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'CYCLOOXYGENASE (COX)' INHIBITORS- A REVIEW.

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ABSTRACT :

The class of medications known as cyclooxygenase (COX) inhibitors targets the enzymes COX-1 and COX-2, which catalyze the transformation of arachidonic acid into prostaglandins and thromboxanes, which are mediators of fever, inflammation, pain, and homeostasis. Non-selective COX inhibitors, such as aspirin, ibuprofen, naproxen, and indomethacin, block both isoforms and effectively reduce fever, inflammation, and discomfort. However, because they inhibit COX-1, they increase the risk of bleeding and gastrointestinal (GI) damage. By preserving COX-1, selective COX-2 inhibitors (such as celecoxib and etoricoxib) lessen gastrointestinal side effects, but they raise cardiovascular risks by upsetting the prostacyclin-thromboxane balance. Acetaminophen and other atypical inhibitors mainly work centrally, providing analgesia and antipyresis with little anti-inflammatory action and a potential for hepatotoxicity. Patient-specific considerations, such as GI and cardiovascular risk profiles, drive the selection of these medications, which are commonly used for gout, arthritis, acute pain, dysmenorrhea, and cardiovascular prophylaxis (aspirin). Their potential to prevent cancer and develop new, safer COX inhibitors are still being investigated.

Keywords: Cyclooxygenase (COX), COX-1, Cyclooxygenase Inhibitor,COX-2, non-selective NSAIDs, selective COX-2 inhibitors.

Introduction

Prostaglandin-endoperoxide synthase, another name for cyclooxygenase (COX), is an enzyme that catalyzes the transformation of arachidonic acid into prostaglandins, thromboxanes, and other eicosanoids. [**1,2**]
Numerous physiological and pathological processes depend on these lipid mediators. There are two primary types of COX enzymes: COX-1 and COX-2. While COX-2 is mostly in charge of inflammation and pain, COX-1 helps to protect the stomach lining and control blood clotting. [**3**]
While COX-2 is inducible and mostly expressed during inflammation, damage, or stress, COX-1 is constitutively expressed in the majority of tissues, preserving baseline physiological activities. Both enzymes are essential membrane proteins found in the nuclear envelope and endoplasmic reticulum. [**2**]

Importance of COX in the Human Body

Control of Inflammation: Prostaglandins (like PGE2) that mediate pain, swelling, and fever are produced when COX-2 is markedly increased in response to inflammatory stimuli. Because of this, anti-inflammatory medications such as nonsteroidal anti-inflammatory medicines (NSAIDs) target COX-2. [**2,4-7**]

Homeostasis Maintenance: COX-1 produces prostaglandins that protect the stomach mucosa, control blood flow to the kidneys, and preserve platelet function (e.g., thromboxane A2 for platelet aggregation). Gastrointestinal ulcers are one of the adverse outcomes of NSAIDs' inhibition of COX-1.

Pain Mediation: COX enzymes create prostaglandins, which make nociceptors more sensitive and intensify pain signals. For this reason, COX inhibitors, like ibuprofen, work well as analgesics.

Fever Regulation: By changing the body's temperature setpoint, prostaglandins produced by COX-2 in the hypothalamus contribute to fever during infections.

Cardiovascular Function: The thromboxanes and prostacyclins produced by COX-1 and COX-2, respectively, have conflicting effects on platelet aggregation and vascular tone. This equilibrium may be upset by COX-2 suppression, raising the risk of cardiovascular events.

Cancer and Cell Proliferation: Because COX-2 prevents apoptosis and stimulates angiogenesis and cell proliferation, it is linked to some malignancies, including colorectal cancer. The possible chemopreventive effects of COX inhibitors are being investigated.

Reproductive Functions: By promoting cervical ripening and uterine contractions, prostaglandins generated from COX are essential for ovulation, implantation, and childbirth.

A class of medications known as COX inhibitors works by blocking the cyclooxygenase (COX) enzymes, which are involved in the synthesis of prostaglandins, which are substances that cause fever, pain, and inflammation. Traditional non-selective NSAIDs and COX-2 selective inhibitors are the two primary categories of COX inhibitors. [**3**]

Classification of COX Inhibitors

Cyclooxygenase (COX) inhibitors are categorized according to their therapeutic effects, mode of action, and selectivity for COX-1 and COX-2 enzymes. Atypical COX inhibitors, selective COX-2 inhibitors, and non-selective COX inhibitors are the three main kinds. [**2,5,7-9**]

1. Non-Selective COX Inhibitors

Definition: Inhibit both COX-1 and COX-2 enzymes with similar potency.

Examples: Aspirin, ibuprofen, naproxen, indomethacin, ketoprofen, diclofenac.

Basis:

Enzyme Inhibition: Equal affinity for COX-1 and COX-2, blocking prostaglandin and thromboxane synthesis.

Mechanism: Reversible inhibition (except aspirin, which irreversibly acetylates COX enzymes).

Clinical Effects: Anti-inflammatory, analgesic, antipyretic, and antiplatelet (via COX-1 inhibition); high GI and bleeding risks.

Applications: Pain, inflammation, fever, cardiovascular prophylaxis (aspirin).

2. Selective COX-2 Inhibitors (Coxibs)

Definition: Preferentially inhibit COX-2, sparing COX-1 at therapeutic doses.

Examples: Celecoxib, etoricoxib, rofecoxib (withdrawn), valdecoxib (withdrawn).

Basis:

Enzyme Selectivity: Higher affinity for COX-2 due to its larger active site (Val523 vs. Ile523 in COX-1).

Mechanism: Reversible inhibition, reducing inflammatory prostaglandins.

Clinical Effects: Anti-inflammatory and analgesic with lower GI toxicity but increased cardiovascular risks.

Applications: Osteoarthritis, rheumatoid arthritis, acute pain, cancer prevention (e.g., familial adenomatous polyposis).

3. Atypical COX Inhibitors

Definition: Indirect or unclear COX inhibition, primarily central effects.

Examples: Acetaminophen (paracetamol).

Basis:

Mechanism: Possible inhibition of COX-3 or modulation of endocannabinoid pathways, with minimal peripheral COX inhibition.

Clinical Effects: Analgesic and antipyretic, no significant anti-inflammatory action; hepatotoxicity risk.

Applications: Mild pain, fever, safe in GI/bleeding risk patients.

Basis for Classification

Selectivity: Non-selective (COX-1 and COX-2), selective COX-2 (COX-2 preference), atypical (central/unclear COX inhibition).

Mechanism: Irreversible (aspirin) vs. reversible; direct (NSAIDs, coxibs) vs. indirect (acetaminophen).

Clinical Effects: Anti-inflammatory (non-selective, COX-2) vs. non-inflammatory (atypical); side effect profiles (GI, cardiovascular, hepatic).

Chemical Structure: Secondary role (e.g., salicylates, propionic acids, coxibs).

Mechanism of Action, Applications, and Specific Drug Examples of COX Inhibitors

The enzymes COX-1 and/or COX-2, which transform arachidonic acid into prostaglandins, thromboxanes, and other eicosanoids, are blocked by cyclooxygenase (COX) inhibitors. These mediators control platelet aggregation, vascular function, inflammation, pain, fever, and gastric protection. With different mechanisms, uses, and adverse effects, COX inhibitors are divided into three categories: non-selective COX inhibitors, selective COX-2 inhibitors (coxibs), and atypical COX inhibitors. A thorough description of each category is provided below, complete with references in Vancouver style, mechanisms, clinical applications, and instances of particular drugs. [**2,5,7-10**]

1. Non-Selective COX Inhibitors

Mechanism of Action:

- • Non-selective COX inhibitors, with the exception of aspirin, bind reversibly to the active sites of COX-1 and COX-2, preventing arachidonic acid from being converted to prostaglandin H2 (PGH2), which is a precursor to thromboxanes (like TXA2) and prostaglandins (like PGE2, PGI2).
- **Aspirin**: Since platelets lack nuclei and are unable to synthesize new COX enzymes, aspirin inhibits both COX-1 and COX-2 irreversibly by acetylating a serine residue (Ser529 in COX-1 and Ser516 in COX-2). This dual inhibition lowers fever, inflammation, and pain (through COX-2) but also interferes with COX-1-mediated platelet aggregation and gastric mucosal protection, raising the risk of gastrointestinal (GI) bleeding and ulcers.
- **Applications**:

- **Pain relief**: Mild to moderate pain (e.g., headaches, muscle aches, dental pain).
- **Anti-inflammatory**: Chronic inflammatory conditions (e.g., rheumatoid arthritis, osteoarthritis).
- **Antipyretic**: Fever reduction in infections.
- **Antiplatelet**: Low-dose aspirin prevents thrombus formation in cardiovascular diseases (e.g., myocardial infarction, stroke prevention).
- **Other**: Dysmenorrhea, gout flares (e.g., indomethacin).

Specific Drug Examples:

1. **Aspirin (Acetylsalicylic Acid)**:
    - **Mechanism**: Irreversible COX-1 and COX-2 inhibition, with a pronounced effect on platelet COX-1, reducing TXA2 and inhibiting platelet aggregation for 7–10 days (platelet lifespan).
    - **Applications**: Low-dose (81–325 mg/day) for cardiovascular prophylaxis; higher doses (500–1000 mg) for analgesia, fever, and inflammation.
    - **Side Effects**: GI bleeding, peptic ulcers, tinnitus, Reye's syndrome (rare, in children with viral infections).
2. **Ibuprofen**:
    - **Mechanism**: Reversible, competitive inhibition of COX-1 and COX-2, with balanced potency.
    - **Applications**: Over-the-counter (200–400 mg) for pain, fever, dysmenorrhea; prescription doses (600–800 mg) for arthritis.
    - **Side Effects**: GI upset, renal impairment (with prolonged use), increased cardiovascular risk at high doses.
3. **Naproxen**:
    - **Mechanism**: Reversible COX-1 and COX-2 inhibition, with a longer half-life (12–17 hours) than ibuprofen.
    - **Applications**: Arthritis, tendinitis, gout, menstrual pain; longer duration allows twice-daily dosing.
    - **Side Effects**: Similar to ibuprofen but potentially less cardiotoxic.
4. **Indomethacin**:
    - **Mechanism**: Potent, reversible COX-1 and COX-2 inhibition, with additional effects on phospholipase A2, reducing arachidonic acid release.
    - **Applications**: Gout, ankylosing spondylitis, patent ductus arteriosus closure in neonates.
    - **Side Effects**: High GI toxicity, headaches, renal dysfunction.

2. Selective COX-2 Inhibitors (Coxibs)

Mechanism of Action:

• The COX-2 active site, which has a bigger binding pocket than COX-1 because valine is substituted for isoleucine, is where selective COX-2 inhibitors preferentially bind. By reducing COX-1 inhibition, this selectivity maintains platelet function and gastro mucosal protection.

• By blocking COX-2, they lower heat, pain, and inflammation by reducing the generation of prostaglandins (including PGE2) at inflammatory sites. The balance between COX-2-derived prostacyclin (PGI2, vasodilatory, and antithrombotic) and COX-1-derived TXA2 (prothrombotic) is upset by

selective COX-2 inhibition, which may raise the risk of cardiovascular events (such as myocardial infarction and stroke).

Applications:

- **Anti-inflammatory**: Chronic conditions like osteoarthritis and rheumatoid arthritis, especially in patients with GI risk factors.
- **Pain relief**: Acute pain (e.g., postoperative, musculoskeletal).
- **Cancer prevention**: Investigational use in colorectal cancer due to COX-2 overexpression in tumors.
- **Other**: Ankylosing spondylitis, acute gout (e.g., etoricoxib in some regions).

Specific Drug Examples:

1. **Celecoxib**:
    - **Mechanism**: Highly selective COX-2 inhibition (COX-2/COX-1 ratio ~30:1), reversible binding.
    - **Applications**: Osteoarthritis (200 mg/day), rheumatoid arthritis (200–400 mg/day), acute pain, familial adenomatous polyposis (adjunctive).
    - **Side Effects**: Lower GI risk than non-selective NSAIDs but increased cardiovascular risk with long-term use; contraindicated in sulfonamide allergy.
2. **Rofecoxib** (Withdrawn):
    - **Mechanism**: Highly selective COX-2 inhibitor, withdrawn in 2004 due to increased cardiovascular events (VIOXX study).
    - **Applications**: Formerly used for arthritis and acute pain.
    - **Side Effects**: Thrombotic events (e.g., myocardial infarction), leading to market withdrawal.
3. **Etoricoxib** (Not available in the U.S.):
    - **Mechanism**: Highly selective COX-2 inhibition, longer half-life (~22 hours).
    - **Applications**: Osteoarthritis, rheumatoid arthritis, gout, ankylosing spondylitis (approved in Europe, Asia).
    - **Side Effects**: Cardiovascular risk, hypertension, less GI toxicity than non-selective NSAIDs.

3. Atypical COX Inhibitors

Mechanism of Action:

- Atypical COX inhibitors have less clear or indirect effects on COX enzymes, often acting centrally or via alternative pathways.
- **Acetaminophen**: Its mechanism is debated but may involve weak inhibition of a COX-1 variant (COX-3) in the central nervous system or modulation of endocannabinoid signaling, reducing prostaglandin synthesis in the brain. It has minimal peripheral COX inhibition, explaining its weak anti-inflammatory effect.

Applications:

- **Analgesic**: Mild to moderate pain (e.g., headaches, osteoarthritis).
- **Antipyretic**: Fever reduction, safe in children and pregnancy (with caution).
- **Other**: Preferred in patients with GI or bleeding risks where NSAIDs are contraindicated.

Specific Drug Examples:

1. **Acetaminophen (Paracetamol)**:
    - **Mechanism**: Likely central COX inhibition, possibly via COX-3 or peroxidase-mediated pathways; minimal effect on peripheral COX-1/COX-2.
    - **Applications**: Pain (500–1000 mg every 4–6 hours, max 4 g/day), fever; first-line in osteoarthritis for patients with GI risks.
    - **Side Effects**: Hepatotoxicity at high doses (>4 g/day or with alcohol), rare skin reactions.

Side effects of each inhibitor drug

The adverse effects of each of the previously listed COX inhibitor medications (aspirin, ibuprofen, naproxen, indomethacin, celecoxib, rofecoxib, etoricoxib, and acetaminophen) are thoroughly explained here, along with substitute medications for their main uses. The response is arranged by medication and includes references in Vancouver style, side effects, and other alternatives. Similar therapeutic indications are used to pick alternatives, taking patient-specific considerations (e.g., cardiovascular or gastrointestinal risk) and safety and efficacy into account. [**5,8,10-13**]

1. Non-Selective COX Inhibitors

Aspirin (Acetylsalicylic Acid)

Side Effects: GI bleeding, gastritis, peptic ulcers, and dyspepsia (caused by the reduction of protective prostaglandins by COX-1 inhibition). increased risk of bleeding (e.g., bruising, epistaxis) as a result of irreversible platelet suppression. In patients who are aspirin-sensitive (aspirin-exacerbated respiratory disease, or AERD), an asthma attack, urticaria, or anaphylaxis may occur. hearing loss (dose-dependent, reversible) and tinnitus. renal

impairment (rare, with large doses) and elevated liver enzymes.

Rare: Reye's syndrome in children with viral infections (e.g., influenza, varicella).

Alternative Drugs:

For cardiovascular prophylaxis (antiplatelet):

Clopidogrel: A P2Y12 inhibitor, less GI bleeding risk but higher cost.

Ticagrelor: Another P2Y12 inhibitor, used in acute coronary syndrome.

For analgesia/fever:

Acetaminophen: Safer GI profile, no antiplatelet effect.

Ibuprofen: Reversible COX inhibition, shorter bleeding risk.

For inflammation (e.g., arthritis):

Celecoxib: COX-2 selective, lower GI risk.

Prednisone: Corticosteroid for severe inflammation, but with systemic side effects.

Ibuprofen

Side Effects: ulcers, dyspepsia, and gastrointestinal bleeding (which is less severe than aspirin because of reversible inhibition). increased risk of stroke and myocardial infarction with long-term or high-dose use. hypertension, fluid retention, and acute kidney damage (particularly in the elderly or those with renal impairment). Rarely, anaphylaxis causes rash. transaminase increase that is mild (rare).

Alternative Drugs:

For pain/fever:

Acetaminophen: Preferred for GI or bleeding risk patients.

Naproxen: Longer-acting, potentially lower cardiovascular risk.

For inflammation (e.g., arthritis):

Celecoxib: Lower GI toxicity.

Methotrexate: Disease-modifying antirheumatic drug (DMARD) for rheumatoid arthritis.

For dysmenorrhea:

Mefenamic acid: NSAID with similar efficacy, shorter duration.

Naproxen

Side Effects:

GI: Ulcers, bleeding, dyspepsia (less than aspirin, similar to ibuprofen).

Cardiovascular: Lower cardiovascular risk compared to other NSAIDs at standard doses, but risk persists with prolonged use.

Renal: Renal impairment, edema, hyperkalemia.

CNS: Headache, dizziness (less common).

Allergic: Rash, rare hypersensitivity reactions.

Alternative Drugs:

For pain/inflammation:

Celecoxib: COX-2 selective, better GI safety.

Diclofenac: Potent NSAID, topical formulations reduce systemic risks.

For gout:

Colchicine: Specific for acute gout, fewer GI effects at low doses.

Prednisone: Short-term corticosteroid for gout flares.

For fever:

Acetaminophen: Safer for children, elderly.

Indomethacin

Side Effects:

GI: High risk of ulcers, bleeding, perforation (more than other NSAIDs).

CNS: Severe headaches, confusion, dizziness (common, limits use in elderly).

Renal: Acute kidney injury, nephrotic syndrome (rare).

Hematologic: Bone marrow suppression (rare).

Cardiovascular: Hypertension, heart failure exacerbation.

Alternative Drugs:

For gout:

Colchicine: Lower GI toxicity, effective for acute attacks.

Allopurinol: For chronic gout (urate-lowering, not acute).

For patent ductus arteriosus (PDA):

Ibuprofen: Equally effective, better safety profile in neonates.

For arthritis:

Celecoxib: Lower GI and CNS side effects.

Etoricoxib: COX-2 selective, available in some regions.

2. Selective COX-2 Inhibitors (Coxibs)

Celecoxib

Side Effects:

Cardiovascular: Increased risk of myocardial infarction, stroke (dose- and duration-dependent, lower than rofecoxib).

GI: Lower risk of ulcers/bleeding compared to non-selective NSAIDs, but not eliminated.

Renal: Edema, hypertension, renal impairment (similar to NSAIDs).

Allergic: Cross-reactivity in sulfonamide allergy (rash, anaphylaxis).

Hepatic: Rare transaminase elevation.

Alternative Drugs:

For arthritis:

Naproxen: Non-selective, potentially lower cardiovascular risk.

Etoricoxib: More selective COX-2 inhibitor (where available).

For acute pain:

Acetaminophen: Safer for short-term use, no cardiovascular risk.

Diclofenac: Topical or oral, balanced efficacy/safety.

For cancer prevention (e.g., familial adenomatous polyposis):

Sulindac: Non-selective NSAID with some evidence in polyp reduction.

Rofecoxib (Withdrawn)

Side Effects:

Cardiovascular: Significantly increased risk of myocardial infarction, stroke (led to withdrawal in 2004 after VIOXX study).

GI: Reduced ulcer/bleeding risk compared to non-selective NSAIDs.

Renal: Edema, hypertension.

Other: Rare hepatic or allergic reactions.

Alternative Drugs (for former indications):

For arthritis/pain:

Celecoxib: Safer COX-2 inhibitor, still available.

Naproxen: Non-selective, lower cardiovascular risk.

For acute pain:

Acetaminophen: No cardiovascular risk.

Ibuprofen: Short-term use, reversible effects.

Etoricoxib (Not Available in the U.S.)

Side Effects:

Cardiovascular: Increased risk of thrombotic events, hypertension (similar to other coxibs).

GI: Lower ulcer/bleeding risk than non-selective NSAIDs.

Renal: Fluid retention, renal impairment.

Hepatic: Mild transaminase elevation (rare).

Other: Headache, fatigue.

Alternative Drugs:

For arthritis/gout:

Celecoxib: Similar COX-2 selectivity, wider availability.

Naproxen: Non-selective, cost-effective.

For ankylosing spondylitis:

Adalimumab: Biologic (anti-TNF), for refractory cases.

Indomethacin: Non-selective, effective but higher GI risk.

3. Atypical COX Inhibitors

Acetaminophen (Paracetamol)

Side Effects:

Hepatic: Hepatotoxicity at high doses (>4 g/day) or with alcohol, acute liver failure (leading cause of drug-induced liver injury).

Allergic: Rare skin reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis).

Renal: Chronic use may cause renal impairment (debated).

Other: No significant GI or cardiovascular risks at therapeutic doses.

Alternative Drugs:

For pain/fever:

Ibuprofen: More effective for inflammatory pain, but GI risk.

Naproxen: Longer-acting, similar indications.

For osteoarthritis:

Celecoxib: Anti-inflammatory, for patients needing NSAID effects.

Topical capsaicin: Non-drug option for localized pain.

Advantages and disadvantages with COX Inhibitor drugs

The benefits and drawbacks of each of the previously mentioned COX inhibitor medications—aspirin, ibuprofen, naproxen, indomethacin, celecoxib, rofecoxib, etoricoxib, and acetaminophen—are outlined in detail below. With benefits and drawbacks specific to their clinical uses and adverse effect profiles, the medications are divided into three classes: non-selective COX inhibitors, selective COX-2 inhibitors, and atypical COX inhibitors. [**5,8,10-14**]

1. Non-Selective COX Inhibitors

Aspirin (Acetylsalicylic Acid)

Advantages:

Effective Antiplatelet: At low doses (81–325 mg/day), irreversible COX-1 inhibition lowers thromboxane A2, preventing cardiovascular events (such as myocardial infarction and stroke) for 7–10 days. Versatile: At larger dosages (500–1000 mg), it effectively reduces pain, heat, and inflammation. Economical: widely accessible, reasonably priced, and over-the-counter (OTC). Anti-Inflammatory: Beneficial for pericarditis, rheumatoid arthritis, and other inflammatory diseases. Cancer Prevention: Research indicates that taking aspirin at low doses may lower the risk of colorectal cancer.

Disadvantages:

Gastrointestinal Toxicity: COX-1 inhibition, particularly at anti-inflammatory dosages, increases the risk of gastritis, ulcers, and GI bleeding. Risk of Bleeding: Irreversible platelet inhibition raises the possibility of cerebral or gastrointestinal bleeding. Allergic Reactions: In aspirin-exacerbated respiratory disease (AERD), it might cause anaphylaxis or asthma. Children who have viral infections run the rare but serious danger of developing Reye's syndrome. Tinnitus: Reversible, dose-dependent hearing problems.

Ibuprofen

Advantages:

Broad Efficacy: Good for fever, inflammation (e.g., arthritis), and mild to moderate pain (e.g., headache, dysmenorrhea). Reversible Action: Compared to aspirin, a shorter duration of platelet inhibition (reversible COX-1 effect) lowers the risk of bleeding. OTC Availability: Easily obtained, reasonably priced, and available in a range of dosages (200–800 mg). youngsters's Use: Safe for fever and pain in youngsters (e.g., 10 mg/kg dosage). Positive Tolerability: Less harmful to the gastrointestinal tract than aspirin or indomethacin.

Disadvantages:

GI Side Effects: Bleeding, ulcers, and dyspepsia are still possible, especially after extended use. Cardiovascular Risk: High dosages or prolonged use increase the risk of myocardial infarction and stroke. Renal Toxicity: The possibility of acute kidney damage, fluid retention, and high blood pressure, especially in individuals who are elderly or have renal impairment. Drug Reactions: increases the risk of bleeding by competing with other medications (like warfarin) for protein binding.

Naproxen

Advantages:

Longer Half-Life: Dosing twice a day is made possible by 12–17 hours, which increases compliance. Reduce the Risk of Cardiovascular Disease: At regular dosages, it may be less harmful to cardiovascular events than other NSAIDs (such as ibuprofen and diclofenac). Beneficial for Inflammation: strong effectiveness in treating ankylosing spondylitis, gout, and arthritis. OTC Availability: Reasonably priced, available for fever and discomfort. Versatile: Used to treat both chronic (like osteoarthritis) and acute (like gout) disorders.

Disadvantages:

GI Toxicity: bleeding, ulcers, and dyspepsia, but not as bad as with aspirin or indomethacin. Effects on the kidneys: hyperkalemia, edema, and renal damage, particularly in those who are at risk. Headache and lightheadedness (less frequent than indomethacin) are CNS effects. Cardiovascular Risk: Lower than with other NSAIDs, but still present with chronic use.

Indomethacin

Advantages:

Potent Anti-Inflammatory: Extremely beneficial for rheumatoid arthritis, ankylosing spondylitis, and acute gout. Specialized Use: Because of its potent COX inhibition, it is preferred for closing the patent ductus arteriosus (PDA) in neonates. Quick Onset: Beneficial for sudden flare-ups of gout. Other Mechanisms: reduces the release of arachidonic acid by inhibiting phospholipase A2.

Disadvantages:

High GI ToxicityNSAIDs have the highest risk of ulcers, bleeding, and perforation. CNS Side Effects: Dizziness, disorientation, severe headaches, and restricted use in older adults. Renal Toxicity: High risk of nephrotic syndrome and acute kidney damage. Hematologic: Infrequent suppression of bone marrow. Limited Chronic Use: Long-term use is limited by poor tolerability.

2. Selective COX-2 Inhibitors (Coxibs)

Celecoxib

Advantages:

Reduced GI Toxicity: Because COX-1 is spared, there is a lower risk of ulceration and bleeding than with non-selective NSAIDs. Beneficial for

Inflammation: approved to treat acute pain, rheumatoid arthritis, and osteoarthritis. Adjunctive use in familial adenomatous polyposis (FAP) to decrease colorectal polyps is one way to prevent cancer. 100–400 mg per day is a flexible dosage that can be used for both acute and chronic illnesses. For patients with GI risk factors (such as a history of ulcers), better tolerability is preferred. Drawbacks:

Cardiovascular Risk: Higher doses or prolonged use are associated with an increased risk of myocardial infarction and stroke. Similar to non-selective NSAIDs, renal effects include edema, hypertension, and renal impairment. Allergic Reactions: Not recommended in cases of rash or anaphylaxis caused by sulfonamide allergies. Cost: Higher than that of non-selective NSAIDs. Residual GI Risk: Particularly at higher dosages, there may still be some GI adverse effects.

Rofecoxib (Withdrawn)

Advantages (Historical):

GI Safety: Significantly reduced ulcer and bleeding risk compared to non-selective NSAIDs. Effective Analgesic/Anti-Inflammatory: Was effective for osteoarthritis, acute pain, and dysmenorrhea. Convenient Dosing: Once-daily dosing due to long half-life. Disadvantages:

Cardiovascular Risk: High risk of myocardial infarction and stroke led to withdrawal in 2004 (VIOXX study). Renal Effects: Edema, hypertension, similar to other NSAIDs. Limited Availability: No longer marketed, reducing relevance. Cost: Was expensive compared to generic NSAIDs. Etoricoxib (Not Available in the U.S.) Advantages:

High COX-2 Selectivity: Lower GI toxicity than non-selective NSAIDs. Long Half-Life: ~22 hours allows once-daily dosing, improving compliance. Broad Indications: Effective for osteoarthritis, rheumatoid arthritis, gout, and ankylosing spondylitis (approved in Europe, Asia). Potent: Higher efficacy in acute pain and gout compared to some NSAIDs. Disadvantages:

Cardiovascular Risk: Similar to other coxibs, increased risk of thrombotic events and hypertension. Renal Effects: Fluid retention, renal impairment. Limited Availability: Not approved in the U.S., restricting access. Cost: More expensive than non-selective NSAIDs. Hepatic Risk: Rare transaminase elevation. 3. Atypical COX Inhibitors Acetaminophen (Paracetamol) Advantages:

Minimal GI Toxicity: Safe for patients with ulcers or bleeding risk, no significant COX-1 inhibition. Safe in Pregnancy/Children: First-line for fever and pain in these populations (with dose caution). No Cardiovascular Risk: Unlike NSAIDs, no increased risk of thrombotic events. OTC Availability: Affordable, widely accessible. Effective Antipyretic/Analgesic: Reliable for fever and mild pain (e.g., osteoarthritis, headache). Disadvantages:

No Anti-Inflammatory Effect: Minimal peripheral COX inhibition limits use in inflammatory conditions. Hepatotoxicity: High doses (>4 g/day) or use with alcohol can cause acute liver failure. Renal Risk: Chronic use may lead to renal impairment (debated). Overdose Risk: Narrow therapeutic index; accidental overdose is a leading cause of liver injury. Rare Allergic Reactions: Skin reactions (e.g., Stevens-Johnson syndrome).

Conclusion

The capacity of cyclooxygenase (COX) inhibitors to inhibit COX-1 and/or COX-2 enzymes, which lowers the synthesis of prostaglandin and thromboxane, makes them essential for treating pain, inflammation, fever, and cardiovascular disorders. Although they are widely effective and reasonably priced, non-selective COX inhibitors (such as aspirin, ibuprofen, naproxen, and indomethacin) are constrained by the risks of bleeding and gastrointestinal (GI) damage. Careful patient selection is necessary because selective COX-2 medications, such as celecoxib and etoricoxib, have higher cardiovascular risks despite having safer GI characteristics. Although hepatotoxicity is still a problem, acetaminophen, an atypical COX inhibitor, is useful for analgesia and antipyresis with little GI or cardiovascular side effects. To maximize safety and effectiveness, the selection of a COX inhibitor should be based on patient-specific criteria, such as GI, cardiovascular, and renal risk profiles, and should be monitored frequently. Prospective investigations into new COX inhibitors and their uses, like cancer prevention, could improve treatment results.

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