Protection against experimental ischemic spinal cord injury

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The authors have studied the protection against ischemic damage to rabbit spinal cord by pretreatment with agents that block neuronal activity and directly or indirectly reduce tissue metabolism. Hypothermia, thiopental, magnesium, lidocaine, and naloxone were used to pretreat the spinal cord prior to ischemia. Hypothermia and thiopental provided comparable protection: they each increased the duration of ischemia required to produce neurological deficits in 50% of the animals from 26 to 41 minutes. They also increased from 10 to 30 minutes the time that the postsynaptic waves of the spinal somatosensory evoked potential (SSEP) could be absent and the animal still have neurological recovery. Hypothermia and thiopental, when used together, increased the duration of ischemia required to produce neurological deficits to 57 minutes in 50% of the animals. Naloxone increased the duration of ischemia required to produce neurological deficits to 36 minutes in 50% of the animals, and increased to 20 minutes the time that the postsynaptic waves of the SSEP could be absent and the animal still have neurological recovery. Magnesium pretreatment improved neurological outcome, possibly by improving collateral circulation as the SSEP did not fail completely during aortic occlusion in all animals. Lidocaine was not beneficial, perhaps because of the prolonged hypotension that resulted.

KEY WORDS • spinal cord ischemia • thiopental • hypothermia • magnesium • lidocaine • naloxone • rabbit

One strategy for increasing the duration of the ischemia that a tissue will tolerate is to decrease the metabolic requirements of the tissue prior to inducing ischemia. If functions of the tissue that are not necessary for survival of the organism during the period of ischemia are suppressed, then energy supplies limited by ischemia might be used for maintenance of tissue integrity, and smaller amounts of toxic products of ischemic metabolism might be produced.

Agents that reduce cerebral metabolism may have at least two different mechanisms of action: direct, by suppression of mitochondrial metabolism; and indirect, by blocking neuronal discharge and synaptic transmission. Some agents may have both or multiple mechanisms of action. Hypothermia results in a generalized reduction of all energy-consuming functions in proportion to the decrease in temperature. Temperatures of 28° to 30°C decrease the central nervous system (CNS) metabolic rate of oxygen (CMRO₂) to 60% of normal and have protective effects in experimental ischemia.¹¹ Barbiturates also depress mitochondrial metabolism and block synaptic transmission. Barbiturates reduce cerebral metabolic rate in proportion to the suppression of the electroencephalogram (EEG), and the CMRO₂ may fall to 58% of normal when the EEG is isoelectric.¹² Magnesium ions block neurotransmitter release at synaptic junctions and will thereby decrease the activity and metabolic rate of the postsynaptic cell. Local anesthetic agents, such as lidocaine, are thought to block membrane channels for ionic fluxes including leak fluxes, resulting in less neuronal activity and energy expenditure. A reduction in CMRO₂ to 65% of normal has been measured with lidocaine.² Barbiturates, magnesium, and lidocaine have been reported to improve neurological outcome from experimental ischemia and injury.¹,³,⁵,⁹,¹¹,¹³

Opiate receptor antagonists such as naltrexone decrease metabolic rate in specific regions of the CNS such as the hypothalamus and pons, although global CMRO₂ may be unchanged.⁶ Endogenous opiates appear to have a role in the CNS response to injury, and naloxone has been reported to have protective effects in some models of ischemia and injury.⁵,⁶

The first purpose of this study was to compare the
protective effects of hypothermia, barbiturates, magnesium, lidocaine, and naloxone during experimental CNS ischemia. The second purpose was to examine the protective effects of combinations of agents that appear to have different mechanisms of action on CNS activity.

Materials and Methods

Animal Preparation

One hundred and thirty-three New Zealand albino rabbits, weighing 3.5 to 4.5 kg each (mean 4.0 kg), were anesthetized with intravenous methohexital sodium, up to 10 mg/kg total dose. They were intubated and ventilated with supplemental oxygen using a volume-cycled ventilator. The tidal volume and rate were adjusted to maintain normal arterial blood gases. Anesthesia was maintained with intramuscular ketamine in an initial dose of 25 mg/kg, followed by 20 mg/kg/hr. At least 90 minutes elapsed between the administration of methohexital and the onset of spinal cord ischemia.

Ischemia Production and SSEP Recording

The methods of producing spinal cord ischemia and of using spinal somatosensory evoked potentials (SSEP's) as a monitor and predictor of neurological function have been described previously. A modified No. 5 French pediatric Swan-Ganz catheter with pressure-monitoring ports proximal and distal to the balloon was inserted through the right femoral artery into the abdominal aorta. The catheter was positioned so that the tip was below the origin of the left renal artery. After other preparations described below, ischemia of the spinal cord was produced by inflating the balloon with 0.4 ml of air. The port distal to the balloon was used for drawing arterial blood gases and monitoring systemic blood pressure; the port proximal to the balloon was used to demonstrate that the occlusion remained complete, and in some cases to infuse drugs directly into the blood vessels supplying the spinal cord. When the desired period of ischemia had been achieved, the balloon was deflated and the catheter withdrawn so that only 2 to 3 cm of the catheter remained in the femoral artery. Heparin, 500 U, was given intravenously prior to femoral catheterization, and 100 to 150 U/hr was given intravenously as long as the catheter remained in place. Systemic metabolic acidosis, measured after deflation of the balloon, was corrected with intravenous sodium bicarbonate.

To record the SSEP's, the left sciatic nerve was exposed just proximal to its bifurcation and a cuff bipolar stimulating electrode was placed around the nerve. The leg-muscle twitch threshold was less than 0.05 mA with a pulse duration of 0.1 msec. Two 0.01-in. diameter Teflon-coated silver wire recording electrodes were inserted just lateral to the spinous processes of the L-5 and L-6 vertebrae so that the tips of the wires rested on the laminae and were sutured in place.

The SSEP's were recorded prior to ischemia, at intervals during ischemia and reperfusion, and at 48 hours after ischemia. The stimuli were square-wave pulses of 0.1-msec duration and 0.5-mA intensity delivered at 3.1 Hz. The potentials were recorded in a bipolar fashion from L-6 to L-5 and were displayed so that a negative potential at L-6 with respect to L-5 was an upgoing deflection. Recordings were made using an Apple Ile computer as the signal averager. The signal was amplified 30,000 times and 50 repetitions were averaged.

Postoperative Care and Assessment

When the animals awakened from anesthesia after the study, they were returned to their cages. They were given normal saline by intraperitoneal injections until they were able to drink adequately, and they received 25 mg/kg of intramuscular cephalothin every 12 hours. The Credé maneuver was used to empty the bladders of the paraplegic animals at least twice daily. Neurological function of the hindlimbs was graded at 24 and 48 hours using the following scale: normal (able to hop normally), weak (paretic, spastic hindlimbs, usually abnormal sensation, variable bladder and bowel function), and paralyzed (flaccid paraplegia with absence of sensation and bowel and bladder function).

After the final neurological examination and SSEP recording, the rabbits were anesthetized and sacrificed by left cardiac perfusion with a buffered solution of 4% paraformaldehyde and 0.5% glutaraldehyde. The spinal cord was removed and the portion caudal to the thoracic cord 1 cm above the lumbar enlargement was cut into cross sections 3 to 5 mm thick, which then were embedded in paraffin. Hematoxylin and eosin-stained sections were prepared and examined for neuronal damage, rarefaction, cavitation, and reaction to injury. Measurements of the total area, gray matter area, and lesion area were made on each section using a computer-assisted image analysis system. The degree of injury for each animal was expressed as the percentage of gray matter destroyed in the single most damaged section.

Control SSEP's, SSEP's recorded during ischemia and reperfusion, and those recorded at 48 hours were compared by measuring the latency and amplitude (from the pretrauma baseline) of each component wave. The duration of ischemia required for the amplitude of each component wave to decrease by 50% (t50) was interpolated from the timed recordings during ischemia. The degree to which the SSEP components returned to their control values after ischemia was expressed by

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† Blood gas analyzer, Model 165/2, manufactured by Corning Scientific Products, Corning, New York.
‡ Swan-Ganz catheter manufactured by Edwards Laboratories, Santa Ana, California.
§ Apple Ile signal averager manufactured by Metraco System, Houston, Texas.
calculating the amplitude of waves $N_3$, $N_4$, and $P_2$ as a percentage of their control values.

**Experimental Groups**

The animals were divided into eight groups: a control group (Group 1), five groups treated with individual agents (Groups 2 to 6), and two groups treated with combinations of agents (Groups 7 and 8).

**Group 1: Control Animals.** In the control group of 31 rabbits, individual animals underwent aortic occlusion for 15 (five rabbits), 25 (eight rabbits), 40 (eight rabbits), 50 (five rabbits), or 60 minutes (five rabbits) with no drug pretreatment.

**Group 2: Hypothermia.** Twenty-two animals were divided into two subgroups, which were treated with either systemic or local hypothermia. Five rabbits underwent aortic occlusion for 25 minutes after rectal temperature had been lowered to 30°C by external body cooling. The other 17 rabbits underwent aortic occlusion for 25 (six rabbits), 40 (six rabbits), or 50 minutes (five rabbits) after local cooling of the spinal cord by infusion of chilled (0° to 5°C) Krebs-Henseleit buffer solution through the Swan-Ganz catheter port proximal to the balloon. The buffer was infused at a rate of 20 ml/min for 7 minutes prior to inflation of the balloon and for the first 5 minutes of the period of ischemia, then at 8 ml/min for the rest of the ischemia time.

**Group 3: Thiopental.** Twenty-two rabbits were divided into two subgroups, which were treated with either systemic or local thiopental. Fifteen rabbits underwent aortic occlusion for 25 (five rabbits), 40 (four rabbits), or 50 minutes (six rabbits), 30 minutes after receiving thiopental, 30 mg/kg, through an ear vein. The seven other rabbits underwent aortic occlusion for 50 minutes, simultaneously with infusion of 30 mg thiopental, diluted to 20 ml with normal saline, through the Swan-Ganz catheter port proximal to the balloon. Four of these seven rabbits also received thiopental, 30 mg/kg, through an ear vein prior to inflation of the balloon.

**Group 4: Magnesium Ions.** Fourteen rabbits underwent aortic occlusion for 25 (five rabbits), 40 (six rabbits), or 50 minutes (three rabbits), 15 minutes after receiving magnesium sulfate, 100 mg/kg, through an ear vein.

**Group 5: Lidocaine.** Five rabbits underwent aortic occlusion for 25 minutes, 15 minutes after receiving lidocaine, 160 mg/kg, through an ear vein.

**Group 6: Naloxone.** Nine rabbits underwent aortic occlusion for 25 (four rabbits) or 40 minutes (five rabbits), 5 minutes after receiving naloxone, 2.5 mg/kg, through an ear vein. Naloxone was continued at 0.25 mg/kg/min during aortic occlusion and for the 1st hour after deflation of the balloon.

**Group 7: Thiopental and Naloxone.** Eight rabbits underwent aortic occlusion for 40 (four rabbits) or 50 minutes (four rabbits), 30 minutes after receiving thio-
blood pressure remained less than 90 mm Hg for a longer time during reperfusion in the animals that developed neurological deficits than in the animals that remained normal (5.4 ± 7.4 and 2.9 ± 3.5 minutes, respectively). Those with a normal outcome required only 0.8 ± 1.3 mEq of sodium bicarbonate to correct acidosis after reperfusion, whereas those that developed weakness or paralysis required 2.8 ± 2.4 mEq.

Table 1 compares the changes in pre-ischemia arterial blood gases and blood pressure that were present in the experimental groups to those in the control animals. Hypothermia resulted in no consistent change in blood pressure. Thiopental and lidocaine transiently decreased arterial blood pressure during infusion but, between the time of administration of the drugs and inflation of the balloon, the arterial blood pressure recovered. The systolic blood pressure of the animals pretreated with intravenous thiopental was actually higher than that of the control animals just prior to the onset of ischemia (121 ± 15 and 101 ± 15 mm Hg, respectively). Infusion of magnesium sulfate resulted in a prolonged hypotension that persisted until inflation of the balloon. In contrast, naloxone increased arterial pressure as it was being infused, and the systolic blood pressure following deflation of the balloon tended to fall further in animals pretreated with thiopental, but these differences were not significant.

Table 2 compares the changes in arterial blood pressure following deflation of the balloon tended to be less in animals that were hypothermic or that were pretreated with thiopental, but these differences were significant only in animals treated with local hypothermia by arterial infusion of cooled Krebs-Henseleit buffer before and during ischemia. Systolic blood pressure returned to at least 90 mm Hg more rapidly in animals pretreated with local hypothermia or intravenous thiopental than in control animals (0.1 ± 0.5, 1.1 ± 1.5, and 4.9 ± 6.4 minutes, respectively). The higher reperfusion pressures, hemodilution, and the buffering of lactic acid that resulted from the volume of Krebs-Henseleit buffer infused in the animals treated with local hypothermia might have contributed to the improved neurological outcome. However, infusion of similar volumes of Krebs-Henseleit buffer at body temperature produced no improvement in outcome, suggesting that the cooling effect was the most important factor. Following deflation of the balloon, blood pressure tended to fall further in animals pretreated with lidocaine or magnesium, and to return to a systolic pressure of 90 mm Hg more slowly with lidocaine (16.2 ± 22.2 minutes compared to 4.9 ± 6.4 minutes in control animals).

**SSEP's During Ischemia and Reperfusion**

Rabbit SSEP's have been described in detail in a previous publication. Briefly, the components of the SSEP recorded from L-6 to L-5 normally consisted of an initial positive wave, four negative waves, and a late long-duration positive wave. The first two negative waves, N_1 and N_2, were present even at low stimulus intensities and remained when stimulus frequencies were high, suggesting a presynaptic origin. The N_1 and N_2 waves were relatively resistant to ischemia and recovery and blood gases that occurred during reperfusion in the experimental and control groups. The fall in blood pressure following deflation of the balloon tended to be less in animals that were hypothermic or that were pretreated with thiopental, but these differences were significant only in animals treated with local hypothermia by arterial infusion of cooled Krebs-Henseleit buffer before and during ischemia. Systolic blood pressure returned to at least 90 mm Hg more rapidly in animals pretreated with local hypothermia or intravenous thiopental than in control animals (0.1 ± 0.5, 1.1 ± 1.5, and 4.9 ± 6.4 minutes, respectively). The higher reperfusion pressures, hemodilution, and the buffering of lactic acid that resulted from the volume of Krebs-Henseleit buffer infused in the animals treated with local hypothermia might have contributed to the improved neurological outcome. However, infusion of similar volumes of Krebs-Henseleit buffer at body temperature produced no improvement in outcome, suggesting that the cooling effect was the most important factor. Following deflation of the balloon, blood pressure tended to fall further in animals pretreated with lidocaine or magnesium, and to return to a systolic pressure of 90 mm Hg more slowly with lidocaine (16.2 ± 22.2 minutes compared to 4.9 ± 6.4 minutes in control animals).
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Figure 1. Graphs showing the effect of agents that inhibit metabolic rate on spinal somatosensory evoked potentials (SSEP). Left: Thiopental, infused intra-arterially (IA) through the aortic catheter at the onset of ischemia, immediately suppressed the late waves of the SSEP without causing systemic hypotension. Center: Lidocaine, administered intravenously (IV) in increasing doses, suppressed the late waves of the SSEP and finally even N1. Right: Reducing the temperature of the spinal cord increased the latency and decreased the amplitude of all component waves of the SSEP proportional to the temperature change.

When spinal cord ischemia was initiated by inflation of the catheter balloon in the aorta of the control animals, the latencies of the component waves of the SSEP progressively increased and their amplitudes decreased until they finally disappeared. Pretreatment with lidocaine and intra-arterial thiopental caused the later waves to be suppressed from the onset of ischemia. Hyperthermia, intravenous thiopental, and naloxone produced no significant change in the length of time during ischemia that the later waves were present nor in the sequence of disappearance of the waves. In the animals pretreated with the combination of intra-arterial thiopental and local hypothermia, the N1 wave, which was the only component wave not suppressed by the drug treatment, had a markedly prolonged t1 during ischemia (a median time of 26.9 minutes compared to 13.6 minutes in the control animals).

When the SSEP's were not suppressed by drug pretreatment, as was the case with hypothermia, intravenous thiopental, magnesium, and naloxone in the doses used, the integrity of the late waves (N3 and N4) served as a monitor of the spinal cord's tolerance to aortic occlusion. If the late negative waves N3 and N4 were still being generated when the balloon was deflated or if the late waves were absent from the SSEP's for less than 10 minutes during ischemia, regardless of the total ischemia time, the SSEP's returned to an almost normal appearance during reperfusion and the animals always had a normal neurological outcome (Fig. 2 upper left).

Three (10%) of the 31 control animals had persistence of the late waves unchanged in appearance for the entire period of aortic occlusion. These animals remained normal despite aortic occlusion times of 40 to 60 minutes. Pretreatment with magnesium sulfate was associated with a higher percentage of rabbits that had persistence of SSEP's during occlusion of the aorta (36%, or five of 14), while the incidence in the remaining treatment groups ranged from 0% to 16%. The most
reason a hypothesis to explain the persistence of the SSEP's and preserved neurological function in these animals is either incomplete aortic occlusion by the balloon or the presence of spinal collateral circulation arising above the point of aortic occlusion. Magnesium may have increased collateral blood flow by its vasodilating actions. 15

In contrast, only one (6%) of the 18 animals that had failure of the late SSEP's for more than 10 minutes during ischemia had a normal neurological outcome, and none was normal after failure of the late potentials for more than 15 minutes (Fig. 2 upper left). Pretreatment with hypothermia, thiopental, and/or naloxone prolonged the period during which failure of the late waves was tolerated by all animals without the development of neurological deficits as follows: to 30 minutes with thiopental and with hypothermia; to 20 minutes with naloxone; and to 25 minutes with the combination of thiopental and naloxone (Fig. 2).

As shown in Table 3, thiopental increased the average recovery of N3 and N4 after 25 minutes of ischemia and of N1 and P2 after 40 minutes of ischemia. The higher dose of thiopental provided by intra-arterial infusion increased the recovery of N3 after 50 minutes of ischemia. Although naloxone increased the average return of P2 following 25 minutes of ischemia, the combination of thiopental and naloxone resulted in no significant improvement over intravenous thiopental alone after 40 and 50 minutes of ischemia. Whole-body hypothermia increased the average return of N3 and N4, and local hypothermia increased the return of N3 and P2 following 25 minutes of ischemia. The combination of thiopental and local hypothermia increased the recovery of P2 after 40 minutes of ischemia and of N3 and P2 after 50 minutes of ischemia. Pretreatment with lidocaine or magnesium did not result in a significant improvement in the recovery of the SSEP following ischemia.

Neurological Outcome

The number of rabbits retaining normal motor function after spinal cord ischemia produced by aortic occlusion was inversely related to the duration of ischemia. All rabbits tolerated 15 minutes of aortic occlusion without motor deficits; hypalgesia, however, was commonly present below L-6. Fifty percent of animals were normal after 25 minutes of aortic occlusion, 25% after 40 minutes, and 20% after 50 and 60 minutes. The two animals that were normal after 50 and 60 minutes of aortic occlusion, and one of the two animals that were normal after 40 minutes of aortic occlusion had persistence of the SSEP relatively unchanged throughout the occlusion time, as discussed above. Thus, few animals that actually developed ischemia of the spinal cord sufficient to suppress the generation of SSEP's tolerated aortic occlusion for more than 25 minutes without sustaining neurological deficit. Six percent of the animals that had evolving deficits; those animals all had either a normal examination or paresis at 24 hours, but exhibited a flaccid paralysis at 48 hours.

Treatment with the different agents caused varying effects on neurological outcome. With hypothermia,
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TABLE 3
Recovery of SSEP and neurological outcome following spinal cord ischemia during aortic occlusion

<table>
<thead>
<tr>
<th>Animal Group</th>
<th>Ischemia Time (min)</th>
<th>No. of Animals*</th>
<th>Recovery of SSEP (%)†</th>
<th>Normal Outcome (%)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N3</td>
<td>N4</td>
</tr>
<tr>
<td>control animals</td>
<td>15</td>
<td>5</td>
<td>93 ± 4</td>
<td>77 ± 23</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>8</td>
<td>61 ± 32</td>
<td>60 ± 41</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>7 (8)</td>
<td>50 ± 39</td>
<td>35 ± 27</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>4 (5)</td>
<td>33 ± 39</td>
<td>37 ± 64</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>4 (5)</td>
<td>41 ± 23</td>
<td>13 ± 16</td>
</tr>
<tr>
<td>hypothermia</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>whole body</td>
<td>25</td>
<td>5</td>
<td>110 ± 17§</td>
<td>102 ± 20§</td>
</tr>
<tr>
<td>local</td>
<td>25</td>
<td>6</td>
<td>112 ± 34§</td>
<td>93 ± 26</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>6</td>
<td>63 ± 29</td>
<td>52 ± 37</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>2 (5)</td>
<td>27 ± 37</td>
<td>34 ± 47</td>
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<td>thiopental</td>
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<tr>
<td>intravenous</td>
<td>25</td>
<td>5</td>
<td>106 ± 10§</td>
<td>119 ± 36§</td>
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<tr>
<td></td>
<td>40</td>
<td>4</td>
<td>98 ± 22§</td>
<td>74 ± 37</td>
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<td></td>
<td>50</td>
<td>4 (6)</td>
<td>55 ± 41</td>
<td>25 ± 25</td>
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<tr>
<td>intra-aortic</td>
<td>magnesium sulfate</td>
<td>25</td>
<td>59 ± 18</td>
<td>83 ± 22</td>
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<tr>
<td></td>
<td>40</td>
<td>3 (6)</td>
<td>72 ± 25</td>
<td>72 ± 33</td>
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<td></td>
<td>50</td>
<td>3</td>
<td>55 ± 19</td>
<td>66 ± 25</td>
</tr>
<tr>
<td>lidocaine</td>
<td>25</td>
<td>5</td>
<td>79 ± 11</td>
<td>63 ± 19</td>
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<td></td>
<td>25</td>
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<td>40</td>
<td>5</td>
<td>56 ± 50</td>
<td>50 ± 41</td>
</tr>
<tr>
<td>thiopental + naloxone</td>
<td>40</td>
<td>4</td>
<td>61 ± 41</td>
<td>35 ± 25</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>3 (4)</td>
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<td>36 ± 45</td>
</tr>
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<td>thiopental + hypothermia</td>
<td>40</td>
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<td>81 ± 18</td>
<td>63 ± 27</td>
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<td></td>
<td>50</td>
<td>5</td>
<td>90 ± 12§</td>
<td>91 ± 31§</td>
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<td>72 ± 35</td>
<td>43 ± 36</td>
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<tr>
<td></td>
<td>70</td>
<td>5</td>
<td>30 ± 43</td>
<td>25 ± 39</td>
</tr>
</tbody>
</table>

* Numbers in parentheses indicate the total number of animals in each group.
† Mean return of spinal somatosensory evoked potentials (SSEP) was calculated at 120 minutes and is given as a percent of the control value.
‡ Figures represent the percentage of animals with a normal neurological outcome as determined by examination at 48 hours or by SSEP recovery at 120 minutes if the animal died before 48 hours.
§ Significantly different from control animals at the same ischemia time (p < 0.05).
|| Significantly different from the group receiving intravenous thiopental at the same ischemia time (p < 0.05).

either local or whole-body, all animals tolerated 25 minutes of ischemia without neurological deficit. Following 40 minutes of ischemia, four (67%) of six were normal and two (33%) were paralyzed. After 50 minutes of aortic occlusion, three (60%) of five were normal and two (40%) were paraplegic. The three animals that were normal after 50 minutes of aortic occlusion had persistence of the SSEP's unchanged throughout the occlusion time. No animals had neurological deficits that evolved. The logistic curve constructed from the animals that suffered spinal cord ischemia sufficient to suppress the SSEP demonstrated an increase in the time of aortic occlusion tolerated by 50% of the animals from 26.1 minutes to 40.8 minutes with hypothermia.

Following intravenous thiopental infusion, aortic occlusion was well tolerated for up to 40 minutes. After 25 minutes of aortic occlusion, all rabbits had a normal motor examination; none had even sensory deficits. After 40 minutes of aortic occlusion, three (75%) of four were normal and one (25%) was weak. After 50 minutes of aortic occlusion, only two (33%) of six were normal, two (33%) were weak, and two (33%) were paralyzed. In the two animals that were normal after 50 minutes of aortic occlusion, the SSEP persisted relatively unchanged throughout the occlusion time. No animals pretreated with thiopental developed neurological deficits. The logistic curve constructed from the animals that suffered sufficient ischemia to suppress the SSEP (Fig. 3) demonstrated an increase in the time of aortic occlusion tolerated by 50% of the animals from 26.1 minutes to 41.2 minutes after pretreatment with thiopental.

Following pretreatment with the higher dose of thiopental provided by intra-aortic infusion, neurological outcome was not significantly different from the lower intravenous dose, with only two (29%) of seven rabbits remaining normal after 50 minutes of aortic occlusion. Because treatment with intra-aortic thiopental suppresses the late waves of the SSEP, the most sensitive monitor of the development of spinal cord ischemia is not available. During extremely long periods of aortic occlusion, however, even N1 disappears and can be a monitor of the development of ischemia. Because the N1 wave, the only SSEP component to remain after the
drug infusion, disappeared at the expected time during aortic occlusion, the animals that remained normal probably did tolerate 50 minutes of actual ischemia of the spinal cord.

Following pretreatment with magnesium sulfate, four (80%) of five animals were normal after aortic occlusion for 25 minutes, and four (67%) of six were normal after 40 minutes of occlusion. There were no normal animals after 50 minutes of aortic occlusion, and no animals had neurological deficits that evolved. Five of the normal animals had persistence of the evoked potentials throughout the time of balloon inflation, two after undergoing 25 minutes and three after undergoing 40 minutes of aortic occlusion. Thus, although the neurological outcome of the entire magnesium sulfate group was improved, the outcome of the animals that actually suffered spinal cord ischemic insult during aortic occlusion was no different from that of the control animals.

Following pretreatment with lidocaine, only two (40%) of five rabbits tolerated aortic occlusion for 25 minutes without developing a motor deficit. Forty percent were weak and 20% were paralyzed. In none of these five animals did neurological deficits develop.

After naloxone infusion, aortic occlusion for 25 minutes was tolerated by most animals, with three (75%) of four remaining normal. After 40 minutes of aortic occlusion, two (40%) of five were normal, one (20%) was weak, and two (40%) were paralyzed. One animal that was normal at 24 hours had developed weakness at 48 hours.

After infusion of thiopental and naloxone together, neurological outcome was no different from the results after thiopental alone; three (75%) of four animals had a normal outcome after 40 minutes and only one (25%) had a normal outcome after 50 minutes of aortic occlusion. In the animal that was normal after 50 minutes of aortic occlusion the SSEP persisted unchanged throughout the occlusion. No animal had neurological deficits. The logistic curve constructed from the animals that suffered sufficient ischemia to suppress the SSEP demonstrated that the combination of naloxone and thiopental provided no greater protection from ischemia than did thiopental alone.

The combination of thiopental and local hypothermia permitted almost all animals to tolerate 40 and 50 minutes of ischemia without a motor deficit. After 60 minutes of ischemia, three (38%) of eight animals were normal, one (13%) was paretic, and four (50%) were paraplegic. After 70 minutes of ischemia, one (20%) of five was normal, one (20%) was paretic, and three (60%) were paraplegic. The logistic curve constructed from these data (Fig. 3) demonstrates an increase in the time of aortic occlusion tolerated by 50% of the animals from 26.1 minutes to 56.7 minutes after pretreatment with thiopental and hypothermia.

**Histopathology of Spinal Cord Ischemia**

Figure 4 demonstrates the relationship between the histological appearance of the spinal cord 48 hours after ischemia, recovery of the SSEP, and their relationship to neurological status. Animals that were clinically normal and had almost normal return of the SSEP had minimal focal cellular infiltration or patchy areas of necrosis and involvement of less than 40% of the gray matter at any level. In contrast, animals that were paralyzed had necrosis of virtually all gray matter in the lumbosacral cord. Exceptions were two animals with selective involvement of the anterior horn cells: these two animals were paraplegic even though only 25% of the cross-sectional area of the spinal cord appeared damaged. Animals with partial neurological deficits had predominantly unilateral or distal confluent lesions. The histological appearance of the lesions in animals with evolving neurological deficits was consist-
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ent with an infarct of 48 hours' duration. There was no vascular thrombosis or any other abnormality that was unique to the animals in which deficits evolved.

Discussion

Other investigators have shown that the rabbit spinal cord is similar to other models of focal ischemia in that blood flow is rarely totally eliminated by occluding its usual blood supply. After ligation of the abdominal aorta for 20 minutes, an average 2% of normal blood flow remains in the spinal cord. In view of this information, some reasonable hypotheses can be generated to explain the behavior of SSEP's during ischemia observed in this study. There was considerable individual variation in the length of time required for the spinal cord to develop sufficient ischemia to lose the ability to generate the postsynaptic waves of the SSEP; an average time of 12.5 minutes elapsed before failure of N3. This time probably reflects the variation in residual blood flow to the spinal cord in each animal after aortic occlusion rather than individual variations in metabolic rate or energy stores, since the distribution of these times was not significantly affected by agents that markedly reduce metabolic rate. However, there was a consistent 10-minute interval during ischemia between failure to evoke the N3 wave of the SSEP and the development of neurological damage in the control animals. Therefore, at the time of N3 wave failure there may be a similar degree of blood flow reduction in the spinal cord gray matter of each animal. The length of time that the N3 wave was absent during aortic occlusion was a more consistent "ischemia time" for all animals than the total aortic occlusion time. The metabolic inhibiting agents that improved neurological outcome following ischemia prolonged the length of time that N3 could be absent during ischemia without neurological damage.

Of the agents studied, only hypothermia and thiopental significantly improved SSEP recovery and neurological outcome following ischemia. Magnesium, in the doses used, did not suppress SSEP's. A possible reason may be that magnesium does not easily cross the blood-brain barrier and may not have blocked synaptic transmission. This is suggested by the fact that the synaptically generated N2 and N4 potentials were not suppressed by magnesium, whereas they were suppressed by intra-aortic thiopental and hypothermia. In the lidocaine-pretreated group, however, SSEP's were markedly suppressed, and some other explanation must be sought for its ineffectiveness. Lidocaine was associated with a prolonged hypotension following deflation of the catheter balloon; the poor reperfusion pressures may have negated any beneficial effects of metabolic suppression. The combination of thiopental and naloxone was not more protective than thiopental alone, and perhaps was even less protective. Naloxone has been reported to reverse the anesthetic actions of barbiturates in some animals, and may have antagonized the metabolic suppressing effects of thiopental in this study. An alternative interpretation is that the same metabolic or neural mechanisms may be acted on nearly maximally by both thiopental and naloxone and that additional protection cannot be obtained by adding the second drug.

The rabbit spinal cord is a reliable model for systematically and rapidly screening agents that might have protective effects during ischemia, as well as intensively investigating therapies that proved effective. Previous studies using this model have commented on the unreliability of the neurological examination on the day of the ischemia; some animals that have spasticity will become quite normal and some animals that are apparently normal will become paraplegic. In addition to being able to predict neurological outcome on the day of ischemia, monitoring SSEP's during aortic occlusion in this model has permitted identification and exclusion of animals that had sufficient collateral blood flow to permit the spinal cord to survive long periods of aortic occlusion.

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