Cardiovascular Safety of Naproxen for Treating Cancer and Noncancer Chronic Pain

Sir,

Nonsteroidal anti-inflammatory drugs (NSAIDs) are in use since 1960. They are non specific cyclooxygenase (COX) enzyme inhibitors. Later, specific COX-2 inhibitors were introduced starting with rofecoxib. NSAIDs and COX-2 inhibitors are common drugs used in the management of mild-to-moderate pain. Although these drugs provide good pain relief, they should be used with caution due to cardiovascular (CVS) side effects associated with its use. Although paracetamol and aspirin are nonopioids recommended by the WHO as the first-line agents for managing cancer pain and non cancer chronic pain, NSAIDs are mostly used instead of aspirin.[1] Of all NSAIDs currently in use, naproxen seems to have a safe CVS profile.

COX-1 and COX-2 enzymes are essential for homeostasis. COX-1 protects gastric mucosa from acid and generates thromboxane A2 (TXA2) by activating platelets in response to injury. Factors precipitating CVS events such as platelet aggregation, vasoconstriction, and increase in vascular and cardiac remodeling are mediated by COX-1 via TXA2. This means that selective COX-1 inhibition will inhibit TXA2 production, thereby preventing adverse CVS events. COX-2 activation leads to prostanoid production due to the release of inflammatory mediators.

Endothelial cells express COX-1 and COX-2, whereas platelet aggregation is mediated by C0X-1 only. NSAIDs are classified as nonselective or selective depending on the COX inhibition caused by their use. The COX-2 inhibitors preferentially inhibit COX-2 enzyme with a very minimal COX-1 inhibition. They do not have any antiplatelet effects due to negligible COX-1 effect. Although COX-2 inhibitors protect gastrointestinal (GI) mucosa, the non-COX- 1 effects lead to thrombotic events which made them notorious.[2]

Among all the nonselective NSAIDs, naproxen has increased selectivity for COX-1 and negligible COX-2 inhibition. This differential selectivity of naproxen is the reason for CVS safety. Naproxen has a long half-life owing to which it strongly inhibits platelet aggregation reversibly by inhibiting COX-1. When compared to other NSAIDs, sodium retention with the use of naproxen is less as a result of which increase in systolic blood pressure is less. Like any other NSAIDs, naproxen also reduces renal blood flow due to prostaglandin inhibition. Therefore, the drug should be avoided in acute and chronic renal failure and in predisposing situations.[3]

In 2004, rofecoxib was banned due to serious adverse CVS events associated with its use.[4] Later, celecoxib was introduced and showed promise due to less CVS events associated with its use. The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen trial showed noninferiority of moderate doses of celecoxib when compared with naproxen or ibuprofen, with regard to the CVS outcome with celecoxib treatment, resulting in lower rates of GI and renal adverse events.[5] Still, naproxen has an edge over celecoxib due to its mechanism of action which is different from other NSAIDs such as ibuprofen and diclofenac.

The present evidence suggests that naproxen is the safest NSAID and might be preferred over celecoxib in patients prone to CVS events. Clinicians should prescribe naproxen at a titrated dose for the shortest possible period.

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Conflicts of interest

There are no conflicts of interest.

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