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COX-2 Inhibitors and Hypercoagulability

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H&O What are the advantages of cyclooxygenase-2 inhibitors over aspirin and other non-selective cyclooxygenase inhibitors?

MF Cyclooxygenase (COX)-2 inhibitors, unlike agents that inhibit both COX-1 and COX-2, provide gastric protection. COX-1 and COX-2 are both involved in the inflammation process, but COX-1 also helps to protect the stomach lining. Therefore, by inhibiting COX-2 but not COX-1, these agents treat inflammation but protect patients from peptic ulcer disease and its complications, including ulcers, perforations, and stomach bleeding.

H&O What are the risks of COX-2 inhibitors?

MF COX-2 inhibitors have risks that were recently brought to light by data from a clinical trial of rofecoxib (Vioxx, Merck), called VIGOR (Vioxx Gastrointestinal Outcome Research). These data showed that the COX-2 inhibitors, by inhibiting prostacyclin, may cause vasoconstriction, which is a hypercoagulable state. Because of this effect on the vasculature, patients may be at risk for coronary disease and for coronary and vascular events, despite having healthy endothelium.

The coronary and vascular events seen in the studies of rofecoxib included more hypertension, more myocardial infarctions, and more thrombotic events. These effects tended to increase in relation to both dose and duration.

H&O How do COX-2 inhibitors cause hypercoagulability?

MF These drugs inhibit the COX-2 pathway, a source of prostaglandins E2 and I2, which mediate inflammation. Therefore, blocking the COX-2 pathway is desirable when treating arthritis. The problem with agents that inhibit both COX-1 and COX-2 is that COX-1 is a source of these prostaglandins in the gastric area, where they afford cytoprotection. The benefit of COX-2 selective agents, then, is that on the one hand they block inflammation, and on the other hand, by not blocking COX-1 they preserve the effect of the prostaglandins on the gastric epithelium.

Given the risks of the COX-2 inhibitors, there is a risk-benefit analysis to be considered. You gain by gastric protection, but you risk vasoconstriction and hyperaggregability of the platelets.

H&O Are these risks the same for all of the COX-2 inhibitors?

MF In clinical trials, it appears that those COX-2 inhibitors that are more selective for COX-2 have both better gastric protection and a greater risk of hypercoagulability. This was demonstrated in the VIGOR study.

We recently conducted a study, called TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial), of lumiracoxib (Prexige, Novartis), which is currently only approved for use in Europe. Lumiracoxib is highly selective for COX-2, and we found that blood pressure was lower than in patients who took nonsteroidal anti-inflammatory drugs (NSAIDs). There was also a slight increase in cardiac events, but this was much lower than that seen in the VIGOR study. In fact, in patients who were at higher risk for cardiac disease and were taking aspirin, lumiracoxib was equally as safe as the NSAIDs. We do not yet know if this was due to differences in the patients or the compounds.

On the other hand, in the trial of celecoxib (Celebrex, Pfizer), which was called CLASS (Celecoxib Long-term Arthritis Safety Study), at 12 months there was no gastric protection difference between celecoxib and the NSAIDs, and there was also no significant difference in cardiac events. This is interesting, because celecoxib is very weakly COX-2–selective, and so it has very little of the risk, and very little of the benefit. However, it is widely used, because it is anti-inflammatory, and it has a much more favorable side effect profile than rofecoxib.

Our trial of lumiracoxib showed that it is a highly selective drug, and we did not see the excess of adverse

events that were seen in rofecoxib. However, there were important differences between the 2 trials: the TARGET study included older patients with osteoarthritis, who were therefore more likely to have coronary disease, while the VIGOR study included younger patients with rheumatoid arthritis who did not take aspirin. Although the low doses of aspirin taken by patients enrolled in the TARGET study who had a history of heart disease reduced the level of gastric protection, they also reduced the incidence of heart attacks. The patients in the VIGOR trial did not have this protection.

H&O Do these findings indicated a need for more studies to determine the safety of the COX-2 inhibitors?

MF Although most of the recent news about COX-2 inhibitors concerns cardiac risk, it is important to maintain some perspective on this risk. In studies of patients at low risk for cardiac events, although an increase in heart attacks has been seen that is double or triple what is considered normal, it has been on the magnitude of increasing from 2 in 1,000 to 4 in 1,000. That is still a very low event rate.

In addition, the differences between patients who also took aspirin and those who did not take aspirin have not been adequately studied. Aspirin helps to protect the heart from the potential negative effects of these drugs, and it interacts safely with COX-2 inhibitors. We now believe that the COX-2 inhibitors can be used safely and are well tolerated if they are given with low doses of aspirin. This combination can still provide some gastric protection, can still prevent heart attacks from occurring in excess, and may be very beneficial for patients' arthritis. Again, this can be seen as a risk-benefit equation.

H&O Has the recent news about rofecoxib affected the approval of lumiracoxib in the United States?

MF Because the data indicates that the risk associated with COX-2 inhibitors increases as the duration of treatment increases, and in some of the rofecoxib trials the risk did not emerge until the patient has been on the drug for 2 or 3 years, we need more data on lumiracoxib.

H&O Is it possible to identify which patients are especially at risk for cardiac events when treated with COX-2 inhibitors?

MF There are 2 groups about whom we are particularly concerned: low-risk patients who do not qualify to be treated with aspirin, but who may be close to having a heart attack without knowing it; and high-risk patients who are not taking aspirin. This latter group includes patients who are allergic to aspirin and those who are just not given it by their doctors. These people are at very high risk for cardiac events when treated with COX-2 inhibitors.

There is a group of intermediate-risk patients who are not widely recognized by doctors. These patients are middle-aged, not under treatment, and on the verge of having a heart attack without realizing it. This small group of patients are the people who may be in danger if they begin taking a COX-2 inhibitor without aspirin.

H&O What does the future hold for COX-2 inhibitors?

MF The future of the COX-2 inhibitors is uncertain. In addition to the increased risk of heart attack associated with rofecoxib, there is the possibility of increased events for patients taking lumiracoxib without aspirin. These numbers are small, and I believe it is a safe drug, but more trials are needed to determine its long-term safety.

In addition to the concern about the safety of the COX-2 inhibitors, we also need to consider the safety of ibuprofen. It has been demonstrated both in the lab and in clinical trials that there is a potentially dangerous interaction between aspirin and ibuprofen. More study needs to be done to determine the extent of this risk.

If all of the COX-2 inhibitors are taken off the market, people will instead take ibuprofen. Those patients at high risk for a heart attack will also take aspirin, and there is a definite risk associated with taking these drugs together.

H&O How can high-risk patients who cannot take aspirin be treated?

MF For high-risk patients who cannot be given aspirin, the safest alternative appears to be naproxen, which is one of the NSAIDs. This is the drug we usually use in our practice.

In fact, because of the risk of interaction between ibuprofen and aspirin, naproxen may also be the best agent even in those who can tolerate aspirin, if the COX-2 inhibitors are not an option. Naproxen has no attenuation of the effect of aspirin, and there does not seem to be a dangerous interaction between naproxen and aspirin.

Suggested Reading

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