Cerebral Vasodilator Therapy in Stroke

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Abstract: Cerebral vasodilating agents have been questioned as an effective form of therapy for the stroke patient and even have been considered by some to be harmful. Animal studies show that often vasodilating agents will cause an intracerebral steal, but such a reaction has rarely been demonstrated in stroke patients. Several studies measuring cerebral blood flow in man have shown that vasodilating agents will increase cerebral blood flow even in ischemic regions in some patients. Significant clinical studies have not been carried out to determine whether these agents will alter the natural history of the disease. On the basis of reported studies of the effect of vasodilating agents on the cerebral circulation, it is suggested that further laboratory and clinical studies be performed. These agents could potentially be an effective form of therapy in some patients with occlusive cerebrovascular disease.

Additional Key Words: cerebral vasodilating agents, cerebral blood flow, occlusive cerebral vascular disease

At the present time we have no specific treatment for patients with acute stroke from occlusive cerebrovascular disease other than the use of vasopressor agents in some patients and anti-edema agents in others. Since one might assume that an improvement in cerebral circulation may be of benefit to a patient with focal cerebral ischemia, cerebral vasodilating agents could be useful in increasing cerebral blood flow. The efficacy of such therapy or the rationale for its use, however, has been questioned. In fact, recently it was stated that "cerebral vasodilating agents theoretically should be harmful to the patient with cerebral ischemia" and "it now seems clear that cerebral vasodilators are worthless or even harmful." Others have suggested that such agents may be contraindicated and that present evidence provides no support for the use of vasodilators to treat acute cerebral ischemia." One must agree that there is "no clinical evidence that . . . vasodilators significantly change the natural history of acute cerebral infarction." These notions are largely based on: (1) experimental observations in animals, and (2) a lack of controlled studies of the effects of vasodilating agents on the clinical course of acute stroke patients. These studies have not been carried out, but some evidence has been obtained that cerebral vasodilating agents should be clinically evaluated. Although the value of cerebral blood flow measurements themselves have been questioned, such measurements in stroke patients have shown that with some agents, in some patients, cerebral circulation even in ischemic regions can be improved. The purpose of this review is to summarize the reported studies of the effects of cerebral vasodilating agents on cerebral blood flow (CBF), particularly in stroke patients.

First, in many animal experiments it has been shown that there is usually vasoparalysis, loss of autoregulation, metabolic acidosis and maximal vasodilatation in experimentally produced acute cerebral ischemic lesions. It was further shown that the administration of a vasodilating agent would often dilate vessels in normal regions and shunt blood from the ischemic area. This paradoxical phenomenon,
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called the “intracerebral steal,” has been demonstrated using various methods by different investigators. Experimental studies in stroke patients demonstrating the intracerebral steal, however, are rare. One explanation for this might be that experiments have not been performed soon enough after the acute episode; another may be that our methods of measurement are not sophisticated enough. Although studies that have been done usually have been carried out several days after the stroke, evidence has gradually accumulated that some vasodilating agents do improve CBF in some stroke patients. The data gathered so far seem to indicate that the use of these agents in man should not be completely dismissed and that further studies should be done.

Other than the use of carbon dioxide, which is discussed elsewhere,15 the cerebral vasodilator that was publicized first for stroke therapy was papaverine.17 In 1952 Jayne et al.18 showed, by the Kety-Schmidt method, that intravenous administration of 200 mg papaverine increased mean cerebral blood flow 13% or from 56.6 to 63.9 ml/100 gm/min in 18 patients. The authors thought that the mechanism whereby papaverine increases cerebral blood flow and decreases cerebral vascular resistance is its direct vasodilating effect on cerebral vessels. In 1961 Aizawa et al.19 reported that seven stroke patients who received 200 mg of intravenous papaverine had a significant increase in cerebral blood flow. Gottstein20 found that intravenous papaverine increased cerebral blood flow from 55.6 to 61.5 ml/100 gm/min, but he21 generally felt that “vasodilator... drugs have no significant influence on cerebral circulation when given intravenously.”

Meyer and his associates82 first gave evidence that suggested papaverine would increase oxygen availability. By continuous measurements of cerebral arteriovenous differences for oxygen pressure and saturation, the intravenous administration of 64 mg of papaverine was shown to cause a significant increase in oxygen availability. Subsequently a controlled clinical study of 79 patients by Gilroy and Meyer23 demonstrated that the course of patients with cerebral infarction could be improved as judged by a scored neurological examination. Meyer et al.24 later found that oral papaverine given to baboons would cause a sustained increase in cerebral blood flow for one hour, that is: control 50.6, 20 minutes 56.6, 40 minutes 59.5, and 60 minutes 63.2 ml/100 gm/min. They concluded that “such an observation should be relevant in the treatment of patients with occlusive cerebrovascular disease.”

In a different type of study regional cerebral blood flow measurements (rCBF) were performed by McHenry et al.25 using the Xenon injection method in six patients with angiographical evidence of focal vascular disease (table 1). Regional CBF was measured before and after administration of 100 mg of intravenous papaverine in 43 brain regions (23 nonfocal and 20 focal). Regional CBF in 8 of the 20 angiographical abnormal or focal regions increased over 20%. The hemispheric mean CBF increased significantly in five of the six individual patients with an average CBF increase for the group of from 34 to 40 ml/100 gm/min or 18%. The focal rCBF rose only 13% from 30 to 34 ml/100 gm/min. From this study one may postulate that intravenous papaverine can cause an increase in rCBF in some focal ischemic regions in some stroke patients.

Also using the Xenon injection method to measure rCBF, Olesen and Paulson8 studied 12 patients with presumed cerebral infarction or occlusive cerebrovascular disease before and after the intracarotid artery injection of 10 mg of papaverine. Although these authors concluded that “vasodilator therapy presumably decreased flow in pathological tissue and such treatment should not be employed in cerebrovascular disease,” their data did not support these conclusions. Others10 concurred that this study showed “no beneficial effects from papaverine.” Re-examination of the Olesen and Paulson data, however, shows the following results: Seven (Nos. 5, 6, 7, 8, 12, 13 and 14) of the 12 stroke patients had vascular disease with areas of focal flow abnormalities similar to those studied by McHenry et al. A focus was defined as an rCBF value 10% to 20% below the mean CBF. The mean rCBF in the focal regions increased 25% or from 27 to 37 ml/100 gm/min, while the nonfocal rCBF increased 87% or from 38 to 70 ml/100 gm/min, after papaverine (table 1). In the remaining five stroke patients (Nos. 9, 10, 11, 14 and 15) in this group, papaverine produced a mean of 103% increase in CBF. No evidence
of intracerebral steal was present in this group. The intracerebral steal was demonstrated once in another patient (No. 17) with transient ischemic attack. It is apparent that intrarterial papaverine had a greater cerebral vasodilating effect than did the intravenous drug. Both Xenon injection rCBF studies show that there is an increase in blood flow in the focal or ischemic regions, but it is less than that in the nonfocal or normal regions.

The other vasodilating agent that has lately received extensive investigation is hexobendine. In two animal studies, hexobendine was shown to increase cerebral blood flow by 15% in dogs and 40% in monkeys. Regli et al., however, found that hexobendine in cats caused a drop in blood pressure and only an increase in blood flow in two out of six animals. The first studies in patients with stroke were reported by Meyer et al. Measuring cerebral hemispheric blood flow (HBF) from bilateral hydrogen clearance curves, they found that intravenous hexobendine caused an increase in HBF in 17 of 20 measurements. The mean HBF increase was 14%, which was accompanied by an 8% fall in mean arterial blood pressure. Since CBF increased in spite of the fall in blood pressure, "the vasodilating effect of hexobendine appears to be more selective in cerebral vessels, indicating that the drug is a potent cerebral vasodilator."

In a study of ten stroke patients using the Xenon injection method to measure rCBF, McHenry et al. found 15 mg of intravenous hexobendine to be an effective vasodilator. Seven of the ten patients had a significant increase in hemispheric mean CBF. For the group, the average increase was 26%, that is, from 34 to 43 ml/100 gm/min, with a fall in cerebrovascular resistance from 3.1 to 2.5 mm Hg/ml/100 gm/min. Cardiohemodynamic measurements performed in these patients demonstrated no change in cardiac index, cardiac work, mean arterial blood pressure or heart rate after hexobendine administration. Thirty-one of the 68 regions measured in these patients had more than a 20% increase in rCBF. Of the remaining 37 regions, 32 rCBF values did not change significantly. No evidence of intracerebral steal occurred in this study of rCBF. In a similar study using the Xenon injection method with a gamma camera, Heiss et al. found that hexobendine "had a significant positive influence on cerebral blood flow." They considered hexobendine "to be a vasodilator acting on cerebral vessels and (it) may be of value in the treatment of cerebrovascular disease. . . ."
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The results of studies of other pharmacological agents alleged to cause cerebral vasodilatation and an increase in blood flow have been less impressive. Although hydergine is considered to be a cerebral vasodilator, Hafkenschiel et al. did not find intramuscular hydergine able to change CBF as measured by the Kety-Schmidt method. Similarly, Gottstein was unable to find a change in CBF after intravenous hydergine. Using the Xenon injection method to measure rCBF, McHenry et al. could not show a change in blood flow after 15 minutes from 0.6 to 1.2 mg of hydergine. Although Szewczykowski et al. found an 8% to 14% increase in CBF after intravenous hydergine, using the carbon dioxide method Meyer et al. found that cyclandelate was not able to change CBF as measured by the Kety-Schmidt method. The patients receiving the cyclandelate had a 6.51 ± 1.55 ml/100 gm/min increase in CBF which was significant. The results of other investigations of cyclandelate have been summarized and give no definitive data on its quantitative influence on CBF.

The effect of oral nylidrin on CBF measured by the Kety-Schmidt method by Eisenberg was variable in patients treated for two weeks or less. In seven patients treated for more than two weeks there was a 43% increase in cerebral blood flow. No comparable control group was tested to determine the natural course of changes in blood flow. Using the nitrous oxide method Meyer et al. found that the intravenous administration of 0.3 to 0.5 mg of nylidrin did not change CBF or oxygen consumption. Similarly Heiss et al. found total CBF to be decreased in 11 out of 15 patients receiving the drug.

The carbonic anhydrase inhibitor, acetazolamide, has been evaluated in two studies on stroke patients. Ehrenreich et al. gave 1 gm of acetazolamide intravenously to each of ten patients with intermittent cerebral vascular insufficiency. The mean CBF measured by the Kety-Schmidt method before the drug was 46.3 ml/100 gm/min. Thirty minutes after the drug the mean CBF was 76.8 and 60 minutes later was 65.4 ml/100 gm/min. The authors considered that acetazolamide acted by inhibiting carbonic anhydrase to increase Po2 and, hence, produce cerebral vasodilatation from hypercapnia. The other study in man was performed by Gotoh et al. in nine stroke patients. In this group the intravenous administration of 500 mg of acetazolamide showed a marked increase in oxygen tension and saturation of the cerebral venous blood which indicates an increase in CBF which occurred within two minutes, reaching its maximum in ten minutes and persisting for 30 minutes. Regli et al. found an increase in CBF after the administration of acetazolamide in cats with acute cerebral ischemia, but had no ready apparent explanation for the increase. These studies show that acetazolamide is an effective cerebral vasodilator to increase CBF, but they do not give evidence that this drug would be effective in altering the course of the disease in a given stroke patient.

In conclusion, in spite of the fact that the results to date of CBF measurements are not startling, they do indicate that further evaluation is worthwhile. One can only partially agree with Waltz who stated that "treatment that leads to an increase of blood flow in ischemic tissue may be of little help to the patient who has suffered a stroke, particularly if the increase of flow occurs days or months after infarction." The latter part of the statement is most likely true, but there is really no evidence that an increase of blood flow might not be of benefit to the patient with acute cerebral ischemia. On the contrary, there seems to be enough evidence to suggest that rCBF measurement should be made in patients with occlusive cerebrovascular disease to determine whether or not there is vasomotor paralysis to cerebral vasodilating agents or loss of cerebral autoregulation. With regional blood flow measurements one might be able to determine whether or not a specific therapy may be of a particular value in a given patient. One cannot accept the pessimism that there is no hope for a more thorough evaluation and a more aggressive management of the patient with an acute stroke. In spite of the tremendous variation in the natural history of acute stroke, there is little or no evidence in man to suggest that there is no potential for an improvement of overall cerebral circulation or more specifically circulation to ischemic regions via collateral circulation. There is no reason to consider that there is little or no evidence in man to suggest that there is no potential for an improvement of overall cerebral circulation or more specifically circulation to ischemic regions via collateral circulation. There is no reason to
believe that a carefully controlled clinical and laboratory evaluation of a suitable group of stroke patients should not be carried out to determine the effectiveness of therapy such as with vasodilating agents. The use of repeated rCBF measurements allows one to evaluate focal and diffuse abnormalities of cerebral circulation and to determine the effect of therapy during the acute stages. The effectiveness of therapy during the ensuing hours or days can be determined clinically and by follow-up measurements of CBF (via the nontraumatic Xenon inhalation method).

When we reach the stage of carefully evaluating the functional abnormality in cerebral circulation in each acute stroke patient, we will have made a further step in an attempt to establish more efficacious therapy to decrease morbidity and mortality from stroke.

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