Aspirin for the Limping Brain

EARLY IN THIS CENTURY J. Ramsey Hunt suggested that occlusive disease of the carotid arteries in the neck was causally related to stroke and noted in passing that one of the symptoms of cerebral disease arising from this relationship was cerebral intermittent claudication, the limping brain. Almost one-half century later a series of reports reaffirmed the relationship of extracranial arterial disease to the most common form of stroke, ischemic cerebral infarction. The term transient cerebral ischemic attack (TIA) was born and such brief attacks of focal cerebral dysfunction were assigned clinically either to the carotid or verteobasilar arterial systems. Emphasis was correctly placed on extracranial arterial stenosis as the most common lesion underlying cerebral infarction. The origins of the internal carotid arteries and vertebral arteries were identified as major sites of extracranial atheromatous disease. The major pathogenetic link, arterial-arterial embolism, connecting extracranial arterial occlusive disease to transient monocular blindness and, by inference, TIA, was provided by careful studies of the ocular fundus during embolization. As early as 1954 surgical remedies were suggested and applied. Anticoagulant therapy was employed to control thrombotic changes superimposed on the extracranial atheromatous disease. The development of new and safe arteriographic contrast agents and the refinement of serial arteriographic equipment removed the study of extracranial and intracranial arterial disease from the pathologist’s domain and made it part of everyday medical practice.

We have now had almost a generation to evaluate the accuracy of these observations and the role of surgical and anticoagulant therapy. Parallel epidemiological studies have attempted to relate the probability of completed stroke to carefully defined criteria for TIA both in the carotid and the verteobasilar territories. Sadly, Kuller’s statement that we continue to have a less than perfect understanding of the natural history of occlusive cerebrovascular disease remains valid. Kuller’s other major observation also remains valid: that prospective clinical trials of vascular surgical and anticoagulant therapy have revealed that both treatment modalities decrease the frequency of TIA’s and that neither has a demonstrated significant impact on mortality or stroke. The current status of antithrombotic therapy in the prevention of ischemic stroke in all clinical studies, controlled and uncontrolled, has very recently been extensively reviewed in this journal. In spite of the expertise of many investigators the therapeutic conclusions reached are, even today, clouded by a host of minor and major methodological errors. The essential problem remains; we still cannot predict whether the patient describing a typical attack of transient monocular blindness or transient focal cerebral ischemia will have a stroke.

Careful population studies suggest that as many as 37% of all patients suffering their first TIA would, if untreated, suffer a completed stroke within five years with approximately one-half of the completed strokes occurring within one year of the first transient episode. Reviews of control populations in therapeutic clinical trials indicated that between 25 and 40% of patients with transient attacks eventually have a cerebral infarction if followed for a period of five years. Thus, while no well defined natural history of ischemic stroke exists, it is now possible to estimate that there is approximately a 7% per year risk of stroke in a patient who presents with multiple TIA’s and that the risk is greatest in the first few months to one year after the presenting attack. While we cannot predict whether a specific individual with transient cerebral or retinal ischemic episodes will have a stroke we are nevertheless obliged to seek predictive indices which will allow the appropriate application of a safe therapy with the highest possible benefit to risk ratio.

Observations of vascular surgeons removing stenotic lesions at the origin of the internal carotid arteries, in England as in America, strongly suggest that it is not the atherosclerotic lesion per se but superimposed thrombotic changes, beginning with platelet aggregation and the development of fibrinoplatelet and mixed clot, which provide the pathogenic basis for most TIA’s and, often, cerebral infarction. In this setting, therefore, the neurological community welcomed with enthusiasm the observations of Mustard’s group and later those of Weiss and Zucker and their colleagues that non-steroidal anti-inflammatory drugs, specifically aspirin and sulfinpyrazone, would inhibit platelet aggregation in vitro and intra-arterial clot formation in vivo.

The Aspirin in Transient Ischemic Attack (AITIA) study was initiated on the basis of these observations. The aim in the three year period of funding of this multiple center effort was to determine whether or not aspirin, a known and safe platelet inhibitor, could significantly reduce the incidence of TIA and, if possible, of stroke in a population at risk when compared to placebo treated controls. The results of this carefully designed study are published in this issue. It is our purpose to assess briefly both the successes and the failures of this effort.

At the beginning of the AITIA study, in spite of numerous anecdotal reports of the effectiveness of aspirin in the reduction of numbers of episodes of transient monocular blindness and TIA, there was considerable doubt that a controlled
trial would reveal any therapeutic effect. The participants, therefore, agreed that the study should be restricted to patients exhibiting the signs and symptoms suggestive of carotid artery territory ischemia occurring within three months of randomization and allocation to treatment with aspirin or placebo. Further, it was recognized that a single TIA could well arise from release of necrotic material from a complex atheromatous internal carotid artery lesion and that multiple episodes were more likely to be related to embolization of superimposed fibrinoplatelet or mixed clot material. It had also been our experience, reconfirmed by this study, that patients were twice as likely to present with multiple attacks when symptoms occurred in the carotid arterial territory. It was expected that at least a third of the cohort would continue to have TIA's if untreated. Thus, a relatively small number of patients allocated either to aspirin or placebo treatment categories might well demonstrate a significant reduction in the frequency of TIA's. Not unexpectedly the major, and indeed, the only significant finding of the study has been the reduction in the lumped number of "unfavorable" outcomes in the six month period following randomization and allocation to aspirin or placebo treatment categories. These unfavorable outcomes included deaths due to cerebral infarction and to cardiovascular disease, death due to intracerebral hemorrhage, non-fatal cerebral infarction, retinal infarction and an excessive ratio of TIA's in the post-allocation period when compared to the pre-allocation period. Of a total of 88 patients treated for up to six months with aspirin, only 15 (19.2%) suffered an unfavorable outcome. Of a total of 90 patients in the placebo treatment category 34 (44.2%) experienced an unfavorable outcome. While there were more non-fatal and fatal cerebral infarctions in the placebo treatment category it is clear from the data that the significant factor favoring aspirin over placebo treatment is the marked reduction in an excessive ratio of TIA's in the aspirin treatment group. Thus, aspirin joins anticoagulant and surgical therapy as an effective means of reducing TIA's.

On the other hand, aspirin continues to share with surgical and anticoagulant therapy an equivocal role in the prevention of completed stroke. Clearly, when the medically treated patients in the AITIA study are taken as a whole, the cumulative probability of death, non-fatal cerebral infarction and retinal infarction is not significantly altered by aspirin therapy. Burdened, however, by the knowledge that a single TIA might not have the same pathogenic mechanism as multiple TIA, the participants have retrospectively stratified the major end points of death and non-fatal cerebral or retinal infarction into groups with either single or multiple attack of TIA. This statistical device has forced an unequal allocation of patients into treatment and control groups with approximately equal numbers of major variables. Nevertheless, from the statistical viewpoint randomization remains "the only game in town." The significant results reported by the AITIA study, therefore, lend validity to the early observations that aspirin has a physiologic effect. It significantly reduced the incidence of TIA. As of this time, however, there is no hard evidence that aspirin offers protection from that most feared consequence of cerebrovascular occlusive disease — completed stroke due to cerebral infarction.

WILLIAM K. HASS, M.D.

References

ASPIRIN FOR THE LIMPING BRAIN/Hass


Controlled Trial of Aspirin in Cerebral Ischemia

WILLIAM S. FIELDS, M.D., NOREEN A. LEMAK, M.D., RALPH F. FRANKOWSKI, PH.D. AND ROBERT J. HARDY, PH.D.

SUMMARY A double-blind trial of aspirin for the treatment of cerebral ischemia was begun in 1972 and continued for 37 months. This was accomplished despite difficulties in controlling a long-term study of a drug which has widespread availability and consumption. This was accomplished despite difficulties in controlling a long-term study of a drug which has widespread availability and consumption.

Patients (178) who had carotid transient ischemic attacks (TIAs) were randomly allocated to aspirin or placebo and followed to determine the incidence of subsequent TIAs, death, cerebral infarction or retinal infarction.

IT IS GENERALLY acknowledged that aspirin (acetylsalicylic acid) alters the aggregation-release reaction of blood platelets.18 Aspirin inhibits collagen-induced platelet aggregation in vivo1 and in vitro.2 The response of platelets to epinephrine-induced release of ADP in the second wave of aggregation is also blocked by aspirin.19 Aspirin inhibits both collagen and ADP-induced activation of platelet factor III (phospholipid-like factor) and the release of ADP of platelet factor IV in vitro and in vivo.3,4 but does

Analysis of the first six months of follow-up revealed a statistically significant differential in favor of aspirin when death or cerebral or retinal infarction and the occurrence of TIAs were grouped and considered together as end points. Significance in favor of aspirin treatment was mainly revealed in patients with a history of multiple TIAs and was most evident in those individuals having carotid lesions appropriate to the TIA symptoms. It cannot be inferred from this study that aspirin prevents stroke because when end points were restricted to death or cerebral or retinal infarction, there was no statistically significant differential between the aspirin and placebo treatments.

not impair the aggregation response to thrombin in minute amounts.5 These effects are uniquely confined to the acetyl moiety of aspirin. Sodium salicylate neither prolongs the bleeding time6,7 nor significantly inhibits platelet ADP release.4 The effect of aspirin on platelets occurs as a consequence of acetylation of the platelet membrane, and this effect lasts for the life of the exposed platelet, normally 8 to 10 days. Recently, the inhibition of the aggregation-release reaction of platelets has been related to specific inhibition by aspirin of the transformation of newly hydrolyzed platelet arachidonic acid to labile cyclic endoperoxide forms of prostaglandins now designated as PGD2 and PGE2. This has been established by radio-labeling the acetyl moiety of aspirin, which in this reaction, persistently acetylates a single platelet protein enzyme of 85,000 molecular weight. This protein copurifies with cyclo-oxygenase.11-18 There have been numerous reports of anecdotal experience
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W K Hass

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