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Reply

To the Editor:

We thank Dr. Sperling and her colleagues from Merck & Co. for their comments on our case reports of thrombosis occurring in temporal proximity to institution of treatment with the selective COX-2 inhibitor celecoxib. Case reports clearly cannot establish a cause-and-effect relationship between these events. However, we used these case reports to propose the hypothesis that in certain individuals who are at increased risk for thrombosis, inhibition of endothelial prostacyclin without concurrent inhibition of platelet thromboxane may alter the coagulation balance toward thrombosis. We believe that this remains a viable hypothesis until such time as it is specifically tested in valid animal models and prospective clinical studies.

Several points made by Sperling et al deserve further comment. They imply in their letter that because high-risk patients are prone to thrombotic events, the hypothesis that selective inhibition of COX-2 could be a contributing factor is invalid. We believe that it is in precisely this high-risk patient population that the first indications of a propensity for prothrombotic risk associated with selective COX-2 inhibition will be identified. Sperling and colleagues note that their marketing data indicate that patients with SLE are prescribed selective COX-2 inhibitors, and that a query of the Merck & Co. database failed to identify patients with adverse events similar to the ones we reported. It is not clear from their letter whether there is a specific effort to prospectively evaluate patients with SLE or other connective tissue diseases for differences in the rate of thrombosis among those receiving selective COX-2 inhibitors compared with those taking traditional NSAIDs, with stratification according to risk for thrombosis at entry into a study. If the database consists only of voluntary adverse-events reporting by individual practitioners, thus introducing the question of reporting bias, Sperling et al are effectively suggesting an alternative hypothesis but have not refuted the hypothesis generated by our report.

Selective COX-2 inhibitors are expected to have a more substantial impact on the ratio of thromboxane to prostacyclin because they inhibit endothelial prostacyclin production without inhibiting platelet thromboxane production (1–4). Sperling and coworkers state that there is no evidence that the degree of prostacyclin synthesis inhibition achieved with selective COX-2 inhibitors can overwhelm the ability of endothelial-derived prostacyclin to prevent formation of a platelet thrombus. There is also no evidence to the contrary. The study cited in support of their argument examined the recovery of endothelial cell prostacyclin production in vitro after treatment with aspirin, an irreversible inhibitor of COX (5). Since endothelial cells continually replenish COX, short-term exposure to aspirin would not be expected to inhibit prostacyclin effectively over time. In the in vivo setting, aspirin has a very short half-life, further reducing the expected effects on endothelial prostacyclin production. This is precisely why aspirin is an excellent antithrombotic agent.

Selective COX-2 inhibitors have demonstrated effects on systemic production of prostacyclin (2,3). This translates into loss of coronary artery vasodilation in response to administration of arachidonic acid in dogs treated with specific COX-2 inhibitors (Hennan JK, Lucchesi B, University of Michigan: personal communication), an observation that confirms the COX-2 dependence of endogenous prostacyclin production in the vasculature. Investigators are beginning to address the important role of prostacyclin as an inhibitor of thrombosis, using genetic models (6) and pharmacologic probes. Further studies must be completed in order to properly examine our hypothesis.

We agree with Sperling et al that specific COX-2 inhibitors are clearly not a substitute for aspirin in cardiovascular prophylaxis. Neither, for that matter, are other NSAIDs. We join them in urging physicians to assess patients individually for thrombotic risk and intervene as medically appropriate. However, we maintain that appropriate vigilance is indicated for patients with thrombotic risk factors who are treated with selective COX-2 inhibitors.

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