The practice implications of cardiovascular risks in NSAIDs

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Non-steroidal anti-inflammatory drugs (NSAIDs) are useful medications for the management of pain. However, Cox-2 NSAIDs have been associated with an increased risk of cardiovascular side-effects and there are now concerns that this increased risk may extend to all NSAIDs. This article outlines the action of NSAIDs and discusses the evidence for a link with increased cardiovascular risk.

Non-steroidal anti-inflammatory drugs (NSAIDs) are recognised as effective analgesics and are used in acute and chronic pain (*Bandolier*, 2005). However, doubts have recently emerged over the safety profile of these commonly used medications.

**Action**

All NSAIDs have analgesic, anti-pyretic and anti-inflammatory actions. They work by inhibiting the action of cyclo-oxygenase (Cox), which is involved in producing prostaglandins.

There are at least two forms of cyclo-oxygenase:

- Cox-1 helps maintain gastric mucosal integrity;
- Cox-2 is produced at sites of inflammation and pain.

The anti-inflammatory effect of NSAIDs is thought to be due to inhibition of Cox-2, while gastrointestinal side-effects are the result of blocking Cox-1 (*Bandolier*, 2005).

Traditional NSAIDs, such as ibuprofen or diclofenac, inhibit the action of both Cox-1 and Cox-2. New generation Cox-2-selective NSAIDs have been developed to try to reduce this side-effect.

**Cardiovascular side-effects**

**Cox-2 NSAIDs**

Concerns regarding cardiovascular side-effects and NSAIDs were first raised when the VIGOR study (Bombardier et al, 2000) was published showing an increase in major cardiovascular events in patients who receive rofecoxib (Vioxx). In September 2004 this resulted in the voluntary worldwide withdrawal of the drug by the manufacturer.

Questions were then raised about whether this effect was specific to rofecoxib or a class effect that was applicable to all Cox-2 NSAIDs. Other Cox-2 NSAIDs were investigated and Nussmeier et al (2005) associated valdecoxib, taken after coronary artery bypass grafting, with an increased incidence of cardiovascular events. Solomon et al (2005) reported an increased risk of cardiovascular events associated with use of celecoxib. Additional trial data on other Cox-2 NSAIDs is forthcoming but the results so far have prompted a Europe-wide review. The Committee on Safety of Medicines (2005) has advised that Cox-2 NSAIDs as a class of drugs may cause an increased risk of cardiovascular events and that the risk may increase with dose and duration of exposure.

The increased risk seems to be higher in those who already have cardiovascular disease and the CSM has made the following recommendations:

- Cox-2 NSAIDs are contraindicated in people with established ischaemic heart disease or cerebrovascular disease, and in people with moderate or severe heart failure;
- In people with risk factors for heart disease (for example, diabetes, hypertension, hyperlipidaemia, obesity, smoking) the balance of gastrointestinal and cardiovascular risk should be considered before prescribing a Cox-2 NSAID;
- People requiring low-dose aspirin should generally not be prescribed Cox-2 NSAIDs because gastrointestinal benefit has not been clearly demonstrated in this group.

It has been suggested that Cox-2 NSAIDs may increase cardiovascular risk because a Cox-2-derived prostaglandin, called prostacyclin, controls the blood-vessel response to stresses such as high blood pressure (Rudic et al, 2005).

**Traditional NSAIDs**

The evidence on Cox-2 NSAIDs points to an increased risk of cardiovascular events being a class effect. This has raised further questions about whether the effect extends to the traditional NSAIDs. A study by Hippisley-Cox and Coupland (2005) has recently suggested that this is indeed the case.

Hippisley-Cox and Coupland (2005) used a new clinical database containing the records of more than 7 million patients registered with 468 UK practices to investigate the risk of myocardial infarction associated with NSAIDs in patients with and without pre-existing coronary heart disease and in those taking, and not taking, aspirin. The data analysis was completed before the announcement of the withdrawal of rofecoxib.
Their results showed a significantly increased risk of myocardial infarction for patients taking rofecoxib compared with those who had not used this within the previous three years. They also found a significantly increased risk with current use of diclofenac and with current use of ibuprofen. Increased risks were also found associated with the other Cox-2 and traditional NSAIDs.

The study concluded that there might be insufficient concern to warrant a reconsideration of the cardiovascular safety of all NSAIDs.

This study does not provide evidence of an increased cardiovascular risk with all NSAIDs. The authors acknowledge that it is only an observational study and may be subject to limitations that could not be fully corrected for. Therefore other explanations for the associations could exist. The authors discuss this and cite the example of the possibility that the NSAIDs may have been given for chest pain that was cardiac rather than musculoskeletal in nature.

In addition, the study does not provide information about the potential cardiovascular risks when taking NSAIDs in low doses, or as required (PRN) doses, or the implications of taking short courses, for instance, postoperatively.

The Medicines and Healthcare products Regulatory Agency (2005) is taking part in a Europe-wide review of the cardiovascular safety of traditional NSAIDs. It has highlighted the fact that a number of studies have not shown any increased risk of cardiovascular disease associated with ibuprofen. It noted that the drug’s excellent safety record resulted in it being made available as an over-the-counter medicine.

Balancing risk

It is important to consider this new risk in light of the needs of the patient groups who rely on this group of drugs. For people who live with chronic conditions such as rheumatoid arthritis, NSAIDs may be essential in order for them to carry out the activities of daily living.

The safety issues regarding Cox-2 NSAIDs were a setback for the management of arthritis (Tadman and Hill, 2005). This information has the potential to further reduce the choice of medication for a large group of patients who may be in desperate need of pain relief. Careful assessment of the risks and benefits associated with the drugs for each individual should be undertaken.

Prescribing decisions should always be made in consultation with the individual patient to discuss the risks and benefits of any medication. Patients will vary in their degree of concern regarding particular possible side-effects and also in their level of desire to alleviate their condition. This must be accounted for during the prescribing consultation and is an important factor in concordance.

The CSM (2005) has said it is not possible to quantify the risk precisely. However, the cardiovascular risk with Cox-2 NSAIDs is considered to be unlikely to exceed one extra serious thrombotic event per 100 patient years, over the rate for no treatment.

It should also be remembered that patients may have concerns regarding other potential side-effects of NSAIDs, such as an increased risk of breast cancer (Marshall et al, 2005), and that patients will vary in their ability to cope with their condition and need for pain relief.

Good practice in management of musculoskeletal pain is to use simple analgesics as first-line treatment. If an NSAID is required then current advice from the MRHA (2005) is that prescribers should use NSAIDs at the lowest effective dose for the shortest period of time.

Conclusion

There is an urgent need for a thorough study to provide more conclusive evidence of any link between the use of NSAIDs and cardiovascular disease. Until this is undertaken there will be doubts about using ibuprofen, which is commonly regarded as one of the safest of all the NSAIDs and has a long history of use.

References


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