"Review of Indole acetic acid derivative-Indomethacin for Osteoarthritis"

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Abstract

Osteoarthritis (OA) is a leading cause of habitual pain and disability, making effective symptom management essential. Indomethacin, a potent nonsteroidal anti-inflammatory drug, plays a crucial role in OA treatment due to its strong inhibition of COX-1 and COX-2 enzymes. This review summarizes the crucial features of indomethacin, including its chemical structure, structure–activity relationship (SAR), mechanism of action, pharmacodynamic, and pharmacokinetic properties. The medicine's indole nucleus, p-chlorobenzoyl group, and acetic acid side chain significantly contribute to its high anti-inflammatory activity, but also to its gastrointestinal, renal, and cardiovascular side effects. While indomethacin remains largely effective for reducing pain, stiffness, and inflammation in OA, its narrow safety periphery requires careful dosing and monitoring. Understanding its pharmacologic profile helps clinicians optimize therapy and supports the design of newer NSAID analogs with advanced safety and efficacy.

Keywords

Indomethacin, non-steroidal anti-inflammatory medicines (NSAIDs), osteoarthritis, pain operation, pharmacokinetics, pharmacodynamics, structural activity relationship (SAR).

Introduction

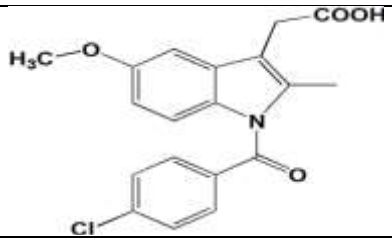
Osteoarthritis (OA) is the most common form of arthritis worldwide and represents a leading cause of habitual pain and disability among adults. Characterized primarily by progressive degeneration of articular cartilage, subchondral bone remodeling, and synovial inflammation, OA significantly impacts quality of life and imposes a substantial socioeconomic burden on healthcare systems. OA is astronomically distributed into primary(idiopathic) and secondary forms. Primary OA is generally associated with aging and inheritable predilection, whereas secondary OA arises from identifiable causes such as common trauma, metabolic diseases, natural abnormalities, or seditious common complaints. Clinically, OA demonstrates pronounced diversity; cases may range from being fully asymptomatic with incidental radiographic findings to passing severe pain, common disfigurement, and major functional impairment. This variability complicates both early opinion and optimal operation. Current OA operation focuses on symptom control and functional enhancement, as no definitive complaint-modifying remedy is yet available. Among the available pharmacologic options, nonsteroidal anti-inflammatory medicines (NSAIDs) remain the most extensively studied.

Agents due to their binary analgesic and anti-inflammatory properties. NSAIDs are recommended as first-line pharmacologic remedy in most international guidelines, particularly for cases that don't achieve acceptable relief from lifestyle revision and physical therapy alone. Indomethacin is a well-established, potent NSAID that has been widely used in the treatment of inflammatory and degenerative common diseases. Its remedial efficacy has been demonstrated in conditions similar to rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis involving large joints. Despite its clinical benefits, indomethacin is also associated with a notable threat profile, challenging careful evaluation of its safety, tolerability, and relative effectiveness within the broader geography of OA pharmacotherapy.

General Background

Indomethacin is a methylated indole derivative belonging to the acetic acid class of non-steroidal anti-inflammatory medicines (NSAIDs). It was first synthesized in 1963 during extensive sweats to develop potent inhibitors of prostaglandin conformation. The U.S. Food and Drug Administration (FDA) approved indomethacin in 1965, marking it as one of the foremost acetic acid-based NSAIDs introduced to clinical practice. This period also saw the development of affiliated agents such as diclofenac and sulindac, which together contributed to the establishment of NSAIDs as foundation curatives for seditious and degenerative rheumatic diseases. Like other NSAIDs, indomethacin exhibits anti-inflammatory, analgesic, and antipyretic properties. These effects are primarily mediated through the inhibition of cyclooxygenase (COX) enzymes, resulting in decreased conformation of prostaglandins, crucial mediators of inflammation, pain, and fever. Indomethacin is distinguished by its fairly potent COX inhibition, which accounts for its strong remedial goods but also contributes to its well-honoured threat profile, including gastrointestinal, renal, and central nervous system adverse effects.

Drug Profile:

Parameter	Description
Generic Name	Indomethacin
Chemical Class	Aryl alkanoic acid derivative (indole acetic acid derivative)
Therapeutic Class	Analgesic, Antipyretic, Anti-inflammatory
Chemical Formula	$C_{19}H_{16}ClNO_4$
Molecular Weight	357.8 g/mol
IUPAC Name	2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid
Structure	

Physical Appearance	white to yellow crystalline powder
Solubility	practically insoluble in water and sparingly soluble in alcohol
Melting Point	158–163 °C
Mechanism of Action (MOA)	Inhibits cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, decreasing the synthesis of prostaglandins responsible for pain, inflammation, and fever
Pharmacological Action	Analgesic, antipyretic, and anti-inflammatory
Route of Administration	oral, rectal, intravenous, and topical (ophthalmic) forms
Dosage Forms	Powder, suppository, suspension, Extended-Release capsules, capsules
Stability	Stable under normal temperature; sensitive to light and moisture
Storage Conditions	Store <25°C, protect from moisture and light

SAR and QSAR of Indomethacin:

Structural Feature	Modification / Observation	Effect on Activity / Rationale
Indole nucleus (core scaffold)	Replacement of indole with other heterocycles reduces activity	The indole ring helps proper orientation into the COX active site via hydrophobic interactions.
	Indole N-methylation	Maintains or slightly increases lipophilicity; essential for optimal COX binding.
p-Chlorobenzoyl moiety (para-chloro substitution)	Removal of the p-Cl group causes a major loss of potency	Para-chloro enhances hydrophobic binding to COX and improves activity.
	Replacement with other halogens (F, Br)	Activity varies; Cl provides optimal size & electronegativity
	Substituting at ortho/meta positions	Lower activity due to steric misalignment in the receptor pocket

Acetic acid side chain (–CH_2–COOH)	Essential: conversion to amide/ester reduces activity	COOH is crucial for ionic bonding with Arg120 at the COX active site
	Removing the α-methyl group (in other arylacetic NSAIDs) reduces activity	α-Methyl increases COX binding affinity (steric & lipophilic effects)
Methoxy group at position-5 of indole	Methoxy-H leads to a significant loss of activity.	Oxygen contributes to electronic distribution and maintains the correct conformation.
	Methoxy-other electron-donating groups	Maintains moderate activity; bulky groups decrease potency
Position of benzoyl group on indole (C-3)	Shifting the benzoyl group to other positions drastically reduces activity	Correct orientation at the COX binding site is lost, required for optimal inhibition
Overall molecule conformation	Rigidification or flexible linkers reduces activity	Proper spatial arrangement between arylacetic acid and aromatic rings is critical
Lipophilicity	Increased lipophilicity improves COX binding but decreases solubility	Indomethacin has an optimal balance via Cl and methoxy groups
Aromaticity requirement	Replacing aromatic rings with saturated rings (cyclohexyl, etc.) reduces activity.	Aromatic stacking interactions are required in the COX channel.

Quantitative Structure-Activity Relationship (QSAR) of Indomethacin:

Quantitative Structure-Activity Relationship (QSAR) methodologies establish mathematical correlations between chemical structure and biological activity, and they have been widely used to model the potency and selectivity of nonsteroidal anti-inflammatory drugs (NSAIDs). QSAR studies often rely on physicochemical descriptors—including lipophilicity, electronic parameters, steric volume, and hydrogen-bonding capacity—to predict cyclooxygenase (COX) inhibitory activity and drug disposition properties.

1. Structural Features of Indomethacin Relevant to Activity

Indomethacin's activity is strongly governed by its methylated indole nucleus, p-chlorobenzoyl substituent, and acetic acid side chain, which collectively enable high-affinity binding within the COX active site.

Key structural features include:

- Indole ring system: Provides hydrophobic anchoring within the COX channel.
- p-Chlorobenzoyl moiety: Enhances lipophilicity and stabilizes ligand–enzyme interaction.
- Acetic acid functional group: Essential for ionic interaction with the catalytic Arg120 residue of COX enzymes.
- Methoxy group: Modifies electron distribution and contributes to optimal molecular conformation.

These features explain indomethacin's potency as a non-selective COX inhibitor.

2. Physicochemical Descriptors Important in QSAR Modeling

QSAR models frequently highlight specific molecular descriptors that contribute to NSAID potency and safety profiles. For indomethacin, important descriptors include:

- Lipophilicity (logP ≈ 4): Predictive of membrane permeability and COX binding strength.
- pKa (~4.5): Favors partial ionization at physiological pH, enhancing ionic interactions within the COX active site.
- Molecular weight (357.8 g/mol): Within the optimal range for oral anti-inflammatory agents.
- Topological polar surface area (TPSA ≈ 68 Å²): Supports favorable oral absorption while maintaining target affinity.
- Melting point (158–163 °C): Relevant for formulation and physicochemical modeling.

These descriptors are commonly used in regression- and machine-learning–based QSAR models to predict potency and pharmacokinetic behavior.

3. QSAR Insights into COX Inhibitory Activity

QSAR studies of NSAIDs show consistent structure–activity patterns reflected in indomethacin's design:

- Electron-withdrawing substituents (i.e., chlorine) strengthen COX binding affinity.
- A planar aromatic scaffold facilitates hydrophobic and π–π interactions within the COX binding cavity.
- A carboxylate moiety is critical for ionic anchoring at Arg120, a well-documented determinant of COX inhibition.
- Appropriate steric bulk around the acyl group improves inhibition but may influence COX-1/COX-2 selectivity.

These QSAR principles collectively explain indomethacin's strong anti-inflammatory efficacy and relatively narrow safety window.

4. QSAR Implications for Osteoarthritis Therapy

QSAR-derived properties of indomethacin translate directly into its clinical performance:

- High lipophilicity and strong COX affinity contribute to potent analgesic and anti-inflammatory action in osteoarthritis.
- Nonselective COX inhibition explains both its therapeutic benefit and its association with gastrointestinal and renal adverse effects.

- Predictive toxicity QSAR models identify increased risks of GI irritation and CNS effects due to its physicochemical profile and COX-1 affinity.

Understanding these QSAR determinants assists in evaluating indomethacin's place among modern NSAIDs in osteoarthritis therapy.

Synthesis:

1. Initial Fischer Indole Synthesis

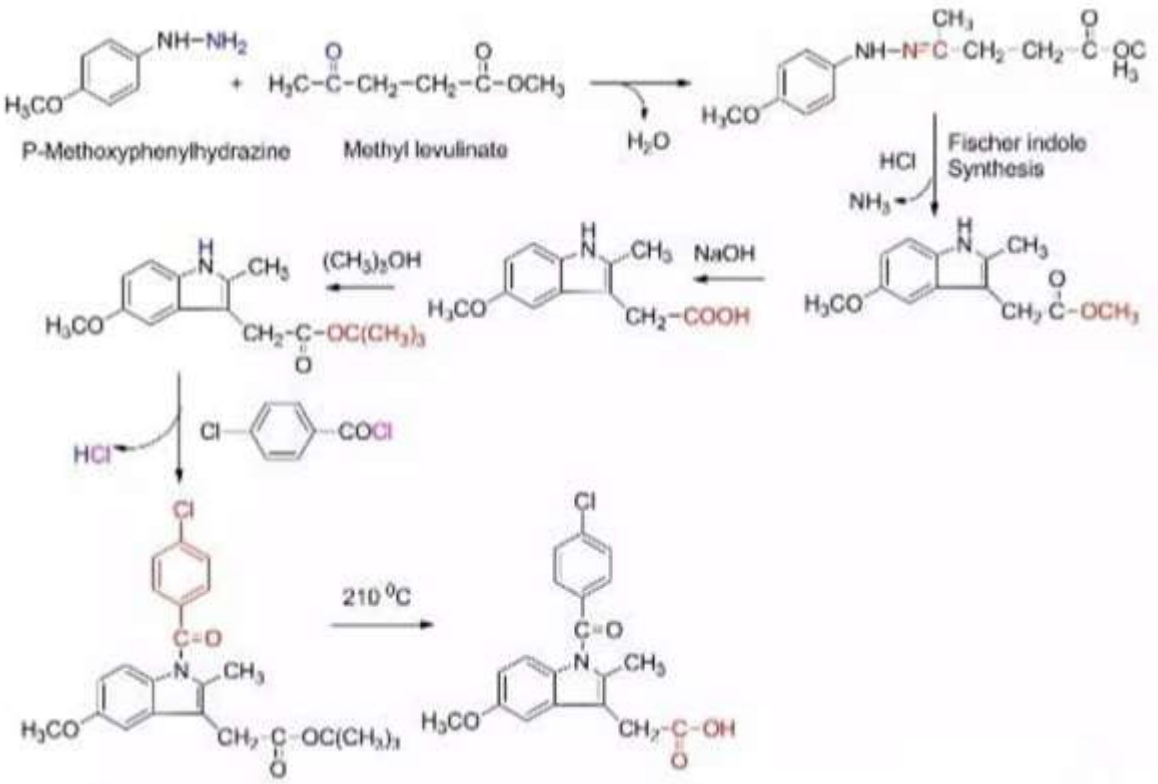
The first part of the reaction involves the condensation of p-methoxyphenylhydrazine and methyl levulinate, followed by a Fischer indole synthesis reaction.

- Hydrazone Formation: P-methoxyphenylhydrazine reacts with the ketone group of methyl levulinate to form a hydrazone intermediate, with the elimination of a water molecule.
- Fischer Indole Cyclization: The hydrazone undergoes an acid-catalyzed cyclization and elimination of ammonia (NH_3) to form a substituted indole ring structure. This is labeled as "Fischer Indole Synthesis" in the diagram.

2. Functional Group Transformations

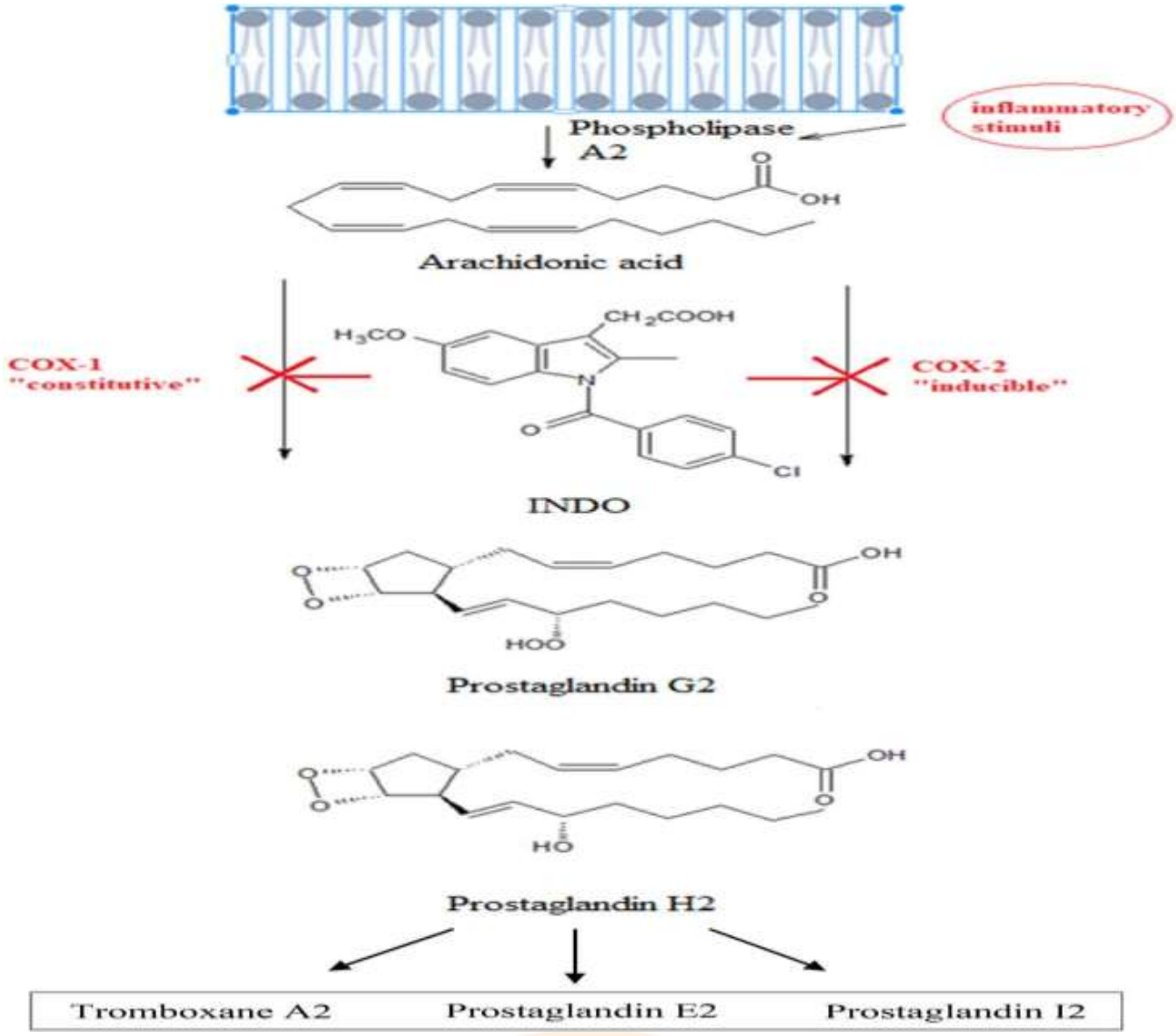
The indole intermediate then undergoes a series of modifications to its functional groups:

- Hydrolysis: The methyl ester group ($CH_2CH_2COOCH_3$) is hydrolyzed to a carboxylic acid group (CH_2CH_2COOH) using sodium hydroxide (NaOH) in methanol (CH_3OH).
- Acylation: The carboxylic acid is then likely converted back into an ester (indicated by the change from COOH to $COOCH_3$ in the structure below it, although the reagents for this step are not explicitly shown). An acylation reaction (addition-elimination process) is a common method for forming esters or amides from carboxylic acid derivatives.
- Chlorination and Ring Closure: The diagram shows a reaction with 4-chlorobenzoyl chloride, resulting in an amide linkage and a new ring structure. This step likely involves an acylation reaction at the nitrogen of the indole ring.
- Final Hydrolysis: The final step involves heating the resulting compound to 210°C, which appears to hydrolyze the ester group back to a carboxylic acid (CH_2CH_2COOH), yielding the final product.



Mechanism of action (MOA):

Indomethacin is a nonspecific and reversible inhibitor of the cyclo-oxygenase (COX) enzyme or prostaglandin G/H synthase. There are two identified isoforms of COX: COX-1 is universally present in most body tissues and is involved in the synthesis of the prostaglandins and thromboxane A2, while COX-2 is expressed in response to injury or inflammation.1 Constitutively expressed, the COX-1 enzyme is involved in gastric mucosal protection, platelet, and kidney function by catalyzing the conversion of arachidonic acid to prostaglandin (PG) G2 and PGG2 to PGH2.1. COX-2 is constitutively expressed and highly inducible by inflammatory stimuli. It is found in the central nervous system, kidneys, uterus, and other organs. COX-2 also catalyzes the conversion of arachidonic acid to PGG2 and PGG2 to PGH2. In the COX-2-mediated pathway, PGH2 is further converted to PGE2 and PGI2 (also known as prostacyclin). PGE2 is involved in mediating inflammation, pain, and fever. Decreasing levels of PGE2 lead to reduced inflammatory reactions. Indomethacin is known to inhibit both isoforms of COX; however, with greater selectivity for COX-1, which accounts for its increased adverse gastric effects relative to other NSAIDs. It binds to the enzyme's active site and prevents the interaction between the enzyme and its substrate, arachidonic acid. Indomethacin, unlike other NSAIDs, also inhibits phospholipase A2, the enzyme responsible for releasing arachidonic acid from phospholipids. The analgesic, antipyretic, and anti-inflammatory effects of indomethacin, as well as adverse reactions associated with the drug, occur as a result of decreased prostaglandin synthesis. Its antipyretic effects may be due to action on the hypothalamus, resulting in increased peripheral blood flow, vasodilation, and subsequent heat dissipation.



Pharmacokinetics:

➢ **Absorption:**

Indomethacin is fleetly and nearly fully absorbed after oral administration, with an oral Bioavailability of roughly 90-100%. Peak tube attention is generally achieved within 1-2 hours. Although food may delay the rate of immersion, it doesn't significantly reduce The total quantum absorbed. The medicine also has rectal and parenteral phrasings, which Give a faster onset of action compared to oral dosing.

Distribution:

Once absorbed, indomethacin is widely distributed throughout the body. It's largely bound to tube proteins, substantially albumin, with binding exceeding 90%, which limits its free Circulating bit. The medicine effectively penetrates inflamed tissues, including the synovial fluid, Making it useful in seditious conditions such as arthritis. It also crosses the placental hedge. And it is sensible in bone milk. The apparent volume of distribution ranges from 0.34 to 1.57 L/ kg.

➢ **Metabolism:**

Indomethacin undergoes extensive hepatic metabolism before elimination. The top metabolic Pathways include O- O-demethylation, N- deacylation, and posterior glucuronidation. These Responses are intermediated primarily by hepatic microsomal enzymes, particularly CYP2C9. The metabolites formed are substantially inactive, though some may contribute to the Medicine's adverse effect profile.

➢ **Excretion:**

Elimination of indomethacin occurs through both renal and biliary routes. Roughly 60% of the administered dose is excreted in the urine as either unchanged medicine or metabolites. Around 33% is excluded through feces via biliary excretion. Only a small The chance of the medicine remaining in its unchanged form during excretion. Impaired renal or hepatic function can protract concurrence and increase toxin threat.

Pharmacodynamics:

Indomethacin works by inhibiting the cyclooxygenase enzymes COX-1 and COX-2, which reduces the synthesis of prostaglandins responsible for pain, inflammation, and fever. This leads to its anti -anti-anti-anti-anti-anti-anti-anti-anti-anti-anti-inflammatory, analgesic, and antipyretic effects. It also decreases neutrophil migration and stabilizes lysosomal membranes, further reducing inflammation. Indomethacin inhibits thromboxane A_2 conformation, causing mild inhibition of platelet aggregation, and is particularly useful. Effective in acute gout because it suppresses prostaglandin- intermediated neutrophil activation around urate chargers. Still, COX1 inhibition in the stomach and feathers contributes to common adverse effects. Effects similar to gastric vexation and reduced renal blood flow.

Marketed Formulations:

Indomethacin Formulation	**Mode of Delivery**	**Strength**	**Adverse Events**
Capsules	Oral	25mg, 50mg	Primarily cardiovascular and gastrointestinal events; rarely neurologic symptoms
Extended-release capsules	Oral	75mg	
Suppository	Rectal	50mg	
Suspension	Oral	25mg/5mL	
Lyophilized powder	Injection (IV)	Dose (0.1-0.25mg/kg) age	Bleeding, transient oliguria, and elevations of serum creatinine

Advantages of Indomethacin in Osteoarthritis

1. **Strong anti-inflammatory effects:** Indomethacin is one of the more potent NSAIDs, helping Reduce synovial inflammation, swelling, and stiffness generally seen in OA flare-ups.
2. **Effective pain relief:** Provides significant analgesic benefit, especially in moderate to severe OA pain that doesn't respond well to milder NSAIDs like ibuprofen or diclofenac.
3. **Useful in acute exacerbation:** Largely effective in acute inflammatory flares of OA where swelling and pain suddenly worsen.
4. **Improves joint function:** By reducing pain and inflammation, it helps patients restore mobility, Enhance day-to-day activity performance and reduce morning/ evening stiffness.
5. **Suitable when other NSAIDs are ineffective:** Indomethacin is frequently used when former NSAIDs give insufficient relief; stronger anti-inflammatory action is needed.
6. **Multiple formulations:** Available as capsules, sustained-release forms, and suppositories, Allowing inflexibility grounded on patient need is useful if oral intake is through.
7. **Cost-Effective:** It is low-cost and broadly available, making it a practical option in Long-term OA care, especially in resource-limited settings.

Drug Interactions of Indomethacin

1. **Anticoagulants & Antiplatelets**

Examples: Warfarin, Heparin, Aspirin, Clopidogrel

Interaction: Increased risk of gastrointestinal bleeding and prolonged bleeding time

Reason: Additive inhibition of platelet aggregation + gastric mucosal damage.

2. **Antihypertensive Drugs**

Examples: ACE inhibitors (enalapril), ARBs (losartan), β-blockers, and Diuretics. Interaction: Decreased antihypertensive effect, increased risk of renal impairment (especially with diuretics)

Reason: NSAIDs reduce renal prostaglandin synthesis → Decreased renal perfusion.

3. **Diuretics**

Examples: Furosemide, Thiazides

Interaction: Reduced diuretic effect increased the threat of nephrotoxicity, hyponatremia, and hyperkalemia.

Reason: NSAIDs blunt diuretic-induced renal prostaglandins.

4. **Other NSAIDs**

Examples: Ibuprofen, Diclofenac, Naproxen

Interaction: Increased risk of nephrotoxicity, GI bleeding, and no added therapeutic benefit.

5. **Alcohol**

Interaction: Increased risk of GI ulcers, bleeding, and liver stress.

Doseage Recommendations:

1. Osteoarthritis & Rheumatoid Arthritis (Adults)

Initial dose: 25 mg 2–3 times daily

Maintenance dose: Adjust according to response

Maximum dose: 150–200 mg/day in divided doses. Use the lowest effective dose for the Shortest duration.

2. Acute Gouty Arthritis

Initial dose: 50 mg 3 times daily, continue until pain is controlled, then taper.

Typical short-course therapy: 3–5 days.

3. Ankylosing Spondylitis

25 mg 2–3 times daily may increase gradually

Maximum: 150–200 mg/day.

4. Patent Ductus Arteriosus (PDA) Closure — Neonates

IV Indomethacin:0.2 mg/kg, then 0.1–0.25 mg/kg at 12-hour intervals × 3 doses. Total dose varies with gestational age and urine output.

Side Effects of Indomethacin:

- **Cardiovascular risk**: NSAIDs, including indomethacin, may increase the risk of serious Cardiovascular thrombotic events (e.g., myocardial infarction, stroke) can be fatal. Use the lowest effective dose for the shortest time.
- **Gastrointestinal risk:** Increased Threat of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach/ bowel, which can occur at any time, with or without warning symptoms (especially in the elderly).
- **Renal risk:** Use in cases with advanced renal complaint isn't recommended; NSAIDs may lead to worsening renal function, fluid retention, and hypertension. Monitor renal function.
- **Haematological effects:** Anaemia, bleeding risk when used with other agents.
- **Hypersensitivity reactions:** Anaphylaxis, serious skin reactions (e.g., Stevens-Johnson syndrome, poisonous epidermal necrolysis) can occur.

Contraindications:

- Hypersensitivity to indomethacin or other NSAIDs
- Includes allergic reactions, anaphylaxis, and NSAID-induced urticaria.
- Aspirin-sensitive asthma / NSAID-induced bronchospasm

- Patients with asthma, nasal polyps, or bronchospasm triggered by NSAIDs must avoid it.
- Active peptic ulcer disease or gastrointestinal bleeding
- I increases the risk of ulceration, perforation, and hemorrhage.
- The third trimester of pregnancy may cause premature closure of the ductus arteriosus and fetal renal dysfunction

Precautions:

- Take with food or milk to avoid stomach irritation.
- threat of GI bleeding/ ulcers; avoid in those with old ulcers.
- May increase BP, oedema, heart attack, stroke risk
- Use cautiously in kidney disease; monitor renal function
- Check liver function if used long-term
- Can cause dizziness or drowsiness; avoid driving primarily
- Avoid aspirin in aspirin-sensitive asthma or NSAID allergy
- Avoid in 3rd trimester of pregnancy
- Use cautiously with anticoagulants, diuretics, ACE inhibitors, lithium, and methotrexate.
- The elderly are at a higher risk of adverse effects.

Applications of Indomethacin:

- **Osteoarthritis –** reduces pain, stiffness, and inflammation.
- **Rheumatoid arthritis** – used to control joint inflammation.
- **Ankylosing spondylitis** – helps relieve spinal pain and stiffness.
- **Acute gouty arthritis –** effective for rapid reduction of gout pain and swelling.
- **Bursitis and tendinitis –** used for inflammatory conditions like shoulder bursitis and tennis elbow.
- **Patent ductus arteriosus (PDA) closure in premature infants –** helps close the ductus arteriosus non-surgically.
- **Dysmenorrhea (menstrual pain) –** reduces pain due to prostaglandin inhibition.

Conclusion:

Indomethacin remains one of the most potent and clinically precious nonsteroidal anti-inflammatory medicines used in the management of osteoarthritis and other inflammatory diseases. Its strong COX-1 and COX-2 inhibitory activity provides effective relief from pain, inflammation, and common stiffness, making it particularly useful in patients who don't respond adequately to milder NSAIDs. The medicine's structural features, similar to the indole nucleus, p- p-chlorobenzoyl group, and acetic acid side chain, play a critical part in its pharmacological activity, as supported by SAR and QSAR analyses. These molecular perceptivities help explain its remedial benefits as well as its safety limitations. Pharmacokinetic properties, including high bioavailability, wide protein binding
Binding and hepatic metabolism contribute to its clinical effectiveness but also increase the liability.
Of medicine relations and adverse responses. While indomethacin offers significant advantages in osteoarthritis, such as strong anti-inflammatory action, multiple formulations, and cost

Effectiveness, its use must be balanced against potential risks, particularly gastrointestinal, cardiovascular, renal, and CNS side effects. Careful patient selection, dosage adjustment, and monitoring are thus essential to ensure safe and optimal use. Overall, indomethacin continues.

to play an important part in OA operation due to its proven efficiency and long-standing clinical Experience. Still, given its risk profile, clinicians are encouraged to use the lowest effective dose for the shortest duration and to customize therapy based on patient comorbidities, concurrent drugs, and treatment goals. Advances in SAR and QSAR exploration may further guide the design of safer, more selective NSAID analogues in the future, eventually improving therapeutic outcomes for Patients with osteoarthritis.

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