Cardiovasc Drugs Ther (2007) 21:77–79
DOI 10.1007/s10557-007-6022-6

EDITORIAL

Cerebrovascular Events After Discontinuation of Rofecoxib Treatment

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Published online: 3 April 2007

The pain-relieving nonsteroidal antiinflammatory drugs (NSAIDs) exhibit different degrees of selectivity for the isoforms COX-1 and COX-2 which differ substantially in their localization and function. While COX-1 plays an important role in the cytoprotection of the gastric mucosa, in platelet activation, and in other homeostatic processes, COX-2 is thought to largely account for prostaglandin formation at the site of tissue injury [1]. With the objective of treating pain and inflammation without affecting gastric mucosa, COX-2 selective NSAIDs ("Coxibs") were developed and introduced on the market. The finding of an excess of thrombotic cardiovascular events, primarily of myocardial infarction, in the VIGOR trial [2] raised concern about the cardiovascular safety of rofecoxib, and also of COX-2 inhibitors in general. The relative risk (RR) of myocardial infarction was 5.00 (95% confidence interval (CI) 1.68–20.13) for patients treated with rofecoxib as compared with naproxen [3]. The proportion of patients with ischemic stroke was similar in both treatment groups (0.2%). The randomized placebo-controlled Adenomatous Polyp Prevention On Vioxx (APPROVe) trial [4] conducted to demonstrate preventive effects of rofecoxib on development of colorectal adenomas ultimately lead to marketing withdrawal of rofecoxib in 2004, since it showed a nearly 2-fold increased risk of confirmed thrombotic events compared with the placebo group. This was statistically significant for cardiac events including myocardial infarction, sudden cardiac death and unstable angina pectoris (RR=2.80; 95%CI 1.44–5.45), but not for cerebrovascular events including ischemic stroke and transient ischemic attack (RR=2.32; 95% CI 0.89–6.74) [4]. In this analysis, only events occurring during treatment or within 14 days thereafter were included. In May 2005, members of the FDA Drug Safety and Risk Management Advisory Committee expressed their concern about this analysis and asked for an additional intention-to-treat analysis which should also include events occurring later than 14 days after the end of study treatment [5]. In May 2006, Merck published the demanded update of the APPROVe trial including extended follow-up data of up to 3 years for some of the patients [6]. This document now also included the demanded intention-to-treat analyses with respect to different cardiovascular endpoints.

In this issue of Cardiovascular Drugs and Therapy, Afilalo et al. highlight one important aspect of these new follow-up data. They analyzed the now available data on ischemic stroke from the APPROVe trial including study extension and concluded that only after inclusion of follow up data later than 14 days after end of study treatment, there was a statistically significantly increased risk of ischemic stroke for rofecoxib as compared with placebo. This is an interesting finding, as it points out the possibility of an increased risk of cerebrovascular events after discontinuation of treatment. In a predefined, secondary analysis of events occurring between 15 days and 1 year after discontinuation of study therapy, there were seven ischemic strokes in the rofecoxib group and 0 in the placebo group (p=0.022) [6]. This was also statistically significant in another predefined analysis using October 31, 2005 as the censoring date (eight events vs. 0 events; p=0.010). However, in a post-hoc analysis of all available follow-up data, which was nearly

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3 years for some patients, this difference was no longer statistically significant (eight events vs. two events; $p=0.134$).

There are some possible explanations for the data derived from the APPROVe extension. Ascertainment bias after unblinding, i.e. preferential detection of events in the group of patients previously treated with rofecoxib, seems to be rather unlikely as ischemic stroke generally causes severe clinical symptoms and leads to hospitalisation. Selective COX-2 inhibitors suppress vascular production of prostacyclin (prostaglandin I2) without affecting thromboxane A2 synthesis [7]. Prostaglandin I2 has been reported to inhibit vascular smooth muscle cell proliferation in vitro [8] and to diminish the proliferative response following vascular injury in vivo [9]. Thus, inhibition of COX-2 may result in accelerated atherogenesis [1] and possibly to delayed cardio- and cerebrovascular events even after the end of pharmacological COX-2 inhibition. Interestingly, in an observational study, we also observed an increased risk of ischemic stroke in patients who terminated their rofecoxib therapy within 15 and 183 days *before* the occurrence of ischemic stroke [10]. However, it should be noticed that animal models investigating the influence of COX-2 inhibition on the development and progression of atherosclerosis revealed contradictory results. While some studies reported acceleration, others reported no effect or even inhibition of atherogenesis (see [11] for an overview). The reasons for these contradictory results are unknown, differences in the experimental setting may have played a role. It cannot be excluded that there are also adverse effects resulting from treatment *cessation*. One study reported a rebound platelet activation after cessation of NSAIDs [12], but was limited because of missing differentiation between patients on COX-2 inhibitors and those on non-selective NSAIDs. Another study reported a rebound of inflammatory markers after cessation of rofecoxib treatment [13]. Finally, an epidemiological study observed an increased risk of myocardial infarction after discontinuation of traditional NSAIDs, which was highest for subjects who had used NSAIDs for a long time previously [14].

What can we learn from these data? 1. Medical events after the end of clinical studies may be related to previous study treatment. This should be considered in design and analysis especially of large clinical trials. 2. The follow-up analysis of APPROVe provides first clinical evidence that adverse cerebrovascular effects of rofecoxib may exceed the duration of treatment. If this also applies to other COX-2 inhibitors, as for instance celecoxib, is unknown. A two-year extension of the placebo-controlled Adenoma Prevention with Celecoxib (APC) trial exploring serious adverse events after discontinuation of celecoxib is ongoing with the last follow up visit expected to be performed in April 2007 [15]. The analysis of this study extension is expected to generate important new data. 3. It is unknown, how long the risk persists after discontinuation of treatment. The analyses of cerebrovascular events which occurred later than 14 days after end of study treatment were statistically significant when using “1 year of follow-up” and “October 31, 2005” as censoring points, but not when the follow-up duration was extended to all available follow up time (i.e. up to 2.9 years for some of the patients). This may be due to enlargement of the observational time beyond the period of an increased risk which reduces the statistical power of the analysis [16]. 4. Unless an increased cerebrovascular risk after cessation of rofecoxib and possibly other NSAIDs has been ruled out, the results of randomized trials and meta-analyses [17, 18] not considering such follow-up data should be interpreted with caution.

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