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Diclofenac from Administration to Adverse Effect a Mini-Review

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Abstract:- Diclofenac, a phenylacetic acid derivative and NSAID with the chemical formula of C14H11Cl2NO2. It shows high effectiveness in order to treat pain and physical disability in rheumatic diseases. There are multiple kinds of adverse effects related to this drug, and it is necessary to know the drug before administration, including its adverse effect. This mini-review is focused on its introduction, efficacy after oral administration, and adverse effect.

Keywords:- *Diclofenac, NSAID, Oral Administration, Adverse Effect.*

I. INTRODUCTION

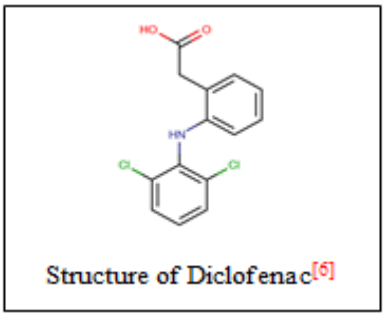
Over the age of 50 years, it is seen that around 70% of the population suffers from diseases related to the Musculoskeletal. It is usually seen that as the age is increased, musculoskeletal tissues show increased bone fragility, loss of cartilage resilience, reduced ligament elasticity, loss of muscular strength, and fat redistribution, decreasing the ability of the tissues to carry out their normal functions. During the treatment it happens, the pain caused by rheumatic diseases gets reduced. The drugs by which rheumatic diseases are treated generally reveal a slow onset of action, which in consequence leads to incorporation of the treatment of the primary diseases, painkillers are stipulated like an additional therapy. In combination with co-analgesics, Analgesics are used for the treatment of pain that occurs due to disease. Drugs such as sedatives, antidepressants, and anti-epileptics are used, so it may help to reduce the dose of analgesic during the treatment. The sufferer of chronic pain is allowed for therapy with high-potency opioids only if their evaluation is at least 50% on the visual analog scale (VAS: 0-100 mm).[1]

Pharmacokinetically and pharmacodynamically, NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) are a diversified class of drug substances that affect different sorts of Cyclooxygenase and which ranges in their mechanism of action distribution to the inflammation site and half-life. Ardent research related to pharmacology and formulation is presently being directed toward obtaining more effective and prudent products.[2]

In various indications, nonsteroidal anti-inflammatory drugs (NSAIDs) are very effective. In rheumatology cases, generally, the treatment proceeds with NSAIDs of different disorders such as lupus erythematosus, rheumatoid arthritis, gout, ankylosing spondylitis, psoriatic arthritis, and rheumatic fever.[3], [4], [5]

II. DICLOFENAC

It is a phenylacetic acid derivative and NSAID with the chemical formula of C14H11Cl2NO2. Cyclooxygenase is inhibited by NSAIDs (COX)-1 and -2(is an enzyme that is behind the production of prostaglandins). Prostaglandins (PGs) give rise to inflammation and pain signaling. In acute and chronic pain, diclofenac is the only drug used in first-line therapy. Diclofenac is used as a first-line drug for inflammation of various causes, like other NSAIDs. The structure of diclofenac is based upon phenylbutazone, mefenamic acid, and indomethacin.[7] At the ortho position of the phenyl ring, there is the addition of two chlorine groups. The phenyl ring locks the ring in maximal torsion, which seems to be linked to increased potency. To prevent the effect of NSAID-induced gastric ulcers, it is frequently used along with misoprostol. The food and drug administration (FDA) first ratified diclofenac in July 1988 under the trade name of Voltaren, marketed by Novartis (previously Ciba-Geigy).[8]



Structure of Diclofenac[6]

III. EFFICACY (AFTER ORAL ADMINISTRATION)

Costa et al. in the year 2017,[9] has brought out the collective data of a study by evaluation of the effectiveness of various drugs and their dosage employed in treating the pain of osteoarthritis which is according to a search of the Cochrane Central Register of Controlled Trials (CENTRAL). The publication of the researchers has reviewed studies that involved around 100 patients from January 1980 to February 2015. There were about entire 8,973 reviewed publications on studies conducted on a total of 58,451 patients. In this cited review, the outcome of efficacy was compared among paracetamol and NSAIDs

(counting ibuprofen, naproxen, celecoxib, diclofenac) used at different therapeutic doses. The comparison was done along with placebo as well as with each other. The study had a conclusion that the diclofenac at a dose of 150 mg/day is the most effective drug in the therapy of pain and osteoarthritis which give rise to physical disability (OA) and is superior to widely used NSAIDs (including ibuprofen, naproxen, and celecoxib) at maximum dose. Its effectiveness in treating physical disability is doubtful, but in the case of treating pain, its maximum dose was 60 mg/day which shows greater efficacy to the diclofenac safety profile, wholly considerable details must be available when diclofenac therapy is selected, and dose should be set on for particular volunteers.[9]

Pavelka[10] gives out mixed well regulated clinical trials, except analysis, n=1 trials, and meta-analyses. Several data-collection were explored (counting Embase, Ovid Medline, and Ovid Medline In-Process & Non-Indexed Citations). After 1999, 263 articles were added up to get published and were reviewed enclosed. This study was on comparing the therapeutic efficacy of diclofenac with other drugs such as lornoxicam, etoricoxib, lumiracoxib, rofecoxib, aceclofenac, acetaminophen, etodolac, meloxicam, nabumetone, nimesulide, dexketoprofen, acetaminophen, tramadol, diacerein, celecoxib, and oxaceprol. As reported by instigator, the therapeutic doses at which diclofenac displayed similar efficacy in almost all studies, and thus diclofenac was framed as a recommended drug of choice in the treatment of osteoarthritis. According to the scrutinization, the efficacious activity of diclofenac is no minimum than newly discovered analgesic drugs that are used in the case of osteoarthritis.[10]

Treatment	Mean visual analogue score (vas) ± SD						% age Reduction
	N	Basal	N	1st week	N	2nd week	
Lornoxicam	50	4.16 ± 1.63	50	2.15 ± 1.46*	41	1.42 ± 1.25*	48
Aceclofenac	50	4.34 ± 1.67	50	1.91 ± 1.24*	39	1.03 ± 0.94*	56
Diclofenac	50	4.48 ± 1.35	50	2.07 ± 1.14*	38	1.03 ± 0.97*	62
F value		0.528		0.448		1.745	
P value		0.591		0.640		0.179	

Table 1: comparative analgesic efficacy between lornoxicam, aceclofenac & diclofenac.

A In 2012, Patnaik et al.[11] published a study where a comparison was made between the effectiveness of lornoxicam and aceclofenac and diclofenac in a person having a musculoskeletal disability. All 50 patients were randomly divided into three consecutive groups. Then they got initiated with the treatment with lornoxicam (dose of 4 mg), aceclofenac (dose of 100mg), diclofenac (dose of 50 mg). Each of the drugs was used twice a day after the meal. Patients were compared while assessment by estimating the extent of pain on the visual analog scale (VAS)[12] from the first day and later for every week for about three weeks. This study determined that lornoxicam, aceclofenac, and diclofenac shows equal analgesic effect which is highly effective for relieving pain.

IV. ADVERSE EFFECT

NSAIDs got more effective therapeutically, as they have a clear-cut mechanism of action. But on other hand, it causes side effects, which are explicitly common after oral administration of the drug. Throughout 21%- 25% of the identified cases of adverse drug reaction (ADR) are because of the NSAIDs. NSAIDs when used for the long-term leads to functional disorders of the gastrointestinal tract, kidneys, cardiovascular, and central nervous system (CNS). Non-steroidal anti-inflammatory drugs, based on adverse effects, showed distinctively.[13], [14], [15], [16], [17]

The good documentation of toxicity of NSAIDs is in the case of upper gastrointestinal disease. The use of NSAIDs is the reason behind the gash to both parts of the intestines and as well as to other parts of digestive organs. It prompts rupture, formation of an ulcer, and constraint of the small intestine which requires operative treatments and may cause enteropathy which leads to inflammation within blood and protein loss from the intestine. The drugs which come under this class may aggravate large-bowel diseases, which reactivate the previous disease which is in the inactive stage or affect the primary episode of inflaming bowel disease.

After treatment with NSAIDs, the chances of liver damage get increased. Typically, this condition occurs when NSAIDs are used, for example, diclofenac and sulindac.[18] The book by Sriuttha et al. evaluated the risk of hepatotoxicity caused by NSAIDs in a review. In that systematic review, [19] 18 randomized controlled trials (RCTs) were rated. Of the 698 studies, 18 of them met the selection process, and 8 studies with NSAIDs (celecoxib, etoricoxib, diclofenac) set up clinically significant hepatotoxicity. Diclofenac was found to be the leading cause of hepatotoxicity but was not associated with an increase in the cause of hospitalization. Human-based disease research was published by Rubenstein in 2004. Contradictory reviews did not provide significant evidence of hepatotoxicity from diclofenac. Both of these identified activities were based on different implantation procedures - from liver damage to enzymes to promote further injury, which ultimately leads to hospitalization and eventual death.[20]

Comparison of diclofenac and omeprazole efficacy compared with celecoxib in patients with OA and RA at high intestinal risk was published in 2013 by Kellner et al.[2] The study was based on a mixed, double-blind design. There

were approximately 4,484 people who were not scheduled for treatment and were included in the analysis for treatment. Approximately 2,238 patients received treatment with celecoxib (200mg dose) and 2,246 patients were given diclofenac plus omeprazole (75 mg dose). Celecoxib was used twice a day, while diclofenac and omeprazole twice a day and a proton pump inhibitor were administered at 20 mg once daily. The test lasted about six months. As the authors point out, celecoxib and diclofenac combined with omeprazole may be somewhat effective in patients with OR and RA with high intestinal risk.

This study also determined that the risk of intestinal problems due to the effect of diclofenac and omeprazole and celecoxib is evident even in patients treated. The test was a standardized measure of intestinal problems, including bleeding, limitation or swelling of the upper intestine, small and large intestines, and significant clinical anemia. 0.9% of patients were treated with celecoxib, while 3.8% of patients were given diclofenac and omeprazole in case of complications.[22], [23], [24]

Lately, rodents showed failure of proton pump inhibitors in bringing out therapeutic benefits but may intensify NSAID- induced enteropathy. The rat those were treated along with proton pump inhibitors (omeprazole or lansoprazole) had a higher frequency of intestinal ulceration and bleeding as compared to the other animals who got treatment with NSAIDs (naproxen or celecoxib) on comparision with the control group receiving just the vehicle and NSAIDs.

In consequence, the studies established the regimen consisting of NSAIDs used in combination with proton pump inhibitors in the prevention of NSAID-induced damage fails to affect the small intestine remarkably. No long time, video capsule endoscopy studies singnify a high incidence (about 55 % to 75 %) of minor intestinal injuries in healthy individual who have been volunteerly taking NSAIDs in combination with proton pump inhibitors for two weeks.[25]

The patients who were being a sufferer of cardiovascular failure, were strictly restricted for the administration of coxibs, diclofenac, and higher-dose ibuprofen should be avoided.[26] Wholly types of NSAIDs may cause cardiovascular complications (excluding acetylsalicylic acid).[27] A review published in the year 2011 manifestes a high dose of coxibs (similar to diclofenac) can increase the risk of cardiovascular issue. For patients who got treatment by naproxen, disssimilar observation were found.[28]

In the year 2013, a paper got published comprises of 280 comparative placebo-controlled studies with 124,513 patients and 474 studies with rest of the NSAIDs in the control group involving 229,296 patients. On the basis of different database diclofenac and ibuprofen in high dose increases the risk of cardiovascular to a degree equivalent to coxibs, considering naproxen relatively safe.[29]

It is significantly seen in the patients who are having coronary heart diseases administering small doses of acetylsalicylic acid often requires concomitant NSAIDs therapy on the basis of coexisting rheumatic disorders. The use of two different types of NSAIDs simultaneously leads to non-medical situation, and care should be taken to ensure that there is a minimum 2-hour interval between acetylsalicylic acid state and another NSAID.[4], [30]

In the medical market, diclofenac is available in many medicinal products and in various dosage forms, and through the various channels through which it can be treated. It is available in a variety of forms such as a chemical form of acid, potassium salt, or sodium salt. They contain oral dosage forms (pills), usually modified exfoliation, rectal dosage forms, injections, products inserted or sprayed into the skin, mucoadhesive dosage forms, and eye drops. The most typical pharmaceutical form of diclofenac is in the form of sodium salt.[31], [32], [33]

V. CONCLUSION

Non-opioid analgesics including paracetamol and non-steroidal anti-inflammatory drugs are most typically used in the treatment of pain in patients with rheumatic diseases. Diclofenac derives from a phenylacetic acid which non-selectively inhibiting cyclooxygenases COX-1 and COX-2. Various meta-analyses have manifested that at therapeutic doses diclofenac is highly effective in treating pain and physical disability in rheumatic diseases. However, keeping in mind the safety profile of diclofenac, all obtainable information of safety measures of the drug should be considered when diclofenac therapy is selected and its dosage is set on for individual patients.

The therapeutic effectiveness of oral dosage forms along with diclofenac is found out not only by the dosage of the drug compound but also by the form of drug formulation and suitable selection of excipients. Tablets released with technological advancement, multi-line tablets or solid capsules containing micropellets that have been developed in the form of drug-based micropellets to improve drug availability and the environment with diclofenac, improve its stability, and reduce side effects.

Another way to reduce the systemic exposure of diclofenac and its adverse reactions is the use of the drug in standard dosage forms. Based on meta-analyzes, topical diclofenac has been found to be very effective in the treatment of chronic pain and chronic musculoskeletal disorders. The transdermal penetration rate of diclofenac can vary, depending on the number of substances such as dosage form (cream, gel, patch, solution), transdermal penetration enhancements, and excipients used in the composition, and body properties of the drug vehicle.

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