Non-acetylated salicylates

Osteoarthitis

For symptomatic OA, UpToDate's pharmacologic approach emphasizes topical NSAIDs (especially for knee and hand OA) and oral NSAIDs when needed (eg, inadequate response to topical therapy, multiple joints involved, or hip OA), with other options such as duloxetine and intra-articular glucocorticoids in selected situations.

Mechanism

Niche for non-acetylated salicylates

Nonacetylated salicylates (eg, salsalate) are described as weak inhibitors of COX. In the context of NSAID hypersensitivity, non-acetyl salicylates are described as weak inhibitors of COX-1, and higher doses may inhibit COX-1 enough to cause symptoms.

It is possibile that non-prostaglandin-mediated mechanisms contribute to their anti-inflammatory effects. Specifically, some studies suggest their anti-inflammatory effects can be similar to non-salicylate NSAIDs, implying that non-prostaglandin-mediated mechanisms may be important for these agents.

A potential niche for non-acetylated salicylates is when an NSAID-like anti-inflammatory is desired but platelet inhibition is a concern, since nonacetylated salicylates (and COX-2 selective NSAIDs) are described as safer alternatives in patients with preexisting platelet defects or thrombocytopenia.

Non-selective NSAIDs (nsNSAID) exert antiplatelet effects through inhibition of the cyclooxygenase (COX)-1 isoform, leading to decreased production of thromboxane A2 (TxA2). TxA2 is released by platelets in response to a number of agonists, amplifying the platelet response and leading to aggregation. These effects have therapeutic applications, such as the use of aspirin as a prophylactic agent in patients with coronary artery disease. However, this same activity has potentially negative consequences in other groups of patients:

- Patients with preexisting platelet defects

Patients with preexisting platelet defects

nsNSAIDs should be avoided in patients with preexisting qualitative or quantitative platelet defects (eg, due to uremia or von Willebrand disease) and in those with thrombocytopenia (platelet count <50,000/microL). Nonacetylated salicylates or selective COX-2-inhibiting agents are safer therapeutic alternatives in these patients. Doses of nonacetylated salicylates should remain within recommended dose ranges (eg, 1.5 to 3 g/day for salsalate) to avoid inhibition of platelet COX, which can occur at high doses.

During the immediate preoperative period – nsNSAIDs should generally be withheld preoperatively for four to five times the drug half-life. However, the elimination half-life correlates poorly with COX inhibition and effects upon platelet aggregation [20,21]. Additionally, the relationship between time of discontinuation of NSAIDs and intra- and postoperative clinical bleeding is not well defined. For most nsNSAIDs, platelet function normalizes within three days of discontinuation, suggesting that nsNSAIDs should generally be discontinued at least three days before surgery. In healthy individuals receiving ibuprofen for one week, platelet function appears to return to normal within 24 hours after the last dose [22]; thus, ibuprofen can be stopped 24 hours prior to surgery. (See "Perioperative medication management", section on

'Nonsteroidal antiinflammatory drugs'.)

Aspirin irreversibly inhibits platelet COX, and platelets lack the machinery to produce new COX. Thus, if aspirin is discontinued preoperatively, patients should stop aspirin for at least one week prior to a planned surgical procedure to allow the body to generate new platelets that have not been exposed to aspirin [19]. (See "Perioperative medication management", section on 'Aspirin'.)

Highly selective inhibitors of the COX-2 isoform of cyclooxygenase have little or no effect on the platelet since COX-2 activity has not been found in platelets.

Concurrent therapy with low-dose aspirin for cardiovascular prophylaxis and a nonsalicylate NSAID for another indication could potentially increase the risk of an untoward gastrointestinal event, but is usually well tolerated, and NSAIDs and low-dose aspirin can generally be used concurrently. However, none of the nonsalicylate NSAIDs have been evaluated for cardioprotective effects in large studies, and they are not a substitute for aspirin therapy.

As mentioned, concomitant use of low-dose aspirin and nonsalicylate NSAIDs may interfere with the beneficial cardiovascular effects of aspirin.

Salicylate-specific effects

While salicylates generally have the same mechanisms of action as other NSAIDs, there are some differences in their effect on COX inhibition. Aspirin and other salicylates barely inhibit the COX enzyme in pure cell-free enzyme systems, and, in cell membrane systems, their effects are not measurable. However, they are very potent inhibitors of both COX-1 and COX-2 in a human whole-cell system, and COX-2 is more sensitive to the effects of the drug than COX-1. Clinical studies have shown that nonacetylated salicylates (such as salsalate) may be as effective as other NSAIDs for patients with rheumatoid arthritis, despite evidence that they are not good prostaglandin synthesis inhibitors in vitro.

eferences

Nonselective NSAIDs: Overview of adverse effects Uptodate