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A Review on Diclofenac Sodium: Pharmacological Properties and Recent Advancements

MuktaMadhavi[1], Harish Sharma[2], Gyanesh Kumar Sahu[2*]

[1]Rungta Institute of Pharmaceutical Sciences
[2]Rungta Institute of Pharmaceutical Sciences and Research
*Professor, Rungta Institute of Pharmaceutical Sciences and Research
*Corresponding author: gyanesh.sahu23@gmail.com

ABSTRACT

Diclofenac is non steroidal anti-inflammatory class of drugs (NSAIDs) which has analgesic , antipyretic & anti-inflammatory properties which is used to treat various diseases like arthritis , osteoarthritis etc. Diclofenac shows its action by inhibition of prostaglandin synthesis by inhibiting COX -1& COX-2 enzyme. It was patented by Ciba-Geigy in 1965 .The Ciba-Geigy 1st introduced the drug diclofenac in 1973. Diclofenac sodium is associated with serious dose dependent gastrointestinal , cardiovascular, & Renal adverse effects. Different Diclofenac containing drug have been developed to Enhance efficacy, tolerability & patient compliance. The different diclofenac contaning drug product like Diclofenac enteric coated tablets, diclofenac spray, diclofenac injection have been developed. The New Drug product consisting of diclofenac potassium was further formulated because of its faster action & lesser side effects. This review Represent that pharmaceutical Technology has been used to modify the pharmacokinetic properties of diclofenac , leading to creation of Novel drug products.

KEYWORDS: NSAIDs, Diclofenac, Pain, COX

INTRODUCTION

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) advocated for use in painful and inflammatory rheumatic and certain non-rheumatic diseases. It is available in a wide number of administration forms which can be given orally, rectally or intramuscularly. The dosage adjustments are not required in the elderly patient or in those patients with renal or hepatic impairment. The drug diclofenac has a short elimination half-life. Diclofenac sodium is a phenylacetic acid derivative, is a non-steroidal, anti-inflammatory, analgesic agent. It is used in rheumatoid arthritis, degenerative joint disease, ankylosing spondylitis and allied conditions, and in the treatment of pain resulting from minor surgery, trauma and dysmenorrhoea. (1)

In numerous clinical trials the efficacy of diclofenac is equivalent to the many NSAIDs with which it has been compared. As an analgesic it has a rapid onset and long duration of action. When administered intramuscularly it is frequently superior to many narcotic and spasmolytic combinations in renal and biliary colic.(2)

Extensive clinical experience has been gained with diclofenac, clearly establishing its safety profile. It is well tolerated compared with other NSAIDs and rarely produces gastrointestinal ulceration or other serious side effects.(3)
Thus, diclofenac can be considered as one of the few NSAIDs of 'first choice' in the treatment of acute and chronic painful and inflammatory conditions.(4)

Published data indicate that diclofenac 75 to 150mg daily (25 to 50mg 3 times daily) is more efficacious as compared with ordinary aspirin 3 to 5g daily and indomethacin 75 to 150mg daily in rheumatoid arthritis and with indomethacin in osteoarthritis. Available data suggest that in patients with osteoarthritis diclofenac sodium is comparable in efficacy and tolerability with naproxen, ibuprofen, sulindac and diflunisal. As oral diclofenac is generally given in 3 divided daily doses it may be at a disadvantage relative to less frequent administration with naproxen, diflunisal and sulindac in rheumatoid arthritis, although there is some evidence of diclofenac's efficacy when administered twice daily, or once daily as a slow release tablet. The drug is also available as suppositories and ampoules for intramuscular injection. No one of the non-steroidal anti-inflammatory agents is the most suitable drug for all patients requiring such therapy, and diclofenac should be considered along with other drugs of its type in the arthritic patient.(5)

Diclofenac was patented in 1965 by Ciba-Geigy; it came into medical use in the United States in 1988. It is available as a generic medication. In 2020, it was the 72nd most commonly prescribed medication in the United States, with more than 9 million prescriptions.It is available as a sodium or potassium salt.(6)

Synonyms: Voltaren, Voltarol, Voldal, Voveran, Orthophen

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

Drug class: Other Nonsteroidal Anti-inflammatory Agents

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

Molecular formula: C14H10Cl2NNaO2

Diclofenac sodium was synthesized by Alfred Sallmann and Rudolf Pfister and first introduced by Ciba-Geigy (now Novartis AG, Basel, Switzerland) in 1973 (7).

PHARMACODYNAMIC PROPERTIES

Diclofenac suppresses acute and chronic inflammation, pain and hyperthermia in various animal models, and in these models the drug has generally proven more potent, than aspirin, ibuprofen, naproxen and phenylbutazone, less potent than piroxicam, and similar to indomethacin. The therapeutic index (ratio of gastrointestinal irritant and therapeutic dosages) of diclofenac is generally good in animals, but varies relative to other non-steroidal anti-inflammatory drugs (NSAIDs) according to the model used. However, controlled studies in healthy subjects show that usual therapeutic dosages of diclofenac cause less gastrointestinal damage than aspirin, feprazone, indomethacin and naproxen but more than fenclofenac.(8)

The anti-inflammatory activity of diclofenac, is inhibition of prostaglandin synthesis. Diclofenac is a potent inhibitor of cyclo-oxygenase in vitro and in vivo, thereby decreasing the synthesis of prostaglandins, prostacyclin and thromboxane products. This is reflected in animals and humans in vivo by reduced concentrations of various prostaglandins in urine, gastric mucosa and synovial fluid during treatment with diclofenac. Also with other NSAIDs, diclofenac is a potent reversible inhibitor of the secondary phase of induced platelet aggregation. However, diclofenac at usual therapeutic dosages has little effect on bleeding time in humans. The drug also affects polymorphonuclear leucocyte function, thereby reducing chemotaxis, superoxide production and protease production.(9)

PHARMACOKINETIC PROPERTIES

Diclofenac is rapidly and efficiently absorbed after conventional oral, rectal or intramuscular administration. After intramuscular administration peak plasma concentrations are attained after 10 to 30 minutes. With the enteric-coated formulation peak concentrations are reached after 1.5 to 2.5 hours, and this is delayed by food to 2.5 to 12 hours. After a single 50mg dose of these formulations, mean peak plasma concentrations of unchanged diclofenac are 0.7 to 1.5 mg/L. No clear peak concentrations are found after a single 100mg dose of sustained release diclofenac, although the mean concentration was about 0.1 mg/L at 2 hours. Peak plasma concentrations and area under the plasma concentration-time curve are linearly related to dose over the range of 25 to 150mg, regardless of administration route, and no accumulation occurs after repeated doses.(10)

Like other NSAIDs, diclofenac is highly (≥ 99.5%) protein bound. The mean total volume of distribution is 0.12 to 0.17 L/kg and that of the central compartment is 0.04 L/kg. The drug efficiently penetrates inflamed synovial fluid where high concentrations are maintained compared with plasma concentrations.

Diclofenac and its metabolites cross the placenta in animals, and small amounts may be found in the breast milk of women.(11)

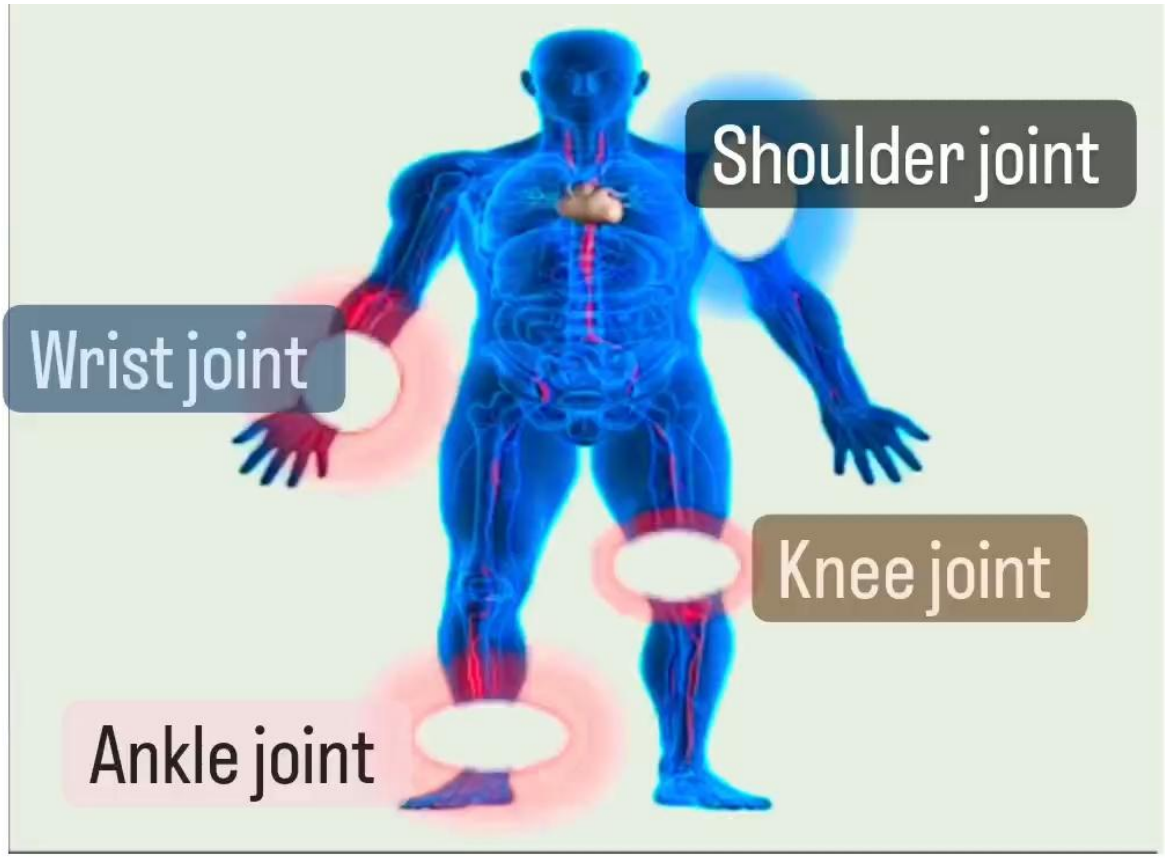
Diclofenac undergoes significant first-pass metabolism and only 60% of the drug reaches systemic circulation unchanged oral administration. It is eliminated by hepatic metabolism and subsequent urinary and biliary excretion of glucuronide and sulphate conjugates of the metabolites. The principal metabolite in humans is 4′-hydroxydiclofenac, which possesses negligible anti-inflammatory activity compared with the parent drug; the amount excreted in urine accounts for 20 to 30% of the dose and that in bile for 10 to 20%. In healthy volunteers, mean plasma clearance of diclofenac is 16 L/h, and the mean elimination half-life of the terminal phase is 1.1 to 1.8 hours. The mean elimination half-life after a radiolabelled dose is about 30 hours for the tracer.(12)

Age and renal or hepatic impairment do not appear to have any significant effect on plasma concentrations of unchanged diclofenac, although metabolite concentrations may be increased by severe renal impairment.(13)

MECHANISM OF ACTION

Diclofenac is a phenylacetic acids belonging to the NSAIDs family and acts to decrease inflammation as other class drugs do.(14)

It has analgesic properties and antipyretic effects. Diclofenac employs its action by inhibiting the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) by inhibiting the synthesis of prostanoids such as prostaglandin-E2 (PGE2), prostacyclins, and thromboxanes, which are essential components of the inflammatory and nociceptive response. It competitively”inhibits arachidonic acid from binding to COX-1 and COX-2. Diclofenac inhibits COX-1 and COX-2 relatively equally, although evidence suggests that it has selective COX-2 inhibition, about four times that of the inhibition of COX-1 during in vitro experimentation. This value is far from the reported 20-fold selectivity of COX-2 inhibition of the more selective COX-2 inhibitors like rofecoxib, but diclofenac’s activity can be compared more accurately to that of celecoxib.(15)



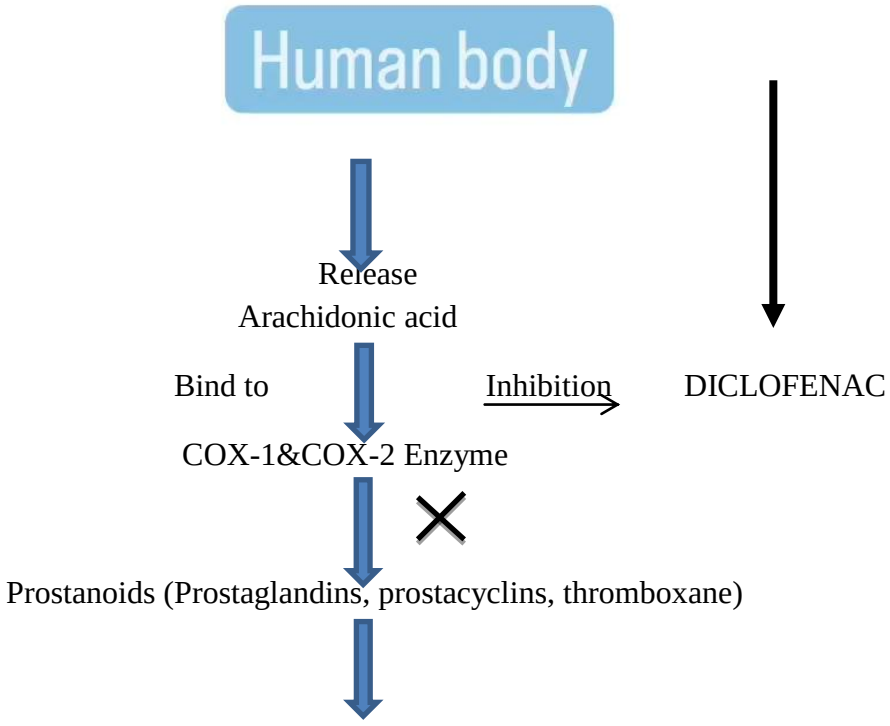


Fig: 1 Mechanism of action of Diclofenac

Diclofenac and other NSAIDs also have effects in blocking the production of thromboxanes, especially thromboxane-B2 (TXB2). Diclofenac is regarded as one of the most effective inhibitors of the production of PGE2; the primary prostanoids are elevated during an inflammatory response.(16)

AVAILABLE MARKETED DOSAGE FORMS OF DICLOFENAC

- Tablet
- Capsule
- Solution
- Injection
- Gel
- Suppository
- Transdermal patch
- Eye drops

Tablet: Diclofenac tablet is a medicine that reduces swelling (inflammation) and pain. It's used to treat aches and pains, as well as problems with joints, muscles and bones. These include: rheumatoid arthritis and osteoarthritis.

Solution : Diclofenac topical solution is used to treat pain and swelling caused by osteoarthritis of the knees. Diclofenac topical patch and topical system is used to treat acute pain caused by minor strains, sprains, and contusions (bruises). This medicine is available only with your doctor's prescription.

Gel:diclofenac topical gel (Voltaren Arthritis Pain) is used to relieve pain from arthritis in certain joints such as those of the knees, ankles, feet, elbows, wrists, and hands.

Injection : Diclofenac injection is a nonsteroidal anti-inflammatory drug (NSAID) used to treat adults with mild to moderate pain. It is used alone or given with other opioid (narcotic) pain medicines to treat adults with moderate to severe pain. This medicine is to be given only by or under the direct supervision of your doctor.

Suppository: Diclofenac suppositories are used to relieve pain, swelling (inflammation), and joint stiffness caused by arthritis. Diclofenac does not cure arthritis, but reducing the symptoms helps you do more of your normal daily activities.

Transdermal patch: Transdermal diclofenac is used to treat short-term pain due to minor strains, sprains, and bruises in adults and children 6 years of age and older.It works by stopping the body's production of a substance that causes pain.

Eye drops: Diclofenac ophthalmic (eye) solution is used to treat pain or swelling of the eye following cataract surger.(17)

ADMINISTRATION

Diclofenac preparations pair the drug with a salt such as sodium, potassium, or epolamine salt. Diclofenac sodium can be administered orally as a tablet or suspension, intramuscular in solution, intravenous in solution, transdermal in gel, or rectal routes as a suppository.Diclofenac potassium is available for oral administration in oral tablet or suspension forms. Diclofenac epolamine is available as a transdermal patch.(18)

When orally administered, diclofenac is absorbed rapidly and binds to albumin in the plasma. The drug concentrates in synovial fluids, where it renders its targeted action as an NSAID for relief musculoskeletal inflammation and ailments.(19)

It is available in both extended-release and immediate-release dosage forms that vary in doses. Oral administration of diclofenac, carries the risk of gastrointestinal upset and is recommended to administered the medication with food or milk in all age groups , as other NSAIDs. In addition, there are formulations of diclofenac combined with misoprostol to mitigate gastrointestinal adverse effects. It is common practice for clinicians to prescribe gastric acid-reducing therapies such as proton pump inhibitors (PPI) for concomitant use with NSAIDs to reduce the risk of more serious gastrointestinal (GI) adverse reactions. Recommendations may include taking over-the-counter (OTC) antacids as a form of gastroprotection(20)

Diclofenacshould be administered at the lowest effective dose to achieve clinical goals to limit the risk of adverse reactions and toxicity. The other NSAIDs also can be used in low dosage(21)

Oral diclofenac sodium can be administered in delayed-release or immediate-release tablets in 25 to 150 mg tablets to achieve a total daily dose of 100-150 mg per day. These doses are for ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis. Topically, diclofenac sodium is available in gel preparations ranging from 1 to 3% concentrations. Gel with 1 to 2% diclofenac sodium is indicated for topical administration for osteoarthritis for up to 16 g per day for monoarthritis joints and up to 32 g per day for polyarthritic joints. The 3% diclofenac sodium preparation is reserved for treating actinic keratosis and is to be applied twice daily as hybrid therapy. Intravenous diclofenac sodium can be administered as a 37.5 mg bolus injection every 6 hours for acute moderate to severe pain. Intramuscular diclofenac solution comes as a 75 mg/3 mL solution for managing moderate to severe pain, and administration is generally by injection into large muscle groups such as the thigh or buttocks. Ophthalmic preparations are to be administered as 1 to 2 drops per affected eye four times daily following cataract surgery and for treatment of photophobia and eye pain.(22)

Generally, diclofenac potassium is administered in either 25 mg or 50 mg doses 1 to 4 times per day for total doses between 50 to 200 mg per day. This treatment is the indicated regimen for migraines, osteoarthritis, generalized pain, primary dysmenorrhea, and rheumatoid arthritis.(23)

Diclofenac epolamine is available as a transdermal patch to be applied twice daily over the affected area to relieve pain and inflammation.(24)

INDICATIONS:

Capsule: Relief of mild-to-moderate acute pain

Immediate-release tablet: Relief of mild-to-moderate pain; primary dysmenorrhea; acute and Chronic treatment of rheumatoid arthritis, osteoarthritis

Delayed-release tablet: Acute and chronic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis

Extended-release tablet: Chronic treatment of osteoarthritis, rheumatoid arthritis

Oral solution: Treatment of acute migraine with or without aura

Suppository (CAN; not available in U.S.): Symptomatic treatment of rheumatoid arthritis and Osteoarthritis (including degenerative joint disease of hip)

Topical gel 1%: Relief of osteoarthritis pain in joints amenable to topical therapy (eg, ankle, Elbow, foot, hand, knee, wrist).

Canadian labeling (not in U.S. labeling): Relief of pain associated with acute, localized Joint/muscle injuries (eg, sports injuries, strains) in patients ≥16 years of age

Topical gel 3%: Actinic keratosis (AK) in conjunction with sun avoidance

Eye drops: Treatment of postoperative inflammation following cataract extraction; temporary Relief of pain and photophobia in patients undergoing corneal refractive surgery.

AVAILABLE DOSAGE FORM IN HOSPITAL

Tablet, oral, as sodium: 50 mg, 75 mg.

Suppository, as sodium: 12.5 mg, 50 mg, 100 mg.

Injection: 75 mg.

Eye drop: 0.1%.

Gel: 1%

Cream, as sodium: 1% + menthol 2.5% + camphor 1.4%.

COMMON SIDE EFFECTS

Oral:

Cardiovascular: Edema

Central nervous system: Dizziness, headache

Dermatologic: Pruritus, rash

Endocrine & metabolic: Fluid retention

Gastrointestinal: Abdominal distension, abdominal pain, constipation, diarrhea, Dyspepsia, flatulence, GI perforation, heartburn, nausea, peptic ulcer/GI bleed, Vomiting

Hematologic: Anemia, bleeding time increased

Hepatic: Liver enzyme abnormalities (>3 x ULN; ≤4%)

Otic: Tinnitus

Renal: Renal function abnormal

Miscellaneous: Diaphoresis increased

LOCAL: APPLICATION SITE REACTIONS (INCIDENSE INCREASED WITH 3% GEL)

- Pruritus (≤52%),
- Rash (35% to 46%),
- contact dermatitis (4% to 33%),
- dry skin (≤27%),
- pain (15% to 26%)
- exfoliation (3% gel; 6% to 24%)
- Parasthesia(≤20%)

Ocular:

- Lacrimation (30%),
- keratitis (28%),
- intraocular pressure increased (15%),
- Transient burning/stinging (15%)(25)

GLOBAL DICLOFENAC SODIUM MARKET:

North America

- U. S
- Canada
- Mexico

Europe

- **Germany**
- UK
- France
- Rest of Europe

Asia Pacific

- China
- Japan
- India
- Rest of Asia

Rest of world

- Latin America
- Middle East and Africa

DERIVATIVES OF DICLOFENAC

- **Diclofenac sodium**
- **Diclofenac potassium**

DICLOFENAC SODIUM *VS* DICLOFENAC POTASSIUM

Diclofenac sodium	Diclofenac potassium
1)it is mainly used to treat arthritis, be it rheumatoid or osteoarthritis	It used to treat mildarthritic pain &swollen joints
2) It not absorbed quickly in body	It absorbed in body faster than diclofenac sodium
3)Diclofenac sodium is delayed release	Diclofenac potassium is quicked release
4)It has more side effects	It has less side effects
5)The side effects include nausea, heartburn, stomach discomfort like diarrhoea	The side effects are light headedness, Constipation, bloating etc
6)Risk factors:developing ulcers, liver problems, and even a heart	Risk factors: cardiovascular problem or

attack.	**stroke**

DRUG INTERACTIONS

Aspirin: When Voltaren isadministered with aspirin, its protein binding is reduced. The Clinical significance of this interaction is not known; however, as with other NSAIDs,Concomitant administration of diclofenac and aspirin is not generally recommended Because of the potential of increased adverse effects.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate Accumulation in rabbit kidney slices. This may indicate that they could enhance the Toxicity of methotrexate. Caution should be used when NSAIDs are administeredConcomitantly with methotrexate.

Cyclosporine: Voltaren, like other NSAIDs, may affect renal prostaglandins and Increase the toxicity of certain drugs. Therefore, concomitant therapy with Voltaren may Increase cyclosporine's nephrotoxicity. Caution should be used when Voltaren is Administered concomitantly withcyclosporine.

ACE Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect Of ACE inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Furosemide: Clinical studies, as well as postmarketing observations, have shown that Voltaren can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During Concomitant therapy with NSAIDs, the patient should be observed closely for signs of Renal failure (Renal Effects), as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and The renal clearance was decreased by approximately 20%. These effects have been Attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully For signs of lithium toxicity.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that Users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.(26)

ADVERSE REACTIONS

In patients taking Voltaren® (diclofenac sodium enteric-coated tablets), or other NSAIDs,the most frequently reported adverse experiences occurring in approximately 1%-10% of Patients are: Gastrointestinal experiences including: abdominal pain, constipation, diarrhea,Dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, GI ulcers (gastric/duodenal) and vomiting.

Abnormal renal function, anemia, dizziness, edema, elevated liver enzymes,headaches, increased bleeding time, pruritus, rashes and tinnitus.

Additional adverse experiences reported occasionally include :

Body as a Whole: fever, infection, sepsis

Cardiovascular System: congestive heart failure, hypertension, tachycardia, syncope**.**
Digestive System: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, gastrointestinal Bleeding, glossitis, hematemesis, hepatitis, jaundice .
Hemic and Lymphatic System: ecchymosis, eosinophilia, leukopenia, melena, purpura, Rectal bleeding, stomatitis, thrombocytopenia
Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, depression, dream abnormalities, Drowsiness, insomnia, malaise, nervousness, paresthesia, somnolence, tremors, vertigo

Respiratory System: asthma, dyspnea

Skin and Appendages: alopecia, photosensitivity, sweating increased

Special Senses: blurred vision

Urogenital System: cystitis, dysuria, hematuria, interstitial nephritis, oliguria/polyuria, Proteinuria, renal failure

other adverse reactions, which occur rarely are:

Body as a Whole: anaphylactic reactions, appetite changes, death

Cardiovascular System: arrhythmia, hypotension, myocardial infarction, palpitations, Vasculitis

Digestive System: colitis, eructation, liver failure, pancreatitis

Hemic and Lymphatic System: agranulocytosis, hemolyticanemia, aplastic anemia, Lymphadenopathy, pancytopenia

Metabolic and Nutritional: hyperglycemia

Nervous System: convulsions, coma, hallucinations, meningitis

Respiratory System: respiratory depression, pneumonia

Skin and Appendages: angioedema, toxic epidermal necrolysis, erythema multiforme, Exfoliative dermatitis, Stevens-Johnson syndrome, urticaria

Special Senses: conjunctivitis, hearing impairment.(27)

THE EFFECT OF DICLOFENAC EXPOSURE DURING PREGNANCY

There are few reports available on the effects of exposure to Diclofenac during pregnancy, these threeStudies involving individuals are Norway, Quebec, and Denmark studies.

From the reviewed studies, evidence has shown that Diclofenac exposure during late pregnancy increases the risk of low birth weight in the fetus; however, no evidence of congenital malformations has beenObserved .(28)

Another study found that taking Diclofenac during pregnancy was strongly connected to an increased risk of Spontaneous abortion. Other studies have found that women exposed to Diclofenac/misoprostol have an Increased risk of miscarriage .Out Of the three studies included, two studies (66.7%) showed exposure to diclofenac during pregnancy increased the risk of spontaneous abortion.(29)

Studies have shown that expectant mothers exposed to Diclofenac had an increased risk of miscarriage(30).

The placenta is a strong connection between mother and fetus, is selectively permeable to a certain extent .(31)

Siu at. Al. reported that Diclofenac Sod. could easily pass through the human placenta during the first trimester of pregnancy. By inhibiting the biosynthesis of prostanoids (prostaglandins , prostacyclins & thromboxanes), NSAIDs cross the placental barrier and enter the fetalcirculation and may thus have teratogenic effects on the Fetus.(32)

Prolonged pregnancy and labor pain are other adverse effects of Diclofenac sodium (NSAID)use observed in the mother and fetus during pregnancy.(33)

Abdominoschisis has been found to be a possible teratogenic effect in the early period of pregnancy as a result of using drugs such as aspirin and ibuprofen .(34)

Teratogenic Effects: Pregnancy Category C

Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Nonteratogenic Effects

Because of the known effects of Diclofenac (nonsteroidal anti-inflammatory drugs) on the fetal cardiovascular System (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery

In rat studies with diclofenac (NSAIDs), as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of Diclofenac on labor and delivery in pregnant women are unknown.

Nursing Mothers

It is not known that drug voltaren (diclofenac) is excreted in human milk. Because many drugs are excreted in **human milk and because of the potential for serious adverse reactions in nursing infants from diclofenac, a** decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (35)

NSAIDs have been prescribed in the symptomatic treatment of many diseases as analgesics, anti-inflammatories, and antipyretics for many years. Due to the widespread use of these drugs, DS was chosen as a pharmacological agent in our study. Studies have shown that these drugs cause early closure of the fetalDA (Ductus arteriosus) and consequently cause adverse effects in the fetus, such as respiratory problems, kidney problems, and pulmonary hypertension dysfunction. (36)

In a study of the toxic effects of NSAIDs, ibuprofen and tolmetin were administered at high doses during the prenatal period, and both of these drugs caused toxic effects in the mother, inhibited intrauterine development, and resulted in developmental variations. (37)

Another study found that Diclofenac Sod. (NSAIDs) and aspirin used in the prenatal period increased the risk of miscarriage. (38)

It has been reported by the United States Food and Drug Administration that DS is a class C drug in terms of the pregnancy risk.(39)

EFFECT OF DICLOFENAC IN BREASTFED INFANTS

In one study, 30 mothers undergoing elective cesarean section (C- section) were allowed to use 25 mg diclofenac suppositories along with either spinal or spinal and epidural anesthesia with a local anesthetic after delivery. The spinal anesthetic group used an average of 56 mg of diclofenac on the day of delivery and 33 mg on the next day whereas the women receiving both spinal and epidural anesthesia used 21 and 18 mg. No mention was made of adverse effects on the breastfed infants.(40)

A breastfed infant developed urticaria on day 15 of life. Her mother had been taking diclofenac (dosage unspecified) for pain since her cesarean section delivery. Diclofenac is a possible cause of the urticaria; however, the infant had also received hepatitis B vaccination 7 days before and the authors thought that it was a more likely cause of the reaction.(41)

EFFECTS OF DICLOFENAC ON LACTATION & BREASTMILK

Excretion of diclofenac into milk are poor, but the drug has a short half-life and little glucuronide metabolite formation. Most reviewers consider diclofenac to be acceptable during breastfeeding.(42)

Diclofenac was not detected in breast milk after a single maternal dose of 50 mg intramuscularly or 100 mg per day orally for one week. However, the drug was measured in the breast milk of a woman who received Diclofenac 150 mg daily but its excretion in breast milk was connsidered too small to be harmful . Diclofenac appears to be a good choice for analgesia in nursing women. (43)

The drugs Ibuprofen, Diclofenac,Indomethacin & naproxen have an acceptably low infants dose & are considered safe to use.Aspirin is contraindicated only because of the theoretical risk ofReye,s syndrome .BothParacetamol and codeine are safe alternatives, although combination containing codeine 30 mg should be used cautiously.(44)

CONTRAINDICATIONS:

Like other selective COX-2 inhibitors, diclofenac is contraindicated with an FDA boxed warning in patients with a history of increased cardiovascular risk such as MI or stroke. Diclofenac should not be used in bypass graft surgery of coronary artery due to a higher risk of MI and stroke. (45)

It Is also contraindicated in patients with a history of anaphylactoid (allergic) reaction to NSAID drugs.(46)

Also, diclofenac is contraindicated in patients with mild or severe renal insufficiency due to potential negative effects of decreased renal perfusion. Clinicians should not use diclofenac or other NSAIDs in patients with a history of GI bleeds or ulcerations. Special monitoring is a consideration in patients with a history of Helicobacter pylori infection. Formulations of diclofenac with misoprostol are contraindicated in pregnant females due to possible side effects involving loss of pregnancy associated with misoprostol.(47)

TOXICITY

Diclofenac's potential for toxicity is associated with polymorphisms of the cytochrome P450 gene family, which affects the patient's potential for drug metabolism. OTC NSAID toxicity is not uncommon but is generally limited to mild symptoms with a low risk of serious effects. These effects are usually limited to GI upset, nausea, and dizziness.(48)

Severe overdose may lead to more serious symptoms involving seizure, coma, cardiovascular events, and metabolic acidosis.(49)

There is no antidote for diclofenac (or other NSAID toxicity). Therefore, treatment is supportive. NSAID toxicity is manageable with the maintenance of circulation and breathing in critical patients. Patients with limited GI toxicity can receive activated charcoal to avoid GI contamination.(50)

Clinicians should address acid-base balance in patients.(51)

DICLOFNAC OVERDOSE

Diclofenac sodium is a prescription medicine used to relieve pain and swelling. It is a nonsteroidal anti-inflammatory drug (NSAID). Diclofenac sodium overdose occurs when someone takes more than the normal or recommended amount of this medicine. This can be by accident or on purpose.
Diclofenac sodium can be harmful in large amounts.

Brand Name:
Diclofenac sodium is a prescription medicine. It is sold under these brand names:

- Voltaren
- Arthrotec
- Solaraze

Other medicines may also contain diclofenac sodium.

Symptoms:
Symptoms of a diclofenac sodium overdose include:

- Diarrhea
- Dizziness (common)
- Drowsiness (common)
- Headache
- Movement problems
- Nausea and vomiting (common, sometimes with blood)
- Blurred vision (common)
- Numbness and tingling
- Ringing in the ears
- Stomach pain (with possible bleeding in the stomach and intestines)
- Rash
- Unsteadiness
- Urination problems (little to no urine output)
- Edema (swelling in the body or legs)
- Wheezing

In very rare cases, severe breathing problems, convulsions (seizures), and coma may occur. (52)

Table:1 Therapeutics uses of Diclophenac sodium

Used for	dosage	Sign & symptoms	Reference
Osteoarthritis	50 mg of diclofenac twice daily.	Joint pain, stiffness, tenderness, loss of flexibility, bone spurs , swelling.	Shep D. , Khanwelkar C. , Gade P, Karad S. Safety & efficacy of curcumin versus diclofenac in knee osteoarthritis: a randomized open – label parallel-arm study.(53)
Ankylosing spondylitis	50 mg of diclofenac tablet were administered orally three times daily.	pain and stiffness in the lower back and hips, fatigue, hunched back, inflamed tendons, inflammatory bowel disease, physical deformity, or sleep disorder	Walker C., Essex Margaret N, Li Chunming ,Park P.W. Celecoxib versus diclofenac for the treatment of ankylosin spondylitis: 12- week randomized study in Norwegian patients. Journal of International Medical Research 2016.(54)
Dysmenorhhea	75 mg of DS (about daily) is effective in reducing the pain at menstruation & bleeding also.	Cramping in the lower abdomen, Pain in the lower abdomen. Low back pain, Pain radiating down the legs. Nausea,Vomiting,Diarrhea,Fatigue.	Riihiluoma P, Wuolijoki E, Pulkkinen M. O. Treatment of primary dysmenorrhea with DS . European journal of Obstetrics & Gynecology & Reproductive Biology . vol. 12 , sep 1981.(55)
Rheumatoid arthritis	150 mg daily of diclofenac sodium is more effective .	Stiffness, swelling, tenderness, or weakness, pain in joint, back &muscles,drymouth, physical deformity, or sensation of pins and needles	Caldwell J.R. Efficacy &safety of diclofenac sodium in rheumatoid arthritis experience in the united states. The American Journal of Medicinr vol.80 Suppl. 2, Apr 28,1986.(56)
Acute Migraine	50 mg&100mg of oral diclofenac potassium tablet & solution is effective in the treatment of acute migrane.	Dizziness, light-headedness, or malaise, irritability, nasal congestion, or scalp tenderness	The Diclofenac –K / Sumatripan Migrane Study Group Acute treatment og migrane attacks: efficacy & safety of a NSAID,diclofenac –pottasium,in comparison to oral sumatriptan & placebo. Cephalagia.1999(57)

Pain	Single injection of 75 mg of diclofenac in 2ml solution by deep intramascular injection in the gluteal region was safe 7 effective as an analgesic agent in the 1st stage of labour.	joint pain. muscle aches.	Al-Assadi A.F. The use of Diclofenac For Pain Relief in 1st stage of labour.jan 2015 (58)

Diclofenac is used to treat pain of :

- Rheumatoid arthritis
- Ocular inflammation
- Ankylosing spondylitis
- Osteoarthritis

Table:2 Different novel formulations of Diclophanc sodium

S.N.	NDDS Formulation	Uses	Method	Dose	Reference
1	Chitosan Microsphere	The controlled release formulation of diclofenac sodium can be developed using chitosan as a polymer.	Emulsion crosslinking, ion induced coagulation, spray-drying method	80mg of DS	Vanessa L.G.,Mauro L,Valfredo T.F. , Rozangela C.P. Effect of crosslinking agents on chitosan microspheres in controlled release of diclofednac sodium. July 14; 2005.(59)

2	Eudragit microsphere	Eudragit microsphere containing DS can be used for sustained release	Solvent evaporation method	50 mg of DS	Momoh M, Kenechukwu F, Adedokun M.O. , Odo C.E. , Attama A. A. Pharmacodynamics of diclofenac from novel Eudragit entrapped microspheres. Oct 2013 (60)
3	Sustained release microcapsules	Used to mask the bitter taste of drug.	Emulsion solvent evaporation technique	50 mg of DS	B. Apparao , M.R. shivalingam , Y.V. Kishore Reddy, N. Sunitha , T. Jyotibasu. Design & evaluation of sustained release microcapsules containing diclofenac sodium; Aug, 2010. (61)
4	Diclofenac transdermal patch	Used to treat minor strains ,sprains, & bruishes in adults & childrens.	Solvent casting method	100 mg diclofenac in the transdermal patch	Chaitanya CSK N, Karunakar P, Garlpati K, Yeladandi M, Bidari P, soni P. A comparative evaluation of diclofenac sodium transdermal patch , oral diclofenac sodium with intramascular injections of DS in patients suffering from oral Pain: A randomized control trial. International Journal of pharmaceutical Investigation ,2017.(62)

5	Niosomes	Improve the solubility & stability of natural pharmaceutical molecules.	Hand shaking method	30 mg of diclofenac sodium	Bhattacharya S. A, Singhai M, Setia A. Preparation & Evaluation of Diclofenac Sodium Using RBF Method. Asian journal of Pharmaceutics; june 2020.(63)
6	Diclofenac Encapsulated Liposomes	It include site-targeting, sustained or controlled release , protection of dugs from degradation & clearance.	Liipid Hydration Technique	1mg/ml	Messa R, Beedha S. Preparation & optimization of diclofenac encapsulated liposomes using lipid hydration technique ; World journal of pharmaceutical Research: oct 2014.(64)

Table: 3 Recent patents of Diclophenac Sodium

S. N	Applicants Name	Diclofenac Products	Patent No.	Inventors	Assignees	Reference
1	Tokuhon Corporation , Tokyo (JP); SSP Co., Ltd., Tokyo (JP); Dojin Iyaku Kako Co., Ltd., Tokyo (JP)	Diclofenacsodium Patches For Topcal Treatment of Pan	US 8,114,434 B2	Yasuhiko Sasaki, Saitama (JP); Yukihiro Matsumura, Saitama (JP); Masaru Yamazaki, Saitama (JP);Hirosi Arai	Tokuhon Corporation, Tokyo (JP); SSP Co., Ltd., Tokyo (JP); Dojin Iyaku	Sasaki Y, Matsumura Y, Yamazaki M, Arai H, Kawabata S, Saito M, Okuyama H, Suzuki M, inventors; Dojin Iyaku Kako Co Ltd, Tokuhon Corp, SSP Co Ltd, assignee. Diclofenac sodium patches for topical treatment of pain. United States patent US 8,114,434. 2012 Feb 14.(65)

				;Gunma (JP); Shogo Kawabata, Saitama (JP); Masaaki saito, Saitama (JP); Hirohisa Okuyama, Chiba (JP). Makoto Suzuki Hayaishi et al. Chiba (JP)	Kako Co., Ltd., Tokyo (JP)	
2	Hsamitsu Pharmaceutical Co., Inc., Tosu-Shi (Jp)	Adhesive Patch Comprising Dclofenac Sodum	Us 9,308,187 B2	Eisuke Hatanaka, Tsukuba (Jp); Yasunori Takada, Tsukuba (Jp); Takaaki Terahara, Tosu (Jp): Naruhito Higo, Tsukuba (Jp)	Hsamitsu Pharmaceutical Co., Inc., Tosu-Shi (Jp)	Taghizadeh SM, Bajgholi S. A new liposomal-drug-in-adhesive patch for transdermal delivery of sodium diclofenac. Journal of Biomaterials and Nanobiotechnology. 2011 Dec 1;2:576.(66)

3	Gavis Pharmaceuticals, Somerset, NJ (us)	Topical Pharmaceutical Gel Composition of Dclofenac Sodum	Us 9.468,618 B2	Bala Chandran Nayar. Somerset, Nj (Us)	Lupin Atlantis Holdingsa (Ch)	Nayar BC, inventor; Lupin Atlantis Holdings SA, assignee. Topical pharmaceutical gel composition of diclofenac sodium. United States patent US 9,468,618. 2016 Oct 18.(67)
4	HZNP Medicines LLC , Hamilton (BM5)	Diclofenac Topical Formulation	US 2020/0237919 A1	Ed KISAK , San Diego , CA (US) ; Jagat SINGH , Toronto (CA	HZNP Medicines LLC , Hamilton (BM)	Pradal J, Vallet CM, Frappin G, Bariguian F, Lombardi MS. Importance of the formulation in the skin delivery of topical diclofenac: not all topical diclofenac formulations are the same. Journal of pain research. 2019 Apr 12:1149-54.(68)
5	HZNP Limited , Hamilton Pembroke (BM)	Treatment of pain with topical diclofenac	US 10 , 058 , 519 B2	Jagat Singh , Scarborough (CA) ; Joseph Zev Shainhouse , North York , CA (US) ; Bradley S . Galer , West Chester , PA (US) ; Robert Dominic King - Smith , San	: HZNP Limited , Hamilton Pembroke (BM)	Singh J, Shainhouse JZ, Galer BS, King-Smith RD, Grierson LM, Burian M, Wilkin J, Kisak E, Newsam JM, inventors; HZNP Ltd, assignee. Treatment of pain with topical diclofenac. United States patent US 10,058,519. 2018 Aug 28.(69)

				Diego , CA (US) ; Lisa Marie Grierson , Richmond Hill (CA) ; Maria Burian , Stolberg (DE) ; Jonathan Wilkin , Columbus , OH (US) ; Edward Kisak , San Diego , CA (US) ; John M . Newsam , La Jolla , CA (US		

CONCLUSION

In summary, the effectiveness & safety of diclofenac depends upon its correct dosage & usage. The diclofenac shows analgesic, anti- pyretic & anti- inflammatory properties with lesser side effects .In lactating women it is poorly secreted in milk which is less harmful for infants. So if she can suffer from pain she can take the diclofenac. It can be summarised as fast – acting, anti- inflammatory, powerful analgesic, rapid onset & widely applicable. It shows more advantages & fewer side effects if we use its correct dose with the suggestion of registered medical practitioner. Because of its less side effects & more advantages it is used in other countries also like Canada, mexico , japan & china etc. So its performance is strong in domestic market as well as international market.

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