Aspirin has emerged as a remarkably safe, inexpensive, and effective drug for the secondary prevention of the complications of atherosclerotic disease. It acts by inhibiting the enzyme prostaglandin (PG) G/H synthase, actually a bifunctional protein that sequentially catalyzes the conversion of arachidonic acid to the highly reactive endoperoxide intermediates PGG2 and PGH2 via its cyclooxygenase (COX) and peroxidase functions. This enzyme, colloquially termed COX, has been crystallized1 and the mechanism of action of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) elucidated.2–4 The catalytic site is buried deep within the core of the enzyme and is accessed by the substrate via a hydrophobic tunnel. Aspirin irreversibly acetylates a serine residue at position 529 in the human enzyme,5 close to but not at the catalytic site, though still blocking access to it by the arachidonic acid substrate. NSAIDs, by contrast, act reversibly as competitive inhibitors at the catalytic site. Indeed, transient occupancy of that site after dosing with an NSAID may mask the serine from the effects of a subsequent dose of aspirin.6

The irreversible acetylation of Ser529 by aspirin in the COX of anucleate platelets explains the cumulative inhibition of the capacity of platelets to generate TxA2, commonly measured as serum concentrations of its hydrolysis product TxB2. Thus, daily administration of 75 mg of aspirin takes 3 to 4 days to inhibit completely serum TxB2 ex vivo.7 Interestingly, like low-dose aspirin, 75 mg of clopidogrel also takes several days to inhibit platelet function ex vivo, perhaps owing to the gradual accumulation of a metabolite that binds to a subclass of purinergic receptors, although this has yet to be established in vivo. As in the case of aspirin, loading doses of clopidogrel have been investigated and are likely to be employed in acute settings of vascular occlusion. Studies designed to assess the potentially additive effects of aspirin with clopidogrel have been initiated. Finally, dipyridamole has been reformulated to correct prior problems with variable and transient bioavailability. This new preparation has been shown to be as effective as low-dose aspirin in the secondary prevention of stroke, and the benefit from a combination of the 2 is roughly additive.8 This has led to the US Federal Drug Administration approval of an aspirin-diprydiamide combination for this indication. Although oral inhibitors of the platelet glycoprotein αIIb/βIII have been disappointing, 3 antiplatelet drugs—low-dose aspirin, clopidogrel, and dipyridamole—have been proven effective in the secondary prevention of cerebrovascular and/or cardiovascular disease. Their mechanisms of action suggest that their benefits might be additive, although this remains to be established in a clinical trial. This has “raised the bar” for the development of potentially novel therapies in this arena.

The advent of pharmacological inhibitors of the TP19–21 inauspiciously coincided with the initial trials establishing the efficacy of aspirin in cardiovascular disease.22–24 This confounded their development in 2 ways. First, as the effects of aspirin were attributed to inhibition of TxA2, TP antagonists had little additional benefit to offer. Perhaps preservation of the ability of the vasculature to generate other PGs such as prostacyclin (PGL2) was a plus, but this was a strictly theoretical concept. Against that, it was difficult for TP antagonists to compete against aspirin at 20 cents a tablet. Two clinical trials of TP antagonists were performed, both addressing the possibility that they might modify restenosis after angioplasty.

In the CARPORT (Coronary Artery Restenosis Prevention on Repeated Thromboxane A2 antagonism) study, the antagonist GR32191, given before percutaneous transluminal coronary angioplasty (PTCA) and for 6 months thereafter, did not differ significantly from the effects of intravenous aspirin given immediately before PTCA on luminal diameter as assessed by angiography performed 6 months after the
intervention. However, the limitations of this uncontrolled experience and of relying on an angiographic end point at a single time were highlighted by the M-HEART (Multi-
Hospital Eastern Atlantic Restenosis Trial) II study. In that study, all patients received aspirin before PTCA due to its role, by then established, in the prevention of periprocedural myocardial infarction but were randomized to continuing treatment with the TP antagonist sulotroban, aspirin, or placebo. In this case, the angiographic estimate of vascular occlusion at 6 months was a secondary end point and did not differ between the groups. By contrast, continued treatment with either aspirin or sulotroban significantly reduced the later myocardial infarction rate in the 6 months after PTCA when compared with the placebo group. These observations left many unanswered questions. First, aside from there being no measure of the degree of synthesis inhibition achieved by aspirin or of TP blockade by either antagonist, the divergence of the time-integrated clinical and “snapshot” angiographic end points in the M-HEART II study illustrated the limited information available from CARPORT. Second, the hypothesis that TP blockade might be superior to aspirin was confirmed on the presence of PGI₂ formation during TP blockade. PGI₂ has significant antiproliferative effects. Both virally delivered PGI synthase and a PGI₂ analogue, bera-
prost, have been shown to reduce significantly the proliferative response to experimental angioplasty. However, the procedure-related increase in PGI₂ biosynthesis, like that in TXA₂, is short-lived and suppressed by aspirin in patients undergoing PTCA, and the patients assigned to sulotro-
ban were receiving aspirin at that time.

Cayette and colleagues now report observations that suggest reconsideration of the role of TP antagonism is timely. Using a newly synthesized TP antagonist, S18886, which is devoid of partial agonist activity, they report that atherogenesis can be retarded in the apoE-knockout (KO) mouse. Oddly, aspirin has no effect. One possibility is that inhibition of other COX products by aspirin, such as PGI₂, might have obscured a benefit from inhibiting TXA₂. We now know that deletion of the PGI₂ receptor—the IP—results in an inhibition of other COX products by aspirin, such as PGI₂, TXA₂, and suppression by aspirin in patients undergoing PTCA, and the patients assigned to sulotro-
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activation in settings previously not considered when these drugs were under development. Finally, TP antagonists may even be worth considering as alternative platelet inhibitors to aspirin in certain circumstances. For example, because platelets express COX-1 only, selective inhibitors of COX-2 do not afford cardioprotection. However, in the absence of any actual clinical data, the empiric combination of these drugs with low-dose aspirin has some theoretical limitations. Even low-dose aspirin causes gastrointestinal side effects, which may erode the postulated benefit of selective COX-2 inhibition on the gastrointestinal tract. By contrast, TP antagonism has been shown to protect against NSAID-induced enteropathy in the rat. Similarly, selective COX-2 inhibitors, NSAIDs, and even low doses of conventionally formulated aspirin depress PGI2 biosynthesis in healthy individuals. Combination of TP antagonists with COX-2 inhibitors would afford at least similar cardioprotection to that of aspirin while sparing PGI2 formation from further suppression.

In summary, the provocative studies of Cayatte et al32 draw attention to a class of compounds that were previously abandoned for reasons that were rational at the time. Now that we know more about the breadth of potential TP ligands and are increasingly informed of the biology of PGs as a result of the availability of receptor-deficient mice, it would seem worthwhile to reconsider the contemporary utility of this interesting class of compounds.

References


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