The Professional Medical Journal
www.theprofesional.com

DOI: 10.17957/TPMJ/16.3252

REVIEW PROF-3252

DICLOFENAC POTASSIUM;
A SAFE AND EFFECTIVE PAIN RELIEVER

Dr. Huma Ali[1], Dr. Farya Zafar[2], Saba A. Baloch[3], Hina Hasnain[4], Safila Naveed[5], Ghazala Raza Naqvi[6]

1. B.Pharm, Pharm.D, M.Phil. Ph.D. Associate Professor Department of Pharmaceutics Faculty of Pharmacy, Ziauddin University
2. B.Pharm, M.Phil. Ph.D. Associate Professor
3. Pharm. D, M.Phil. (Scholar) Senior Lecturer
4. Pharm.D. M.Phil. (Scholar)
5. B.Pharm, M.Phil. Ph.D. Jinnah University for Women, Karachi, Pakistan.
6. Assistant Professor Faculty of Pharmacy Federal Urdu University

Correspondence Address:
Dr. Huma Ali
B.Pharm, Pharm.D, M.Phil. Ph.D.
Associate Professor
Department of Pharmaceutics
Faculty of Pharmacy,
Ziauddin University
humaali80@live.com

Article received on:
15/01/2016
Accepted for publication:
03/03/2016
Received after proof reading:
12/04/2016

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.

Article Citation: Ali H, Zafar F, Baloch SA, Hasnain H, Naveed S, Naqvi GR. Diclofenac potassium; a safe and effective pain reliever. Professional Med J 2016;23(4):358-363. **DOI:** 10.17957/TPMJ/16.3252

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.[1,2] The chemical name of diclofenac potassium is 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid. Figure-1[2] showing the structure:

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

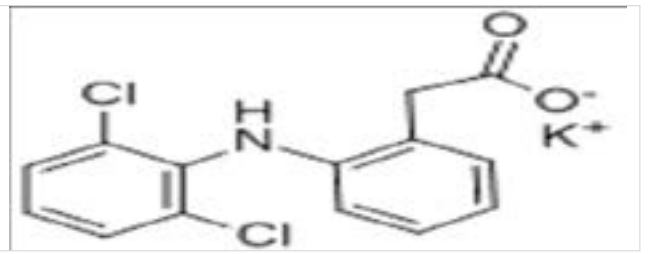

Figure-1: Structural presentation of diclofenac potassium,
(M = sodium (Na^+) or potassium (K^+) salt, respectively

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

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 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 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 (ED_{50} = 43 mg/kg) to decrease cortical neuronal activity and prompt anticonvulsant response via 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 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 morbidities (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 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 admistered as a single dose (12.5 & 25 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

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.[3,12] NSAIDs do not influence blood pressure and can be used in combination with most other migraine agents.[13] 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.[46]

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.[14] Diclofenac-K, relieves ETH when given in doses of 12.5 and 25mg which is comparable to ibuprofen 400mg.[15,16]

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.[18] Yet another trial showed that patients medicated with diclofenac K were significantly improved than those in patients treated with piroxicam.[19]

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.[20] Diclofenac potassium is safe and effective for treating OA and has good tolerability.[21,22]

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.[23] 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 adequetly.[24] Within 30 minutes of administration Diclofenac potassium brings about rapid pain relief when assessed for postoperative dental pain studies.[25]

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.[26] Diclofenac potassium helps to improve physical performance in women by effectively relieving menstrual pain.[27] It also improves sleep quality with effective decrement in nighttime dysmenorrheic pain.[28]

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.[29]

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).[30]

Other uses

Diclofenac may be used for uncomplicated UTI it is effective against numerous multidrug-resistant *E. coli* strains, with 25 micrograms/ml MIC.[31] It showed efficacy in treating *Salmonella* diseases in mice,[32] and is under scrutiny for the therapy of tuberculosis.[33] It also inhibits the excretion of uric acid in the urine.[34]

DRUG-DRUG INTERACTIONS

Aspirin (acetylsalicylic acid), digoxin, cyclosporin, lithium, cholestyramine, methotrexate and colestipol exhibit considerable drug interactions.[8] When given simultaneously with cardio active compounds, the concentration of potassium was increased however the frequency of doses

did not affect diclofenac concentrations.[35] The cimetidine (H_2-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 [36].

ADVERSE EFFECTS

Abdominal pain, fatigue and nausea are most frequent adverse effects reported.[3] 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.[9] Diclofenac decreases hematocrit by 50% and dose-dependently damages the stomach.[3] Since prostaglandins form a part of normal physiology, NSAID's, as a result, possess predictable therapeutic adverse effects so should be used safely.[38]

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.[3,24,39] 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.[47]

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.

REFERENCES

1. Hinz B, Chevts J, Renner B, Wuttke H, Rau T, Schmidt A, Szelenyi I, Brune K, Werner U. **Bioavailability of diclofenac potassium at low doses.** British journal of clinical pharmacology. 2005, 59(1):80-4.

2. Chuasuwan B, Binjesoh V, Polli JE, Zhang H, Amidon GL, Junginger HE, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. **Biowaiver monographs for immediate release solid oral dosage forms: Diclofenac sodium and diclofenac potassium.** Journal of pharmaceutical sciences. 2009, 98(4):1206-19.

3. McNeely W, Goa KL. **Diclofenac-potassium in migraine.** Drugs. 1999, 57(6):991-1003.

4. Van Den Abeele J, Brouwers J, Mattheus R, Tack J, Augustijns P. **Gastrointestinal Behavior of Weakly Acidic BCS Class II Drugs in Man□Case Study Diclofenac Potassium.** Journal of pharmaceutical sciences. 2015, doi: 10.1002/jps.24647.

5. Dastidar SG, Ganguly K, Chaudhuri K, Chakrabarty AN. **The anti-bacterial action of diclofenac shown by inhibition of DNA synthesis.** International journal of antimicrobial agents. 2000, 14(3):249-51.

6. Scholer DW, Ku EC, Boettcher I, Schweizer A. **Pharmacology of diclofenac sodium.** The American journal of medicine. 1986, 80(4):34-8.

7. Barros NR, Chagas PA, Borges FA, Gemeinder JL, Miranda MC, Garms BC, Herculano RD. **Diclofenac potassium transdermal patches using natural rubber latex biomembranes as carrier.** Journal of Materials. 2015, Article ID 807948.

8. Davies NM, Anderson KE. **Clinical pharmacokinetics of diclofenac.** Clinical pharmacokinetics. 1997, 33(3):184-213.

9. Moore N. **Diclofenac Potassium 12.5 mg Tablets for Mild to Moderate Pain and Fever.** Clinical drug investigation. 2007, 27(3):163-95.

10. Brooks PM, Day RO. **Nonsteroidal anti-inflammatory drugs - differences and similarities.** New England Journal of Medicine. 1991, 324(24):1716-25.

11. Zuniga JR, Malmström H, Noveck RJ, Campbell JH, Christensen S, Glickman RS, Tomasetti BJ, Boesing SE. **Controlled Phase III Clinical Trial of Diclofenac Potassium Liquid-Filled Soft Gelatin Capsule for Treatment of Postoperative Dental Pain.** Journal of Oral and Maxillofacial Surgery. 2010, 68 (11): 2735–2742.

12. Herrera JA, Millán A, Ramos R, Fuentes P, González M. **Evaluation of the effectiveness and tolerability of controlled-release diclofenac-potassium versus immediate-release diclofenac-potassium in the treatment of knee osteoarthritis.** Current Therapeutic Research. 2007, 68 (2): 82–93.

13. Marry-Jette K. **Rasmussen and Michael Binzer: Non-Steroidal Anti-Inflammatory Drugs in the Treatment of Migraine.** 2001, 17 (1): 26-29.

14. Ashina S, Ashina M. **Current and potential future drug therapies for tension-type headache.** Current pain and headache reports. 2003, 7(6):466-74.

15. Kubitzek F, Ziegler G, Gold MS, Liu JM, Ionescu E. **Low□dose diclofenac potassium in the treatment of episodic tension□type headache.** European Journal of Pain. 2003, 7(2):155-62.

16. Bendtsen L, Evers S, Linde M, Mitsikostas DD, Sandrini G, Schoenen J. **EFNS guideline on the treatment of tension□type headache–Report of an EFNS task force.** European Journal of Neurology. 2010, 17(11):1318-25.

17. Gehanno P, Dreiser RL, Ionescu E, Gold M, Liu JM. **Lowest effective single dose of diclofenac for antipyretic and analgesic effects in acute febrile sore throat.** Clinical drug investigation. 2003, 23(4):263-71.

18. Saavedra HC. **Comparison of the analgesic and anti-inflammatory effects of diclofenac potassium versus piroxicam versus placebo in ankle sprain patients.** Journal of international medical research. 1990, 18(2):104-11.

19. Morán M. **An observer-blind comparison of diclofenac potassium, piroxicam and placebb in the treatment of ankle sprains.** Current medical research and opinion. 1990,12(4):268-74.

20. Herrera JA, Millán A, Ramos R, Fuentes P, González M. **Evaluation of the effectiveness and tolerability of controlled-release diclofenac-potassium versus immediate-release diclofenac-potassium in the treatment of knee osteoarthritis.** Current therapeutic research. 2007, 68(2):82-93.

21. Jianhua X, Guihua S, Zongwen S. **Clinical trial of diclofenac potassium in treatment of osteoarthritis.** Acta Universitis Medicinalis Nahui. 2000, 6:022.

22. Wen SZ, Pei LX, Jian WU. **Effectiveness and safety of 1% diclofenac potassium gel for external application in the treatment of patients with osteoarthritis.** Anhui Medical and Pharmaceutical Journal. 2002, 1:012.

23. Hersh EV, Levin LM, Adamson D, Christensen S, Kiersch TA, Noveck R, Watson G, Lyon JA. **Dose-ranging analgesic study of prosorb® diclofenac potassium in postsurgical dental pain.** Clinical therapeutics. 2004, 26(8):1215-27.

24. Kubitzek F, Ziegler G, Gold MS, Liu JM, Ionescu E. **Analgesic efficacy of low-dose diclofenac versus paracetamol and placebo in postoperative dental pain.** Journal of orofacial pain. 2002, 17(3):237-44.

25. Zuniga JR, Noveck RJ, Schmidt WK, Boesing SE, Hersh EV. **Onset of action of diclofenac potassium liquid-filled capsules in dental surgery patients.** Current Medical Research & Opinion. 2011, 27(9):1733-9.

26. Chantler I, Mitchell D, Fuller A. **The effect of three cyclo-oxygenase inhibitors on intensity of primary dysmenorrheic pain.** The Clinical journal of pain. 2008, 24(1):39-44.

27. Chantler I, Mitchell D, Fuller A. **Diclofenac potassium attenuates dysmenorrhea and restores exercise performance in women with primary dysmenorrhea.** The Journal of Pain. 2009, 10(2):191-200.

28. Iacovides HS, Avidon I, Bentley A, Baker FC. **Diclofenac potassium restores objective and subjective measures of sleep quality in women with primary dysmenorrhea.** Sleep. 2009, 32(8):1019.

29. Olson NZ, Sunshine A, Zighelboim I, DeCastro A. **Onset and duration of analgesia of diclofenac potassium in the treatment of postepisiotomy pain.** American journal of therapeutics. 1997, 4(7-8):239-46.

30. World Health Organization. **WHO's pain ladder for adults.** World Health Organization. 2013.

31. Mazumdar K, Dutta NK, Dastidar SG, Motohashi N, Shirataki Y. **Diclofenac in the management of E.** coli urinary tract infections. In vivo. 2006, 20(5):613-9.

32. Dutta NK, Annadurai S, Mazumdar K, Dastidar SG, Kristiansen JE, Molnar J, Martins M, Amaral L. **Potential management of resistant microbial infections with a novel non-antibiotic: the anti-inflammatory drug diclofenac sodium.** International journal of antimicrobial agents. 2007, 30(3):242-9.

33. Dutta NK, Mazumdar K, Dastidar SG, Park JH. **Activity of diclofenac used alone and in combination with streptomycin against Mycobacterium tuberculosis in mice.** International journal of antimicrobial agents. 2007, 30(4):336-40.

34. Naidoo V, Swan GE. **Diclofenac toxicity in Gyps vulture is associated with decreased uric acid excretion and not renal portal vasoconstriction. Comparative Biochemistry and Physiology Part C: Toxicology &**

Pharmacology. 2009, 149(3):269-74.

35. Jakovljevic V, Sabo A, Tomić Z, Milijašević B, Popovic M, Vasovic V, Rašković A. **Interaction of diclofenac and ketoprofen with cardioactive drugs in rats. European journal of drug metabolism and pharmacokinetics.** 2009, 34(1):11-7.

36. Verbeeck RK. **Pharmacokinetic drug interactions with nonsteroidal anti-inflammatory drugs.** Clinical pharmacokinetics. 1990, 19(1):44-66.

37. Wallace JL, Caliendo G, Santagada V, Cirino G, Fiorucci S. **Gastrointestinal safety and anti-inflammatory effects of a hydrogen sulfide–releasing diclofenac derivative in the rat.** Gastroenterology. 2007, 132(1):261-71.

38. Kubitzeka F, Zieglerb G, Goldc MS, Liuc JMH, Ionescu E. **Low-dose diclofenac potassium in the treatment of episodic tension-type headache.** European Journal of Pain. 2003, 7 (2): 155–162.

39. Grebe W, Ionescu E, Gold MS, Liu JM, Frank WO. **A multicenter, randomized, double-blind, double-dummy, placebo-and active-controlled, parallel-group comparison of diclofenac-K and ibuprofen for the treatment of adults with influenza-like symptoms.** Clinical therapeutics. 2003, 25(2):444-58.

40. Ortiz MI, Granados-Soto V, Castañeda-Hernández G. **The NO–cGMP–K+ channel pathway participates in the antinociceptive effect of diclofenac, but not of indomethacin.** Pharmacology Biochemistry and Behavior. 2003, 76(1):187-95.

41. Ortiz MI, Torres-López JE, Castañeda-Hernández G, Rosas R, Vidal-Cantú GC, Granados-Soto V. **Pharmacological evidence for the activation of K+ channels by diclofenac. European journal of pharmacology.** 2002, 438(1):85-91.

42. Peretz A, Degani N, Nachman R, Uziyel Y, Gibor G, Shabat D, Attali B. **Meclofenamic acid and diclofenac, novel templates of KCNQ2/Q3 potassium channel openers, depress cortical neuron activity and exhibit anticonvulsant properties.** Molecular pharmacology. 2005, 67(4):1053-66.

43. Gan TJ. **Diclofenac: an update on its mechanism of action and safety profile.** Current Medical Research & Opinion. 2010, 26(7):1715-31.

44. BP, British Pharmacopoeia. 2007. **Great Britain, Directorate of Medicine and Health;** 665.

45. Sarfraz A, Sarfraz M, Ahmad M. **Development and Validation of a Bioanalytical Method for Direct Extraction of Diclofenac Potassium from Spiked Plasma.** Tropical Journal of Pharmaceutical Research. 2011, 10(5):663-9.

46. Garnock-Jones KP. **Diclofenac potassium powder for oral solution: a review of its use in patients with acute migraine.** CNS Drugs. 2014, 28(8):761-8.

47. Ungprasert P, Matteson EL, Thongprayoon C. **Nonaspirin Nonsteroidal Anti-Inflammatory Drugs and Risk of Hemorrhagic Stroke: A Systematic Review and Meta-Analysis of Observational Studies.** Stroke. 2015, 47:1-9 pii: STROKEAHA.115.011678.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Huma Ali	Equally Contributed	
2	Dr. Farya Zafar		
3	Saba A. Baloch		
4	Hina Hasnain		
5	Safila Naveed		
6	Ghazala Raza Naqvi		