional 45–60 min with 70 per cent N_2O and O_2, a time sufficient to reduce end-tidal halothane concentration to 0.04 per cent or less, as determined by mass spectrometry. All surgery was completed before halothane was stopped and the animal was handled as little as possible thereafter. At the end of this period, a wire was placed into the right atrium via the catheter already in place. Its position was reconfirmed by EKG, and ventricular fibrillation (VF) induced with a 2–5-s pulse of 60 Hz AC current (20 V RMS) passed between the wire and a subcutaneous electrode placed over the apex of the heart. The ventilator was disconnected and the endotracheal tube occluded. On occasion, repeated AC shocks were required to maintain VF, but any animal with a spontaneous heart beat occurring more than one minute into the arrest was deleted from further study.

Circulatory arrest was continued for 12, 14, or 16 min (timed from the onset of VF). At the end of the desired ischemic period, the ventilator was reconnected (FI_{O_2} = 1.0) and closed chest CPR begun. Over the next one minute, each cat received 1) 2 mEq/kg sodium bicarbonate, 2) 15 μg/kg epinephrine, and 3) 10 mg/kg $CaCl_2$ (all given via the RA catheter). Manually generated BP was kept at or above 125/50 mmHg, and defibrillation (15–25 joules) was first attempted 1.0–1.25 min after starting CPR. If unsuccessful, CPR was continued and additional bicarbonate (1 mEq/kg) and epinephrine (15 μg/kg) was given with repeated DC shocks until successful. Resuscitation was considered complete when a spontaneous systolic pressure over 100 mmHg was achieved and maintained. Either before or immediately after defibrillation 0.05 mg/kg atropine and 1 mg/kg lidocaine were given intravenously to stabilize cardiac rhythm. To minimize problems due to variations in resuscitation times, any cat requiring more than four minutes of CPR was discarded.

Post-resuscitation

During the first hour post-resuscitation (PR-timed from the start of CPR), mean arterial pressure (BP) was maintained at or above 90–100 mmHg, using intravenous fluids (lactated Ringer's solution) and dopamine if needed. Thereafter mean BP was kept above 85 mmHg. No animal arrested for 12 or 14 min required dopamine unless given thiopental (see below), but all cats arrested for 16 min (control and thiopental treated) required transient pharmacologic support. Arterial blood gases were drawn 5, 15, 30, 45, and 60 min PR and at least every two hours thereafter. Ventilation was adjusted to return Pa_{CO_2} into the control range as quickly as possible. Bicarbonate, 1 mEq, was given every 5 min until pH was above 7.30; it was not given faster to avoid problems with transient hypercapnia, hyperosmolality, and acute Na^+ overload. FI_{O_2} remained at 1.0 until one hour PR and then reduced until Pa_{O_2} was between 150–300 mmHg. PEEP was kept at 2–4 cmH_2O and the trachea suctioned as needed. Transient pulmonary edema (frothy sputum) was common, but rarely lasted more than 15 min.

All animals received intensive care support as described below. This consisted of paralysis (pancuronium), mechanical ventilation (P_{CO_2} 30–35 mmHg guided by blood gases drawn q 2 h), intravenous fluids sufficient to maintain BP, RAP and urine output, as well as aggressive respiratory care (turning, chest physical therapy, and suctioning every two hours). At the end of the ICU period, cats received 0.04 mg/kg atropine and 0.06 mg/kg prostigmine intravenously and were extubated when able to maintain P_{CO_2} below 35 mmHg. Electrodes and catheters were removed and the animals transferred to a warmed (27–28°C) Plexiglas® cage with an O_2-supplemented atmosphere (FI_{O_2} = 0.5) where they remained for an additional 24–45 h (depending on the length of their prior ICU period) until being moved back to regular cages (room air). The total period of oxygen supplementation (ICU and post-ICU periods combined) was 40–48 h for all cats.

Animals were observed for a total of seven days. During the entire post-ICU period, nursing care was pro-

TABLE 1. Post-arrest Treatment Groups

Arrest Times	Number Arrested	Number Resuscitated	n	EEG Flat (s)	Resuscitation Time (min)	EEG Return (min)
12 Minutes	38	34 (89 per cent)				
Rapid wean			11	23 ± 2	2.5 ± 0.2	27.3 ± 1.2
Control			12	22 ± 1	2.7 ± 0.3	33.4 ± 4.5
Thiopental			11	27 ± 4	2.3 ± 0.2	63.6 ± 7.8*
14 Minutes	15	13 (87 per cent)				
Control			8	22 ± 2	2.5 ± 0.2	31.0 ± 1
Thiopental			5	24 ± 1	2.3 ± 0.2	82.8 ± 18.8*
16 Minutes	23	21 (91 per cent)				
Control			11	23 ± 1	2.7 ± 0.2	35.6 ± 1.7
Thiopental			10	22 ± 2	2.4 ± 0.2	90.5 ± 5.6*
Totals/Means	76	68 (89 per cent)		23 ± 1	2.5 ± 0.1	

All values are means ± SEM. EEG flat times are from the onset of VF. Resuscitation is timed from the start of CPR, and equals the time until spontaneous systolic BP is over 100 mmHg. Time to EEG return is the time until the first EEG activity seen. The duration of burst suppression in barbiturate treated cats was generally about three times the EEG return time.

* $P < 0.01$ thiopental-treated *vs.* control.

vided, which included frequent turning, chest physical therapy, mouth, eye, and wound care, *etc.* Five per cent dextrose in 0.2 per cent normal saline was given subcutaneously to maintain urine output until the animal was taking oral fluids. Solid food was provided only after oral fluid intake had resumed. At the end of the observation period, the animals were anesthetized with intraperitoneal pentobarbital and the brains fixed by perfusion (via the left ventricle) with warmed (37°C) Trump's solution (4 per cent formalin-1 per cent glutaraldehyde in phosphate buffer). Brains were removed and stored in fixative at 4°C for an additional 2 weeks before embedding and sectioning. However, neuropathologic results are not currently available.

Autopsies were performed for animals which died before the end of the seven-day period to determine, as accurately as possible, the cause of death (see below).

Post-arrest Treatment Groups

Cats successfully resuscitated from 12, 14, or 16 min of VF were assigned to either control or thiopental treatment groups. Within each time period, allocation to control or treatment groups was done randomly. All animals (control and thiopental) received 20–24 h of ICU care, except for one group of cats arrested for 12 min who received only three hours of ICU care (to determine the effects of ventilatory support alone). Thiopental was given in a total dose of 60 mg/kg beginning five minutes after resuscitation was complete. Cats arrested for 12 min received a loading dose of 25 mg/kg during the first five minutes of the infusion with the rest given over the next 29 min. However, such rapid barbiturate loading was not well-tolerated by cats arrested for 14 and 16 min. Instead, they received the initial 25 mg/kg over 10 min with infusion completed over the next 29 min. All thiopental-treated cats required transient dopamine support to maintain BP within the desired limits. With the exception of the use of dopamine, there were no differences in post-arrest care between control and thiopental treated animals. The groups are summarized in table 1. An additional six *unarrested* cats received 60 mg/kg thiopental (infusion schedule identical to cats arrested for 12 min) followed by 12–24 h of mechanical ventilation. These served as drug controls.

Neurologic Assessment

Neurologic damage in each cat was assessed daily by at least two observers who were unaware of the circumstances surrounding the arrest or the treatment received. A neurologic deficit score (NDS) was assigned by each examiner, based on a predetermined scale (table 2), where NDS = 0 refers to a normal animal, and NDS = 100 is a maximal injury, indicating a brain dead cat (apneic, areflexic, *etc.*). The daily score for each animal was the average of the scores given by the different examiners. Unarrested, untreated normal cats occasionally were scored to insure the accuracy of the examiners, particularly at the low end of the scale. No attempt was made to assign an arbitrary score (for statistical purposes) to animals which died.

Mortality

Because the NDS ignores dead animals, an attempt was made to determine the cause of death in each cat dying before the end of the seven-day period. Based on clinical examination and autopsy findings, four categories were used to classify the causes of death: 1) *Cardiovascular*: Deaths attributed to any form of severe cardiovascular disorder, including recurrent VF, refractory

hypotension with high right atrial pressures (cardiogenic shock), myocardial infarction (discovered postmortem), or severe pulmonary edema. 2) *Neurologic*: Deaths occurring in any severely neurologically damaged animal, without evidence for significant cardiovascular pathology at autopsy. This category includes deaths occurring during or immediately after a witnessed major-motor seizure. All animals in this group had NDSs of 75 or greater recorded shortly before death. 3) *Technical*: Deaths attributed to technical error or equipment failure. 4) *Unknown*: Includes any death not readily placed in another category.

Statistics

Comparisons of NDSs were performed using an unpaired t test. Mortality data were evaluated using either a χ_c^2 (corrected for continuity) or Fisher's exact test depending on group sizes.

Results

A total of 85 cats was used. Seven were lost as a result of pre-arrest problems and two were discarded because of "failed" arrests (spontaneous defibrillation), leaving 76 successful *arrests* (38-12 min; 15-14 min; 23-16 min). The AC current resulted in almost instantaneous VF, with non-pulsatile blood pressure falling below 15 mmHg in about 30 s. The EEG was flat in 23 ± 2 s (SEM) and the pupils were dilated and unreactive within 2.0 min (table 1). Eight cats could not be resuscitated within the four-minute limit (4–12 min; 2–14 min; 2–16 min), and, therefore, a total of 68 successfully *resuscitated* cats was entered into the various treatment groups. This represents an overall resuscitation rate of 89 per cent, with a mean resuscitation time of 2.5 ± 0.2 (SEM) min. Resuscitation times and the percentage of successful resuscitations did not vary significantly between the different experimental groups (table 1).

There were no differences in pre-arrest mean blood pressures or arterial blood gases between any of the groups (BP = 125–145 mmHg). Post-arrest BP in animals arrested for 12 and 14 min (control and treatment groups) were back to pre-arrest values within 5 min PR, and then gradually decreased to 100–140 mmHg. Cats arrested for 16 min were slower to recover (BP at five minutes PR 100–115 mmHg), but normalized by 15 min PR. All cats were hypercarbic (Pa_{CO_2} 38–60 mmHg) and acidotic (pH 7.15–7.25) immediately following resuscitation, but these values were normalized rapidly (Pa_{CO_2} 28–35 mmHg, pH 7.31–7.37 by one hour PR). There were no significant intergroup differences (control *vs.* thiopental). There were no episodes of hypoxia ($Pa_{O_2} < 100$ mmHg) or hypotension (BP < 95 mmHg).

TABLE 2. Neurologic Assessment

	Points	Maximum Points
Level of Consciousness		
Normal	0	
Clouded or delerious	5	
Stuporous	10	
Comatose	15	15
Respirations		
Normal	0	
Abnormal	5	
On ventilator	10	10
Cranial Nerves		
Pupil size (normal = 0/abnormal = 1/fixed = 2)	0–2	
Light reflex (present/weak/absent)	0–2	
Oculocephalic (present/weak/absent)	0–2	
Corneal reflex (strong/weak/absent)	0–2	
Facial sensation (strong/weak/absent)—hemostat applied to nasal mucosa	0–2	
Auditory (strong/weak/absent)—loud clap	0–2	
Gag reflex (strong/weak/absent)—tongue blade to posterior pharynx	0–2	14
Spinal Reflexes		
Muscle tone		
Trunk: normal/spastic/flaccid	0–5	
Limbs: normal/spastic/flaccid	0–5	
Flexor reflex to pain—pressure exerted on base of toenail with hemostat		
Front: normal/depressed/absent	0–3	
Hind: normal/depressed/absent	0–3	16
Behavioral Reactions		
Wheelbarrowing—gait on forelimbs when hind limbs held off ground, note head position and symmetry)	0–3	
Extensor postural thrust—lower animal to floor with hind limbs to touch, allow walking and observe symmetry	0–3	
Placing—paws to contact table edge, simultaneously and individually; observe for placement onto table		
Front: normal/ataxic/absent	0–3	
Hind: normal/ataxic/absent	0–3	
Feeding—yes = 0/swallows when fed = 2/absent = 4	0–4	
Cleaning—yes = 0/absent = 4	0–4	20
Gait		
Normal	0	
Minimal paresis and ataxia; able to walk	5	
Able to stand and independently support self, but stumbles and falls frequently	10	
Unable to stand independently; stumbles and falls frequently when supported	15	
Unable to stand, purposeful movement when supported by tail—severe paresis	20	
Absence of purposeful movement	25	25
Maximum Possible Score		100*

* 100 points = the most severe neurologic deficit; 0 points = normal.

All cats were transiently hyperkalemic in the early post-resuscitation period (K^+ 5–7 mEq/l), again with no intergroup differences. There were no differences in Na^+, Hct, glucose, or osmolality.

EEG Recovery

In control animals, initial EEG activity reappeared 20–25 min PR, (regardless of the duration of VF Table 1). Thiopental therapy significantly delayed the reappearance of initial activity, and usually resulted in 2–7 h of a burst-suppression pattern (*e.g.*, fig. 1*A*).

Two different EEG recovery patterns were seen in control animals. In one group (26 cats, all arrest times combined) arbitrarily designated as "normal" recovery, initial slow activity was quickly followed by brief spindles which faded quickly into continuous background activity that gradually increased in frequency over the next 12–18 h (fig. 1*B*). However, in a second subgroup of control animals (16 cats, all arrest times combined), the initial post-arrest slow-wave activity abruptly changed into episodic bursts of rhythmic, high-frequency waves (13–20 Hz) beginning 20–30 min PR with bursts recurring 1–4 × per min (fig. 1*C*). This persisted for 30–60 min before fading into a continuous but slower background. This group has been designated as "abnormal" recovery. Three (of 26) thiopental treated cats showed similar "abnormal" patterns (although the onset of the described bursts was delayed until 1.5–3.0 h PR). The difference in the incidence of this "abnormal" activity between control and thiopental-treated groups is significant (16/42 *vs.* 3/26, $\chi_c^2 = 4.4$, $P < 0.05$.).

We were unable to determine any pre-arrest differences between animals with "normal" *vs.* "abnormal" EEG recovery patterns (BP, blood gases, weight, sex, *etc.*) and there were no post-arrest difference in BP, blood chemistries, resuscitation times, *etc.* However, there was a relationship between the pattern of EEG recovery and eventual neurologic outcome (see below).

Outcome

The results of thiopental therapy were assessed by three measurements: mortality rate, cause of death, and the neurologic function of survivors (NDS).

Mortality

Mortality data are summarized in Table 3. There were no significant differences in overall mortality between control animals (16/42, 38 per cent) and thiopental-treated animals (7/26, 26 per cent) when all arrest times were combined (χ_c^2). Deletion of the two technical deaths from the treated groups lowered mortality to 21 per cent (5/24) but significance was still not achieved by the χ_c^2 statistic ($\chi_c^2 = 1.38$). The size of the groups precluded accurate statistical comparisons of mortality rates for any single arrest time (12, 14, or 16 min).

Causes of Death

The causes of death are discussed below. The categories have been presented under Materials and Methods.

Cardiovascular Deaths

Ten cats (six control, four thiopental) died from cardiovascular (CV) causes, with eight of these belonging to the 16-min arrest groups (four control, four thiopental). All CV deaths in the 16-min arrest groups were associated with large myocardial infarctions. The remaining two animals showed no apparent areas of infarction, but died from 1) recurrent VF, in spite of normal electrolytes and blood gases, and 2) myocardial failure (falling BP with rising RAP). All but one CV death occurred within 36 h PR. Therapy had no effect on the incidence of CV deaths.

Neurologic Deaths

A total of 10 control cats died with severe neurologic disability, four of these deaths occurring during or following a witnessed major motor seizure. There were no neurologic deaths among treated animals. When expressed as a fraction of the total deaths (10/16, *vs.* 0/7) this difference is significant, even if technical deaths are deleted (10/16 *vs.* 0/5, Fisher's Exact Test, $P < 0.02$).

All neurologic deaths occurred in cats that had demonstrated "abnormal" EEG recovery patterns early in the PR period. Of the 16 control animals with "abnormal" EEG's 11 (69 per cent) died before the end of the 7-day period (10 neurologic, one CV). By contrast, only 5/26 (19 per cent) "normal" EEG recovery animals died (all due to CV causes). This difference is significant ($\chi_c^2 = 8.3$, $P < 0.01$).

In thiopental-treated groups, only three cats showed "abnormal" EEG patterns, but all survived 7 days. However, all three were severely damaged neurologically (NDS > 60).

Technical Deaths and Death Due to Unknown Causes

Two cats (both in thiopental-treated groups) died from technical errors. The cause of death in one remaining treated cat could not be accurately determined, but the animal was improving neurologically (falling NDS).

All sham animals survived the full 7 days.

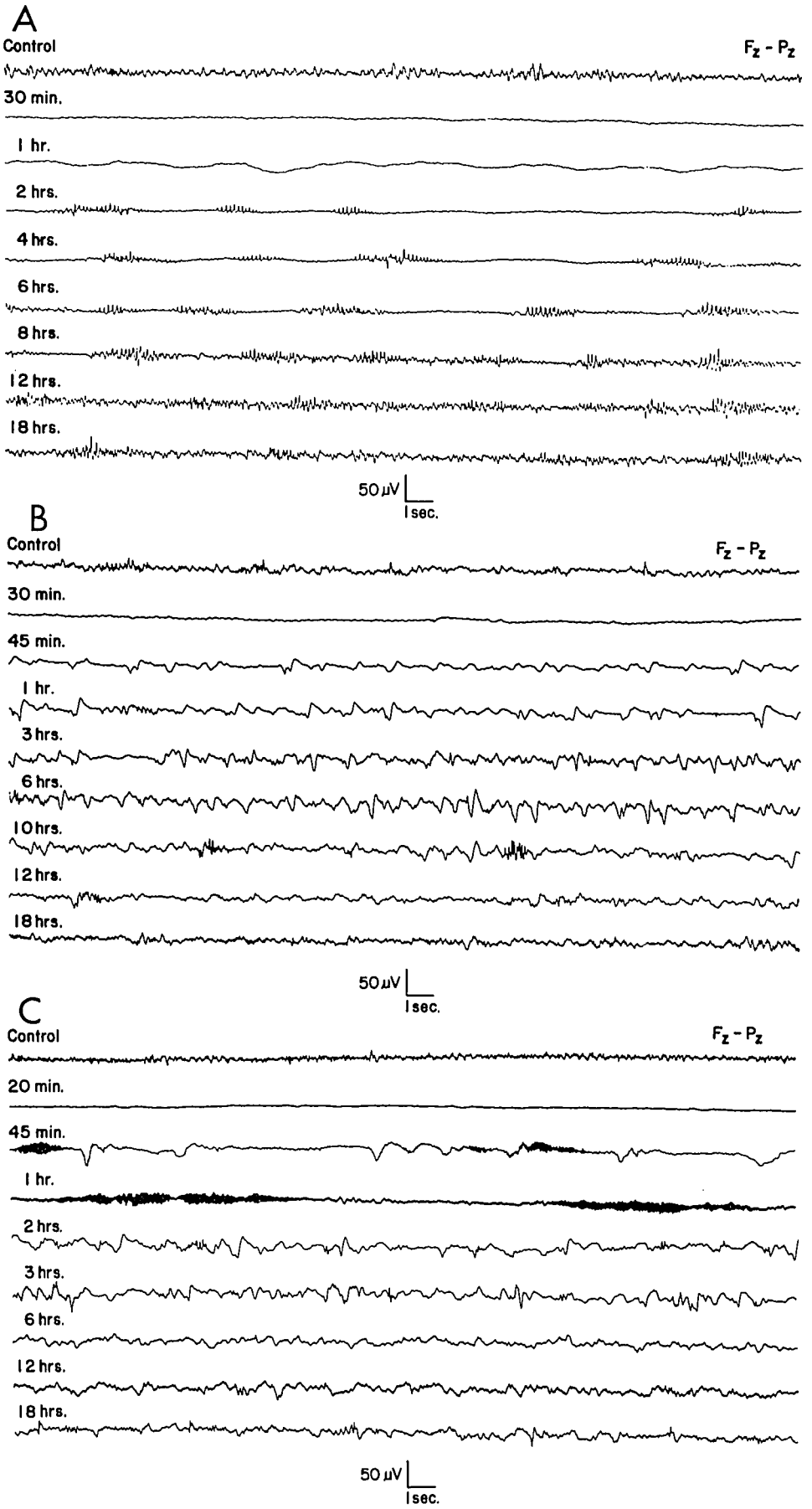

FIG. 1. Excerpts from pre- and post-arrest electroencephalograms (EEGs) of a thiopental-treated animal (*A*) a "normal" control, (*B*) and a control animal showing an "abnormal" EEG recovery pattern (*C*). All tracings were obtained at a gain of 5 μv/mm at a paper speed of 10 mm/s using subcutaneous platinum needle electrodes. Times refers to minutes or hours post-resuscitation. (*A*) 16-min arrest, thiopental-treated cat. Initial EEG activity returned between 1 and 2 h post-resuscitation but a burst-suppression pattern disappeared only between 6 and 7 h. (*B*) 16-min arrest, "normal" EEG recovery. Initial activity appeared between 25–35 min post-arrest, usually with episodic delta waves, and occasionally with brief spindles (not shown) similar to those seen in figure 1*A* (at approximately two hours post-arrest). The remaining 17 h is characterized by a progressive increase in frequency. (*C*) 14-min arrest "abnormal" EEG recovery. The "abnormal" pattern is characterized by repetitive bursts of rhythmic high-frequency activity such as that seen at 45 min and one hour post-resuscitation. By 2–3 h post-arrest there were no consistent differences between the EEGs in the "normal" and "abnormal" animals. However, an "abnormal" EEG recovery pattern was invariably associated with either death or a poor neurologic outcome (see text).

TABLE 3. Mortality

	12 minutes			14 minutes		16 minutes	
	"Rapid Wean"	Control	Thiopental	Control	Thiopental	Control	Thiopental
Number resuscitated	12	11	11	8	5	11	10
Cause of death							
Neurologic	3	2	0	3*	0	2*	0
Cardiovascular	0	1	0	1	0	4	4
Technical	0	0	1†	0	1†	0	0
Unknown	0	0	1‡	0	0	0	0
Mean time of death (days)	2.5	1.5	2.5 (1)	1.8	2.5 (1)	1.7	1.3
Total deaths	3 (25%)	3 (27%)	2 (18%)§	4 (50%)	1 (20%)§	6 (55%)	4 (40%)

* Includes 2–14 min and 2–16 min cats dying during or immediately after witnessed seizures. *All* "neurologic deaths" were in the "abnormal" EEG recovery group.

† One death due to endotracheal tube obstruction, one due to O_2 disconnect.

‡ Death occurred at 2.5 days PR, in an animal with rapidly improving NDS, with no significant abnormality on autopsy (found dead).

§ In the 12 and 14 minute thiopental-treated groups, mortality becomes 9 per cent and 0 per cent, respectively if technical deaths are deleted.

NEUROLOGIC DEFICIT SCORES

The NDS data for the various groups are summarized in figure 2 (*A*, *B*, and *C*). In all groups, the 7-day observation period was characterized by a gradual improvement in neurologic function. Some of this improvement in mean NDS resulted from the deaths of damaged cats, but a similar pattern was typical of individual animals as well. There were no differences between control and treatment groups, regardless of the duration of arrest.

This method of expressing neurologic morbidity is biased by the mixing of living cats and cats destined to die, as well as cats with "normal" and "abnormal" EEG recovery patterns. However, if cats which died before the end of the seven-day period are deleted (as described by Bleyaert *et al.*[1]), and only cats with "normal" EEG recovery patterns are compared, therapy was again seen to have no effect on NDS. At day seven, NDS values for these subgroups were as follows: 1) 12-min arrest, control = 20.6 ± 10 (SE); rapid wean = 15.9 ± 4.8, thiopental = 10.2 ± 3 (no significant differences); 2) 14-min arrest, control = 15.8 ± 2 *vs.* thiopental = 23.4 ± 4.7; and 3) 16-min arrest, control = 29.8 ± 3.5 *vs.* thiopental = 32.0 ± 4.0.

There were no differences between the 12-min "rapid wean" (3 h mechanical ventilation PR) and controls (20–24 h ventilation). Unarrested cats given thiopental were normal (NDS = 0) within 3–4 days.

PLASMA THIOPENTAL LEVELS

Plasma thiopental levels during the initial 48 h following resuscitation are shown in figure 3. The curve is constructed from values obtained in 11 cats, with each point representing 4–6 animals. Levels of 41 ± 4.1 (SEM) μg/ml were found upon completion of the drug infusion (designated "45 min") and there were no apparent differences between 12, 14, or 16 min arrest groups. Levels had fallen to 16.9 ± 3.0 μg/ml by six hours, a time at which essentially all cats showed continuous EEG activity. No drug was detected at seven days.

Discussion

Over the last 30 years, many methods have been used to produce severe global cerebral ischemia compatible with survival in laboratory animals. These can be divided into two general categories. In the first group are techniques designed to halt brain perfusion without impairing flow to other vital organs. These include surgical occlusion of the subclavian, innominate, carotid and/or vertebral/basilar arteries,[11–14] or procedures that compress the extracranial vessels with a high-pressure neck tourniquet.[15] An alternative involves elevating intracranial pressures to levels exceeding arterial pressure.[16] The second group includes methods of producing complete circulatory arrest, either by occlusion of the ascending aorta[17,18] or by ventricular fibrillation.[8–10] Problems exist with all approaches. The brain is supplied by numerous collaterals, and in studies utilizing isolated brain/head ischemia, flow may still persist. Methods of minimizing collateral perfusion have included neck dissections[14] or profound systemic hypotension,[11–13] but these add certain confounding variables to the picture (*e.g.*, large doses of halothane reduce BP but also reduce

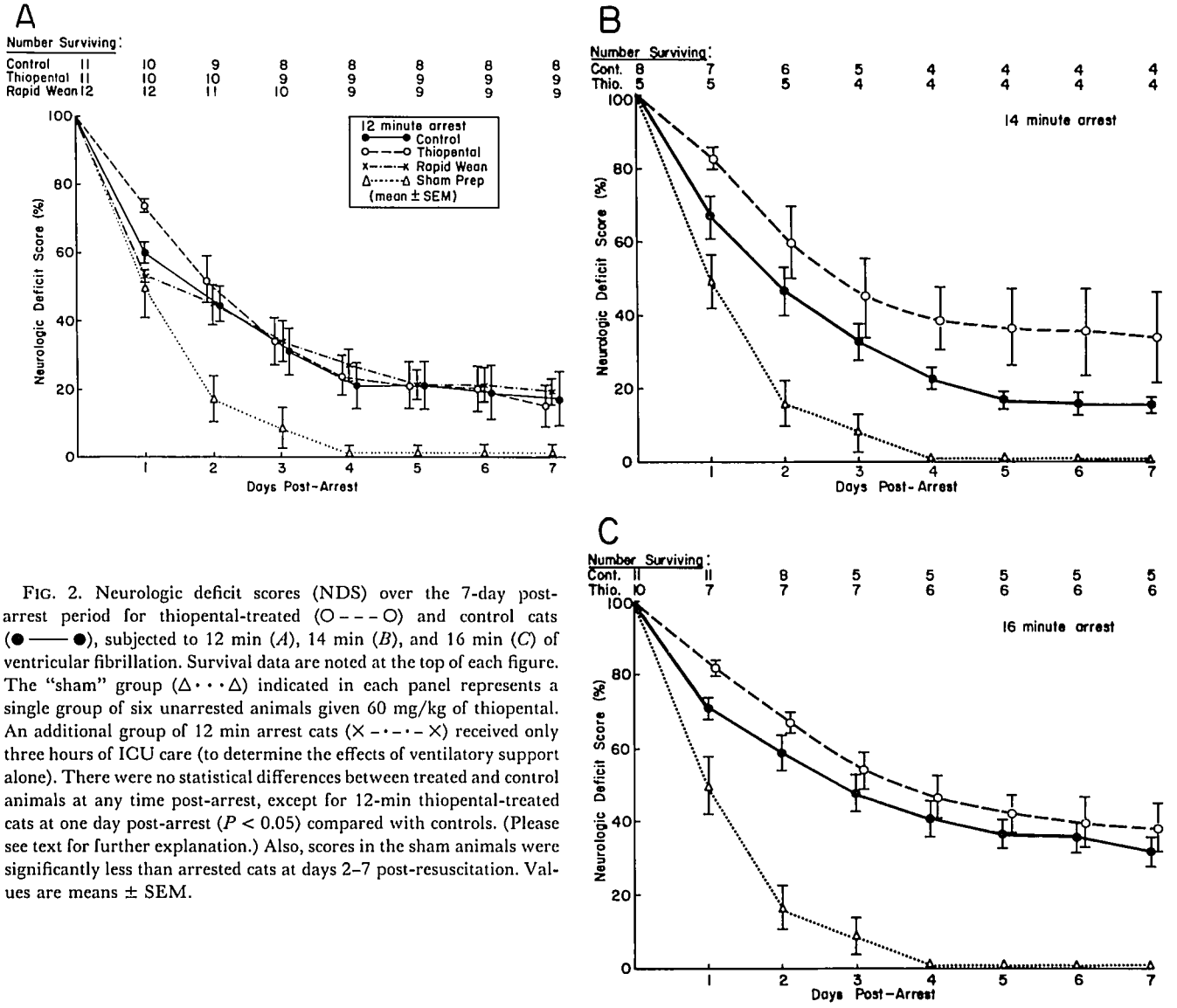

FIG. 2. Neurologic deficit scores (NDS) over the 7-day post-arrest period for thiopental-treated (O - - - O) and control cats (● —— ●), subjected to 12 min (*A*), 14 min (*B*), and 16 min (*C*) of ventricular fibrillation. Survival data are noted at the top of each figure. The "sham" group (Δ • • • Δ) indicated in each panel represents a single group of six unarrested animals given 60 mg/kg of thiopental. An additional group of 12 min arrest cats (× - • - • - ×) received only three hours of ICU care (to determine the effects of ventilatory support alone). There were no statistical differences between treated and control animals at any time post-arrest, except for 12-min thiopental-treated cats at one day post-arrest ($P < 0.05$) compared with controls. (Please see text for further explanation.) Also, scores in the sham animals were significantly less than arrested cats at days 2–7 post-resuscitation. Values are means ± SEM.

cerebral metabolism and cerebrovascular resistance). Circulatory arrest techniques are not plagued by questions of collateral flow, but generally require extensive surgery, *e.g.*, a thoracotomy or sternotomy and/or are complicated by high cardiovascular mortality rates.[18] This has been particularly true of previous experiments utilizing ventricular fibrillation.[8-10]

These factors were taken into consideration during the development of the cat model of ventricular fibrillation/resuscitation described herein. Our goals were to 1) simplify the surgical preparation; 2) provide pre-arrest analgesia/anesthesia while insuring that more potent volatile agents had been eliminated; 3) to produce a clinically relevant form of total circulatory arrest, followed by standard resuscitation procedures; 4) to carefully define the resuscitation protocol and resuscitation times so that the ischemic insult was as standardized as possible; 5) to provide post-ischemic monitoring and supportive care to all animals; and 6) to minimize subjective bias in quantitative neurologic assessment. The neurologic deficit scoring techniques are relatively crude, and are weighted toward motor function. Therefore, it is possible that more sophisticated methods of testing learning, memory, social behavior, etc. would reveal abnormalities with arrests even shorter than 12 min. For example, this system ignores visual abnormalities and it was clear that transient blindness was common in our animals. It may also be true that a cat with an NDS of five is equivalent to a human with a severe intellectual deficit. Nevertheless, within the confines of the experimental laboratory, the model is workable, and its results appear to have some relevance to clinical practice.

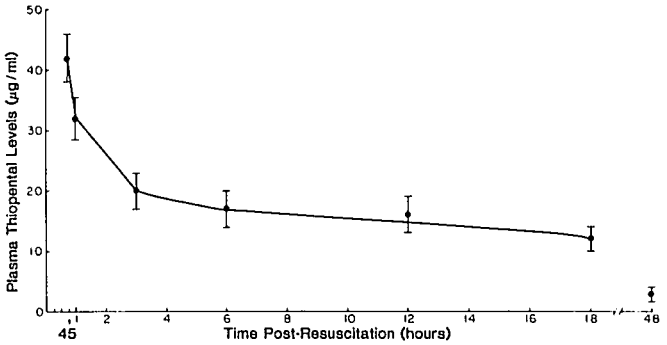

FIG. 3. Plasma thiopental levels post-arrest. Note that the level at "45 min" was drawn approximately 1 min after stopping the drug infusion, although the actual time post-resuscitation varied between 40 and 50 min.

Many years ago, barbiturate anesthesia was shown to prolong the survival (time until death) of small animals subjected to hypoxia (*not anoxia*).[19] The most likely mechanism for such "protection" is the reduction in cerebral and/or whole body metabolic activity.[20] Subsequently, barbiturates were shown to minimize the metabolic signs of ischemia in animals subjected to severe hypotension and/or hypoxia[21–23] and to reduce the size of the infarct resulting from the experimental occlusion of the common carotid and/or middle cerebral artery.[24,25] However, in contrast to the consistently beneficial effects of barbiturates in cases of hypoxia, hypoperfusion, and/or focal cerebral ischemia, the role of these drugs in *total global* cerebral ischemia remains controversial. In 1964, Wright and Ames[14] showed that intracarotid pentobarbital given just before occlusion of the carotid and vertebral arteries improved survival in cats. However, it is unclear whether ischemia was truly complete, and no details were provided concerning neurologic morbidity. In 1966, Goldstein *et al.*[26] produced complete ischemia by cross-clamping the ascending aorta for periods of 8–12 min and noted that animals operated on under pentobarbital anesthesia did better than those receiving only procaine infiltration. Unfortunately, immobilization without general anesthesia may result in an altered cerebral metabolism in animals,[27] and, in 1978, Steen *et al.* were unable to reproduce these findings in dogs made analgesic with nitrous oxide (with or without added pentobarbital).[4] Therefore, the value of barbiturate treatment started *prior* to an episode of complete ischemia remains unproven. In 1978, Bleyaert *et al.* suggested that large doses of thiopental (up to 120 mg/kg) given to primates as late as one hour *after* a 16-min period of ischemia could dramatically improve neurologic function *among survivors*.[1] Serious criticisms have been raised concerning the model used to produce ischemia, and certain aspects of post-resuscitation care.[2] Careful examination of the model indicates that the ischemia may not have been complete, and that the duration of ischemia was possibly variable. Furthermore, thiopental-treated monkeys received prolonged post-ischemic ICU support while "control" monkeys did not. Interpretation of their results is further complicated by the inability of investigators from the same institution to reproduce these findings.[28] An additional study by Snyder *et al.*[3] failed to confirm the therapeutic benefits of thiopental (in dogs), although their results may have been biased by a failure to provide post-ischemic supportive therapy, as well as the use of a complex cerebral insult (asphyxia leading to circulatory arrest). Thus, the utility of barbiturates given following a period of severe global ischemia is not proven.

Our results are complex and can perhaps be subjected to various interpretations. Part of the difficulty stems from the fact that a given period of VF did *not* yield a uniform group of animals, but instead produced at least two distinct subgroups. These could be distinguished by their post-resuscitation EEG patterns. In terms of the neurologic *function* of survivors (assessed by NDS), thiopental therapy had no detectable effect, even if the groups are subdivided according to EEG recovery patterns (*e.g.*, controls with "normal" EEGs *vs.* treated cats with "normal" EEG). This is clearly different from the results of Bleyaert *et al.*[1] although comparable to that of Gisvold *et al.*[28] However, this approach does not fully describe the data. Both of these authors discarded dying animals from their data and did not evaluate either the causes of death nor make any extensive mention of electroencephalographic activity in the post-arrest period. As noted, our arrests yielded at least two populations of cats, and therapy clearly altered the distribution of animals between these groups ("normal" *vs.* "abnormal" EEG). Thirty-eight per cent of controls developed the unusual, repetitive rhythmic high-frequency EEG activity we have called "abnormal," 10 of these animals (10/16) eventually died from neurologic causes. By contrast, there were only three treated animals (12 per cent) demonstrating such abnormal EEG events, and there were no neurologic deaths. The incidence of abnormal EEGs and the incidence of neurologic deaths (expressed as a fraction of the total deaths) were clearly reduced by therapy. The change in *overall* mortality did not reach statistical significance although this would probably have occurred with a slightly larger experimental population.

These findings suggest that the thiopental-mediated reduction in neurologic mortality is related to the suppression of the described "abnormal" EEG event, although it is possible that the effects of therapy on the EEG are parallel, but unrelated to, a drug effect on some other undefined factor. We have been extremely cautious in labeling the observed "abnormal" EEGs. However, one possibility is that this represents seizure activity. Our

caution stems from the fact that the electrical patterns do not resemble any previously described form of seizure, and we could not determine if there were accompanying motor signs (as a result of the use of pancuronium). It is possible that the ischemic insult altered the electroencephalographic appearance of a seizure, possibly as a result of decreased cortical excitability. For example, Goor *et al.*[29] were able to convert typical electroencephalographic epileptic discharges (induced in cats by intramuscular penicillin) into rhythmic spindles by either hypoxia or by direct suppression of cortical excitability using topical KCl. Support for the "seizure" theory also stems from other studies in our laboratory (unpublished) showing that the "abnormal" EEG patterns could be suppressed by other anticonvulsants (diazepam, phenytoin) and could be evoked in post-arrest cats by the injection of small doses of pentylenetetrazol. Furthermore, four cats with this "abnormal" EEG pattern went on to develop (and die from) obvious seizures in the post-ICU period, and repetitive tremors were commonly seen in other "abnormal" animals following reversal of paralysis. The fact that such activity has not been reported previously may be species-related, or may be due to the common use of barbiturate anesthesia or the presence of halothane at the time of the insult. There have also been relatively few careful descriptions of the *evolution* of post-arrest encephalograms. Since the events seen by us were transient (rarely lasting more than 30 min) they may also have been missed by other workers.

Post-ischemic seizures are commonly seen in the clinical setting[30,31] and are associated with both an increased mortality[30] and neurologic morbidity.[31] Furthermore, laboratory studies have indicated that seizure suppression can improve outcome in gerbils subjected to temporary unilateral carotid occlusion.[32] Post-ischemic therapy with phenytoin has also been reported to alter outcome following global ischemia, although there are no descriptions of EEG activity.[33] The beneficial effects of thiopental noted in our study may therefore have been the result of the drug's anticonvulsant activity. These observations have several implications. They suggest that drugs with less cardiovascular and respiratory depressant effects (*e.g.*, diazepam, phenytoin) may prove equally useful. More importantly, however, it indicates that certain definable events in the post-arrest period can contribute to the ultimate outcome, and that such events can be altered (*e.g.*, seizure suppression). Such an observation supports the belief of many clinicians that something can be done to aid a patient's resuscitation from a severe ischemic insult. Perhaps continuous EEG monitoring and aggressive seizure suppression (or seizure prophylaxis with a drug less toxic than thiopental) may indeed be of value.

In summary, our results can be considered as both supporting and rejecting the use of barbiturates following a global cerebral ischemic event. Treatment reduced the incidence of neurologic deaths, and this apparently was related to suppression of a unique post-resuscitation electroencephalographic event (? seizures). However, therapy failed to improve the neurologic function of survivors beyond that seen in controls. When thiopental *failed* to suppress the observed EEG activity, animals survived but in a severely damaged state (NDS > 60). The work clearly does *not* support the "routine" use of large doses of barbiturates in post-arrest patients. It might, however, be considered as support for aggressive intervention in certain patients if such seizures or EEG indicators can be identified in humans, particularly in the early post-resuscitation period.

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APPENDIX

Thiopental Assay

The gas chromatographic assay for plasma thiopental was developed in the laboratory of one of the investigators (R.D.), and the methodologic details will be published shortly. They are available upon request. In summary, frozen, heparinized plasma was thawed, and 0.5- or 0.25-ml aliquots were extracted with benzene (after the addition of secobarbital as an internal standard). The extract was then dried, and the residue reconstituted in isopropyl alcohol. Three-microliter samples were chromatographed on a Hewlett-Packard HP 5710A GC®, using a nitrogen-phosphorus flame ionization detector. Peak areas were obtained with a HP 3385A integrator.