Modification of Cerebral Ischemic Damage by Anesthetics

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SUMMARY The yield of infarcted hemispheres following unilateral carotid ligation in gerbils under ketamine anesthesia substantially exceeded that occurring under pentobarbital anesthesia. In addition to increasing the gerbil stroke model's efficiency, ketamine provided a shorter recovery period, thus allowing earlier observation of clinical signs of brain injury. These results support the contention that anesthetic agents may modify the response of central neuronal tissues to acute ischemia.

THE MONGOLIAN GERBIL has been extensively employed in studies of cerebrovascular disease. The usefulness of this model derives from the absence of a significant anastomosis between the verteobasilar and carotid arterial circulations in approximately 40 percent of adult gerbils. Because of the circle of Willis defect, unilateral carotid artery ligation often produces cerebral infarction. The yield of infarcted cerebral hemispheres has ranged between 30% and 50%.1-7

Agents used to provide anesthesia during carotid ligation in the gerbil have included ether,8 hydrogen cyanide vapor,2 nitrous oxide,7 nitrous oxide-oxygen mixtures,1 halothane-nitrous oxide-oxygen mixtures,1 halothane alone,4 and various barbiturates.2-4,6 Choice of anesthetic affects the ability to make clinical observations postoperatively, since anesthetic agents differ markedly in the relative duration of their soporific activity. Moreover, experimental evidence indicates that anesthetics may influence the extent or nature of ischemic injury. For example, nitrous oxide produces anesthesia by inducing generalized anoxia,4 which may alter the consequences of focal ischemia. Barbiturates, on the other hand, reportedly protect cerebral tissues against the deleterious effects of ischemia.9

In an attempt to assess the effects of anesthesia in the gerbil stroke model, observations were made of the neurologic and neuropathologic changes following unilateral carotid ligation performed under two different agents.

Methods

One hundred and thirty adult gerbils (Meriones unguiculatus) weighing 50-70 gms were studied. Through a ventral midline cervical incision, the right common carotid artery was ligated with 4-0 silk. Interruption of flow was assured visually and the skin closed with a single silk mattress suture. Total operative time was less than three minutes. Sixty-six gerbils were anesthetized with 44 mg/kg of ketamine HCl (Ketalar8, Parke-Davis) by single intramuscular injection, while the remaining animals received a single intraperitoneal injection, 60 mg/kg, of sodium pentobarbital.7 Ketamine produced surgical anesthesia within two to three minutes; signs of recovery appeared within five minutes and locomotion resumed 10 to 12 minutes following injection. Pentobarbital also provided anesthesia within two to three minutes; however, responses to startle reappeared only after 1.5 to 2 hours and normal locomotion resumed after a delay of approximately three hours. Locomotor circling was used as a sign of unilateral hemispherical injury.8

Surviving gerbils were killed by exsanguination 24 hours after carotid ligation. These animals were perfused in situ with 10% buffered formalin via intracardiac puncture. The brains were harvested by blunt craniectomy and stored in formalin for one to two weeks. Paraaffin-impregnated, hematoxylin- and eosin-stained coronal sections were examined for microscopic evidence of ischemic injury9 at four, equally spaced anteroposterior levels. Brains were recovered as quickly as possible from gerbils that died spontaneously within 24 hours, then processed in a similar manner.

Results

Fifty-two of the 66 ketamine-treated gerbils survived the 24-hour period of observation as opposed to 51 of the 64 receiving pentobarbital. Thus, both groups had approximately the same 20% mortality rate (X2 = 3.4; p > .05). Substantial differences between the two treatment groups were observed, however, in the incidence of neurologic and neuropathologic evidence of brain injury. When evaluated three hours after carotid ligation, circling behavior was observed in 59% of ketamine-treated gerbils but in only 29% of those receiving pentobarbital (table 1). Among gerbils surviving 24 hours, microscopic evidence of infarction appeared in 40 (77%) of the ketamine-treated animals and in 19 (37%) of those receiving pentobarbital (X2 = 23.2; p < .001). Brains from animals not surviving the 24-hour period showed microscopic evidence of ischemic injury. Thus, for the entire group studied, the incidence of cerebral infarction in ketamine-treated gerbils is 64% greater than the incidence in gerbils having carotid occlusion under pentobarbital anesthesia (table 2). No distinction in histopathological features could be seen when contrasting the animals given ketamine with those given pentobarbital.

Discussion

The above results indicate that incidence of neurologic or histopathologic evidence of cerebral infarction in gerbils receiving unilateral carotid ligation under pentobarbital anesthesia is substantially less than in gerbils subjected to the same procedure during ketamine anesthesia. The incidence of infarction in barbiturate-anesthetized gerbils closely matches that reported in previously published studies.2-4 Although no reports of gerbils undergoing uni-
lateral carotid ligation with ketamine anesthesia are available for comparative purposes, a primate model of cerebral infarction shows cerebral ischemic injury to be significantly more extensive in rhesus monkeys receiving middle cerebral artery occlusion under ketamine than under barbiturate anesthesia.11

Two possibilities may explain the differences noted with ketamine and pentobarbital use. First, several earlier studies suggest that barbiturates protect central nervous tissues against ischemic damage, possibly by exerting a direct inhibitory effect on cerebral metabolism.12 The protection afforded by pentobarbital noted in the present investigation may merely reflect the relatively prolonged duration of its pharmacologic action, since the length of barbiturate-induced anesthesia far exceeded that produced by ketamine. On the other hand, the lower incidence of circling at three hours in the pentobarbital-treated group may reflect barbiturate depression of motor activity leading to a falsely low clinical indication of hemispherical injury. Unfortunately, neither the present nor previous studies permit definitive interpretation of pentobarbital’s protective qualities. A second explanation of the varying ketamine-pentobarbital effects recognizes ketamine as a phenothiazine derivative capable of elevating both cerebral blood flow and the cerebral metabolic rate for oxygen.13-16 This property of ketamine may foster a drug-induced increase in cerebral energy requirements that could aggravate ischemic injury.

The findings of this study suggest that barbiturate anesthesia may substantially decrease the incidence of infarction in various animal stroke models. It follows that use of non-barbiturate anesthetics may lead to a higher yield of infarcted hemispheres in experimental studies. Additionally, these studies should assist in the development of new pharmacologic approaches to limiting ischemic brain injury in man.

References
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