Progress Review:
The Relationship Between Dose of Aspirin, Side-Effects and Antithrombotic Effectiveness

JACK HIRSH, M.D.

CLINICAL TRIALS over the last decade have demonstrated that aspirin is an effective antithrombotic agent. The antithrombotic effect of aspirin has been attributed to its inhibition of platelet function. Aspirin irreversibly inhibits the enzyme cyclo-oxygenase which in the platelet is responsible for the conversion of arachidonic acid to thromboxane A$_2$ and in vascular wall cells is responsible for the conversion of arachidonic acid to PGI$_2$. Thromboxane A$_2$ induces platelet aggregation and vasoconstriction while PGI$_2$ inhibits platelet aggregation and induces vasodilatation. Thus aspirin has the potential to be both antithrombotic and thrombogenic.

The optimal antithrombotic dose of aspirin is controversial. There are both theoretical and practical reasons to choose the lowest effective dose of aspirin. Low doses of aspirin (300 mg and less) have a selective inhibitory effect on thromboxane A$_2$. Low doses of aspirin would also be desirable (if effective) because the side-effects of aspirin are dose dependent and many of the clinical conditions in which aspirin is effective require that the drug be used long term, or even indefinitely.

Differential Effects of Aspirin on Thromboxane A$_2$ and PGI$_2$ Production

Investigations have been performed seeking to determine if there is a dose of aspirin which blocks thromboxane A$_2$ production without inhibiting PGI$_2$ production. Results of early studies performed by Burch et al., indicated that platelet cyclo-oxygenase is more sensitive to the inhibitory effects of aspirin than cyclo-oxygenase in vascular wall cells. Studies by other investigators reported that PGI$_2$ production by vascular wall cells is restored more quickly after aspirin administration than is thromboxane synthesis by platelets, presumably, because vascular wall cells can synthesize new cyclo-oxygenases while platelets cannot. More recently the relative effects of aspirin on platelet thromboxane A$_2$ production and vessel wall PGI$_2$ production have been studied using human vessel wall fragments in patients treated with aspirin and by measuring the urinary excretion of metabolic products of PGI$_2$ and thromboxane A$_2$ in patients who have ingested aspirin.

Studies using vascular wall fragments indicate that doses of aspirin of 40 mg per day or greater inhibit both vascular wall PGI$_2$ production and platelet thromboxane A$_2$ production but that the effect of aspirin on thromboxane A$_2$ is greater. Patrignani et al. measured the metabolic products of PGI$_2$ and thromboxane A$_2$ in urine and showed that at doses of 0.45 mg per day of aspirin, thromboxane A$_2$ production was inhibited by 95% without affecting the basal levels of the PGI$_2$ metabolic product 6-keto-prostaglandin-F$_1$-alpha. Fitz-Gerald et al. reported that doses of aspirin of less than 100 mg per day totally inhibited urinary excretion of thromboxane metabolites while the metabolites of PGI$_2$ persisted at 25-40% of their baseline value even with doses of aspirin of 2.6 grams per day.

Both types of studies have shortcomings. Direct measurement of PGI$_2$ from vascular wall cells that have been excised at operation may not reflect PGI$_2$ production by intact vessels, while studies of urinary excretion of metabolites of PGI$_2$ and thromboxane A$_2$ may reflect the synthesis of these metabolic products from tissues other than platelets and vascular wall cells. Despite these shortcomings, it appears that platelet cyclo-oxygenase is more sensitive than vascular wall cyclo-oxygenase to aspirin, that the effect of aspirin on platelet cyclo-oxygenase lasts longer than its effect on vascular wall cells, but that even low doses of aspirin inhibit PGI$_2$ synthesis in human vessels.

The therapeutic importance of inhibiting PGI$_2$ is uncertain. Experimentally, aspirin is only thrombogenic at extremely high doses (200 mg/kg) which far exceed the minimum dose required to inhibit PGI$_2$ production suggesting that inhibition of PGI$_2$ alone may not be the mechanism for the thrombogenic effect of very high doses of aspirin. Additional studies in rabbits indicate that the thrombogenicity of aspirin may be contributed to by the effect of the salicylate moiety on a
second unidentified substance produced by vascular wall cells. Epidemiologic studies of patients with rheumatoid arthritis treated with very large doses of aspirin do not indicate that there is an increase in thrombosis of atherosclerosis, suggesting that even high doses of aspirin are not thrombogenic in man. Finally, patients with congenital cyclo-oxygenase deficiency who both lack PGI₂ and thromboxane A₂ do not suffer thrombotic episodes but rather have a mild bleeding tendency. It is likely, therefore, that the importance of vascular wall PGI₂ production to the resistance of endothelial cells to thrombosis has been over emphasized, and that aspirin is not thrombogenic in the therapeutic doses used in man.

Relationships Between Dose of Aspirin and Side Effects

There is good evidence both from randomized trials and from a case control study that regular aspirin ingestion produces side-effects which are mainly gastrointestinal.

An association between aspirin ingestion and gastrointestinal bleeding was suggested by the results of a case control study. In this study, a relationship was sought between long-term regular use of aspirin and hospital admissions for major upper gastrointestinal bleeding and for newly diagnosed peptic ulcer disease. A statistically significant association was found between heavy, regular aspirin use and major bleeding. A similar association was found in patients with newly diagnosed benign gastric ulcer but there was no corresponding association with duodenal ulcer. There was no evidence of a significant association with either upper GI bleeding or peptic ulcer disease when less heavy use of aspirin was considered. A number of randomized trials comparing aspirin with placebo or oral anticoagulants in coronary artery disease and cerebrovascular disease have demonstrated that long-term aspirin ingestion produces gastrointestinal side-effects. Patients with coronary heart disease have been treated with an aspirin dose of between 100 mg per day and 1500 mg per day. All six studies in which aspirin was administered in a dose of at least 900 mg per day reported an increase in side-effect when aspirin was compared with placebo (in 5 studies) or with oral anticoagulants in one study. Symptoms of stomach pain, heart burn, nausea, constipation, hematemesis, and melena all occurred more frequently in the aspirin group than in the control group in the majority of studies. In two studies there was a statistically significant increase in acute gout, and in uric acid and in blood urea nitrogen. Both of these biochemical abnormalities were clinically minor. There was no evidence of a generalized bleeding tendency in the aspirin treated patients, although in one study there was a statistically significant increase in hematuria.

Three studies were performed with an aspirin dose of 324 mg per day or less and in none was there evidence of a higher frequency of side effects in the aspirin group than in the placebo group.

Aspirin has been evaluated in placebo-controlled randomized studies in patients with cerebrovascular disease. Aspirin was administered in a dose of approximately 1 gram/day and there was an increase in gastrointestinal side effects. The combination of aspirin and warfarin has been associated with a greater frequency of clinically important generalized bleeding than warfarin therapy alone. There is also evidence that the combination of aspirin and heparin is more hemorrhagic than heparin alone.

The published data are consistent with the conclusion that the side-effects of aspirin are dose related, and that when given in a dose which does not exceed 324 mg per day, aspirin is not associated with clinically important side effects. Aspirin does not appear to produce a generalized bleeding abnormality unless it is combined with anticoagulant therapy.

The Effects of Aspirin on Gastric Mucosa

Endoscopic studies have demonstrated that aspirin produces erythema of the gastric mucosa in approximately 80% of patients with rheumatic diseases, gastric erosions in approximately 40% and gastric ulcer in 15%. Topically applied aspirin damages gastric mucosa and induces occult gastrointestinal bleeding. Aspirin administered by injection may also produce effects on gastric mucosa, but the damaging effect of aspirin on gastric mucosa is much less with parenteral administration. Oral administration of dilute solutions of aspirin cause considerably less bleeding than similar doses in tablet form and aspirin solutions containing antacids with sufficient buffering capacity cause no measurable blood loss in normal subjects.

There is some evidence that the effect of aspirin on the gastric mucosa is through inhibition of synthesis of prostaglandins. The synthesis of prostaglandins by gastric mucosal preparations is blocked by aspirin. The effect of aspirin on gastric mucosa is reduced by treatment with cimetidine, antacids and by the use of enteric coated aspirin. Buffered preparations of aspirin do not contain enough alkali to neutralize the effects of 650 mg of aspirin and do not protect against aspirin-induced gastric mucosal erosions.

Relationship Between Aspirin Dose and Clinical Efficacy

Most clinical trials demonstrating benefits of aspirin have dealt only with a single dose of the drug selected arbitrarily. In the studies comparing two doses of aspirin, no differences were observed in most. Hynes reported that thrombotic occlusion of the brachial artery complicating cardiac catheterization occurred with equal frequency after 325 or 650 mg aspirin per day. O'Brien was unable to show a difference in the antithrombotic effectiveness of 600 mg or 2400 mg aspirin per day in patients undergoing thoracotomy; he found no benefit at either dosage. McKenna et al. studied patients undergoing knee replacement operations and found significant protection against venous thrombosis at a dose of 3600 mg/daily but no therapeu-
tic benefit at 900 mg daily; the conclusion of this study is somewhat weakened by the small number of patients involved. Harris et al. subsequently studied the effect of 1200 mg daily compared with 3600 mg per day in patients undergoing total hip replacement and found no difference in the therapeutic effectiveness of the two doses. In a more recent study, Harris et al. found that postoperative thrombosis occurred with equal frequency (approximately 50%) with 1200 mg and 300 mg of aspirin per day in total hip replacement.

A study comparing two aspirin doses is currently reaching completion in patients with transient cerebral ischemia in the U.K. and the preliminary results indicate that the high doses of aspirin (approximately 1000 mg/day) produces more side effects than the low dose (approximately 300 mg/day). Thus there is no convincing evidence from comparative studies that any one dose of aspirin is more or less effective than another.

Antithrombotic effects of aspirin have been reported with doses which have varied between 100 mg per day to over 1 gram per day. Low doses of aspirin have been effective in preventing aorto-coronary by-pass shunt thrombosis (100 mg per day), thrombosis of arterial venous shunts in patients undergoing chronic hemodialysis (160 mg per day), and in patients with unstable angina (320 mg per day). Aspirin has also been shown to be effective in reducing complications in patients with transient ischemia in doses of approximately 1 to 1.5 grams per day. In the Canadian Study, this effect was only seen in males but in the French Study benefit was found in males and females. In this latter study, the addition of dipyridamole to aspirin did not improve the effectiveness of aspirin.

There is suggestive but less conclusive evidence that aspirin is effective in preventing reinfarction and death in patients who have suffered acute myocardial infarction in doses of between 300 mg and 1.5 grams per day. Thus aspirin has been shown to be an effective antithrombotic agent in doses which have varied between 100 mg per day to over 1 gram per day. There is no convincing evidence that low doses (300 mg/day or less) are either more effective or less effective than high doses (1000 mg/day). There is evidence, however, that low doses produce fewer side effects. Because the thrombogenic stimulus may not be the same in the different thromboembolic disorders in which aspirin has been evaluated, the successful results obtained with low doses of aspirin in unstable angina, aortocoronary bypass surgery and in patients with sialastic arterio-venous shunts should not be extrapolated to disorders such as cerebral ischemia in which only high doses of aspirin have been evaluated. On the other hand, the results of biochemical studies on its mechanism of action, the dose-related side effects of aspirin and the results of clinical studies evaluating antithrombotic efficacy all support the use of low doses of aspirin in the treatment of most thromboembolic disorders in which the drug has been found to be effective. The result of the Oxford Study in transient cerebral ischaemia comparing low and high doses of aspirin is awaited with great interest. Although a greater benefit for aspirin has been reported in males in some studies, this has not been a consistent finding. At present, there is no evidence from clinical studies that the addition of dipyridamole to aspirin improves its clinical efficacy.

References


46. Warlow C: Personal Communications.


Progress review: the relationship between dose of aspirin, side-effects and antithrombotic effectiveness.

J Hirsh

Stroke. 1985;16:1-4
doi: 10.1161/01.STR.16.1.1
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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/16/1/1.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/