Ephedrine-Induced Intracerebral Hemorrhage and Central Nervous System Vasculitis

To the Editor:

A 68-year-old right-handed man was admitted to the emergency room 2 hours after developing headache, dysphasia, and right hemiplegia. Computed tomography demonstrated a left temporo-parietal hematoma with rupture into the lateral ventricle. On admission, his wife reported his use of an over-the-counter antiasthma pill containing theophylline 0.025 gm, ephedrine 0.01 gm, caffeine 0.015 gm, and theobromine 0.025 gm. He had taken this medication for 10 years, four to six tablets a day, and had used it 2 hours before the onset of ictus. His medical history consisted of chronic obstructive pulmonary disease for 40 years. Neurologic examination demonstrated nuchal rigidity, confusion, and hemiplegia on his right side.

On the second hospital day, his level of consciousness deteriorated, and he showed an obvious dilatation of the left pupil. The hematoma was evacuated. Pathological examination demonstrated necrotizing angitis of the small vessels with infiltration of polymorphonuclear leukocytes, especially prominent in the intima. Congo red stain was negative. Angiography showed irregularity at the siphon and diffuse segmental irregularity of the intracranial medium-sized and small arteries. The patient improved with prednisone.

Ephedrine is a sympathomimetic agent and popular bronchodilator, similar to amphetamine and phenylpropanolamine in its effects. A drug-induced vasculitis is often associated with intracranial hemorrhage, while vasculitides of the central nervous system (CNS) rarely produce this finding. The features, benign course, and histologic findings of drug-induced vasculitides are also similar to each other and unlike the fatal and evolving disease seen in polyarteritis of the CNS.

The acute onset in our case is similar to another reported case of drug-induced vasculitis. This rapid onset of symptoms and the infiltration of polymorphonuclear leukocytes, particularly in the intima, seem more likely to be correlated with an immune complex-mediated process in its pathogenesis.

While the pathogenesis of drug-induced vasculitis is still unknown, withdrawal and discontinuation of the offending agent is mandatory. Our case underscores that a patient with intracerebral hematoma and no obvious etiology should be evaluated for drug-induced vasculitis.

DR. PU-AN YIN
Department of Neurology
China Medical University
Shenyang, Liaoning
The People's Republic of China

References

Pulmonary Arteriovenous Fistulas Are at High Neurologic Risk

To the Editor:

The development of neurologic complications from a pulmonary arteriovenous fistula in a case described by Reguera et al has recently been reported in two additional case reports. The suggested mechanism of paradoxical embolism from leg veins in the case of Reguera et al is interesting, but unfortunately remains unsubstantiated. While accepting the reported figures of a low incidence of pulmonary arteriovenous fistula in young stroke patients, one should not assume that neurological complications are rare in this condition; rather, it is because pulmonary arteriovenous fistulas are uncommon that they remain a small contributor to the overall burden of stroke.

The cerebral complication rate is high, particularly in untreated cases. There were three fatal strokes in 19 of 47 conservatively managed young patients; in another series of 76 patients, there was a history of cerebral abscess in 9%, stroke in 18%, and transient ischemic attacks in 37%. Embolization or surgery for pulmonary fistulas is appropriate in nearly all cases to reduce these high risks.

D.G. Grosset, BSc, MRCP(UK)
Neurology Department
Institute of Neurological Sciences
Glasgow, Scotland

References

Effect of Hyperoxia Differences During Ischemia and Reperefusion

To the Editor:

Recently, Reitan et al reported the beneficial effect of hyperbaric oxygen following ligation and section of the left carotid artery in the Mongolian gerbil. In discussing these results, the authors state, "The effects of oxygen therapy on experimental subjects is paradoxical. On one hand oxygen causes marked tissue damage and toxicity, while on the other hand it provides apparent treatment for neuronal ischemia, depending on the total dose and pressure." They then cited our work2 on the deleterious effect of therapy with 100% normobaric oxygen during reperfusion.

The following discussion may show that the results of the study by Reitan et al and the results of our studies are not necessarily contradictory or paradoxical. During ischemia, increased oxygen dissolved in plasma may supply the penumbra that surrounds the area of total ischemia with sufficient oxygen to prevent glycolysis and subsequent intracellular lactic acidosis. In other words, aerobic...
metabolism may be maintained in areas where it might otherwise be compromised. However, during reperfusion, increased oxygen dissolved in plasma supplies cells whose mitochondrial function is impaired so that reduced capacity for aerobic metabolism exists. Under these circumstances, increased oxidative stress occurs, as demonstrated in the increased production of pentane (a marker for lipid peroxidation) during hyperoxic reperfusion.

In the Mongolian gerbil, 3 hours of normobaric hyperoxic reperfusion results in greater preservation of cortical neurons as well as relative preservation of axons within the area of prior ischemic injury, but it also is associated with greater damage to white matter in the lateral corpus striatum, lateral thalamus, and mesencephalon. Macrophages are seen within the pencil-like myelinated bundles of the corpus striatum as early as the first day after ischemia. Myelin damage becomes increasingly more obvious from the sixth day to the eleventh day after ischemia.3

The areas of observed myelin damage after hyperoxic reperfusion lie in proximity to dopaminergic neurons. Brannan et al4 reported the massive release of dopamine into the corpus striatum after 15 minutes of bilateral carotid occlusion in the Mongolian gerbil. The fate of the released dopamine is not known. On the one hand, the released dopamine might be oxidized enzymatically by monoamine oxidase, a reaction that also forms hydrogen peroxide, which, in turn, inhibits the uptake of dopamine by synaptosomes. On the other hand, dopamine, which functions as a neurophysiological antioxidant,4 might be oxidized nonenzymatically to form reactive intermediates, which are able to promote oxygen free radical formation and result in further oxidative damage. Oxidation promoted by dopamine might provide an explanation for the selective sites where myelin damage is found.

The pathological finding of myelin damage and preservation of axons associated with oxidative stress concurs with the hypothesis that myelin damage results from peroxidation of lipids and oxidation of proteins. Oxidative stress may provide a common pathway for myelin damage from a variety of pathological processes.7-9

Based on this hypothesis, possible benefit of hyperbaric oxygen in multiple sclerosis (MS), a possibility mentioned in the paper by Reitan et al,1 might stem from induction of the antioxidant enzymes: superoxide dismutase, catalase, glutathione peroxidase, and other antioxidant proteins. Discrepancies in findings reported for the use of hyperbaric oxygen in MS may result from variations in the genetic capability of production of these antioxidant proteins, in dietary antioxidant and general nutritional status of the patients, and on whether the patients were in an acute phase (proposed to be associated with oxidative stress) or in a chronic phase (proposed to be associated with autoimmune mechanisms) of their illness. None of these variables have been controlled or studied in any of the reports of use of hyperbaric oxygen in MS.

Similarly, the effect of hyperbaric oxygen on reperfusion after ischemia has not been studied carefully. If, under hyperbaric conditions, dopamine were oxidized rapidly to aminochrome, with subsequent radicals, oxidative stress concurs with the hypothesis that myelin damage results from increased lipid peroxidation.2

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REFERENCES


The following is in reply:

To the Editor:

We would like to thank Dr. Mickel for an interesting discussion concerning the differing effects of oxygen therapy on experimental subjects. In our article, we mentioned that, on one hand, hyperoxia at normobaric conditions seemed to accelerate neuronal degeneration during reperfusion; yet, in our study, hyperoxia at hyperbaric conditions and with no postinsult reperfusion appeared to reduce the untoward effects of cerebral ischemia in the gerbil.2 Dr. Mickel's explanation of this seeming disparity is thoughtful and appears to have substantial merit. We never proposed that the apparent paradox was enigmatic, and Dr. Mickel's letter of enlightenment proposes a solution to the mystery.

In our animals there was an attempt to reduce the significant oxidative forces that evolve after ischemic insult in that we treated the gerbils with superoxide dismutase. Interestingly, the treatment with this free radical scavenger was not successful in long-term attenuation of the effects of permanent carotid artery interruption. Quite possibly, superoxide dismutase is a treatment substance that should be investigated during reperfusion protocols instead.

John A. Reitan, MD
Department of Anesthesiology
University of California School of Medicine
Davis, California

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Effect of hyperoxia differs during ischemia and reperfusion.

H S Mickel

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