Barbiturate effects on acute experimental intracranial hypertension

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Acute intracranial hypertension was induced in cats by progressive inflation of an epidural balloon. Changes in intracranial pressure (ICP), mean arterial pressure (MAP), cerebral perfusion pressure (CPP), heart rate (HR), electroencephalogram (EEG), and pupil size were studied in untreated animals and in animals that had received barbiturates at different stages during the experiment. In animals pretreated with barbiturates, the increase in ICP during balloon expansion was significantly less than in untreated animals (p < 0.001). The CPP, initially higher in untreated animals, was not significantly different (p < 0.05) as the mass lesion pressure-volume curve exceeded the inflection point. In the postdeflation period, the untreated animals developed a significant increase in ICP, whereas, in the barbiturate-pretreated group, the ICP returned to preinflation values, suggesting a protective effect of barbiturates against postcompression brain swelling. Barbiturates affected ICP and CPP differently in animals with intracranial hypertension due to the presence of an epidural balloon that was maintained inflated compared to those with postdeflation brain swelling. In the latter group, pentobarbital reduced ICP (p < 0.05) without significantly decreasing the CPP, whereas, in the mass lesion group, barbiturates failed to reduce the ICP and caused a deterioration in CPP (p < 0.025). Brain gross pathological changes were significantly less in the pretreated animals as compared with all other groups. The results suggest that if barbiturate treatment is to have therapeutic value, the timing of the therapy and the criteria for its initiation should be determined.

KEY WORDS • intracranial hypertension • mass lesion pressure-volume curve • brain swelling • barbiturate • acute head injury • intracranial mass lesion

Experimental studies using models of cerebral infarction or anoxia,3,4,15,20,33,37,50,55 vasogenic cold-induced edema,7,16 and trauma21 support the effectiveness of barbiturates in reducing raised intracranial pressure (ICP), and demonstrate a protective effect on the brain. In the clinical setting, barbiturate coma was initially introduced to protect the brain from ischemic and anoxic insults1,5,18 and has been extended to treat severe head injury associated with elevated ICP.26,27,29,30-32 Of particular interest is the reported experience28,47 in which high-dose barbiturate therapy has led to the control and normalization of ICP in three-fourths of patients exhibiting resistant intracranial hypertension.

Despite this experimental and clinical evidence, neurosurgeons are cautious in advocating the widespread use of barbiturate therapy.6,28,39,40,44 The indication relied on for initiation of this treatment has been the presence of elevated ICP not controlled by so-called "standard measures." Two important questions arise: is the treatment initiated too late to avoid irreversible brain damage? and should intractable elevation of ICP, irrespective of its cause, be the sole indication for this treatment? We therefore undertook a study to evaluate the acute response to barbiturates when given before, during, or after epidural brain compression. Comparison of these results may yield clinical clues regarding the timing and the indications of barbiturate therapy.

Materials and Methods

Preparation of Animals

Forty adult cats of either sex, weighing from 3.2 to 4.6 kg, were studied. A cephalic vein was catheterized for administration of medications and maintenance solution of saline. Prior to anesthesia, 0.2 mg of atropine was given intramuscularly. Anesthesia was...
induced in all animals with a single dose of 1% methohexital sodium (Brevital). Each cat was intubated, paralyzed with 1.5 mg/kg of gallamine triethiodide (Flaxedil), and then maintained on controlled ventilation* with a mixture of nitrous oxide and oxygen adjusted to ensure arterial blood gases constant at normal levels. Additional doses of gallamine (1 mg/kg) were given at 30-minute intervals. Before the start of the operative manipulations, surgical sites and external auditory canals were infiltrated with 1% lidocaine (Xylocaine), which was repeated intermittently throughout the duration of the experiment. A Teflon catheter was placed into the abdominal aorta via the femoral artery to monitor systemic arterial pressure and for periodic sampling of blood gases. With the animals in the sphinx position and head elevated and immobilized in the stereotaxic frame, the scalp and temporalis muscles were reflected from the skull. Using a high-speed drill, appropriate holes were made for placement of: 1) a silicone rubber catheter into the left lateral ventricle to monitor ICP; 2) a Fogarty arterial embolectomy catheter† into the epidural space over the right temporal lobe to induce brain compression; and 3) five screw electrodes with their tips in contact with the dura to obtain bipolar frontoparietal electroencephalograms (EEG) from both sides. When necessary, the burr holes were sealed with dental acrylic. A rectal probe was placed, and body temperature was kept at 37 ± 1°C by use of a heating blanket. Autopsies were subsequently performed on all animals for confirmation of catheter placement and gross pathology examination of the brain.

Protocol

All animals received the same brain compression. Using a Harvard infusion pump,‡ the epidural Fogarty balloon was gradually inflated at a constant rate of 0.1 ml/min until a 1.5-ml volume was obtained (1.5 ml in 15 minutes) which is approximately 8% to 10% of the cat's intracranial volume. The balloon was maintained at the constant volume of 1.5 ml for 15 minutes after which the balloon was deflated. Monitoring was continued for 2 to 3 hours before the animal was sacrificed.

A 45- to 90-minute period of baseline recordings prior to inflation allowed for stabilization of parameters and an awake appearance of the EEG. The animals were then randomly divided into four groups. The first group (control group) consisted of 20 cats that received no additional treatment until the postdeflation period. The second group (pretreated group) consisted of 10 cats and differed from the control group in that they received an initial dose (40 mg/kg) of pentobarbital (Nembutal) by slow intravenous infusion 15 minutes prior to balloon inflation. Additional doses were given hourly to maintain an almost flat or silent EEG. The third group (brain swelling group) contained 14 of the 20 cats in the control group that showed increased ICP above 35 mm Hg in the postdeflation period. Nine of these received an initial dose of barbiturate (40 mg/kg) at this time, while the other five cats served as controls. The last group (mass lesion group) consisted of 10 cats and differed from the other groups in that the balloon was not deflated once 1.5-ml volume was reached. Then, after 15 minutes, seven cats received the same initial dose of barbiturates as given in Groups 2 and 3, while three cats were maintained for control.

Data Collection and Analysis

The ICP, mean arterial pressure (MAP), heart rate (HR), respiration, and EEG were continuously monitored on the chart paper of a 6-channel analogue recorder.§ The MAP and ICP were measured by means of Statham strain gauge transducers¶ via Gould coupler couplers.§ At the end of the experiment the drift of the ICP transducer was less than ± 2 mm Hg. The HR was recorded via Gould Bio-Tach coupler§ and the breathing by a temperature probe* inserted into the tracheal tube via a telethermometer and a Gould universal probe.§ The two-channel EEG was recorded via a Gould EEG coupler§ at a sensitivity of 10 µV/division filtered between 0.2 and 50 Hz. In addition, any modifications of the pupils were carefully noted. The EEG, for practical purposes, was divided into four patterns: 1) normal, 2) abnormal, 3) flat, and 4) silent. The criteria for these groups were arbitrarily defined as "abnormal" when the amplitude was decreased by 30% to 70% of normal, usually accompanied by slowing of the frequency, and "flat"

* Harvard animal ventilator pump manufactured by the Harvard Apparatus Co., 150 Dover Road, Millis, Massachusetts.
† Fogarty arterial embolectomy catheter manufactured by Edwards Laboratories, 1722 Red Hill Avenue, Santa Ana, California.
‡ Harvard infusion pump manufactured by Harvard Apparatus Co., 150 Dover Road, Millis, Massachusetts.
§ Brush mark 260 analogue recorder and Gould couplers manufactured by Gould, Inc., Instruments Division, 3631 Perkins Avenue, Cleveland, Ohio.
¶ Statham 23dB, manufactured by Statham Instruments, 2230 Statham Boulevard, Oxford Mills, Massachusetts.
* YSI temperature probe 511 manufactured by Yellow Springs Instruments Inc., Yellow Springs, Ohio.
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when the amplitude was decreased to less than 30% of normal. Suppression bursts and/or epileptic discharges were included in both flat and silent patterns.

Data for all animals were entered at 1-minute intervals for the analysis of inflation and compensatory phases, and at 2- or 5-minute intervals thereafter. Each pressure was expressed as mean: diastolic plus 1/3 pulse pressure. For each animal, a plot was constructed of ICP and MAP versus balloon volume during the brain compression and versus time thereafter. The cerebral perfusion pressure (CPP) was calculated as the difference between MAP and ICP. The inflection or breakpoint of the mass lesion pressure-volume curve was identified using the criteria of Sullivan, et al., as the intersection point of the two lines representing the slopes of the two major parts of the curve. Means, standard deviations, and t-test analysis were calculated as usual.

Results

Mass Lesion Pressure-Volume Curve

The data obtained from the barbiturate-pretreated animals were compared with those obtained from the untreated animals. For both groups, the plot of ICP versus balloon volume (Fig. 1) followed the classical configuration of an initial relatively flat segment, an inflection point, and a final steep segment. In the baseline observations, prior to balloon inflation, the ICP was 9 ± 4.1 mm Hg (standard deviation) in the untreated and 6 ± 2.1 mm Hg in the barbiturate-pretreated animals. The inflection point occurred at 0.6 ± 0.3 ml balloon volume in the untreated and 0.8 ± 0.2 ml balloon volume in the pretreated animals. The ICP at this point was 16.0 ± 5.5 mm Hg in the untreated, and 14 ± 5.1 mm Hg in the barbiturate-pretreated animals. The differences in the ICP and inflection points of the two groups were not significant. With balloon volume increasing beyond 1.0 ml, the magnitude of the elevation in ICP became significantly greater in the untreated group compared with the barbiturate-pretreated group (p < 0.05). At the cessation of balloon expansion with an equivalent volume (1.5 ml) loaded in the epidural space in the same inflation time (15 minutes), the ICP was 99.0 ± 4.8 mm Hg in the untreated group, and 60 ± 3.9 mm Hg in the barbiturate-pretreated group (p < 0.01). Barbiturates significantly decreased the rate of the rise of ICP, modifying the slope of the steep segment of the mass lesion pressure-volume curve such that the shape became flatter as the ICP rose.

The MAP in the baseline observation (before balloon inflation) was 105 ± 3.0 mm Hg in the barbiturate-pretreated group and 140 ± 9.0 mm Hg in the untreated group, the latter of which included three spontaneously hypertensive cats (MAP > 150 mm Hg). Thus, prior to balloon inflation, because of the significant difference in MAP with almost equal ICP (< 10 mm Hg) in both groups, the CPP was significantly greater in the untreated group (p < 0.01). During balloon inflation, there was no variation in the MAP of the barbiturate-pretreated cats, whereas the MAP started to rise in the untreated cats when a balloon volume of 0.9 ml was reached. By the end of the inflation period, the mean increase in MAP in all the untreated animals was +16 mm Hg, but a large

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Fig. 1. Intracranial mass lesion pressure-volume curve and sequential changes in mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) for untreated and barbiturate-pretreated animals. The arrows indicate the inflection point of the intracranial pressure (ICP) versus balloon volume curve. The data derived from all cats are condensed to show mean and standard deviation. Values contained between two asterisks are significantly different (p values at least < 0.05) from control.
The decrease in CPP in the barbiturate-treated cats during balloon inflation was dependent only upon the change in ICP. Because in the untreated animals the ICP rose more than the arterial pressure, there was a noticeable decrease in CPP. When the values of CPP are compared, there was no difference at a level of significance of \( p < 0.05 \) between the two groups after a 0.9-ml balloon volume was reached. The changes in HR during balloon inflation and throughout the remainder of the experiment were not significant.

After cessation of inflation and while the injected volume was maintained, a gradual decline of ICP was observed in both the barbiturate-pretreated and the untreated animals (Fig. 2). This reduction in ICP began immediately, but continued at a different rate and magnitude in the two groups. In the untreated cats, the mean ICP, which had risen to 99 mm Hg at 1.5-ml balloon volume, fell to 54 ± 5.1 mm Hg in 8 minutes and then stabilized. In the barbiturate-pretreated animals, the ICP exhibited a more limited and gradual decline from 60 mm Hg to 41 mm Hg over 15 minutes. Although the ICP values appeared higher in the untreated group, this difference was not significant after 6 minutes, due to spontaneous compensation. The MAP remained stable in the barbiturate-pre-
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which this response was present, the EEG became flat and the pupils became fixed and dilated. In the compensatory phase, the EEG showed improvement proportional to the amount of time the tracing was flat in the inflation period.

Postcompression Phase

Immediately after balloon deflation, the ICP fell to 0 ± 5 mm Hg in both the barbiturate-pretreated and the untreated groups. It then slowly began to rise but remained at 15 mm Hg in all the barbiturate-pretreated animals. In the untreated animals, there was a more rapid and greater increase in ICP, reaching 45 mm Hg in 15 minutes, where it remained (Figs. 2 and 3). At the end of the observation time, the mean ICP was 12 ± 3 mm Hg in the barbiturate group, essentially the same as the baseline value measured prior to balloon inflation. At this time, the ICP in untreated animals was 40 ± 12 mm Hg, not significantly different from the predeflation value (51 mm Hg) but significantly higher than both the baseline preinflation value of the same group (p < 0.001) and the postdeflation value of the treated group (p < 0.01). The pattern of the ICP response to deflation was homogeneous in the barbiturate group in that no cat exhibited a significant rise in ICP. In the untreated group however, the ICP response of each cat was variable, with values widely scattered from the mean (SD ± 17 mm Hg). Six of the 20 cats never showed ICP above 35 mm Hg. Immediately after balloon deflation, the untreated group showed a transient fall in MAP paralleling the decrease in ICP. This was followed by a tendency of the MAP toward the predeflation value, while in the barbiturate group the arterial pressure remained unchanged.

Thus, balloon deflation resulted in a significant improvement of CPP in the barbiturate group. If we look at the cats of the untreated group individually, however, five cats in which the ICP never rose above 35 mm Hg also showed a significant improvement in CPP. Balloon deflation induced a normalization of the pupillary abnormalities in all but two of the pretreated group, and these maintained ipsilateral dilatation. In the untreated animals, there was no significant improvement in the pupillary abnormalities. Those cats that exhibited a postdeflation rise in ICP maintained bilateral fixed and dilated pupils. In cats in which the ICP remained at less than 35 mm

Fig. 3. Recordings of intracranial pressure (ICP) and systemic arterial pressure (SAP) at the time of balloon deflation from a barbiturate pretreated cat (upper) and an untreated cat (lower).
Hg, there was some improvement in the pupillary abnormalities and, rarely, dramatic reversal of the dilation.

**Brain Swelling and Mass Lesion**

In the postdeflation period, 14 of the 20 cats in the untreated group developed sustained intracranial hypertension (greater than 35 mm Hg). These animals were considered to have substantial brain swelling (the brain swelling group), and nine were treated with pentobarbital while the other five were used as controls. The results are contrasted to those obtained from the mass lesion group, in which barbiturate-treated animals were compared to untreated animals while the epidural balloon was maintained inflated (Figs. 4, 5, and 6). The barbiturate administration resulted in a simultaneous sharp decline in ICP and MAP in all animals of both groups. The effect was of short duration but of considerable magnitude, and paralleled a temporary improvement in pupillary dilatation in the mass lesion group. The decrease in MAP was greater than the reduction in ICP, hence the CPP showed a deterioration in both groups. This effect, initially similar in both the groups, began to differ at 10 minutes. After 10 minutes, the ICP began to increase, attaining the pretreatment values in the mass lesion group but remaining 30% lower than the pretreatment values in the brain swelling group. Paired t-test analysis revealed that barbiturates significantly (p < 0.05) reduced the ICP in the brain swelling group throughout the entire experiment. In contrast, similar analysis of the mass lesion group showed that after the initial decrease, the ICP was not significantly affected by barbiturate therapy. Thus,
barbiturates favorably affected the ICP only in the brain swelling group. In order to substantiate these results, in several cats of the brain swelling group, monitoring continued for 3 more hours. During this time, the decrease in ICP continued to be significant in the barbiturate group, although the untreated cats tended to show a slow decline in ICP. When monitoring was continued in the mass lesion group, the effect of barbiturates on ICP was not significant compared with both the control and the pretreated group values.

After the initial decrease in CPP, concurrent with the administration of barbiturates, the CPP continued to deteriorate in the mass lesion group and remained significantly decreased as compared with the untreated (p < 0.025). In the brain swelling group, however, the decrease in CPP following the barbiturate administration was not significant compared to the untreated cats (−15 mm Hg). Barbiturate treatment in the brain swelling group resulted in a significant decrease of ICP without a deterioration in CPP. In the mass lesion group, however, barbiturate treatment not only failed to reduce the ICP but also markedly reduced the CPP.

**Brain Pathology**

All animals demonstrated a focal depression over the right temporal lobe (at the site of balloon inflation) with evidence of subarachnoid and subpial hemorrhage and, occasionally, minor local contusion. In five animals, the dura was violated. Sections through the brain revealed no intraparenchymal or extraparenchymal hematoma. Brain swelling, most often in the right hemisphere, and midline shift were observed in all cats but were more pronounced in the untreated group. Seven of the 10 cats in the pretreated group demonstrated no additional gross pathological changes. The other three showed transtentorial herniation of various degrees and minor changes, consisting of scattered petechiae in the posterior thalamic region and in the midbrain. The majority of the other 30 cats showed transtentorial herniation (28 cats), scattered petechiae or hemorrhages in the posterior thalamic region (22 cats), and midbrain hemorrhages or necrosis (20 cats). The brain appeared nearly normal in five cats, three of which were pretreated with barbiturates.

**Discussion**

The results of our study concerning the effects of barbiturates on intracranial hypertension induced by epidural brain compression show that pretreatment with barbiturates results in a lesser increase in ICP when equivalent volumes are loaded in the same craniospinal compartment at the same rate. These barbiturate-pretreated brains sustain the same compression as in untreated cats, but escape postcompression brain swelling. Barbiturates given during postcompression brain swelling alleviated the intracranial hypertension without decreasing CPP, whereas barbiturates given in the presence of an expanding mass lesion failed to reduce the ICP and decreased the CPP.

The primary mechanism of barbiturate action has not been established. Its effect has been ascribed to a

![Fig. 6. Recordings of the response of intracranial pressure (ICP) and systemic arterial pressure (SAP) to barbiturates in a cat from the brain swelling group (upper) and a cat from the mass lesion group (lower).](https://example.com/image)
reduction of cerebral metabolic rate, to a decrease in the functional activity of brain, and to an inhibition of the brain-stem neurogenic mechanism for vasoparalysis. A sealing effect on membranes and a scavenging of free oxygen radicals are also proposed. Whatever the mechanism, the result is an increase of cerebral vascular resistance, with a decrease in cerebral blood flow and cerebral blood volume. Our data show that barbiturates modify the ICP versus epidural mass volume curve by inducing a flattening and a shift to the right.

Because the elevation of ICP is related to the exhaustion of craniospinal volume reserves, the most likely explanation for the observed modification of the ICP versus balloon volume curve is the increase of these reserves. The decrease in cerebral blood volume best accounts for improvement in the compensatory reserve, which allowed our barbiturate-tumor animals to better accept the intracranial mass lesion. By reduction of blood volume, barbiturates postpone the exhaustion of the compensatory reserve, thereby altering the steep segment of the pressure-volume curve. The same mechanism can be invoked to explain the ICP decrease when barbiturates were given during postdeflation brain swelling but not when given in the presence of an expanding mass lesion. In the former instance, the source of the intracranial hypertension is ischemic vasoparalysis associated with cerebral vasodilatation, which leaves the brain unprotected from the adverse effects of systemic hypertension on ICP. In this setting, barbiturates induce a pharmacological internal decompression by decreasing cerebral blood volume via their vasoconstrictive properties. Their systemic hypotensive effect cooperates to further decrease the ICP. In the mass lesion group, however, the intracranial hypertension results mainly from the expanding mass lesion. The barbiturates are given at a time when the cerebral blood volume has presumably already been expelled as part of the spontaneous early compensatory response and before the ICP has risen to the vasopressor threshold. Therefore, at this time only a minor reduction in ICP can be expected by the cerebral vasoconstrictor effect of the barbiturates. Their systemic effects, however, combined with no parallel decrease in ICP, resulted in severe deterioration of the CPP.

The most interesting observation in this series is the reversal of the intracranial hypertension with balloon deflation in the barbiturate-pretreated animals, while the untreated animals exhibited postdeflation brain swelling, as evidenced by elevated ICP. The fact that there was no statistical difference in CPP between treated and untreated animals at the end of inflation indicates that the brains of both groups were exposed to the same degree of ischemia. Therefore, the escape from postcompression brain swelling seen in the treated group can be attributed to barbiturate protection against cerebral ischemia. A decrease in cerebral metabolic rate cannot fully explain the protective effects of barbiturates seen in our series, as both groups exhibited silent EEG's consistent with a marked decrease in brain metabolism. Furthermore, the model used in our study introduces brain distortion; thus, other factors as well as ischemia are in operation, and the mechanism of the barbiturate protection becomes more complex. Barbiturates, by maintaining lower levels of ICP, prevent brain-stem compression and distortion which could result in the vasopressor response and eventual vasoparalysis. Their systemic effect of lowering arterial blood pressure, along with the consequent fall in the intravascular pressure across the blood-brain barrier, reduce the formation of brain edema as proposed by Matsumoto, et al. The decrease in cerebral blood volume, as originally suggested by Shapiro, et al., appears to be the primary mechanism that best explains the beneficial effect of barbiturates observed in our model.

The results obtained when barbiturates were given at different stages of our experiment show that a greater protective effect occurred when the therapy preceded brain compression: treated animals exhibited not only a significant reduction of ICP but also a diminution of ocular signs and brain lesions. After brain compression had occurred, barbiturates favorably influenced only the ICP parameter, without any demonstrable amelioration in pupillary abnormalities and brain pathology. Furthermore, barbiturates appeared potentially dangerous in the presence of an expanding mass lesion because of their adverse effect on CPP.

Although these results are derived from acute animal experiments, the possibility arises that similar patterns of response to barbiturate therapy may occur in head-injured humans. The management of intracranial hypertension must not only control the ICP but also improve the CPP and avoid the brain shift and distortion. Its true efficacy is best judged by the final outcome, reflecting the actual brain damage. Our findings of a significant reduction in the number of pupillary abnormalities, and in the severity of the brain lesions seen in the barbiturate-pretreated group are evidence supporting the effectiveness of barbiturates in alleviating the brain damage caused by an acutely expanding intracranial mass.

From this study, we conclude that the efficacy of
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barbiturates in the treatment of acute intracranial hypertension is related to the timing of the initiation of therapy and to the mechanism by which the ICP has become elevated.

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