UNIT NO. 4

COX2 INHIBITORS AS ANTI-INFLAMMATORY AGENTS

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ABSTRACT

Pain and inflammation are common problems in clinical practice. Anti-inflammatory drugs are one of the most often prescribed groups of medications. The issue is that they carry gastrointestinal (GI) and cardiovascular (CV) risks. Therefore, anti-inflammatory drugs should be used mostly in the setting of inflammation. Non inflammatory pain can be managed with other groups of drugs and therapies. For patients who do need anti-inflammatory agents, the choice is dependent on the GI and CV risk profile of the patient. Where possible, efforts should be directed to the underlying cause of the pain and inflammation.

Keywords: NSAID; Coxib; Anti-inflammatory;

SFP2017; 43(1): 19-20

INTRODUCTION

Pain and inflammation are common problems in the management of many types of patients. Inflammation can be intense, such as in acute gout or severe flares of rheumatoid arthritis. This requires treatments which reduce inflammation and pain while waiting for other treatments to take effect which will modify and control the underlying disease. On the other hand, there are causes of pain which have a minimal component of inflammation. An example is osteoarthritis which is essentially a degenerative non-inflammatory condition. These occur in older patients who are more prone to peptic ulcers and cardiovascular events. Non-steroidal anti-inflammatory drugs (NSAIDs), including COX2 inhibitors, can give rise to these two categories of side effects. In addition, they have an adverse impact on control of hypertension, may worsen renal function, and cause fluid retention.

Aspirin was discovered in the late 19th century but it was not until the 1970s that the mechanism of the cyclo-oxygenase enzyme inhibiting prostaglandin production was clarified by John Vane and other workers in the field.[1] This gave rise to the development of NSAIDs and subsequently the COX2 inhibitors. However with time, it became clear that although COX2 inhibitors reduce the incidence of gastrointestinal (GI) side effects, some of them like rofecoxib, which has been withdrawn, increased cardiovascular (CV) events. Currently, some parts of the world have given approval to the continued use of etoricoxib and most parts of the world continue to use celecoxib.

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GUIDELINES FOR CHOICE OF MEDICATION

Therefore, when choosing a medication to reduce pain and inflammation, there are a few considerations. **First, does the pain have a significant inflammatory component?** If not, it may be better to opt for other alternatives such as simple analgesics, e.g. paracetamol, or short-term opioid derivatives, e.g. tramadol. An example of such a condition is osteoarthritis. **Second, is there a treatment for the underlying cause?** If there is, then all efforts should be directed at treating the underlying disease. An example is gout. For those with tophi, renal stones, and frequent arthritic flares, the therapeutic goal is to drive the serum uric acid to below the saturation point of 6 mg/dl or 360 mmol/l. Another example is rheumatoid arthritis. There are now so many effective Disease Modifying Anti-Rheumatic Drugs (DMARDs), including the newer and more effective biological DMARDs targeting TNF, IL6, CD20, and JAK3. **Third, what is the risk profile of the patient regarding NSAIDs and coxibs?** If the patient has significant GI or CV risk and still needs an NSAID or coxib, then the choice is for one that minimises these side effects.

The question then arises. Are all NSAIDs and coxibs the same with regards to GI and CV risks?

In the CONDOR trial (**C**elecoxib versus **O**meprazole **aN**d **D**iclofenac in patients with **O**steoarthritis and **R**heumatoid arthritis),[2] comparing celecoxib with diclofenac in patients with rheumatoid arthritis and osteoarthritis, they studied patients with existing GI risk. Earlier studies had shown that in such patients, there are similar upper GI outcomes for coxibs alone versus NSAIDs plus proton pump inhibitor (PPI). In CONDOR, risks to both upper and lower GI tract were assessed and the celecoxib performed better than NSAID plus PPI.

In the MEDAL study,[3] etoricoxib was compared with diclofenac. Etoricoxib had fewer GI events but more renovascular adverse events compared to diclofenac, especially hypertension. The 2 drugs were comparable for CV events.

Another trial looking at CV events was the CNT trial (Coxib and traditional NSAID Trialists' Collaboration Trial).[4] This was a meta-analysis of 280 trials which compared NSAID vs placebo and 474 trials of one NSAID versus another NSAID. The findings were that high-dose diclofenac, ibuprofen, and coxibs increased CV risk but naproxen had a lower risk than other NSAIDs, including coxibs. Heart failure risk was doubled and interestingly all treatment groups including coxibs had increased GI risk compared to placebo.

A large-scale trial was started in 2006 and was completed in

2016. This trial, PRECISION (**P**rospective **R**andomised **E**valuation of **C**elecoxib **I**ntegrated **S**afety versus **I**buprofen **O**r **N**aproxen) recruited 24,222 patients with primary outcomes of first occurrence of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Secondary outcomes include clinically significant GI events. The trial should further clarify the choice of NSAIDs or coxibs in the management of patients with GI or CV risk.

For osteoarthritis, a consensus guideline published in 2015[5] suggested the following approach:

For patients with l**ow GI and low CV risk**, any non-selective NSAID (ns-NSAID) is acceptable.

For l**ow GI and high CV risk**, naproxen is preferred as it has lower CV risk than other ns-NSAIDs or coxibs. Celecoxib at 200 mg once daily is also acceptable.

For **high GI and low CV risk,** a coxib alone or ns-NSAID with PPI is acceptable. Only celecoxib has benefit for both upper and lower GI tract.

For **high GI and high CV risk**, it is best to avoid the use of NSAIDs and coxibs altogether.

In conclusion, anti-inflammatory agents such as NSAIDs and coxibs are one of the most often used groups of medications in clinical practice. It is important for the doctor to be vigilant about the appropriate use of these drugs to gain the maximum benefit/risk ratio for their patients.

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LEARNING POINTS

- **For non-inflammatory causes of pain, avoid NSAIDs and coxibs. Opt for other groups of medications such as simple analgesics.**
- **If there is an underlying illness causing the pain and inflammation, direct efforts at treating the condition adequately.**
- **For those who do need anti-inflammatory agents, choose a specific drug based on the patient's risk for GI and CV events.**