Low-Dose Aspirin and Stroke

"It Ain’t Necessarily So"

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Most clinicians have assumed that very low doses of aspirin might be effective in preventing stroke and death in patients presenting with transient ischemic attacks (TIAs) and stroke. In fact, 325 mg/day or less are often advocated despite the large numbers of well-designed, prospective controlled studies involving stroke-threatened patients that demonstrate the effect of doses greater than 975 mg/day and the paucity of studies using lower doses.

The Antiplatelet Trialists\(^2\) concluded that "... if aspirin is to be used prophylactically in routine medical practice there appears to be no good reason to use a dose higher than 300–325 mg/day..." This was based on a meta-analysis of studies of a heterogeneous group of clinical trials (TIA, stroke, surgical trials, myocardial infarction, unstable angina) using a heterogeneous group of end points (definite stroke, probable or definite nonfatal myocardial infarction, and all deaths that might have been vascular or hemorrhagic). In addition, studies using any drug thought to have a platelet antiaggregant effect were included. The authority of this group is impressive. Nevertheless, we have serious reservations that low dose might not be as effective as high dose. Of course, if the side effects were not different and it were possible that the higher dose was more effective, it would be used. Unfortunately, evidence exists that higher dose has significantly more gastrointestinal complications. Therefore, if the doses are equally effective and high dose is used, some harm might result.

The designers of the first trials of aspirin in stroke prevention decided on a daily dose in the absence of any available guidelines. It was assumed that any beneficial effect would be related to the prevention of platelet aggregation by aspirin’s inhibition of platelet thromboxane A\(_2\) synthesis. In subsequent years, when it was established that as little as 40 mg a day could produce this effect, it was assumed by many that the original doses were too high. These studies in conjunction with the introduction of the homogenizing meta-analyses led some to believe that we can now recommend the appropriate dose of aspirin for stroke prevention. Others of us still consider the issue to be as yet unresolved.

In this issue of Stroke, Tohgi and his coworkers\(^3\) report that the effect of low-to-high doses of aspirin on platelet aggregability necessary to prevent thrombogenesis varies in poststroke patients, depending on methods of evaluation. Different doses may be necessary to prevent thrombogenesis induced by different triggers of different strengths.

Aspirin After Transient Ischemic Attack and Minor Stroke

Our first concern is that none of the lower-dose studies in the original review of the Anti-platelet Trialists were of cerebrovascular disease.\(^4\) These were primarily heart studies. None of the studies of cerebrovascular disease at that time demonstrated a statistically significant effectiveness of a dose of aspirin less than 975 mg/day.\(^5\) In the one direct comparison of 300 versus 1,200 mg/day, the United Kingdom Study,\(^5,6\) the numbers of patients in each aspirin group were far too small to rule out a type II error. Therefore, the recommendation that “if aspirin is to be used prophylactically in routine medical practice there appears to be no good reason to use a dose higher than 300–325 mg/day...” does not appear to be well founded.

Part of the bias for assuming that 325 mg aspirin or less a day is equivalent to or better than 975 mg or more is based on an assumption. Low doses, possibly as low as 30 mg/day, will block cyclooxygenase and the release of thromboxane A\(_2\) in platelets and have very little or no effect on the prostacyclin system in the endothelium. Therefore, low dose might induce a desirable combination effect. This has not been established by a properly
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