Efficacious Experimental Stroke Treatment With High-Dose Methylprednisolone

Gabrielle M. de Courten-Myers, MD; Marla Kleinholz, BS; Kenneth R. Wagner, PhD; Guohua Xi, MD; Ronald E. Myers, MD, PhD

Background and Purpose Recent studies reveal success in treating spinal cord trauma with early, high-dose methylprednisolone. As in spinal cord research, failure to find therapeutic effects with steroids in studies of acute stroke treatment may reflect institution of treatment too late and at too low dosage. We presently test the efficacy of stroke treatment with methylprednisolone administered early and at high doses using a cat temporary middle cerebral artery occlusion model.

Methods We occluded the middle cerebral artery for 4 hours in 24 pentobarbital-anesthetized cats. To enhance the probability of brain injury, we maintained the cats’ serum glucose concentrations at high levels both during occlusion and for 6 hours afterward. Using a blinded, randomized study design, we treated 12 cats with methylprednisolone (30 mg/kg IV infused over 15 minutes starting 30 minutes after occlusion followed by 5.4 mg · kg⁻¹ · h⁻¹ IV for the next 23 hours) and 12 control cats with vehicle. During and for 8 hours after occlusion, we monitored cerebral blood flow, brain and rectal temperatures, and multiple cardiovascular and blood compositional parameters. We assessed brain pathological outcome after animal survival for 4 days or after acute death from hemispheric edema.

Results Experimental and control animals showed similar early mortality rates (treated, 3/12; controls, 4/12). However, surviving methylprednisolone-treated cats (n=9) showed a mean infarct size more than six times smaller than in the control animals (n=8) (mean±SEM, 2.4±0.7% versus 15.6±6.2% of the ischemic territory, respectively; P<.05). The methylprednisolone-treated animals also showed less marked reduction in cerebral blood flow during ischemia than did the controls (mean±SEM, 58±5% versus 74±4%; P<.005).

Conclusions Administering methylprednisolone at high doses early after onset of ischemia significantly reduces tissue injury in cats that survive 4 days of temporary middle cerebral artery occlusion. This improvement in outcome occurs in the setting of significant increases in ischemic cerebral blood flow. However, methylprednisolone treatment did not reduce hemispheric edema in animals that died early after temporary middle cerebral artery occlusion. (Stoke. 1994;25:487-493.)

Key Words • brain edema • methylprednisolone • corticosteroids • cats

Although it was earlier believed that corticosteroids might be useful for stroke treatment, recent opinion holds they are ineffective in treating either the cytotoxic or the vasogenic edemas of ischemia. However, several clinical and animal experimental studies have described definite therapeutic benefits of methylprednisolone (MP) treatment in protecting the brain from injury caused by ischemia. Braughler and Lainer demonstrated MP to be effective only when administered before cerebral ischemia was produced by neck vessel occlusion. The lack of effectiveness when administered after vessel occlusion was due possibly to limited drug access to the ischemic brain caused by marked hypoperfusion during the reperfusion phase. A stroke model with a well-developed ischemic penumbra (as displayed by the cat with middle cerebral artery [MCA] occlusion and also by humans subject to major ischemic strokes) should provide drug access to the brain during ischemia. With this access, MP treatment may be effective even though the drug is administered only after occlusion has occurred.

The presence of an ischemic penumbra in a model in which a short duration of ischemia produces no neuronal injury, but in which damage progresses as the ischemia is prolonged, is important for studies of pharmacologic stroke treatment because such a model provides the possibility for a clinically relevant amelioration of outcome. MCA occlusion in cats provides a substantial ischemic penumbra in the affected hemisphere; decreasing percentages of cats remain brain-intact after 4 and 8 hours of temporary and after permanent occlusion, ie, 50%, 30%, and <10%, respectively.

487
The present study uses a hyperglycemic, 4-hour MCA occlusion model in cats to study early, high-dose MP treatment effects corresponding in timing and dose to MP used in spinal cord injury in humans. In this model, cats without treatment develop infarcts the mean size of which encompasses about 50% of the MCA territory. This infarct size readily permits drug effects to alter outcome in either direction. Indeed, some authors have suggested that use of steroids for stroke treatment may be deleterious.

Methods

We tested the efficacy of high-dose MP in treating stroke using a blinded, random study design that included 12 MP-treated animals and 12 vehicle controls. The experimental model involved a 4-hour temporary MCA occlusion in cats in which hyperglycemia was maintained during and for 6 hours after MCA occlusion. Maintaining hyperglycemia in the animals increases their vulnerability to injury from reversible focal ischemia. The details of the methods used in the present study follow those already described.

MP Treatment

We structured the MP treatment regimen used in the present study after that described for treatment of acute spinal cord trauma in humans. Thus, we infused MP 30 mg/kg body weight IV over 15 minutes starting 30 minutes after MCA occlusion. We followed this initial high dose with a maintenance dose of 5.4 mg/kg • h⁻¹ starting 90 minutes after occlusion and lasting for the next 23 hours. We administered the same volumes of the control animals as we gave of the drug to the experimental animals. All members of the investigative team carrying out the experimental procedures were blinded regarding the composition of the solutions administered; the code was broken only after all end points had been assessed.

Anesthesia and Physiological Monitoring

The conditioned cats used in the present study were deprived of food for 48 hours (but allowed free access to water) to provide stable serum glucose concentrations during the study period. On the day of the procedure, we anesthetized the cats with pentobarbital 35 mg/kg IV. Thereafter, we provided 2 mg • kg⁻¹ • h⁻¹ pentobarbital supplements during the period of MCA occlusion and throughout the ensuing 8 hours of postoperative monitoring. We catheterized the right femoral artery and vein to monitor the mean arterial blood pressure (MABP) and heart rate, to sample the arterial blood for acid-base and respiratory gas determinations, to infuse 10% glucose solutions intravenously to administer drugs or vehicle, and to transfuse donor blood periodically to compensate for blood loss caused by sampling or surgery. We started 100% glucose infusions intravenously an estimated 1 hour before MCA occlusion and adjusted the infusion rate to maintain the serum glucose concentration at 20 to 22 mmol/L during and for 6 hours after occlusion. We maintained the cats' body temperature at 38.5±0.5°C by applying external heat as needed. We also monitored multiple cardiovascular and blood compositional parameters and brain temperature throughout the same period. We estimated the ages of the animals using the 5-point scoring system described by Tomita et al.

Animal Exclusion

Animals were excluded from the study if they sustained >10 mL blood loss during surgery; for persistent bleeding into the subarachnoid space; because of uncertainty of aneurysm clip placement during surgery; for intercurrent viral illnesses (pneumonias) during animal survival; for deviant physiological values including MABP reductions <85 mm Hg; for a body temperature <37.5°C or >40.0°C; for a PaO₂ <80 mm Hg; for a PaCO₂ <50 mm Hg; or for a blood pH <7.10. Those cats that died from hemispheric edema and brain stem compression during the first days after MCA occlusion were included in the study because such brain edema development and acute animal death represents one of the expected outcomes of MCA occlusion.

Postoperative Care and Neurological Evaluation

All cats received routine postoperative care until they either (1) died within the first 2 days of hemispheric edema and brain stem compression or (2) recovered from anesthesia and their condition stabilized. We maintained surviving cats for 4 days in a standard animal-care setting. During the period of postoperative maintenance, they received intramuscular analgesics (nalbuphine hydrochloride 1 mg/kg TID). We evaluated each animal's neurological status daily following the procedure. After the cats survived for 4 days, they were deeply anesthetized with pentobarbital 60 mg/kg IP. After they reached deep anesthesia, we perfused their bodies with 10% buffered formalin. We removed their brains and the brains of animals that died spontaneously from hemispheric edema and fixed or post-fixed them for 2 weeks in buffered formalin.

Brain Pathological Examination

We examined the formalin-fixed brains grossly for evidence of edema, tissue herniation, and areas of cortical softening or discoloration. Furthermore, we assessed the extent of brain herniation (a measure of brain edema in fixed brains) semiquantitatively using the sums of 0 to 4+ scores depicting the degrees of herniation at five locations: posterior cingulate cortex, herniation past the tentorium ipsilaterally (1) and contralaterally (2) to MCA occlusion, (3) orbitalfrontal cortex herniation through the parachiasmatic bone opening used for MCA occlusion, (4) herniation of the vermis through the foramen magnum, and (5) shift across the midline of the ischemic hemispheric tissue. We then sliced the brains coronally into six standard sections and embedded them in paraffin. Whole-mount sections were stained with hematoxylin and eosin and examined microscopically.
We estimated infarct sizes morphometrically from the microscopic brain sections in all cats killed electively after 4 days of survival. Areas of tissue injury or infarction and total ipsilateral cerebral hemispheric areas were measured on each of the six standard brain sections using computer-assisted morphometry (BioQuant, Nashville, Tenn.). The sum of the total brain parenchymal areas in the affected hemisphere was set as 100%, and the sum of the infarcted areas was expressed as a percentage of the whole hemisphere. Because the area measurements are taken from standard brain sections encompassing the entire hemisphere, the area measurements are proportionate to volume. By expressing the infarct as a percentage of hemispheric volume, the influence of the variable tissue shrinkage that develops during dehydration and paraffin embedding is minimized. Finally, we expressed the volume of an infarct as a percentage of the MCA territory assuming this to be one half of the total hemispheric volume (based on unpublished carbon black injection studies).

We defined two distinct categories of brain pathological outcome in the present study: (1) instances in which the cats died in the first 2 days after MCA occlusion from marked edema of the ischemic MCA territory causing herniation of brain tissue and brain stem compression, and (2) instances in which the cats survived and were killed electively 4 days later to measure infarct size. We also used a third measure of outcome in which the animals of the first two outcomes were combined, including those that died early from hemispheric edema and those that survived with microscopically well-defined infarcts. In this third measure of outcome, cats that died early from hemispheric edema were assigned maximal infarct volume values of 100% since all such animals showed both the gross and the microscopic findings of edema and acute tissue infarction (pale-staining vacuolated brain with acute neuronal changes) that affected the entire estimated MCA territory.

Statistical Analyses

We compared the two animal groups with respect to five different physiological and CBF values measured at six separate time points using ANOVA. We used median infarct volumes in those instances when we made comparisons between groups that also included cats that died early from hemispheric edema. We used median values in these comparisons because median values are not affected by the values of animals that died acutely because (1) the percentage of tissue infarcted in such animals likely is higher than that in the surviving animals and (2) the percentage of animals that died acutely from hemispheric edema is less than 50% of each group. For comparisons of infarct size, we used the square root transformation to approximate the normality condition and performed the one-way ANOVA procedure with the transformed and nontransformed values both for the survivor and combined fatal and survivor groups.

Results

The MP-treated and the control animal groups were closely comparable regarding the values of their cardiovascular and blood compositional parameters, their brain and core temperatures, and their estimated volumes as can be seen from the Table. Only one group comparison was significant: The MP-treated group at 8 hours after MCA occlusion showed a significantly higher serum glucose concentration compared with the untreated controls (glucocorticoid effect). Because elevated serum glucose concentration adversely affects the brain's pathological response to focal ischemia,11 the smaller infarct sizes in MP-treated surviving animals occurred despite, rather than because of, this difference in glycermia.

The rates with which the cats of the two comparison groups died in the first 2 days from hemispheric edema and brain stem compression and the infarct sizes of the surviving animals of the two groups are presented in Fig 1. The 12 MP-treated cats showed a mortality rate of 25% and an infarct size in the 9 surviving animals of 2.4±0.7% (mean±SEM) of the MCA territory. The 12 animals that served as vehicle controls displayed a 33% mortality rate, whereas the 8 surviving animals in this group showed an infarct size of 15.6±6.2%. This difference in infarct size was statistically significant (P<.05, one-way ANOVA with square root transformation; P=.02, one-way ANOVA without transformation). The median infarct size for the combined fatal and survivor groups was 3.8% compared with 30.2% of the ischemic territory in MP-treated and control groups, respectively (P>.10). The herniation scores of the animals that died acutely were similar in the MP-treated and the untreated control groups, respectively: n=3, 12.7±4.2 versus n=4, 11.0±2.6 (mean±SD).

The MP-treated cats experienced significantly higher CBFs during ischemia than did the vehicle control animals, whereas the CBF rates for the two groups during reperfusion were similar (Fig 2). Thus, the treated and the control cats showed average reductions in CBF during ischemia of 58.0±4.7% and 73.8±3.6%, respectively (mean±SEM; 32 and 33 measurements, P<.05). As in the two groups as a whole, the subgroup of 3 treated cats that died acutely from hemispheric edema showed less marked reduction in CBF during ischemia (69±2.8% [8 measurements]) than did the 4 control animals that similarly died acutely (96±2.5% [9 measurements]), P<.05.

The MP-treated cats that died from hemispheric edema survived longer after MCA occlusion than did the vehicle controls that similarly died acutely (7 to 25 hours versus 4.25 to 10 hours, respectively). The MP-treated animals also manifested an average ischemic and early reperfusion brain temperature that was significantly higher than in the controls (37.6±0.17°C [53 measurements] versus 37.1±0.4°C [28 measurements]; mean±SEM; P<.05). The 8 surviving animals in the MP-treated group showed more preserved ischemic CBF in the MP-treated group. Because even small reductions in brain temperature can reduce ischemic neuronal injury,16 smaller survivor infarct of the MP group occurred despite, rather than because of, this group's higher brain temperature. Finally, the treated cats showed significantly lower MAP values after clip release (pooled values at 4, 6, and 8 hours) than did the vehicle controls, ie, 125±3 mm Hg (35 measurements) versus 141±4 mm Hg (32 measurements), P<.01.

Discussion

The present study demonstrates that high-dose MP, administered shortly after cerebrovascular occlusion, causes a sixfold reduction in mean infarct size in cats that survive a 4-hour temporary MCA occlusion. This beneficial effect was achieved with a treatment schedule that started with a rapid MP infusion of 30 mg/kg body weight beginning 30 minutes after occlusion, followed by MP infusion of 5.4 mg·kg⁻¹·h⁻¹ for 23 hours.

This effect of MP in protecting the brain from MCA occlusion parallels its efficacy in protecting the spinal
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time</th>
<th>MP Group</th>
<th>Vehicle Group</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain temperature, °C</td>
<td>-1 hour</td>
<td>37.1±0.7</td>
<td>37.3±0.7</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0 hour</td>
<td>37.1±0.7</td>
<td>37.3±0.7</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>2 hours</td>
<td>37.7±1.1</td>
<td>36.9±1.3</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>4 hours</td>
<td>37.5±0.8</td>
<td>37.0±1.3</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>6 hours</td>
<td>37.9±0.9</td>
<td>37.3±0.7</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>8 hours</td>
<td>37.4±0.9</td>
<td>37.2±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Age score</td>
<td></td>
<td>4.08±1.26</td>
<td>3.58±1.73</td>
<td>NS</td>
</tr>
</tbody>
</table>

MP indicates methylprednisolone; MABP, mean arterial blood pressure; bpm, beats per minute; and NS, not significant.

*Two-way ANOVA.
The treated cats of the present study showed higher CBF rates in the ischemic brain territory during ischemia than did the controls, not only in those cats that survived to develop the smaller infarcts but also in the animals that died early of hemispheric edema. MP treatment did not reduce the frequency with which the cats died acutely after temporary MCA occlusion and did not affect the extent of brain herniation exhibited by these animals. Enhancement of blood flow caused by MP treatment during MCA occlusion may partly explain the reduction in tissue infarct size. However, the deaths of the treated animals took place at ischemic CBF levels that untreated animals survived. Thus, the mechanism responsible for infarction and fatal ischemic edema may be distinct in this temporary MCA occlusion model. We did not determine whether MP increased ischemic CBF by dilating cerebral blood vessels. However, such blood vessel dilation may be inferred since MP administration reduced MABP.

The finding that MP treatment fails to reduce mortality from hemispheric edema in the present investigation is surprising because other studies with dexamethasone have described reductions in both focal and global brain edema in cerebral ischemia.25-27 Thus, Tosaki et al27 showed that dexamethasone (2 mg/kg given 5 hours before bilateral carotid occlusion in rats) significantly reduces mortality by suppressing the development of brain edema as measured by changes in brain water and electrolyte contents. Also, in acute head trauma in humans, early high-dose MP treatment (30 mg/kg every 6 hours given twice, then 250 mg every 6 hours given eight times, then tapering over 8 days) markedly reduced the mortality rate.28 Thus, the pathophysiologic effect of dexamethasone from trauma may be more susceptible to be reduced by high-dose MP than is the edema associated with ischemic brain reperfusion.

The present study suggests that protection of the brain from ischemia by high-dose MP is mediated in part by improvements in blood flow. However, other studies suggest that glucocorticosteroids can protect the brain without such changes in CBF.29,30 Dexamethasone administered at low doses to newborn rats 24 hours (but not 3 hours or immediately) before exposure to 3 hours of hypoxia (8% O2) plus carotid artery occlusion protects the brain. This effect was seen only in newborns; adult treatment failed to show such benefits. However, dexamethasone treatment of the type described profoundly affects the rat pups’ glucose metabolism, which may explain its brain-protective effects. Both the rat pup controls and those pretreated immediately or 3 hours before exposure all developed a marked hypoglycemia (to approximately 2 mmol/L blood glucose concentration) by the end of exposure, whereas the pups treated 24 hours before exposure maintained their blood glucose concentrations in the normal-to-slightly hyperglycemic ranges. Since reduction in serum glucose concentration below normal is detrimental during exposure to focal cerebral ischemia, regarding exposure to both temporary and permanent cerebral blood vessel occlusion,31-33 the fact that dexamethasone preserves normoglycemia in a model that otherwise becomes markedly hypoglycemic (during hypoxia/ischemia) likely accounts for the reported amelioration of outcome. The basis for this effect being restricted to newborns may reflect the newborn’s restricted glucose reserves, which appear to
be increased by dexamethasone administration 24 hours
earlier. Thus, the beneficial effects that pretreatment
with low-dose dexamethasone present appear ade-
quately explained by this drug’s effects on glucose
metabolism. In contrast, it seems likely that the benefi-
cial effects of high-dose MP in the present model are
mediated in part through the role of MP in increasing
CBF during ischemia.

Conclusion
The present findings indicate that early treatment
with high-dose MP during 4 hours of temporary MCA
occlusion in the cat significantly reduces the brain
damage produced in animals that survive. This evidence
that high-dose MP limits ischemic brain damage in
animals suggests that it may act similarly in humans.
Thus, the possibility that early high-dose steroid use
may be effective for the treatment of stroke in humans
needs to be reevaluated. However, the encouragement
gendered by the present results is dampened by the
fact that high-dose MP treatment fails to reduce early
mortality from infarct edema. The challenge remains as
to how to control the edema development in brain areas
injured by ischemia after reestablishment of blood flow.
A solution to this problem would provide the basis to
enable stroke patients to fully benefit from reestab-
lished blood flow in areas of focal ischemia. Control of
such edema would make it possible to prevent a major
portion of acute, stroke-related mortality and to im-
prove stroke outcome as a whole and not only in a
subgroup of patients.

Acknowledgments
This work was supported by a Grant-in-Aid from the
American Heart Association cosponsored by the National
Center and the Ohio Affiliate (91-4890). The authors thank Dr
Edward Hall, CNS Disease Research Unit, at the Upjohn
Company, Kalamazoo, Mich, for kindly supplying the methyl-
ated solution. 9. Heiss WD. Flow thresholds of functional and morphological

References
1. Meyer FB, Sundt TM Jr, Yanagihara T, Anderson RE. Focal
cerebral ischemia: pathophysiology mechanisms and rationale for
3. Anderson DC, Cranford RE. Corticosteroids in ischemic stroke.
4. Braughler JM, Lainer MJ. The effects of large doses of methyl-
prednisolone on neurologic recovery and survival in the Mongolian
gerbil following three hours of unilateral carotid occlusion. CNS
5. Braughler JM, Hall ED. Current application of “high-dose”
6. Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W,
Baskin DS, Eisenberg H, Flamm E, Leo-Sommers L, Maroon J,
Marshall LF, Petos PL, Piekmeier M, Songstad VCH, Wagner FC,
Wilberger JE, Winn HR. A randomized controlled trial of methyl-
prednisolone or naloxone in the treatment of acute spinal-cord
7. Astrup J, Siegjo BK, Symon L. Thresholds in cerebral ischemia: the
8. Marcoux FW, Morawetz RB, Crowell RM, DeGirolami U, Halsey
HJ Jr. Differential regional vulnerability in transient focal cerebral
9. Heiss WD. Flow thresholds of functional and morphological
10. de Courten-Myers GM, Myers RE, Kleinholz M, Wagner KR.
Effects of normo- and hyperglycemia on reversibility and exacer-
batation of outcome after clip release after MCA occlusion in cats.
11. de Courten-Myers GM, Kleinholz M, Wagner KR, Myers RE.
12. Sapolsky RM, Pulsinelli WA. Glucocorticoids potentiate ischemic
injury to neurons: therapeutic implications. Science. 1985;229:
1397-1400.
13. de Courten GM, Myers RE, Schoolfield S. Hyperglycemia enlarges
14. Passzor E, Symon L, Dorsch NMC, Brandt NM. The hydrogen
clearance method in assessment of blood flow in cortex, white
perfusion hyperemia” following middle cerebral arterial occlusion
16. Busto R, Dietrich WD, Globus MW-T, Valdes I, Scheinberg P,
Ginsberg MD. Small differences in intraschismic brain tem-
perature critically determine the extent of ischemic neuronal
17. Anderson DK, Saunders RD, Demediuk P, Dugan IL, Braughler
JM, Hall ED. Lipid hydrolysis and peroxidation in injured spinal
cord: partial protection with methylprednisolone or vitamin E
and selenium. CNS Trauma. 1985;5:257-267.
18. Braughler JM, Hall ED, Means ED, Waters TR, Anderson DK.
Evaluation of an intensive methylprednisolone sodium succinate
19. Sandler AN, Tator CH. Effect of acute spinal cord compression
1976;45:660-676.
20. Anderson DK, Means ED, Waters TR, Green ES. Microvascular
perfusion and metabolism in injured spinal cord after methylpred-
21. White YJ, Yen V, Blight A. Extracellular calcium ion activity in
high doses of dexamethasone on cerebral blood flow in patients
with cerebral tumors. In: Hartmann A, Brock M, eds. Treatment of
23. Chyatte D, Rusch N, Sundt TM Jr. Prevention of chronic experi-
mental cerebral vasospasm with ibuprofen and high-dose methyl-
24. Hall ED, Travis MA. Attenuation of progressive brain hypo-per-
fusion following experimental subarachnoid hemorrhage by large
intravenous doses of methylprednisolone. Exp Neurol. 1988;99:
594-606.
25. Bartko D, Reulan HJ, Koch H, Schuurmann K. Effect of dexa-
methasone on the early edema following occlusion of the middle
cerebral artery in cats. In: Strickler and Brain Edema. New York,
26. Okamatsu S, Peck RC, Lefer AM. Protective actions of dexam-
Takai I, Szekeres L. Actinomycin D suppresses the protective
effect of dexamethasone in rats affected by global cerebral
clonidine in the management of severe head injury. Neuro-
29. Barks JD, Post M, Todor UI. Dexamethasone prevents hypoxic-
ischemic brain damage in the neonatal rat. Pediatr Res. 1991;29:
558-563.
30. Tuor UI, Simonse CS, Barks JDE, Post M. Dexamethasone
prevents cerebral infarction without affecting cerebral blood flow
31. de Courten-Myers GM, Kleinholz M, Wagner KR, Myers RE.
Mild insulin hypoglycemia increases fatal hemispheral edema from MCA
of plasma glucose on infarct size in focal cerebral ischemia-
33. de Courten-Myers GM, Kleinholz M, Wagner KR, Myers RE.
Normoglycemia (not hypoglycemia) optimizes outcome from
Efficacious experimental stroke treatment with high-dose methylprednisolone.
G M de Courten-Myers, M Kleinholz, K R Wagner, G Xi and R E Myers

Stroke. 1994;25:487-492
doi: 10.1161/01.STR.25.2.487

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/25/2/487

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/