Cardiovascular effects and the use of nonsteroidal anti-inflammatory drugs

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) include the nonselective and the cyclo-oxygenase-2-specific inhibitors. These agents are used for pain associated with musculoskeletal conditions. The nonselective anti-inflammatory drugs are still widely used, and are also freely available as over-the-counter analgesics. However, they carry the risk of serious cardiovascular adverse effects, especially in patients who have a high, pre-existing cardiovascular risk profile. It is imperative that physicians are aware of these risk factors and choose agents that have the best benefit-to-risk profile, while taking into consideration the patient's individual risk profile.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used worldwide to treat pain and inflammation.[1] In 2007, the American Heart Association published a warning in a focused update on the use of NSAIDs in patients with established cardiac disease.[2] Cardiovascular side-effects relating to NSAIDs first became apparent in clinical trials in which the effects of selective cyclo-oxygenase-2 inhibitors (COX-2 inhibitors) were investigated. Follow-up studies subsequently suggested an increase in cardiovascular risk in nonselective NSAIDs, e.g. ibuprofen and diclofenac. NSAIDs are widely used across the globe, and many of them can be purchased as over the-counter-drug analgesics, e.g. ibuprofen, diclofenac and mefenamic acid.[3]

Diclofenac was identified by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee as a high-risk NSAID with regard to its effect on the heart and circulation when administered systemically, i.e. using capsules, tablets or injections.[4] Individual drugs have different degrees of risk. Naproxen and low-dose ibuprofen carry the lowest cardiovascular risk. Diclofenac has a higher risk in dosages that are available over the counter. The available data for etoricoxib are still sparse, but it has a higher relative risk compared to naproxen or ibuprofen. Indomethacin has a range of gastrointestinal and central nervous system side-effects. It has a cardiovascular risk profile that is similar to that of diclofenac.[5]

The physiology involved in cardiovascular side-effects is explained in the sebsequent section.

Both COX-1 and COX-2 are found in the blood vessels, stomach and kidneys.[6,7] The physiological action of COX-1 includes normal physiological regulation and the production of the prostanoids which are responsible for maintenance of the following:[6,7]

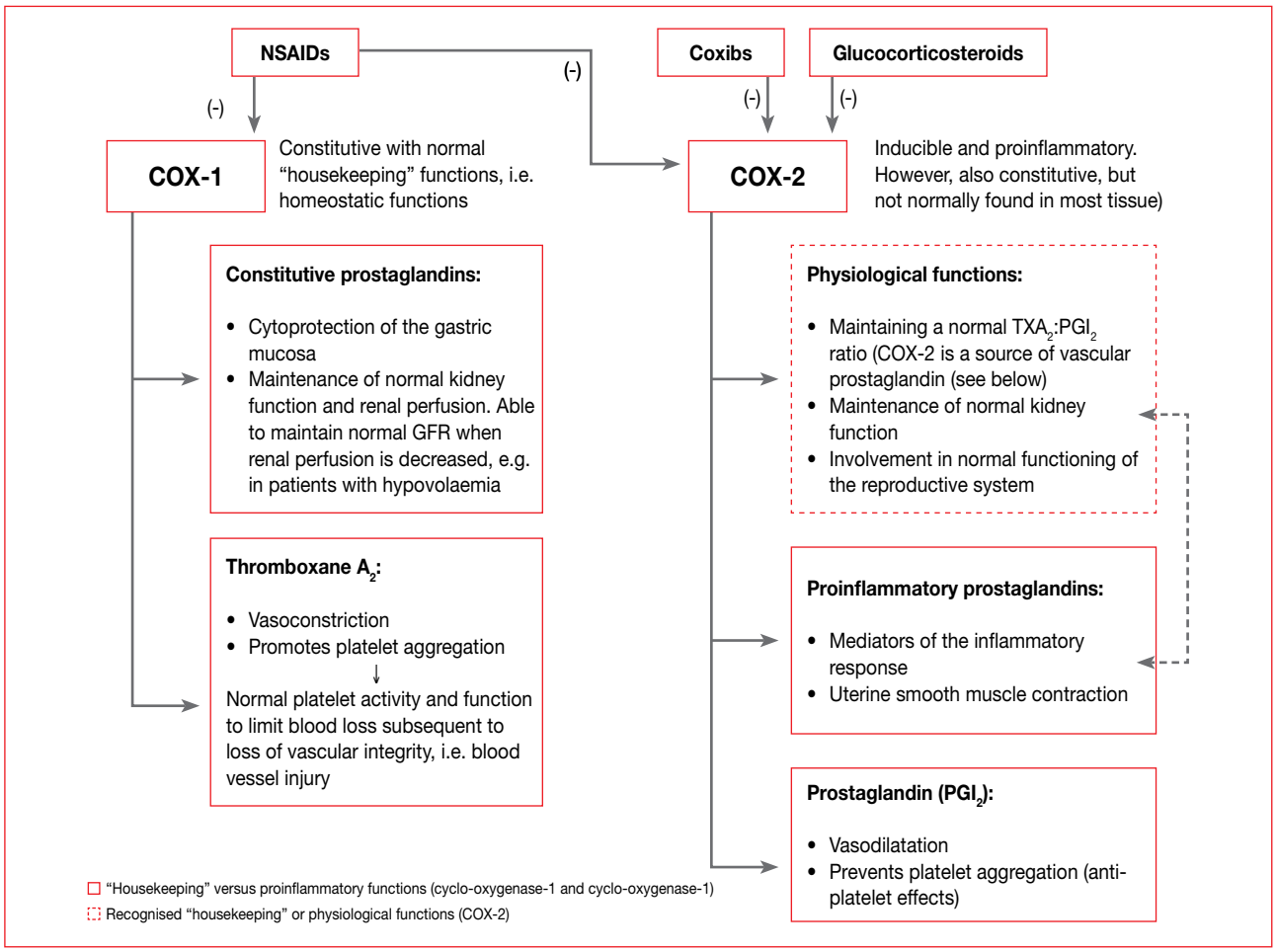
- *The gastrointestinal mucosa:* The production of bicarbonate and mucus from the gastrointestinal mucosa, blood flow regulation and epithelial proliferation.
- Platelet aggregation.
- *Renal prostaglandin synthesis:* The two prostaglandins found in the kidneys include PGE_2 and PGI_2. PGE_2 is involved in sodium reabsorption in the thick ascending loop of Henle, as well as the collecting tubules, and also seems to antagonise the antidiuretic effect of vasopressin in the collecting tubule.

COX-2 is expressed in the adult mammalian renal cortex, macula densa, thick ascending limb, interstitial cells in the inner medulla, and in the papilla and podocytes.[6,7] COX-2 is detected upon stimulation in monocyte, macrophage, neutrophil and endothelial cells.[6,7] COX-2 release is triggered by cytokines, mitogens and endotoxins in inflammatory cells, and is responsible for prostaglandin production in inflamed tissue.[6,7]

Figure 1 is a comparison of COX-1 and COX-2 isozymes.

Cardiovascular events

Individual factors may contribute to the relative risk of cardiovascular events. Underlying pathologies, including



Coxibs: cyclo-oxygenase inhibitors, COX-2: cyclo-oxygenase-2, GFR: glomerular filtration rate, NSAIDs: nonsteroidal anti-inflammatory drugs, PG: prostaglandin, TXA_2: thromboxane A_2

Figure 1: A comparison of cyclo-oxygenase-1 and cyclo-oxygenase-2 isozymes

pre-existing hypertension, renal impairment and concomitant therapy may exacerbate cardiovascular toxicity.[8-10]

Cardiovascular-related toxicity includes: (Figure 2):[8-10]

- An increase in blood pressure of approximately 4-6 mmHg; especially in susceptible individuals, i.e. patients who are known to be hypertensive or those who are already on antihypertensive treatment.
- New onset and recurrence of congestive cardiac failure.
- Sodium and water retention that is primarily owing to the effects of COX-2. (COX-2 is produced in the macula densa of the proximal tubule of the kidney. Inhibition can lead to sodium and water retention).
- *Atrial fibrillation or flutter:* The use of non-aspirin NSAIDs has an increased risk of atrial fibrillation and flutter. The highest incidence was found in new users. (The risk increases in specific relation to COX-2 inhibitors).

Mechanisms involved in fluid retention, heart failure and hypertension with non-selective nonsteroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors.

This may be because of the presence of COX-2 in the kidneys, and the effect of COX-1 in maintaining a normal glomerular filtration rate (Figure 1). Inhibition of these

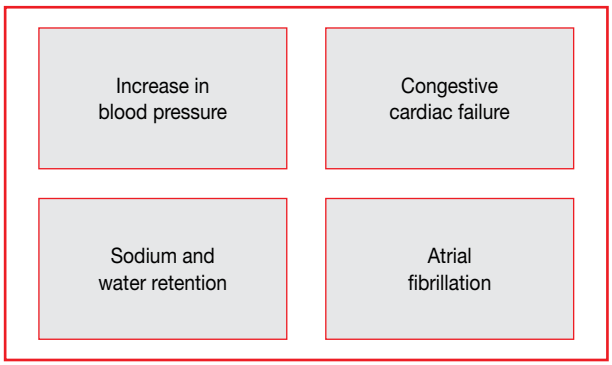
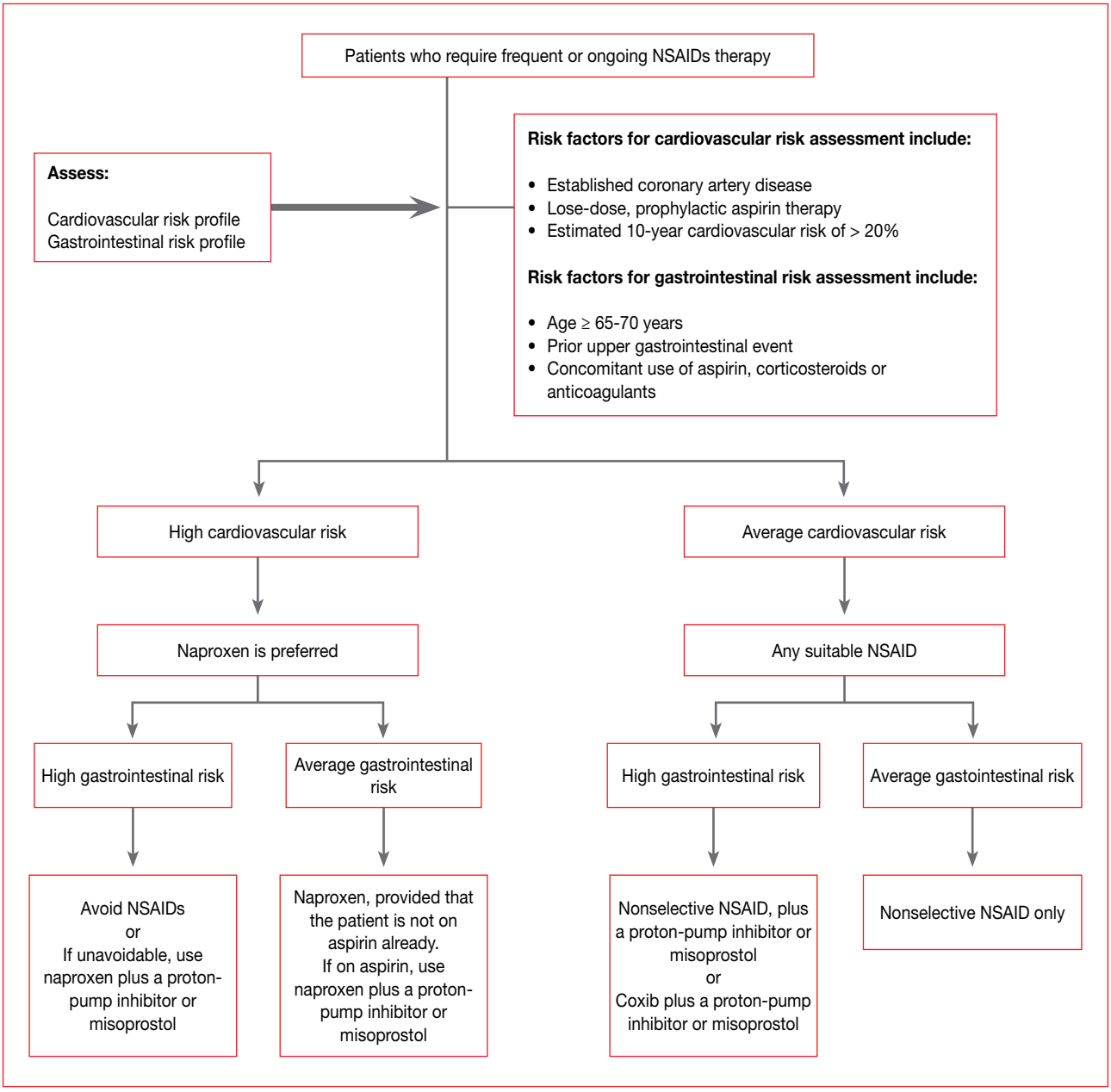


Figure 2: Cardiac effects which relate to nonsteroidal anti-inflammatory drugs

enzymes by nonselective NSAIDs and selective COX-2 inhibitors will result in renal effects, with different degrees of sodium and fluid retention, depending on the agent.[6] Prostaglandins are synthesised in the kidneys, and disruption of their synthesis by NSAIDs can result in acute renal failure, acute nephritis, electrolyte imbalances and a reduction in renal perfusion.[6,8] Fluid retention might increase peripheral vascular resistance, with deleterious effects on the heart, including hypertension and heart failure. However, only a small proportion of patients who develop fluid retention will eventually develop congestive heart failure.[6,8]



Coxib: cyclo-oxygenase inhibitor, NSAID: nonsteroidal anti-inflammatory drug

Figure 3: Management algorithm for frequent or ongoing nonsteroidal anti-inflammatory drug therapy[11]

NSAIDs may have varying degrees of influence on blood pressure. Indomethacin, the most potent inhibitor of the prostaglandins, is also associated with the highest incidence of heart failure, and provides considerable challenges in blood pressure control. The NSAIDs (both nonselective and selective) antagonise most of the important agents that are used to manage hypertension, thus aggravating the condition.[6,8]

As previously stated, the cardiovascular risk profile of NSAIDs differs between drugs. Currently, naproxen seems to be the safer choice (Figure 3), particularly when compared to diclofenac, which carries a warning, especially when given to patients with an existing cardiovascular risk profile, such as those with high blood pressure, raised blood cholesterol, diabetes or those who smoke.[4,6,8]

Conclusion

The use of NSAIDs should be reserved for patients who suffer from debilitating musculoskeletal conditions, e.g. osteoarthritis, and only when the benefit outweighs the risk. NSAIDs (both nonselective and selective) should be used with caution in patients with pre-existing cardiovascular conditions, and the physician should select the NSAID that has the lowest risk when the patient's current condition is taken into consideration. It should be used at the lowest dose and for the shortest possible time.

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