Outcome Following Subarachnoid Hemorrhage

TO THE EDITOR: The recent article by Juul, et al. (J Neurol 41:99-103, January, 1986) is a well-documented investigation of an often-asked question. The authors have accomplished a thoughtful study to answer it.

We were disappointed, however, that no reference was made to our review of such cases.1 Compared to the authors' review and follow-up of 32 patients with subarachnoid hemorrhage (SAH) of unknown etiology over a period of “1 to 6 years,” we believe that our study of more than 10 times the number of patients who were followed for 20 years is more comprehensive. We did not specifically analyze functional status in our long-term report, although the information was in the research material. We saw no need to pursue that because most of those patients left the hospital neurologically intact. Unless they rebled, which they rarely did, they were not subsequently disabled by the SAH.

CARL J. GRAF, M.D.
Sea Island, Georgia

RESPONSE: We are thankful for Dr. Graf's comment on our article, as it gives the opportunity to right a wrong. To our knowledge, the study by Nishioka, et al.,2 is the most comprehensive work on the subject of subarachnoid hemorrhage (SAH) of unknown or "undetermined" etiology. The purpose of their study was to "determine the incidence of recurrent bleeding and the patterns of mortality during a 20-year follow-up."

These matters were, of course, also an important part of our study. Our main topics of discussion, however, addressed the problems of false-negative findings on angiography, treatment with antifibrinolytic drugs, and the functional status of the surviving patient. In disagreement with Dr. Graf, we did see the need to "specifically analyze functional status." As far as false-negative angiographic findings are concerned, Nishioka, et al.,2 stated that "unless there is evidence of a localized hemorrhage or unless SAH recurs, there is little to be gained by routinely repeating angiography." Their conclusion is, in our view, not necessarily supported by the facts, since they also stated that "in 72 patients, either a carotid or vertebral study was repeated, revealing aneurysms in 13 patients." However, they referred to a study by Forster, et al.,1 in support of their view. This latter study specifically addressed the problem of false-negative findings and is referred to in our article.

The two other main topics of discussion in our article are not dealt with by Nishioka, et al.2 This, together with a general wish to limit the number of references, led us to omit their work from our bibliography. We do, however, agree with Dr. Graf that a "study of more than 10 times the number of patients who were followed for 20 years is more comprehensive." As the study with the largest number of cases and the longest follow-up period, their article is, in our view, the most important work on the matter of rebleeding and mortality in SAH of unknown etiology.

ROAR JUUL, M.D.
TORBJORN A. FREDRIKSEN, M.D.
ROLF RINGJOEB, M.D.
University of Trondheim
Trondheim, Norway

References

Opiate Antagonists in Experimental Stroke

TO THE EDITOR: The recent paper by Baskin, et al., reports prolonged survival following experimentally induced cerebral ischemic deficits in cats treated with opioid antagonists (Baskin DS, Hosobuchi Y, Grevel JC: Treatment of experimental stroke with opiate antagonists. Effects on neurological function, infarct size, and survival. J Neurosurg 64:99-103, January, 1986). Although cerebral blood flow (CBF) was not measured in their experiments, secondary parameters possibly related to the sequela of ischemia (including infarct size, motor abnormalities, and degree of survival) were emphasized. We have the following reservations about these results:

1. With respect to the methodology used in their investigation, it has been conclusively shown that ketamine significantly alters cerebral oxygen consumption and CBF as well as increases intracranial pressure.10 Thus, the use of ketamine may have produced early metabolic derangements that had subsequent implications, making the comparison of treated and control animals of uncertain value.

2. With respect to the survival time of these animals, we have difficulty agreeing with the implication that the opioid antagonists acted on the process of cerebral ischemia in some way as to affect the survival. Since there was no description of the etiology of death in these animals, it is conceivable that shock preceded their death. In this context, opiate antagonists are known to improve the survival rate6 by a mechanism...
postulated to involve hypothalamic functions. Thus, the survival rate of the animals could represent a mechanism associated with shock rather than reflect ischemic damage to focal cerebral areas.

3. With respect to the acute improvement of focal motor functions purportedly related to the ischemic regions, these may indeed not necessarily be associated with effects of naloxone on focal cerebral ischemia as the authors stated. However, we postulate that opiate antagonist-induced reversal of neuronal electrophysiological depression may be detrimental to the survival of neurons. Since the release of endorphins during the ischemic process may serve to protect the "idling neurons" in a zone bordering on areas of infarct, administration of opiate antagonists could perhaps impair eventual functional recovery. Although this hypothesis has not previously been extended, circumstantial evidence supporting it includes the knowledge that opioids or opiates suppress neuronal activity, reduce the cerebral metabolic rate (CMRO2) up to 85% with smaller reductions of CBF, and inhibit depolarization-induced release of noradrenaline from cerebral slices, implying that reversal of these possible protective functions of the opioids could be potentially harmful to the recovery of these neurons. Indeed, Cutler, et al., have reported worsening of neurological deficits following administration of naloxone to humans with stroke. Thus, concepts of the use of opioid antagonists in the therapy of ischemia may need to be reconsidered.

Finally, in attempting an explanation of the potential effects of opiate antagonists on cerebral ischemia, the central role of the hypothalamic-locus ceruleus (LC) endorphinergic-noradrenergic axis should be mentioned. Endorphinergic inhibitory projections from the arcuate nucleus of the hypothalamus to the LC may have an impact on neurogenic control of CBF. The LC is known to control CBF and to be associated with the induction of rapid eye movement sleep, a state reported to be related to significant increases in CBF. Thus, blockade of endorphin activity would be expected to increase noradrenergic activity, with possible changes in CBF partially accounting for some of the observed effects of naloxone on ischemia.

References

RESPONSE: We appreciate the comments of Drs. Iacono and Sandyk and are gratified to see others speculate on the mechanism of action of opiate antagonists in cerebral ischemia. This important effect must be understood at the molecular level before therapeutic strategies can be appropriately designed for patients with cerebral ischemia. We cannot, however, agree with their conclusions.

Iacono and Sandyk correctly stated that cerebral blood flow (CBF) was not measured in our experiments. However, as referenced in our report, we have previously measured CBF in primates with focal cerebral ischemia before and after naloxone administration and have detected no changes.

Ketamine, in anesthetic doses, can alter cerebral metabolism, but recent reports suggest a protective effect in ischemia through interactions with the N-methyl-D-aspartate receptor. Moreover, the dosage used in our studies was only mildly sedating, and the effects of ketamine were present in both the control and experimental groups since both received equal doses of ketamine at the same time.

We are aware of the role of opiate antagonists in the treatment of shock. However, as referenced in our paper, several investigators have previously shown that opiate antagonists have no effect on blood pressure, heart rate, arterial blood gases, cardiac output, or cardiac filling pressures in primates with focal cerebral ischemia.

The neurological deficits "purportedly related to the ischemic regions" were due to classic middle cerebral artery infarctions, documented histologically in every animal. While it is interesting to speculate that opiate antagonists could, under certain contrived conditions,
worsen neurological function, there is no experimental or clinical evidence that this can ever occur.

The report by Cutler, et al., showed no statistically significant difference in motor function in patients with cerebral ischemia who were treated with naloxone. The two patients in their study who became slightly worse were critically ill with progressive deterioration before treatment, prompting the authors to conclude that “no cause and effect relationships between naloxone and subsequent deterioration were established.” Indeed, their dosage and timing of therapy could be expected to produce no effect, as the doses were too low and treatment was, in general, too late.

We are puzzled by the final point made by Drs. Iacono and Sandyk, as they propose a mechanism of action for opiate antagonists in cerebral ischemia, after implying that there is no such effect. It is not correct that the locus ceruleus is “known to control CBF . . .”. but even if it did, no one has measured a change in CBF in focal cerebral ischemia after the administration of opiate antagonists.

The fact that opiate antagonists can improve motor function under certain conditions of focal cerebral ischemia provides us with a clue to as to how this occurs, and continued detailed laboratory investigation is very much needed to systematically test various hypotheses.

References

Dexamethasone in Severe Head Injury

To THE EDITOR: The recent article by Dearden, et al., was very interesting (Dearden NM, Gibson JS, McDowall DG, et al: Effect of high-dose dexamethasone on outcome from severe head injury. J Neurosurg 64:81-88, January, 1986). I agree with the authors that it is still unclear whether glucocorticosteroids were able to counteract traumatic brain edema under nonexperimental conditions. Yet, because of the literature cited the reader expects to find a discussion of some principles that are not taken into full account in this study:

1. Over 50% of the patients had a Glasgow Coma Scale (GCS) score of 3 to 5 before intubation, and 22% of those in the steroid group had scores of 8 or more. There are no exact data for making a prognostic categorization of survival rate after head injury differed considerably. It would seem to be more useful to separate patients into several age groups, especially with regard to very young and very old patients.

2. Forty-one percent of the patients received their first dose of steroid more than 6 hours after trauma, 26% more than 8 hours after trauma, and probably 26% within the first 4 hours after trauma. This is not only inhomogeneous but also partially exceeds the current pharmacological recommendations for the timing of glucocorticoid treatment after head injury.

4. The regimen of 1.4 mg/kg/day of dexamethasone on Days 1 to 3 in adults is much less than the minimum dose of 6 mg/kg/day now demanded.

No one expects dexamethasone to be a panacea, but it probably holds some benefit for a yet-to-be-defined subgroup of patients. From a statistical point of view, it is impossible to evaluate the respective differences if a study includes a large number of patients with too poor or too good a prognosis: nothing will help the first group, and steroids will not help the second.

References

TO THE EDITOR: We read with interest the article by Dearden, et al., which reported the results of a large double-blind trial of the effects of high-dose dexameth-