Minimal Daily Dosage of ASA for Platelet Inhibition

To the Editor:

Acetylsalicylic acid (ASA) has the property of inhibiting cyclo-oxynegene of both platelets and vessel wall intima. However, a differential inhibition of the cyclo-oxynegene in the platelets has been claimed possible by low doses of ASA. Preservation of the vessel wall production of prostacyclin, which is a potent inhibitor of platelet aggregation, would seem a therapeutic benefit. ASA in large doses of one gram daily or more has not shown convincing protective effect against thromboembolism, and the possibility that small doses of aspirin might be more effective remains to be thoroughly investigated.

We studied the lowest daily dose of ASA necessary to inhibit platelet aggregation in 40 patients with cerebrovascular disease of a mean age of 61 years. Platelet aggregation was studied in a Born aggregometer after adding sodium arachidonate to platelet-rich plasma.

Over a treatment period averaging 118 days, 13 patients showed full inhibition of platelet aggregation on a daily ASA dose of 25 mg. In 85 per cent of the patients the daily requirement was below 75 mg ASA. The highest dose needed was 125 mg daily in 2 patients.

It is concluded that the ASA dosage used in the large controlled studies are far in excess of what is needed. For future controlled studies of the effect of ASA on thromboembolism it is suggested to use minimal daily doses and to monitor the effect on platelet function individually.

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References
5. Fields WS, Lemak NA, Frankowski RF, Hardy RJ: Controlled trial of aspirin in cerebral ischemia. Stroke 1977; 8: 301–16

Editor’s Note: This communication was sent to Dr. C. P. Warlow, Principal Investigator of the United Kingdom TIA Trial, and the following response has been obtained.

To the Editor:

Thank you for allowing me to comment on the above letter by Dr. Boysen and colleagues. The question ‘how much aspirin?’ has concerned neurologists and others ever since its anti-platelet effects were discovered in the late 1960’s. It is not, therefore, a new question which has only appeared in response to the more recent discovery of the prostacyclin pathway of prostaglandin metabolism in the vessel wall and its possible protective role against thrombosis.

Reconciling the balance between the ‘good’ prostaglandins in the vessel wall and the ‘bad’ prostaglandins in the platelet, and the fact that aspirin inhibits the production of both is a matter which has generated much debate. It seems to me, however, that pharmacologists, on the basis of experiments in animals or in normal human volunteers, can only tell us the best guess at the dose of aspirin to be used in middle aged and elderly individuals with cerebrovascular, or indeed cardiovascular, disease. This guess at the dose which will inhibit maximally the ‘bad’ prostaglandins, but inhibit minimally the ‘good’ prostaglandins, must then be validated by clinical trials. The Canadian TIA Trial in threatened stroke patients, and practically all the other major trials of aspirin, used a dose of about 1 gram daily because that was the best guess in the early 1970’s when these trials were designed. Whether this dose of aspirin really does increase the survival period free of stroke TIA has been vigorously debated and in response to this debate, and in response to the dose issue, the UK-TIA Aspirin Trial was initiated in 1978 and the first patient randomized in August 1979. In this trial TIA patients are randomised three ways, and the males and females are being analysed separately or together. Aspirin 600 mgs. b.d. is being compared to placebo to investigate whether the result of the Canadian Trial is correct and, in a third treatment arm, aspirin 300 mgs. daily is being used since, back in 1978, this was the best guess at the most effective antithrombotic dose regime. To date just over 1200 patients have been randomised and the aim is to recruit about 2000 by the end of 1983. So far 92 end points have occurred (stroke, myocardial infarction, death) and the stopping rules have not yet had to be invoked. Only 2 patients have been lost to follow-up although many are no longer taking their trial medication.

From the results of this trial it should be possible to answer the question whether 1200 mgs. or 300 mgs. of aspirin daily has a clinically useful effect on the risk of stroke, myocardial infarction, and death after TIA. If there is little to choose in therapeutic effectiveness between the two doses it would be an advantage to use the lower one since it is cheaper, and almost certainly associated with fewer gastrointestinal side effects. Obviously one concern is that 300 mgs. daily will still be ‘too much’ and that neither dose of aspirin will have a clinically useful effect. However, it is only by doing trials such as this that the best dose will emerge and, importantly, become believable in real clinical practice. Naturally we look to our pharmacological colleagues to provide some idea of the best dose and hope that the number of their guesses will not be excessive — for each guess at the dose of aspirin, or indeed any other antithrombotic drug, many hundreds of TIA patients need to be randomised to have a reasonable degree of certainty of turning a guess into clinical reality.

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Editor’s Note: The above communication was sent to Dr. J. Hirsh of the Canadian Co-operative Study Group, and his comments follow.

To the Editor:

I agree that the doses used in the two stroke studies cited (reference 4 and 5) were greater than the minimum amount required to inhibit platelet prostaglandins synthesis. It cannot be assumed, however, that the antithrombotic effect of aspirin is limited to this single action of the drug. Thus, in the study by McKenna and associates, very large doses of aspirin were found to be more effective than moderate doses of aspirin in preventing venous thrombosis after knee surgery and there is experimental evidence that very high doses of aspirin have additional effects on platelet function. It is known that salicylate inhibits the platelet lipoxigenase pathway which may also be important in platelet aggregation. For these reasons, it is inappropriate to conclude that doses of ASA used in the studies cited (although unconvinced to Boysen and associates) were excessive.

I agree, however, that it would be highly appropriate to do further studies using smaller doses of ASA to determine whether these are more
Which Circulates Faster Through the Cerebral Microcirculatory System, Red Cells or Plasma?

To the Editor:

In a recent paper describing interesting experiments to measure the plasma and red cell transit in a cerebral ischemic area of the cat brain (Stroke 12: 218–223, March-April, 1981), Little et al. reported that the transit time of plasma as represented by 131I albumin was shorter than that of red cells labeled with 99Tc even in the control State. This is just the opposite of data reported by us1 in the cat brain using our photoelectric method. It also contrasts with the results of other groups including Larsen & Lassen in the brain,2 Pappenheimer & Kinter in the kidney,3 Rapaport et al. in the lung,4 Moore & Baker in the skeletal muscle,5 and Freis et al. through the forearm.6 All these authors found that the velocity of red cells exceeded that of plasma. These findings were supported by the larger plasma volume than red cell volume in the tissue.7–9 Such observations have led to the concept of a lower value of tissue hematocrit than large vessel hematocrit (Hct2). The relationships in this situation can be explained mathematically as follows.

The equation for the tissue hematocrit (Hct2) derived by Larsen & Lassen2 from the basic definition of the hematocrit value (Hct) as Hct = 100 × V_r/(V_r + V_p), where V_r is the red cell volume and V_p the plasma volume, is

\[ Hct_2 = 100 \times \frac{1 + MCT_p \times (100 - Hct_1)/Hct_1}{MCT_r \times Hct_1} \]

where MCT_r is the mean circulation time which is by definition volume divided by flow, and is therefore equivalent to the mean transit time (t). If we consider the "relative" tissue hematocrit which means Hct, relative to Hct1 expressed in percentage, or rHct = 100 × Hct2/Hct1, and if we neglect the term Hct1 × (1 – MCT_p/MCT_r) which is much smaller than 100 × MCT_p/MCT_r when MCT_p/MCT_r is close to unity, the Larsen & Lassen equation reduces to

\[ rHct = 100 \times \frac{t_{r / p}}{t_2} \]

In other words, the ratio of the mean transit time for red cells and that for the plasma is approximately the tissue hematocrit relative to that of the large vessels.

The data of Little et al. would imply therefore that the cerebral tissue hematocrit is higher than the large vessel hematocrit, which is incredible. A closer examination of their analytical method shows that the transit time was determined by them from measurements of the total peak time. We believe that the tissue concentration curve which they recorded was a cumulative distribution function, whose peak time represented only the arterial phase, and by no means the microcirculatory phase as they claimed. Even with any contribution from the arterial phase, their data are dubious due to the existence of the Fahrensu-Lindqvist effect. We recommend that they recheck their data pertinent to the above criticism.

References
8. Sklar FH, Burke Jr. EF, Langfitt TW: Cerebral blood volume: values obtained with 51Cr-labeled red blood cells and RISA. J Appl Physiol 24: 79–82, 1968

Editor's Note: The above correspondence was sent to the author cited and his comments follow.

To The Editor:

The objectives of the investigation were to study plasma and erythrocyte transit in an area of acute focal cerebral ischemia and define their relationship to developing microcirculatory obstruction as determined by morphological techniques. The results indicated: (1) progressive delay of albumin and erythrocyte transit with longer periods of middle cerebral artery occlusion in cats developing cortical infarction; (2) absence of complete microcirculatory obstruction despite absence of carbon filling in infarcted cortex; and, (3) no findings to suggest plasmapheresis.

The technique used to measure albumin and erythrocyte transit involved the measurement of radionuclide activity over the sylvian region (i.e., core area of ischemia) ipsilateral to the middle cerebral artery occlusion following ipsilateral intracarotid injection of 131I albumin and 99Tc labeled erythrocytes. Measurement of the interval from the arrival to disappearance of radionuclide activity in cortex together with analysis of the radionuclide activity curve should provide an index of transit for these two elements. I agree that the relationship of the albumin to erythrocyte transit as demonstrated in the investigation was at variance with the previously-described Fahraeus-Lindqvist effect. This may have been related partly to greater resistance in the syringe with 99Tc-erythrocyte injection and consequently slightly longer injection times. The technique used to measure albumin and erythrocyte transit involved the measurement of radionuclide activity over the sylvian region (i.e., core area of ischemia) ipsilateral to the middle cerebral artery occlusion following ipsilateral intracarotid injection of 131I albumin and 99Tc labeled erythrocytes. Measurement of the interval from the arrival to disappearance of radionuclide activity in cortex together with analysis of the radionuclide activity curve should provide an index of transit for these two elements. I agree that the relationship of the albumin to erythrocyte transit as demonstrated in the investigation was at variance with the previously-described Fahraeus-Lindqvist effect. This may have been related partly to greater resistance in the syringe with 99Tc-erythrocyte injection and consequently slightly longer injection times. The objective of the study, however, was not specifically directed towards comparing absolute transit times of albumin and erythrocytes per se but to the relative changes in the transit of these two elements. I think that the objectives as stated in the paper have been fulfilled.

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Practical Considerations in Antifibrinolytic Therapy
To the Editor:

In the conclusions of a recent review of antifibrinolytic therapy in aneurysmal subarachnoid hemorrhage (SAH) appearing in STROKE, Dr. Adams states: "Complete bed rest with a quiet environment, sedatives, analgesics, anticonvulsants and stool softeners are also necessary." These recommendations raise 2 practical clinical questions. Should these patients be initially monitored in an intensive care unit (ICU)? In many hospitals, a quiet, dark environment is not available...
Minimal daily dosage of ASA for platelet inhibition.
G Boysen, J Bøttcher and J S Olsen

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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/13/5/721.citation

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