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Aging
HEALTH

NSAIDs in elderly patients with heart failure: stuck between a rock and a hard place?

“In many countries, NSAIDs are sold over-the-counter...without any provision of medical advice on their use or potential adverse effects. This practice is worrying and symptomatic of the widespread misinterpretation that NSAIDs are harmless drugs that are safe for everyone.”

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used effectively for the treatment of pain and inflammatory conditions over the last 100 years and are among the most commonly used drugs worldwide. However, during the last decade there has been increased concern regarding the cardiovascular safety profile of NSAIDs, primarily because of results from studies demonstrating increased cardiovascular risk with selective cyclooxygenase (COX)-2 inhibitors, the newer generation of NSAIDs developed with the aim of providing a more favorable gastrointestinal risk profile. Recently, there has been accumulating evidence from several large observational studies and meta-analyses indicating that nonselective NSAIDs are also associated with increased cardiovascular risk.

The main action of NSAIDs is inhibition of COX enzymes that catalyze synthesis of prostaglandins from arachidonic acid. Prostaglandins are mediators of an array of physiologic and pathophysiologic functions, for example, vascular tone, blood pressure, gastric protection, body salt and water homeostasis, inflammation and thrombosis [1]. In brief, traditional NSAIDs inhibit prostaglandin synthesis and thereby suppress pain, inflammation and fever, but they also predispose to gastrointestinal ulceration and bleeding. COXs exhibit two main isoforms – COX-1 and COX-2 – both of which are inhibited by NSAIDs, although to a varying degree. There are two products of COX prostaglandin synthesis that mainly influence the cardiovascular system, namely, thromboxane A_2 (TXA $_2$) and prostaglandin I_2 (PGI $_2$ or prostacyclin). TXA $_2$ is a powerful vasoconstrictor and a potent stimulator of platelet aggregation, and the antithrombotic effect of low-dose aspirin is achieved by selective and irreversible inhibition of constitutive COX-1 in

platelets. On the other hand, PGI $_2$ is a potent vasodilator and inhibitor of platelet function that appears to be predominantly produced by inducible COX-2 in vascular cells. However, there are several other effects of prostaglandins that can influence the cardiovascular risk associated with modulation of COX activity by NSAIDs. For example, TXA $_2$ can increase renal salt and fluid retention, augment systemic blood pressure and enhance negative myocardial and vascular remodeling, while PGI $_2$ can facilitate renal salt and fluid excretion, and lower blood pressure. In the healthy cardiovascular system there is an favorable equilibrium between TXA $_2$ and PGI $_2$ and it is likely that NSAIDs, to a varying degree, can tip the TXA $_2$ /PGI $_2$ balance and thereby increase cardiovascular risk.

“Several large observational studies and meta-analyses have now indisputably demonstrated an increased cardiovascular risk with the use of nonselective NSAIDs...”

The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial was the first major study to demonstrate increased cardiovascular risk with the selective COX-2 inhibitor, rofecoxib [2]. These results were confirmed in several other studies for rofecoxib as well as for other selective COX-2 inhibitors [3–9]. Traditional nonselective NSAIDs have been used uncritically for decades without any concern for a potential cardiovascular risk and there has been an alarming lack of randomized studies aimed at examining the cardiovascular safety of these agents. However, several large observational studies and meta-analyses have now indisputably demonstrated an increased cardiovascular risk with the use of nonselective NSAIDs [5,6,10–13]. There

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exists, however, considerable variability in the risk associated with individual NSAIDs, which is related to the capacity of the individual drug to inhibit COX-1 and/or COX-2. Hence, non-selective NSAIDs with high COX-2 inhibition potential (e.g., diclofenac) appear to convey a higher cardiovascular risk, whereas nonselective NSAIDs with high COX-1 inhibition potential (e.g., naproxen, aspirin and ibuprofen) appear to be associated with higher gastrointestinal toxicity [1,14].

“Although the current evidence undeniably points to increased cardiovascular risk of NSAIDs, total abandonment of their use is not likely or even possible at present...”

The discussion of the cardiovascular risk of NSAIDs has predominantly focused on the risk of thrombotic events. However, it is common knowledge among physicians that NSAIDs increase the risk of fluid retention and peripheral edema and that these drugs can destabilize and worsen pre-existing heart failure. Accordingly, international treatment guidelines have generally advocated caution with the use of NSAIDs in patients with heart failure. Furthermore, NSAIDs may decrease renal perfusion and glomerular filtration rate, leading to acute renal failure in susceptible patients [15]. Hypertension is a major cardiovascular risk factor and one of the main causes of heart failure, and NSAIDs have been shown to increase blood pressure and counteract blood pressure control in patients with hypertension receiving antihypertensive treatment [16–19]. In addition, several studies have demonstrated that among patients with established cardiovascular disease or those who are at increased cardiovascular risk (e.g., owing to ischemic heart disease), NSAIDs carry an even larger cardiovascular risk [7,20–22]. Indeed, in two separate cohorts of patients with myocardial infarction and chronic heart failure, we have demonstrated that treatment with the selective COX-2 inhibitors, rofecoxib and celecoxib, and the nonselective NSAID, diclofenac, as well as ibuprofen and naproxen in high dosages, increased the risk of death and rehospitalization for myocardial infarction and heart failure. This excess risk was prevalent early after treatment initiation and persisted during long-term use [11,12].

Epidemiological studies have demonstrated extensive prescription use of NSAIDs in the general population and among patients with

established cardiovascular disease [11,12,23]. Furthermore, in many countries, NSAIDs are sold over-the-counter in supermarkets, convenience stores and gas stations, without any provision of medical advice on their use or potential adverse effects. This practice is worrying and symptomatic of the widespread misinterpretation that NSAIDs are harmless drugs that are safe for everyone. Although the current evidence undeniably points to the increased cardiovascular risk of NSAIDs, total abandonment of their use is not likely or even possible at present, since some patients suffering from pain conditions are relieved by these drugs exclusively. Nevertheless, there is an unmet need among clinicians to focus on the balance between the treatment risk and benefit before initiating any NSAID treatment. This is particularly important in patients with established cardiovascular disease, where alternative pain treatment with drugs carrying a lower cardiac risk (e.g., acetaminophen or weak opiates) should be considered as the treatment of choice. In patients with indications for NSAID after careful risk–benefit assessment, great caution should be exerted and NSAIDs with the highest COX-1 selectivity (e.g., naproxen, ibuprofen or aspirin) are the preferred agents and they should be used in the lowest dosages and for the shortest periods of time as possible. In the elderly and in patients with heart failure or hypertension, close monitoring of blood pressure, renal function, bodyweight, symptoms of fluid retention and worsening of heart failure is recommended during NSAID treatment. Furthermore, a competitive interaction exists between COX-1-selective NSAIDs and aspirin with regard to binding to the COX-1 active site, which may abrogate the cardioprotective effect of low-dose aspirin in patients receiving dual NSAID therapy [24,25]. Thus, in patients taking aspirin for atherothrombotic prophylaxis, the other NSAID should be administered at least 2 h after the intake of aspirin. When a stronger analgesic effect is required, combination therapy with other types of analgesics (e.g., acetaminophen or opiates) should be considered. For patients with increased risk of gastric ulcers that require NSAIDs, a proton-pump inhibitor should be coadministered. There is, in fact, only a marginal benefit of selective COX-2 inhibitors as compared with traditional NSAIDs regarding the risk of gastric ulcers or bleeding, and this benefit is questionable during long-term treatment and might even be abrogated if low-dose aspirin is administered simultaneously. If,

however, a COX-2 inhibitor is required, treatment with celecoxib in low dosages (i.e., below 200 mg daily) may be considered.

“It is important to consider the value of nonpharmacological therapeutic measures...as a supplement and potential substitute for analgesic pharmacotherapy.”

In conclusion, re-evaluation of the current promiscuous use of NSAIDs is clearly warranted, not least in elderly patients with hypertension, heart failure or ischemic heart disease who often suffer from coexisting arthritis or rheumatic disease and are therefore in need of adequate analgesic treatment. This may pose a significant therapeutic dilemma and individual assessment and tailoring of pharmacotherapy is required, with careful consideration of the balance between risk and benefit. Furthermore, it is important to consider the value of non-pharmacological therapeutic measures, such as

physiotherapy and physical exercise, as a supplement and potential substitute for analgesic pharmacotherapy. The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) study is currently underway, and may provide more definitive information regarding the safety of NSAIDs in high cardiovascular risk patients [26]. Unfortunately, until these results become available in 2011, elderly patients with heart failure requiring NSAIDs remain stuck between a rock and a hard place.

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