Protection from Cerebral Ischemia by a New Imidazole Derivative (Y-9179) and Pentobarbital. A Comparative Study in Chronic Middle Cerebral Artery Occlusion in Cats

AKIRA TAMURA, M.D., TAKAO ASANO, M.D., KEIJI SANO, M.D., TATSUMI TSUMAGARI, AND AKIRA NAKAJIMA

SUMMARY For the purpose of investigating the protective action against cerebral ischemia by a new imidazole derivative (Y-9179) and pentobarbital, regional cerebral ischemia was produced in 53 cats by permanent occlusion of the middle cerebral artery (MCA) via the transorbital approach. In 20 cats, the clips were applied at the origin of the right MCA whereas in the remaining 33 they were applied laterally. The administration of Y-9179 (6.25 and 12.5 mg/kg/day), pentobarbital (25 mg/kg/day) and saline was started 30 min after MCA occlusion and continued for 3 days. The cats were observed for 7 days and then sacrificed. Since there was a remarkable difference in mortality between the medial (65%) and the lateral occlusion groups (15%), the evaluation of drug effects was based only on the results obtained with the lateral occlusion group. The brains were sliced at 4 fixed coronal planes, in which the ratios of the infarcted area in the 2 hemispheres were obtained by planimetry. A statistically significant decrease in the infarction rate was found both in Y-9179 and pentobarbital-treated groups compared to the control group. Since the CNS depressant action of Y-9179 is far less potent than that of pentobarbital, the present results indicate the potential usefulness of Y-9179 in the management of strokes.

THE PROTECTIVE EFFECT of barbiturates against cerebral ischemia or anoxia has been widely reported in animal experiments.\textsuperscript{11-15} Clinical trials with barbiturates have recently been reported with favorable results.\textsuperscript{13, 14} In these experimental, as well as clinical studies, very high doses of barbiturates were administered. Such doses require that patients and animals be given intensive care because of the severe respiratory depression and the deterioration of the level of consciousness that follow administration.\textsuperscript{9, 13} In view of this fact, an alternative drug with less adverse effect on the condition of patients has been sought.

Recently a new imidazole derivative Y-9179 (1-(2-(2-Chlorobenzoyl)-4-nitrophenyl)-2-(diethylamino-methyl) imidazole fumarate) was found to possess remarkable protective action against cerebral anoxia, or ischemia, in animal experiments using mice and rats. The anti-hypoxic, or anti-anoxic effect of this compound was observed with very small doses which might vary considerably from animal to animal. In view of this fact, an alternative drug with less adverse effect on the condition of patients has been sought.

To investigate the possibility of clinical application of this compound, a comparative study with Y-9179 and pentobarbital was carried out in cats using the chronic middle cerebral artery occlusion model.

Materials and Methods

Fifty-three adult cats of both sexes weighing 2.3 to 4.6 kg (average: 3.0 kg) had the following operative procedures. Cats were fasted for 24 hours prior to the operation. Atropine sulfate (0.75 mg/kg) was intra-muscularly administered 30 min before induction of anesthesia by halothane inhalation. The cats were then intubated and adequate depth of anesthesia, as judged by respiratory rate and volume, was maintained by varying the concentration of halothane (2.0–3.5%) inhaled during operative procedures. The cats were extubated after recovery from anesthesia with an average duration of halothane anesthesia of about 40 min.

The horizontal portion of the right middle cerebral artery (MCA) was clipped by Sugita clips\textsuperscript{16} which have short, straight blades. The clip was applied using an operating microscope under aseptic conditions and a transorbital approach reported previously.\textsuperscript{12, 13} It was anticipated that the exact site of the clip might vary considerably from animal to animal. In order to estimate the possible influence of the site of MCA clipping on the overall results, the animals were divided into 2 groups which underwent 2 different operative procedures.

In the first group, clips were applied in as medial a position as possible, i.e., immediately lateral to the origin of the MCA from the intracranial portion of the internal carotid artery (medial occlusion group: MOG). The eyeballs were enucleated in all the animals to facilitate medial exposure of the MCA.

In the second group of animals, the clips were applied in a more lateral position than was the case with the first group, in the vicinity of the origin of the lateral striate artery (lateral occlusion group: LOG). The eyeballs were not enucleated in this group because sufficient exposure of the lateral portion of the horizontal MCA was obtained merely by retracting the orbital contents (fig. 1). The average duration of each operation was 30 min for the first group and 40 min for the second. In both operative groups, the dural
defects were packed with pieces of Gel Foam and sutures were not used. About 100 mg of kanamycin powder was topically applied in the orbital cavity. The skin incision and the orbital fissure were tightly closed. With this technique no external leakage nor intraorbital pooling of CSF was observed in any of the animals.

Immediately after termination of the operative procedures, the animals were given 20 ml of 5% dextrose solution by subcutaneous injection and 200 mg of kanamycin by intramuscular injection. The animals were then transferred to an observation cage, where the room temperature and humidity were maintained between 24-27°C and 50-60%, respectively. The posture, respiratory rate, heart rate, rectal temperature, pinna reflex, pupillary light reflex, pain reflex and body weight were regularly checked at 3, 6, 24, 48, 72, 96, 120 and 144 hours following operation. Neurological evaluation was carried out at the same time intervals (see below). A complete blood count was also obtained on the preoperative, first and sixth postoperative days (table 1).

The scale for neurological evaluation is the same as reported by Smith et al. (table 2). The scoring was undertaken by 2 observers who had no knowledge of the drug administered, and the scores of the 2 observers were later compiled.

The importance of intensive care for animals in the

Table 1  Experimental Schedule Showing the Time-Intervals Between Each Postoperative Observation and the Administration of Drugs (left). The Observations are Shown Top Right. The Schedule of Drug Administration is Shown Lower Right.

<table>
<thead>
<tr>
<th>Time (Hr)</th>
<th>Observation(A-K)</th>
<th>Observation Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>-25.5</td>
<td>Fasting</td>
<td></td>
</tr>
<tr>
<td>-1.5</td>
<td>Atropine 0.75mg/kg i.m.</td>
<td></td>
</tr>
<tr>
<td>-1.0</td>
<td>Halothane Anesthesia</td>
<td></td>
</tr>
<tr>
<td>-0.5</td>
<td>MCA Clip 5% Dextrose 20ml s.c. Kanamycin 200mg i.m. Halothane Turn Off</td>
<td></td>
</tr>
</tbody>
</table>

Drug Administration(3 Days) Cont. Y-9179 PBT*

| 0       | --- i.p. 2.5 5.0 10 |
| 3       | --- s.c. 1.25 2.5 5  |
| 9       | --- s.c. 1.25 2.5 5  |
| 16      | --- s.c. 1.25 2.5 5  |

(* mg/kg/day, -:Vehicle)

| 96      | Observation(A-K) Evans Blue 2.5ml/kg i.v. |
| 120     | " (A-K) |
| 144     | " (A-K) |
| Brain Perfusion |

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Table 2 Criteria for Neurological Evaluation Scores. Smith's Score Was Partially Modified. For Each Observation, the Scores of 2 Observers Were Later Added to Obtain a More Objective Evaluation.

- **0:** No neurological deficit
- **1:** Hemiplegia (left side), can stand without support and circles
- **2:** Hemiplegia (left side), can stand with support, decreased spontaneous activity
- **3:** Hemiplegia (left side), cannot stand with support, no spontaneous activity
- **4:** Dead

Postoperative period has been stressed in previous papers.6, 19 Since, however, artificial ventilation, forced feeding, parenteral fluid supply and body warming were considered in the present study to hamper drug evaluation, they were not carried out. The cats were allowed to take food and water after the operation.

On the 7th postoperative day, all the surviving cats were again anesthetized with halothane and the brain was fixed in situ by perfusion of 240-300 ml of Karnovsky solution at a pressure of 100 mm Hg via the common carotid arteries. Prior to the perfusion fixation, 2.5 ml/kg of 2% solution of Evans blue was intravenously administered. Then the brain was removed and immersed in 10% formalin for a week.

The brains were sliced at 4 fixed coronal planes, i.e., Slice I: A 19.0 ± 2 mm, Slice II: A 14.0 ± 2 mm, Slice III: A 9.0 ± 2 mm, Slice IV: A 4.0 ± 2 mm, according to Snyder's atlas.20

In each section, the ratio of the infarcted area (determined by microscopical examination with Hematoxylin-Eosin and Klüver-Barrera stains) to the total area of both hemispheres was obtained. Those cats which died within 6 days following the initial operation were immediately autopsied.

Histological specimens were examined by one of the authors (A.T.). The specimens examined were given the examiner randomly by the other authors, so that the examiner did not know which drug had been administered.

The schedule of drug administration is shown in Table 1. The drug to be administered to the animals was randomly predetermined by one of the authors (T.T.). Therefore, the administration of drugs and postoperative observations were carried out by persons with no knowledge of which drug was being, or had been administered to which cat. Five percent dextrose solution was given the control group. The amount of any drug given at any one time remained constant, i.e., 1 ml/kg body weight for intraarterial and 0.5 ml/kg for subcutaneous injections.

In several cats in each group (3 in the control group, 5 in the Y-9179 group and 5 in the pentobarbital group), an EEG was recorded pre- and postoperatively with epidural electrodes which had been implanted 2 weeks prior to the experiment under pentobarbital anesthesia. The preoperative EEG recordings all revealed normal awake patterns without any local abnormalities. All the EEG recordings were stored in a magnetic tape recorder (TEAC R-260) for computer analysis.

Results

Influence of Clip Application Site

A remarkable difference in mortality was observed between the groups in which the clip had been medially applied and those in which application had been lateral. No significant differences in mortality were seen in relation to the drug administered. Ton-sillar herniation, which was seen in each of the autopsied brains, was considered to be the major cause of death, while unilateral and/or bilateral transtentorial herniation was observed in 9 of the 18 deaths. The relationship between mortality and the site of clip application is shown in Figure 2. The calculated infarction ratio in those cats which succumbed unexpectedly was considered inadequate for statistical evaluation because of the lack of perfusion fixation of the brain and the inconsistency in the time interval between clip

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Position of MCA Clipping</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>▲▲</td>
<td>2/3</td>
</tr>
<tr>
<td>Y-9179</td>
<td>▲▲▲▲▲</td>
<td>6/10</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>▲▲▲▲▲▲</td>
<td>5/7</td>
</tr>
</tbody>
</table>

▲▲Dead, ▲▲Survived for one week

Position of MCA Clipping: MOG: 0.41 ± 0.03 cm (20)

Mean ± SE (N) LOG: 0.75 ± 0.03 cm (30)

Figure 2. Influence of the site of clip application on mortality. The mortality rate was higher in the medial occlusion group (65%) than in the lateral occlusion group (15%). The overall mortality for both groups was 34%. There was no statistically significant difference in the mortality rate between the control, Y-9179 and pentobarbital treated groups.
application and death. Therefore, the following statistical analysis of the experimental results was carried out based solely on the group with lateral occlusion.

Time Course of Vital Signs and Neurological Scorings

As shown in figure 3, there were no significant differences among the cats with lateral clipping given 3 separate treatments in regard to respiration rate, heart rate, rectal temperature and body weight, and there was no difference in the duration of operative procedures or anesthesia.

There was, however, a significant difference in the neurological evaluation scores between the control group and both the Y-9179 and the pentobarbital treated group 6 hours after the operation. This was considered to be due to the sedative, or muscle relaxant, action of Y-9179 and the CNS depressant action of pentobarbital. Later neurological scores tended to be similar and there were no differences during the period from discontinuation of drugs until the day of sacrifice.

Pathological Evaluation

In the examination of each coronal section, the normal, moderately affected (area B) and the severely affected (area A) areas were defined according to the criteria shown in figure 4. The typical appearance of each area and its histological definition is shown. The width of each area and of both hemispheres was measured with a planimeter. An infarction ratio of each specimen was calculated as the proportion of area A, area B and area A plus B to the sum of the areas of both hemispheres. The values obtained were grouped according to the drug which had been administered. A statistical analysis, by the analysis of variance method, was carried out on each coronal plane as well as on the average of the infarction ratio of the 4 planes (table 3, fig. 5).

A statistically significant decrease of infarction ratio was seen in the severely affected area (area A) in the Y-9179 group. A tendency for a decreased infarction ratio was also found in the pentobarbital-treated group, although it did not reach statistical significance. More distinct results were obtained with the infarction ratios of the severely affected areas plus the moderately affected areas (area A + area B). In both the Y-9179 and pentobarbital-treated groups, there were statistically significant reductions in the infarction ratios compared to the control group. It also
FIGURE 4. Representative pathological specimens (H.E. stain, \( \times 50 \)) of the moderately (area B, perifocal) and the severely (area A, necrotic focus) affected areas. The pathological definitions of each area are given to the right of the photographs. Moderately affected area (area B, perifocal area): The normal cytological architecture is maintained whereas the neurones show varied ischemic cell changes. Presence of edema in the white matter is also noted. Severely affected area (area A, focus of necrosis): Complete loss of the normal cytological architecture.

appeared that a higher dose of Y-9179 was more effective in reducing the infarction ratio. The infarction ratio of each coronal plane in each group is also shown in figure 5.

EEG Findings

In the majority of animals which had their EEG recorded, EEG activity in the right hemisphere disappeared immediately after application of the clips. Through the postoperative period, the slowing of the basal rhythm in the infarcted side tended to be less severe in both the Y-9179 and the pentobarbital-treated groups as compared to the control group.

Discussion

Site of Clip Application

Since the original report of transorbital clipping of the MCA in cats by Sundt et al.,\(^4\) clips have, in the succeeding experiments,\(^5\) been applied as medially as possible, just lateral to the origin of the MCA. As has been demonstrated in clinical data,\(^1\) the site of clip application is considered to have a great effect on the localization and extent of cerebral infarction. Moseley et al.,\(^7\) showed no differences in infarction ratios according to the site of the MCA occlusion. Michenfelder et al.,\(^8\) reported a significant occurrence of diabetes insipidus in monkeys when the clips were medially applied. There was a remarkably high mortality rate in the present study, as compared to that of previous reports,\(^5\) in the medial occlusion group. The primary cause of death in cats dying after medial clipping was invariably massive brain edema which resulted in transtentorial and/or tonsillar herniation. In these cats, no other causes of brain damage, such as surgical trauma, infection or accumulation of blood, was observed. The duration of operative procedures differed only slightly. The higher mortality rate in the medial occlusion group, as compared to the lateral occlusion group, was considered to be due not to a difference in operative technique, but a difference in the site of clip application. The mortality rate in the medial occlusion group of the present study is considerably higher than reported for previous experiments which had employed essentially the same approach. This discrepancy in experimental results may well be attributed to the absence of postoperative intensive care in the present experiment.

Intensive postoperative care would inevitably have varied the experimental conditions. In the present study, neither artificial respiration nor forced feeding was carried out to maintain fixed experimental conditions in the postoperative period. Only minimal care was given, such as maintaining adequate room temperature and humidity, and applying mild constriction to an animal in the case of behavioral excitation. Parenteral fluid was never given, except for the initial administration in the immediate postoperative period. The minimal changes in body weight and hematocrit value indicate that the care given could be considered adequate. Consequently, the difference in the mortality rate between the 2 different operations probably reflects the influence of the site of clip application.

Measurement of Infarcted Area

Exact pathological definition of an infarcted area has seldom been presented in previous papers.\(^5\) In the present study, the areas severely affected (area A, focus of infarction) and moderately affected (area B, perifocal area) were defined as stated. The area of the homolateral hemisphere is subject to considerable variation due to the presence or absence of diffuse cerebral edema and cortical or subcortical atrophy. The infarction ratio calculated as the ratio of the infarcted area to the summed area of both hemispheres, as in the present study, is considered to give a better
 estimation of the severity of ischemic insult than the infarction ratio as calculated in previous reports.3, 6, 9

### Schedule of Drug Administration

In most previous reports,3, 4, 10 drugs have been administered prior to clip application. In the recent papers by Michenfelder et al.8 and Bleyart et al.,29 a statistically significant protective effect of barbiturates, administered in the postoperative period, was reported. Clinically, pre-ictal or prophylactic use of these agents is impractical except for preoperative administration. In estimating the benefits of clinical application, only the cerebral protective effect of drugs

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**TABLE 3-1 Infarction Ratios of All Coronal Sections of the Cat Brains Which Were Divided According to the Drug Administered. All the Statistical Analyses in the Present Study Were Based on this Table.**

<table>
<thead>
<tr>
<th>Cat Sex B.W.</th>
<th>Coronal Section</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>Total</th>
<th>b/a (e/a) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>3.10</td>
<td>3.40</td>
<td>4.30</td>
<td>4.79</td>
<td>15.59*</td>
<td></td>
</tr>
<tr>
<td>Male 3.2 kg</td>
<td></td>
<td>0.45</td>
<td>0.60</td>
<td>0.65</td>
<td>0.00</td>
<td>1.70*</td>
<td>10.90</td>
</tr>
<tr>
<td>Male 4.2 kg</td>
<td></td>
<td>2.90</td>
<td>4.45</td>
<td>5.05</td>
<td>5.30</td>
<td>17.70</td>
<td></td>
</tr>
<tr>
<td>Male 4.1 kg</td>
<td></td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
<td>0.00</td>
<td>0.30</td>
<td>1.69</td>
</tr>
<tr>
<td>Male 4.0 kg</td>
<td></td>
<td>0.60</td>
<td>0.75</td>
<td>0.90</td>
<td>0.23</td>
<td>2.38</td>
<td>12.00</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>3.40</td>
<td>3.83</td>
<td>5.60</td>
<td>6.05</td>
<td>18.58</td>
<td></td>
</tr>
<tr>
<td>Female 2.5 kg</td>
<td></td>
<td>0.43</td>
<td>0.50</td>
<td>0.40</td>
<td>0.10</td>
<td>1.43</td>
<td>7.54</td>
</tr>
<tr>
<td>Male 2.6 kg</td>
<td></td>
<td>1.00</td>
<td>1.50</td>
<td>0.90</td>
<td>1.00</td>
<td>4.40</td>
<td>21.28</td>
</tr>
<tr>
<td>Male 2.5 kg</td>
<td></td>
<td>3.00</td>
<td>3.65</td>
<td>4.55</td>
<td>4.40</td>
<td>15.60</td>
<td></td>
</tr>
<tr>
<td>Male 2.4 kg</td>
<td></td>
<td>0.35</td>
<td>0.70</td>
<td>0.60</td>
<td>0.40</td>
<td>2.05</td>
<td>13.14</td>
</tr>
<tr>
<td>Male 2.0 kg</td>
<td></td>
<td>0.70</td>
<td>1.05</td>
<td>1.00</td>
<td>1.00</td>
<td>3.75</td>
<td>24.04</td>
</tr>
<tr>
<td>Female 2.5 kg</td>
<td></td>
<td>3.30</td>
<td>4.15</td>
<td>5.33</td>
<td>4.82</td>
<td>17.60</td>
<td></td>
</tr>
<tr>
<td>Female 2.4 kg</td>
<td></td>
<td>1.10</td>
<td>1.30</td>
<td>1.40</td>
<td>0.53</td>
<td>4.33</td>
<td>24.60</td>
</tr>
<tr>
<td>Female 2.0 kg</td>
<td></td>
<td>3.03</td>
<td>3.37</td>
<td>5.00</td>
<td>4.95</td>
<td>16.35</td>
<td></td>
</tr>
<tr>
<td>Female 1.8 kg</td>
<td></td>
<td>0.50</td>
<td>0.60</td>
<td>0.40</td>
<td>0.10</td>
<td>1.60</td>
<td>9.79</td>
</tr>
<tr>
<td>Female 1.6 kg</td>
<td></td>
<td>1.00</td>
<td>1.50</td>
<td>0.90</td>
<td>1.00</td>
<td>4.40</td>
<td>21.28</td>
</tr>
<tr>
<td>Female 1.4 kg</td>
<td></td>
<td>3.00</td>
<td>3.65</td>
<td>4.55</td>
<td>4.40</td>
<td>15.60</td>
<td></td>
</tr>
<tr>
<td>Female 1.2 kg</td>
<td></td>
<td>0.35</td>
<td>0.70</td>
<td>0.60</td>
<td>0.40</td>
<td>2.05</td>
<td>13.14</td>
</tr>
<tr>
<td>Female 1.0 kg</td>
<td></td>
<td>0.70</td>
<td>1.05</td>
<td>1.00</td>
<td>1.00</td>
<td>3.75</td>
<td>24.04</td>
</tr>
<tr>
<td>Female 0.8 kg</td>
<td></td>
<td>3.30</td>
<td>4.15</td>
<td>5.33</td>
<td>4.82</td>
<td>17.60</td>
<td></td>
</tr>
<tr>
<td>Female 0.6 kg</td>
<td></td>
<td>1.10</td>
<td>1.30</td>
<td>1.40</td>
<td>0.53</td>
<td>4.33</td>
<td>24.60</td>
</tr>
<tr>
<td>Female 0.4 kg</td>
<td></td>
<td>3.03</td>
<td>3.37</td>
<td>5.00</td>
<td>4.95</td>
<td>16.35</td>
<td></td>
</tr>
<tr>
<td>Female 0.2 kg</td>
<td></td>
<td>0.50</td>
<td>0.60</td>
<td>0.40</td>
<td>0.10</td>
<td>1.60</td>
<td>9.79</td>
</tr>
</tbody>
</table>

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*Area of coronal section.
*Area A (Severely affected area).
*Area A + Area B (Moderately affected area).
administered starting 30 min after clip application was evaluated in the present study. The drugs were administered for 3 days following the operations.

As reported in previous papers, tissue destruction due to ischemia is considered to proceed most rapidly in the first few days after clip application. As striking protection was obtained with both Y-9179 and pentobarbital in the present study, the continuation of drug administration did not seem necessary.

Cerebral Protection by Pentobarbital and Y-9179

The protective action by barbiturates against cerebral hypoxia and/or ischemia has been repeatedly reported. In most of the studies previously reported, however, a very high dose of barbiturates was required to obtain protection. Such a high dose of barbiturates inevitably carries significant disadvantages. During postoperative care artificial respiration and parenteral fluids were indispensable adjuncts to cope with severe respiratory and generalized CNS depression. In the recently reported clinical study by Marshall et al., using barbiturates in severe head injury, such respiratory and circulatory treatment as artificial ventilation or use of pressor amines, was necessary. Such intensive care is not always possible or even desirable when broader clinical application of these agents to less severely affected patients is contemplated. Consequently, the importance of developing new agents with minimal adverse effects has been repeatedly stressed by many authors.

Definite protection from cerebral ischemia was achieved by Y-9179 which was similar to that of pentobarbital. Y-9179 was produced in the process of developing various imidazole derivatives, and in routine screening tests for drugs useful against hypoxia, anoxia and ischemia, the remarkable protective action of Y-9179 was discovered. The compound is water-soluble for parenteral administration. If a massive amount of Y-9179 is given intravenously, no respiratory depression has been observed in dogs and cats (Tsumagari, T., et al. unpublished). The agent acts as a potent muscle relaxant, which may be
Y-9179 AND PENTOBARBITAL IN ISCHEMIA/Tamura et al. 133

Possible Mechanism of Y-9179 Action

A number of interpretations of the protective action of barbiturates have been postulated, but they are still unproven.26–28 The mechanism of action of Y-9179 is not clarified by the present experiment but the depression of the cerebral metabolic rate (CMR) by Y-9179 has been demonstrated in a complete ischemia model using mice following the method of Lowry et al.15, 27 This diminution of the CMR may be one of the principal reasons for its protective action. Recent studies by Michenfelder et al.8 and Nordström et al.,13 however, indicate that the protective action of barbiturates is not necessarily based on its depressant effect of the CMR. According to Michenfelder et al.8 and Moseley et al.,7 the protective action of barbiturates can only be expected in those cerebral areas where the minimum blood supply is maintained to ensure neuron survival. The apparent decrease in the infarction ratio of the mildly affected (perifocal) areas by pentobarbital in the present study is consonant with the above observation. For Y-9179 a statistically significant reduction of the infarction ratio was observed both in the mildly (area B, perifocal areas) and severely (area A, focus of infarction) affected areas. This may indicate that the mechanism of Y-9179 is in some way different from that of barbiturates in protection against ischemia.

The antioxidant action of barbiturates, proposed by Demopoulos and associates,39–41 seems to deserve further investigation, and the antioxidant effect of Y-9179 is currently being studied.

References

4. McGraw CP: Experimental cerebral infarction. Effects of pen-
23. Michenfelder JD: The interdependency of cerebral functional and metabolic effects following massive doses of thiopental in the dog. Anesthesiology 41: 231-236, 1974
29. Smith AL, Marque JJ: Anesthetics and cerebral edema. Anesthesiology 45: 64-72, 1976
Protection from cerebral ischemia by a new imidazole derivative (Y-9179) and pentobarbital. A comparative study in chronic middle cerebral artery occlusion in cats.
A Tamura, T Asano, K Sano, T Tsumagari and A Nakajima

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