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Is There a Higher Risk of Thrombotic Vascular Events due to NSAIDs?

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Non-steroidal anti-inflammatory drugs (NSAIDs) by inhibiting the cyclooxygenase (COX) enzyme and thus prostaglandin synthesis are potent analgesics. They also ameliorate some of the other clinical manifestations of inflammation. Their efficacy is reflected in their very frequent prescription; they are one of the most commonly prescribed drugs and are also available over the counter in many countries.

COX ISO-ENZYMES AND THEIR INHIBITION

Two COX iso-enzymes have been identified, despite their close homology; they have distinct functional physiological roles. The COX-1 iso-enzyme is widely expressed, having a 'house keeping' role whereas the COX-2 enzyme is induced during inflammation.

INHIBITION OF COX ENZYMES

The traditional NSAIDS inhibit both COX-1 and 2, although the extent varies between agents. The adverse effects of these agents on the gastro-intestinal system arise from COX-1 inhibition where as the benefit is due to inhibition of COX-2. The development of specific COX-2 inhibitors potentially overcomes the adverse gastrointestinal effects of the traditional NSAIDs whilst providing similar efficacy. However COX-2 inhibitors also reduce vascular prostacyclin production and thus may tilt the eicosanoid balance towards a pro-thrombotic profile.

COX-2 INHIBITORS AND THROMBOTIC EVENTS

Concerns of the potential pro-thrombotic effects of COX-2 inhibitors were first appreciated in 2000. In 2004, the VIGOR trial showed a five fold increase in the risk of acute myocardial infarction (AMI) with rofecoxib, a COX-2 inhibitor compared with naproxen. It has been calculated that rofecoxib resulted in one AMI for every complicated gastro-intestinal event prevented. Subsequently a two-fold increase in AMI was found with rofecoxib in the APROVe compared to placebo. These observations resulted in the worldwide withdrawal of rofecoxib. The risk of pro-thrombotic events with other COX-2 inhibitors will be discussed.

NSAIDs AND THROMBOTIC EVENTS

Several studies have now questioned the received wisdom that NSAIDs increase the risk of thrombotic events. These include:

- A meta-analysis which we and others have undertaken of observational studies which interrogated prescription databases.
- A meta-analysis of randomized studies which compared COX-2 inhibitors with NSAIDs.
- Two double blind randomized studies of two new COX-2 inhibitors lumiracoxib and etoricoxib show that they carry the same risk of thrombotic events similar to ibuprofen and diclofenac.

All these studies suggest that NSAIDs result in a small absolute risk of thrombotic events.

CONCLUSION

1. Current evidence indicates that use of COX-2 inhibitors is associated with higher risk of thrombotic CVS events. Current opinion is that this is a class effect. They should thus be used with caution in patients with pre-existing CVS disorders or in those with significant risk factors for CVS disease.

2. The concomitant use of aspirin with a COX-2 inhibitor reduces their potential beneficial gastrointestinal benefits.
3. There is accumulating evidence from observational studies that NSAIDs also increase the risk of CVS events. Although the absolute risk is small, because of the large numbers of patients prescribed NSAIDs the overall risk is high.
4. There also appears to be a difference in the CVS thrombotic risk of NSAIDs. This may be due to differences between NSAIDs in their relative inhibition of COX-1 to COX-2.

It has therefore been advocated that the increased thrombotic risk of specific COX-2 inhibitors and NSAIDs be considered a class effect. The guidelines suggested for COX-2 inhibitors should also be applied to the use of all NSAIDs.