"Navigating the Double- Edged Sword of Diclofenac: Pain Relief and Associated Cardiovascular Safety"

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ABSTRACT: Diclofenac sodium (DFS) is a widely prescribed nonsteroidal anti-inflammatory drug (NSAID) effective in managing pain and inflammation in patients with arthritis and musculoskeletal conditions. While DFS is known for its rapid analgesic effects and broad therapeutic indications, it also poses significant cardiovascular (CV) safety concerns. Research highlights that prolonged or high-dose use of diclofenac increases the risk of myocardial infarction, stroke, and thrombotic events. Despite clinical guidelines discouraging its use in patients with heart conditions, a large percentage of individuals continue its use after hospital discharge. This review explores the dual nature of diclofenac's benefits for pain relief and its associated cardiovascular risks, discussing pharmacokinetics, therapeutic indications, adverse effects, and regulatory recommendations.

Key words: Diclofenac, Nonsteroidal Anti-inflammatory Drugs (NSAIDs), Cardiovascular Risk, Pain Relief, COX-1 and COX-2 Inhibition, Myocardial Infarction, Prostaglandins, Thrombosis, Atherosclerosis

INTRODUCTION:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications for alleviating pain and inflammation associated with arthritic conditions. Diclofenac sodium (DFS), a widely prescribed NSAID globally, is particularly effective in managing pain and inflammation related to conditions such as rheumatoid arthritis and osteoarthritis. According to Danish data, around 15% of the population fills at least one prescription for non-aspirin NSAIDs each year, a number that rises to over 60% within a 10-year period. This high usage is concerning due to the associated risk of myocardial infarction and even death, even among otherwise healthy individuals.

Surprisingly, despite clinical guidelines recommending against it, around 35% of patients with myocardial infarction or chronic heart failure continue to use non-aspirin NSAIDs after being discharged from the hospital [1,2].

Diclofenac, first patented in 1965 by Ciba-Geigy, was introduced for medical use in the United States in 1988. It is now available as a generic drug. By 2020, it ranked as the 72nd most prescribed medication in the U.S., with over 9 million prescriptions filled. The drug is offered in both sodium and potassium salt forms [3].

Brand names: Cambia, Flector, Licart, Pennsaid, Voltaren, Zipsor

Drug class: Other Nonsteroidal Anti-inflammatory Agents

Molecular formula: C14H10Cl2NNaO2 [4]

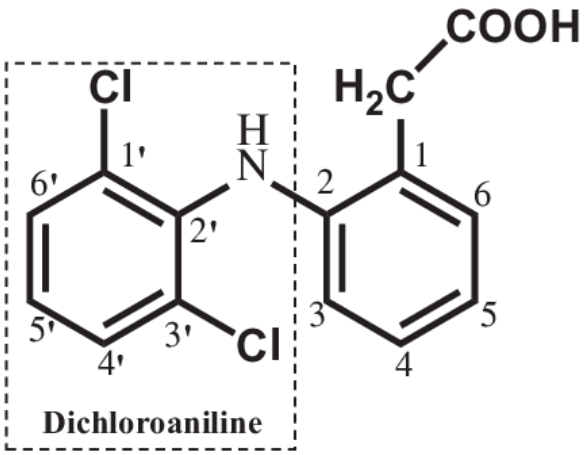

Figure: 1shows *the chemical structure of diclofenac*

Chemical name: 2-[(2,6-dichlorophenyl) amino] benzene acetic acid, monopotassium salt [5]

Dosages of Diclofenac:

Adult Dosage Forms & Strengths

- Tablet, Enteric Coated: 50 mg
- Tablet, Extended Release: 100 mg
- Capsule: 18 mg, 25mg, 35mg
- Powder for Solution: 50 mg
- Solution for IV injection: 37.5mg/mL (Dyloject) [6,7]

Mechanism of Action:

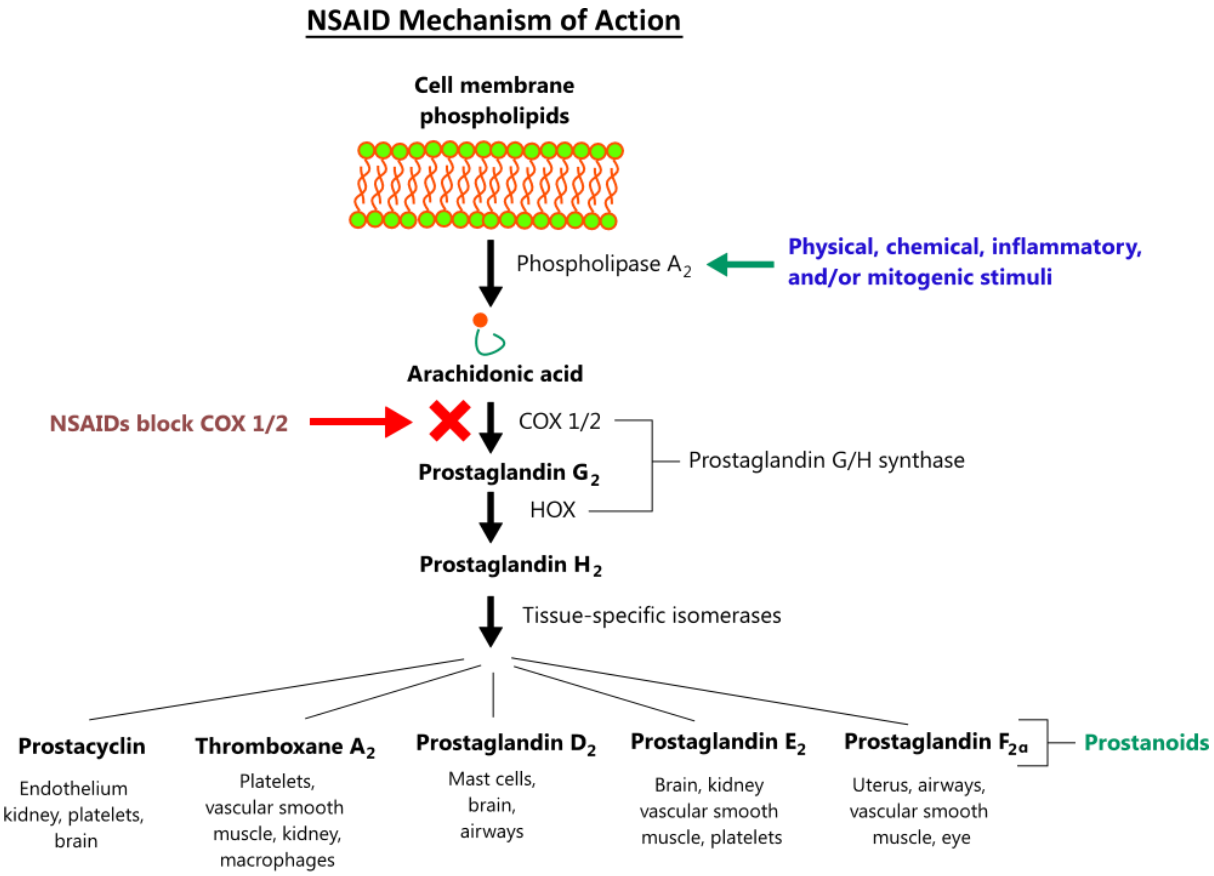

Figure:2 Explains the mechanism of action[8]

Pharmacokinetics of Diclofenac:

1. **Absorption**:
   - Rapidly absorbed after oral, rectal, or intramuscular administration.
   - **Intramuscular**: Peak plasma levels within 10–30 minutes.
   - **Enteric-coated**: Peaks at 1.5–2.5 hours (delayed by food to 2.5–12 hours).
   - Sustained-release forms show no clear peak, but a mean plasma level of 0.1 mg/L at 2 hours.
2. **Plasma Concentrations**:
   - Peak levels range from 0.7–1.5 mg/L after a single 50 mg dose.
   - Dose and plasma concentrations are linearly related (25–150 mg range).
   - No accumulation occurs with repeated dosing.
3. **Distribution**:
   - Highly protein-bound (≥99.5%).

- Volume of distribution: 0.12–0.17 L/kg (total) and 0.04 L/kg (central).
- Efficiently penetrates inflamed synovial fluid, maintaining high concentrations.
- Crosses the placenta and appears in small amounts in breast milk.

4. **Metabolism and Elimination**:
   - Significant first-pass metabolism; 60% of oral dose reaches systemic circulation unchanged.
   - Eliminated mainly by hepatic metabolism; metabolites excreted in urine (20–30%) and bile (10–20%).
   - Main metabolite (4′-hydroxydiclofenac) has minimal anti-inflammatory activity.
   - Plasma clearance: 16 L/h; elimination half-life: 1.1–1.8 hours (terminal phase); tracer elimination: ~30 hours.
5. **Special Populations**:
   - Age, renal, or hepatic impairment generally do not significantly affect diclofenac levels.
   - Severe renal impairment may increase metabolite levels[9].

Therapeutic Indications:

Diclofenac is utilized to manage rheumatic complaints and serves as an analgesic in the following cases:

- Post-injury or post-surgery pain relief
- Treatment of acute or chronic joint inflammation
- Relief of mild-to-moderate pain; primary dysmenorrhea; acute and Chronic treatment of rheumatoid arthritis, osteoarthritis
- Management of degenerative diseases
- acute migraine
- Actinic keratosis (AK) in conjunction with sun avoidance[10&11]

Key Properties:

- Rapid onset of action compared to other NSAID’S
- Short elimination half-life of 3–4 hours[10]

ADVERSE EFFECTS:

 General **Risks with NSAIDs**:

- Diclofenac, like other NSAIDs, can cause dose-related serious side effects, including gastrointestinal (GI), cardiovascular (CV), and renal issues.

 GI **Adverse Effects**:

- GI side effects occur due to reduced prostanoid synthesis, which decreases protective mucus and bicarbonate secretion in the stomach.
- NSAIDs with higher COX-1 selectivity generally pose a higher risk of GI toxicity, but diclofenac has a relatively low risk, especially at low doses (≤75 mg daily).
- High systemic levels of diclofenac contribute to its GI toxicity.

 Role **of PGI2 and CV Risks**:

- PGI2, a product of COX-2, functions as a vasodilator and platelet inhibitor.
- Suppression of PGI2 increases the risk of hypertension and thrombosis.
- High doses of diclofenac (≥150 mg daily) are associated with a greater risk of thrombotic events, including heart attacks.

 Comparison **with Other NSAIDs**:

- The CV risk of diclofenac at doses ≥150 mg daily is similar to that of rofecoxib, celecoxib, and high-dose ibuprofen.
- The likelihood of myocardial infarction depends on the extent of COX-2 inhibition by the NSAID [12].

Clinical significance of diclofenac associated with cardiovascular risk:

1. **Risk Comparison with COX-2 Inhibitors**:
   - The European Medicines Agency's PRAC found that systemic diclofenac poses cardiovascular risks similar to selective COX-2 inhibitors, particularly when used in high doses or over extended periods.
   - It is recommended to apply the same precautions for minimizing blood clot risks associated with COX-2 inhibitors to diclofenac use.

2. **Regulatory Recommendations for NSAIDs**:
   - Diclofenac and other NSAIDs slightly increase the risk of arterial blood clots, such as heart attacks or strokes, especially in individuals with existing heart or circulatory conditions.
   - To mitigate risks, regulatory authorities advise using the **lowest effective dose for the shortest necessary duration** [13].

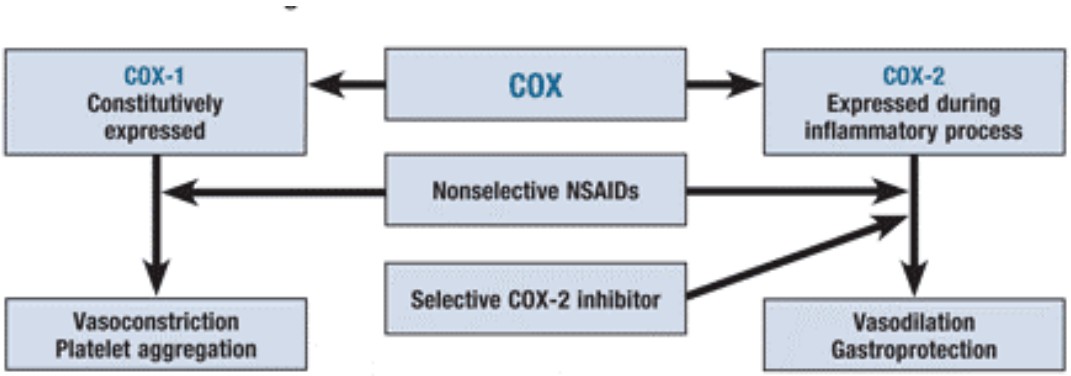

Figure: 2 shows the mechanism of Cox enzymes [14]

Diclofenac has a short half-life (1–2 hours) but is prescribed at high doses to maintain effective pain relief throughout the dosing interval. Initially, its plasma concentration is high enough to inhibit both COX-2 and COX-1 (selectivity shifts). As the concentration decreases, diclofenac sustains COX-2 inhibition while COX-1 inhibition fades, creating a "window" of selective COX-2 inhibition.

Mechanisms of CV Risk:

1. **Selective COX-2 Inhibition**:
   - Inhibits COX-2–derived prostacyclin (a vasodilator and platelet inhibitor) while sparing COX-1–mediated thromboxane A2 (a vasoconstrictor and platelet aggregator), promoting thrombosis.
   - This contrasts with ibuprofen and naproxen, which inhibit COX-1 more persistently.
2. **Other Factors**:
   - Acceleration of atherosclerosis.
   - Blood pressure destabilization or elevation.
   - Risk of heart failure decompensation.
   - Increased susceptibility to arrhythmias (e.g., atrial fibrillation) due to reduced prostacyclin-mediated anti-arrhythmic effects.

- Impaired balance of thromboxane and prostacyclin during myocardial ischemia, increasing infarction size and arrhythmia risk [15].

Conclusion:

Diclofenac is an effective NSAID for managing pain and inflammation in various musculoskeletal and arthritic conditions. However, its dual-edged profile presents significant cardiovascular risks, especially at high doses and prolonged use. Clinicians and patients should be cautious about these risks, particularly in individuals with underlying heart conditions or cardiovascular vulnerabilities. Adherence to clinical guidelines, regulatory recommendations, and evidence-based dosing protocols can help mitigate diclofenac's adverse cardiovascular outcomes. Continuous research and patient education remain essential to ensure the safe and effective use of diclofenac while prioritizing long-term cardiovascular health.

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