DICLOFENAC POTASSIUM; 
A SAFE AND EFFECTIVE PAIN RELIEVER

ABSTRACT: Diclofenac potassium is efficiently utilized in treating pain during migraine, episodic tension headache, ankle sprain, osteoarthritis and dental pain etc. This review article covers the clinical aspects, pharmacokinetics, different therapeutic applications, drug-drug interactions, related adverse effects, safety and efficacy of diclofenac potassium.

Key words: Diclofenac potassium, Episodic tension headache, Osteoarthritis, Pharmacokinetics and Adverse effects.

INTRODUCTION
Diclofenac Potassium is a nonsteroidal anti-inflammatory (NSAID) compound. It is benzene-acetic acid derivative, showing cyclooxygenase-2 enzyme inhibition. It is launched as an immediate release tablet in order to provide quick pain relief.\textsuperscript{1,2} The chemical name of diclofenac potassium is 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid. Figure-1\textsuperscript{2} showing the structure:

Owing to its property of inhibition of prostaglandin synthesis, diclofenac is used as an antipyretic and analgesic agent.\textsuperscript{3} Globally it is one of the most extensively prescribed NSAID.\textsuperscript{4}

SOLUBILITY AND PHYSICAL PROPERTIES
Diclofenac potassium (DP) belongs to class II drug category (high permeability, low solubility) according to biopharmaceutics classification system (BCS). It has high solubility in the acidic environment of stomach which makes it a quick pain reliever. It is a yellowish white, absorbent and inodorous powder. It is not soluble in chloroform, is relatively soluble in ethanol and water but has highest solubility in methanol. Reported dissociation constant (pKa) is found to be 4.0 ± 0.2 at 25°C in water while the partition coefficient

Figure-1: Structural presentation of diclofenac potassium,
(M = sodium (Na\textsuperscript{+}) or potassium (K\textsuperscript{+}) salt, respectively

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in n-octanol at pH 7.4 is 13.4 and at pH 5.2 is 1545.44-45

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION
The mechanism which is responsible for the anti-inflammatory, analgesic and antipyretic activity is via restricting prostaglandin synthesis by inhibiting cyclooxygenase (COX) however the exact mechanism is still not clear. Besides this it also possesses bacteriostatic activity owing to its property of inhibiting bacterial DNA synthesis.5 It is the most potent NSAID because it has additional functions of inhibiting both phospholipase A2 and leukotrienes synthesis (also pro-inflammatory autacoids).6 Diclofenac prompted peripheral reduction in sensitivity to painful stimuli involves the \( \text{L-arginine–NO–cGMP–potassium channel pathway}. \)\(^{40}\) This peripheral reduction in sensitivity to painful stimuli is brought about by the stimulation of numerous types of \( \text{K}^+ \) channels, which hyperpolarize marginal terminals of primary afferents.41 Diclofenac acts by producing the following effects: (1) constrains the thromboxane-prostanoid receptor, (2) influences the taking up and emission of arachidonic acid, (3) triggers pathways of nitric oxide–cGMP antinociceptive and (4) confines lipoxygenase enzymes.44 In Peretz in 2005 studied a new method of diclofenac \((\text{ED}_{50} = 43 \text{ mg/kg})\) to decrease cortical neuronal activity and prompt anticonvulsant response via \( \text{KCNQ2/Q3 potassium currents enhancement}, \) making it suitable for the utilization in migraine epilepsy and neuropathy.43

PHARMACOKINETICS
The absorption of diclofenac potassium is quickly accomplished after oral intake. Its apparent volume of distribution is reported to be 1.3 L.kg\(^{-1}\).2,7 The area under the plasma concentration-time curve (AUC) of diclofenac potassium is directly related with the dose \((25 – 150 \text{ mg})\). Despite the fact that it bounds extensively to plasma albumin it still attains substantial concentrations in synovial fluid.8 Half an hour following administration, the peak plasma drug concentration is achieved, and the mean terminal half-life is 60 – 120 minutes, providing a 240 - 360 minutes stretch of activity, determined by the situation.9

After biotransformation to glucoroconjugated and sulphate metabolites diclofenac is eliminated via urine, with only little removed unaltered. Renal function is responsible for the excretion of conjugates, depicting build-up in end-stage renal disease but build-up did not occur while comparing young and elderly individuals. Dosage adjustments for patients with co morbities (for instance liver disease or rheumatoid arthritis) or ages in extremes of life may not be required.9

THERAPEUTIC APPLICATION
The non-steroidal anti-inflammatory drugs are very often prescribed for managing rheumatic diseases. The indications of NSAIDs are numerous and are still increasing, and are now prescribed for postoperative analgesia, pain associated with cancer, treatment of dysmennorhea and proteinuria and for thrombosis prevention.10

The major therapeutic applications of diclofenac potassium are as follows:

For Pain and Fever
Around 13 randomized double-blind, placebo-controlled trials have revealed that diclofenac K \((12.5 \text{ mg tablets})\) have effectiveness in disease situations such as, severe pain in lower back and pain after dental removal, headache, pain in manifestations of cold and influenza (including fever) and in menstruation.9 When administered as a single dose \((12.5 & 25 \text{ mg})\) Diclofenac K remarkably diminished fever and throat pain. In patients with sore throat and fever diclofenac potassium produces significant decrement in pyrexia and sore throat.17

Acute Treatment of Migrain Attack
Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms.11 Diclofenac-potassium is well tolerated, induces quick solace from pain (within 1 - 1.5 hours), and brings about decrease in the co-existing
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manifestations in patients with migraine. According to some trials, diclofenac K imparts as solace from pain as sumatriptan; however it has more rapid onset of action and its effect on nausea and vomiting is greater than sumatriptan. Diclofenac-potassium may in future be useful as first-line alternative in the treatment of severe migraine. NSAIDs do not influence blood pressure and can be used in combination with most other migraine agents. Diclofenac potassium powder was found to be efficient in placebo controlled trials in patients with migraine. Scientists reported that diclofenac potassium powder is more effective as compared to diclofenac potassium tablets related to the primary endpoint i.e. 2 hr pain relief also in numerous secondary endpoints.

Episodic tension type headache
One of the common primary headaches is Tension-type headache which requires accurate diagnosis before treatment, with immense socioeconomic impact. NSAIDS is used for the management of episodic tension-type headache. Diclofenac-K, relieves ETH when given in doses of 12.5 and 25mg which is comparable to ibuprofen 400mg.

Ankle sprain
In a clinical trial comparing the anodyne and anti-inflammatory effects of Diclofenac potassium and piroxicam, the former was found to more effective than piroxicam or placebo in reducing pain at rest and upon walking. Yet another trial showed that patients medicated with diclofenac K were significantly improved than those in patients treated with piroxicam.

Osteoarthritis
Small study in a Venezuelan population showed that both IR and CR formulations of diclofenac K are effective in medical care of knee osteoarthritis. Diclofenac potassium is safe and effective for treating OA and has good tolerability.

Post-surgical dental pain
Single dose of diclofenac K (ProSorb; 25, 50, and 100 mg) were more effective than placebo in reducing the pain following dental surgery. Other trials conducted with diclofenac-K (2 × 12.5 mg) or paracetamol (2 × 500 mg) also depicted that it relieves the most intense postoperative pain adequately. Within 30 minutes of administration Diclofenac potassium brings about rapid pain relief when assessed for postoperative dental pain studies.

Primary dysmenorrheal
In previous studies cyclooxygenase inhibitors were compared and it was determined that Rofecoxib and diclofenac potassium were found to be similarly efficient in reducing pain associated with primary dysmenorrhea. Diclofenac potassium helps to improve physical performance in women by effectively relieving menstrual pain. It also improves sleep quality with effective decrement in nighttime dysmenorrheic pain.

Post episiotomy pain
Diclofenac potassium is more efficient in providing long lasting analgesic for managing post episiotomy pain as compared to aspirin in several range of doses.

Cancer
Diclofenac is frequently used to treat chronic pain associated with malignancy, particularly if inflammation is present additionally (Step I of the World Health Organization (WHO) scheme for treatment of chronic pain).

Other uses
Diclofenac may be used for uncomplicated UTI it is effective against numerous multidrug-resistant E. coli strains, with 25 micrograms/ml MIC. It showed efficacy in treating Salmonella diseases in mice, and is under scrutiny for the therapy of tuberculosis. It also inhibits the excretion of uric acid in the urine.

DRUG-DRUG INTERACTIONS
Aspirin (acetylsalicylic acid), digoxin, cyclosporin, lithium, cholestyramine, methotrexate and colestipol exhibit considerable drug interactions. When given simultaneously with cardio active compounds, the concentration of potassium was increased however the frequency of doses
did not affect diclofenac concentrations. The cimetidine (H₂-receptor blocking agent) restricts the oxidative metabolism of several concurrently administered compounds i.e. different NSAIDs. Cholestyramine decreases the oral absorption of NSAIDs, while corticosteroid causes plasma salicylate concentrations to decrease. Interactions can also occur between NSAIDs, antihypertensive and diuretics compounds.

ADVERSE EFFECTS
Abdominal pain, fatigue and nausea are most frequent adverse effects reported. When diclofenac K was compared to ibuprofen in a safety study for a duration of 90 days in individuals with knee osteoarthritis, neither hepatic injury nor cardiovascular safety-related issues were noted however the pattern of other adverse effects were same. Diclofenac decreases hematocrit by 50% and dose-dependently damages the stomach. Since prostaglandins form a part of normal physiology, NSAID’s, as a result, possess predictable therapeutic adverse effects so should be used safely.

EFFICACY & SAFETY
According to several clinical trials and post marketing surveillance studies, the safety and efficacy profiles of low doses of diclofenac potassium and ibuprofen (200-1200 mg in divided doses) in episodic tension like headache were found to be similar. When compared to 100 mg dose of sumatriptan, the therapeutic efficacy of 50 – 100 mg doses of immediate release tablets of diclofenac potassium are just as efficacious as sumatriptan. Ungprasert in 2015 reported that the use of different NSAIDs is not related with an elevated risk of hemorrhagic stroke, although this risk was moderately considerably high in users of diclofenac and meloxicam.

CONCLUSION
Because of its potency, diclofenac potassium could be useful as an alternative oral therapy for migraine attacks. The diversity in diclofenac’s mechanism of action indicates more effective profile as compared with other NSAIDs.

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