NSAIDS and Coxibs update

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The identification of two cyclooxygenase isoforms (COX-1 and COX-2) a mere 10 years ago resulted in the remarkably rapid development of drugs that selectively inhibit COX-2 (coxibs). Lack of gastrointestinal adverse effect with long-term use was seen as the main advantage of the coxibs. Lack of antiplatelet effect was perceived as an advantage in acute perioperative pain management, particularly with ketorolac being restricted to use in low risk patients. However, recently a number of coxibs have been withdrawn due to unforeseen side effects. In contrast lumiracoxib, the latest in the coxib series, is at last being launched in the UK in October 2005. This review will summarise current understanding of new COX variants and the place of COX-2 inhibitors in clinical practice.

The COX isoenzymes are currently derived from two distinct genes. However, there are a number of variants of COX-1 and COX-2. Alternative splicing of COX mRNA is functionally significant; retention and deletion of introns and exons (stretches of the mRNA sequence) alter the amino acid sequence of the isoenzymes which could possibly change protein folding and active site conformation. In addition both the COX-1 and COX-2 gene have demonstrated single nucleotide polymorphism (SNPs) sequences with rare polymorphisms being identified. For the COX-1 isoform there are at least 18 SNPs identified with seven resulting in amino-acid changes. Preliminary allele frequencies suggest these SNPs are all rare and found in less than 4% of the population.

The first two selective inhibitors of COX-2 (celecoxib and rofecoxib) were approved by the American FDA in 1999 with claims of greater gastrointestinal safety than conventional NSAIDs. It is now apparent that selective COX-2 inhibitors reduce the production of antithrombotic prostacyclin without changing the production of prothrombotic thromboxane and as a result are associated with an increased risk of serious cardiovascular events (APPROVe trial, APC Study, CABG surgery study). Rofecoxib and valdecoxib have now been withdrawn, lumiracoxib's launch was initially abandoned and the prescribing advice for celecoxib and etoricoxib now markedly restricts their indications for use. Furthermore other non-coxib selective COX-2 inhibitors such as meloxicam and etodolac, are under scrutiny. Interestingly valdecoxib was withdrawn as a result of serious cutaneous reactions and not because of adverse cardiovascular effects. In a further twist to the story aspirin has been shown to increase the risk of adverse cardiovascular events whilst lumiracoxib demonstrates comparable cardiovascular safety to ibuprofen and naproxen (TARGET study).

It has been suggested that the deleterious cardiovascular effects of coxibs may be a class effect. However, alternative mechanisms have been suggested. Thus coxibs with a

sulphone structure such as rofecoxib seem to be implicated more than coxibs with a sulphonamide structure such as celecoxib.

The coxib story continues to evolve and there is much confusion regarding their place in clinical practice. It is important to remember that adverse cardiovascular events with coxibs relate to their long-term use. There is currently no information on the incidence of such events with short-term perioperative use.

Further Reading:

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