reason for this was that the lesions of the right hemisphere affect the functions of visuomotor, temporal and spatial concepts.

References

Cerebral Infarction in the Mongolian Gerbil
Exacerbated by Phenoxybenzamine Treatment

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SUMMARY In a double-blind study, the effects of a large dose (20 mg per kilogram) and a small dose (2 mg per kilogram) of phenoxybenzamine (PBZ) on cerebral infarction were evaluated in 120 Mongolian gerbils. The left common carotid artery was ligated in 100 animals; a sham operation was done in 20 animals. One hour later, 25 animals were given 2 mg per kilogram of PBZ, 25 animals were given 20 mg per kilogram of phenoxybenzamine, and 50 animals were given 0.5 cc of normal saline, all doses being repeated at 24, 48, and 72 hours. Five sham-operated animals were given 2 mg per kilogram of phenoxybenzamine, five were given 20 mg per kilogram of phenoxybenzamine and ten were given 0.5 cc of normal saline on the same treatment schedule. Morbidity and mortality were recorded for one week and then all surviving animals were killed. All brains were studied for signs of infarction. Of the saline-treated animals, 32% had cerebral infarction and 81% of these died. Of the animals treated with phenoxybenzamine, 36% of those receiving 2 mg per kilogram and 68% (p < 0.05) of those receiving 20 mg per kilogram had cerebral infarction and all of those with infarction died during the observation period. The animals receiving phenoxybenzamine had a larger stroke index than those treated with saline. The authors concluded that phenoxybenzamine is harmful in post-ischemic treatment of strokes.

WHEN ISCHEMIA develops after brain or spinal cord trauma or hemorrhage, monoamine neurotransmitters may leak from neurons that have lost their structural integrity as a result of that ischemia.1,2 These neurotransmitters have been postulated to alter nerve cell metabolism, depress neuronal function, produce cerebral edema,4,5 cause cerebral arterial vasospasm,5,6,7,8,10 and increase platelet aggregation.1,11,12 Mechanisms that normally inactivate these neurotransmitters, namely presynaptic re-uptake and oxidative deamination, are attenuated due to the lack of oxygen, and the accumulation of these substances in the extracellular space exacerbates the damage caused by the initial ischemia.1,2,7

This information suggests several approaches to the pharmacological therapy of stroke: (1) inhibition of neurotransmitter synthesis, (2) suppression of the release of neuro-
transmitters from nerve terminals, (3) blockade of the receptors upon which the neurotransmitters act, and (4) removal of excess neurotransmitters. In this study, we investigated the third of these mechanisms by studying the effect of phenoxybenzamine (PBZ), a known potent inhibitor of alpha-adrenergic activity, on the morbidity and mortality associated with cerebral ischemia. Our study was done in Mongolian gerbils (Meriones unguiculatus) in which, because they have an incomplete circle of Willis, cerebral infarction develops in a high percentage of cases after ligation of the carotid artery. \(^{14-18}\)

**Methods**

One hundred twenty adult Mongolian gerbils weighing 47 to 75 gm were anesthetized with ether. A ventral midcervical incision was made, and in 100 animals the left common carotid artery was doubly ligated and transected. In 20 animals, the artery was exposed but not ligated. The wound was closed and each animal received an intraperitoneal injection of 0.7 cc of 1% trypan blue. \(^{19}\) One hour later, 25 gerbils with carotid artery ligation and five sham-operated animals were treated with a 20 mg per kilogram intraperitoneal dose of phenoxybenzamine in 0.5 cc of saline, 25 gerbils with carotid artery ligation and five sham-operated animals were treated with a 2 mg per kilogram intraperitoneal dose of phenoxybenzamine in 0.5 cc of saline, and 50 gerbils with carotid ligation and ten sham-operated animals were treated with 0.5 cc of saline intraperitoneally. The same animals were treated with the same doses 24, 48 and 72 hours later.

Each animal was examined every eight hours for the first three days, then daily for the next three days. Morbidity and mortality were evaluated and scored by an investigator unaware of the drug or dosage used. Morbidity was evaluated on the following: a decrease in alertness and movement, ptosis, cocked head, circling behavior, hindlimb splaying and rotation, seizure behavior, piloerection and tremor. A stroke index was devised, in which each of these characteristics was given a numerical weight (fig. 1). The time of death was recorded.

Animals that survived the study were killed on the seventh day. The cranium was removed from all animals and fixed in 10% formalin for 24 hours. The brain was removed from the skull and examined for softness, staining with trypan blue, and swelling. The location and extent of the infarct were determined by gross section.

Deaths due to cerebral infarct during the test period of observation were totaled for each group. Chi-square analyses were done comparing the total number of deaths in each group. The average time of death for each group was calculated, and the Student \(t\)-test was used to determine if there was a significant difference in survival time between groups. The stroke index for each eight-hour examination was calculated for each animal. These values were averaged for each group, so that an average group stroke index was obtained for each eight-hour examination period. The Student \(t\)-test was used to compare average group stroke index for each group at eight-hour intervals.

**Results**

Of the 20 animals with sham operations, three had clinical and pathological signs of stroke, probably due to manipulation of the carotid artery. Two of these three had been treated with saline, one with the lower dose of phenoxybenzamine.

Table 1 shows the total number of infarcts and mortality due to infarction in each group. There is no statistical significance in mortality between the group treated with the low dose of phenoxybenzamine and the group treated with saline. However, the difference in mortality between the high-dose phenoxybenzamine and the saline group is significant at the 5% level, as is the difference in the number of infarctions between the low-dose phenoxybenzamine group and the high-dose phenoxybenzamine group.

The average times of death were 31.4 ± 16.5 hours\(^*\) for the group treated with saline, 30.2 ± 15.4 hours for the low-dose phenoxybenzamine group and 43.4 ± 29.0 hours for the high-dose phenoxybenzamine group (p < 0.08).

Figure 2 is a graph of average group stroke index versus time to 72 hours, no statistically significant change in group stroke index first occurring later than 72 hours. There was no significant difference between the average group stroke index of the saline group and that of the low-dose phenoxybenzamine group except at 32 hours (p < 0.09). However, the difference between the saline group and the high-dose phenoxybenzamine group was significant at each hour, and the difference between the low-dose group and the high-dose group was significant at the first hour and became consistently significant at 40 hours (p < 0.05).

Gross examination of the brains indicated that all lesions occurred in the left hemisphere. Most lesions were cortical, although four involved the subcortex as well. The average lesion size (expressed as percentage of total brain size) of the saline group was 12.85 ± 11.79%, that of the low-dose phenoxybenzamine group was 11.12 ± 12.70%, and that of

\*Represents 1 SD.
the high-dose phenoxybenzamine group was 21.50 ± 14.94%. No significant differences with respect to percentage of lesion size, location, or percentage of animals with large lesions could be determined between any of the groups. However, when lesion size was graded from 1 to 4, a significant difference appeared between lesions in the saline group and those in the large-dose phenoxybenzamine group (p < 0.08).

Discussion

Pretreatment of animals with phenoxybenzamine has been shown to reduce hemorrhagic necrosis and lesion size after spinal cord trauma,1,19 thus preserving somatic and visceral motor function.20 Phenoxybenzamine is known to inhibit platelet aggregation,12,21 to reduce brain edema,22 to reduce the duration,23 extent,24,25 and clinical manifestations26 of vasospasm, and to slow cerebral metabolic activity in patients with cerebral infarction by decreasing hemispheric oxygen consumption and carbon dioxide production while increasing the glucose:oxygen utilization ratio.14 Thus it would appear to have potential value in the treatment of stroke.

However, in our study, phenoxybenzamine increased the number of cerebral infarctions and the mortality from infarction when given daily to experimental animals after an ischemic event. These effects were seen at both high (20 mg per kilogram) and low (2 mg per kilogram) doses of the drug, and were statistically significant at the 20 mg per kilogram dosage. Although they were not statistically significant at the 2 mg per kilogram level, they did occur more frequently in that group than in the saline control group. There also was an increase in the average size of infarction with increasing dosage. However, the animals receiving the larger dosage still took longer to die (p < 0.08) than the other animals, which suggests that there may be a possible benefit from the large dosage that was offset by the increased number of infarctions and deaths.

The detrimental effects in our study compared to more favorable results in other studies may have been due largely to the time of administration of the drug (postligation in our study), to the repeated treatments given in our study, or to both factors. Since, with stroke patients, there is usually a time lag between the ischemic insult and any treatment, we delayed the administration of phenoxybenzamine for one hour to more closely approximate a clinical situation. Hedeman and Ranajit20 showed that while phenoxybenzamine preserved somatic and visceral motor function in dogs when given as a 10 mg per kilogram dose one hour before spinal cord trauma, it provided no protection when given 15 minutes after trauma. Osterholm19 reported significant reduction in hemorrhagic necrosis and lesion size when 10 mg per kilogram of phenoxybenzamine was given one hour before experimental spinal cord injury in cats. We found no similar reduction with repeated post-trauma treatments in gerbils.

The high dose (20 mg per kilogram) of phenoxybenzamine used is the same as that shown by Nelson22 to reduce brain edema in mice when given one-half hour before a hemorrhagic lesion was induced. It is also the same as that given by Anden et al.24 intraperitoneally to rats 24 hours after spinal cord transection, a dose that blocked norepinephrine receptors of effector neurons in the cord.

The low dose (2 mg per kilogram) of phenoxybenzamine is slightly higher than the 1.5 mg per kilogram dose given intravenously by Kawamura et al.29 to decrease vasoconstrictor tone in cerebral vessels during hypocapnia and increased cerebral perfusion pressure, and slightly higher than the 0.7 mg per kilogram dose given via the carotid artery to stroke patients by Meyer et al.,14 which appeared to decrease hemispheric metabolism. We slightly increased the dosage to compensate for any loss due to our use of an intraperitoneal route.

The mechanism of action of phenoxybenzamine that caused the detrimental effects in our animals may have been: (1) a decrease in cerebral perfusion pressure, (2) a cerebral vascular steal from the ischemic area to normal areas, or (3) CNS effects of the drug.

(1) Phenoxybenzamine is known to lower systemic blood pressure,13,14,15,16,17 and to cause cerebral vasodilation1,18,19,20 A lowered mean arterial blood pressure (MAPB) in combination with cerebral vasodilatation would decrease the microvascular perfusion pressure within the brain. The report of Meyer et al.,14 that phenoxybenzamine increases mean intracranial pressure (ICP) by increasing mean intracranial venous pressures tends to support the concept of dilatation of large capacitance vessels which also would tend to decrease the microvascular perfusion pressure.

(2) In addition to contributing to a decreased perfusion...
pressure throughout the brain, the ability of phenoxybenzamine to dilate both normal and spas tic vessels could effect a cerebrovascular steal of blood away from the ischemic area to normal areas. One would suspect that, due to decreased blood flow to the infarcted area, these vessels would receive less phenoxybenzamine than those in normal areas and the latter vessels would dilate more and steal blood from the ischemic area. This, in turn, would increase the size of the infarction.

(3) Nickerson has reported that phenoxybenzamine can cause nausea, vomiting, hyperventilation, motor excitability, and convulsions, as well as sedation or stimulation. These effects are unrelated to peripheral alpha-adrenergic blockade, and appear to be direct CNS effects. Alone or in combination, they could contribute to the morbidity and thus the mortality of cerebral infarction.

It would seem that the vascular effects of lowered MABP, vasodilation, and decreased cerebral perfusion pressure, in addition to the effects on intracranial dynamics of increased ICP and intracranial venous pressure, and possibly the inhibitory effects on the CNS are all effects that outweigh whatever benefit alpha-adrenergic blockade may have in post-insult treatment of cerebral anoxia. More work in the area of post-CNS insult treatment with alpha-adrenergic blockers needs to be done to determine if their detrimental effects in stroke are specifically those of phenoxybenzamine or are a general property of this class of drugs. Our study indicates that post-ischemic studies with systemic phenoxybenzamine could be harmful when done in human stroke victims.

References

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