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A Review on New Uses of Ketoprofen and Its Role in Clinical Practices.

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Abstract: -
Ketoprofen was synthesized in 1968 and it is belonging to the family of non-steroidal anti-inflammatory drug (NSAIDs) and has analgesic, anti-inflammatory and antipyretic properties. The present review examines the main available clinical evidence of ketoprofen in the treatment of acute and chronic pain, of both rheumatic and traumatic origin, as well as postoperative pain. Ketoprofen was introduced in 1973 in France and the United Kingdom for anti-inflammatory use. Today the drug is available in about 80 countries and has recently been approved in the United States for treatment of rheumatoid arthritis and osteoarthritis. The therapeutic experience with ketoprofen is estimated to have exceeded 3 million patient years. Ketoprofen has a short half-life, a simple metabolism, and a broad therapeutic window, and does not accumulate with multiple doses. These features contribute to a rapid onset of action, flexible dosing, and a reliable tolerance profile.
Keywords: -*Ketoprofen, gastric mucosa, rheumatic arthritis, osteoarthritis.*

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I. Introduction: -

Ketoprofen was synthesized in 1968. It belongs to the family of propionic acid derivatives. The mechanism of action of ketoprofen is inhibits the prostaglandin synthesis by non- specific blocking cyclooxygenase-1(COX-1) and cyclooxygenase-2 (COX-2). COX-1 is responsible for the synthesis of prostaglandin and COX-2 is responsible for the synthesis of pro- inflammatory prostaglandin at the site of inflammation. It is readily distributed into the central nervous system passing the blood brain barrier and inhibiting prostaglandin synthesis in hypothalamus. Ketoprofen is a chiral molecule and only the S- enantiomer has COX inhibiting activity. It is metabolized in liver and is mainly excreted in the urine and to the minor extent, in the feces. It does not accumulate. It is well absorbed after oral and rectal administration. It can be taken in by injection (intravenously, intramuscularly) and trans dermally. It is available as an over the counter drug in the form of 50 mg capsules and as a prescription drug in various pharmaceutical forms: capsules (100mg, 150mg, 200mg), tablets (100mg, 150 mg). suppositories (100mg), gels (25mg/g) and injection solution (50mg/ml).

Side effects of ketoprofen are associated with its effects on COX. Chronic use of ketoprofen includes; headache and drowsiness, depression nervousness, nightmare, sleepiness, cardiovascular reactions (peripheral edema), dermatological problems like photosensitization after topical use and skin sensitization. It causes platelets dysfunction, increase liver enzyme activity, gastro intestinal problems such as vomiting, diarrhea, gastric and duodenal irritation, ulcers, and bleeding. Side effects of ketoprofen include renal impairment, electrolyte imbalance and hypertension. The pain due to sensitisation does not only come from the site of injury, but also from neural messages or impulses. Nerve damage can lead to neuropathic pain, which lasts much longer than the in-jury itself, greatly exceeds a “normal” response to a painful stimulus, and may also spread to other parts of the body. This process plays a major role in the development of chronic pain. The spinal cord mechanism of pain amplification is transmitted to the nociceptive neurons in the dorsal horn through unmyelinated C fibers. The N-methyl-D-aspartate (NMDA) receptors of second-order neurons are activated during the course of the C-fibre transmission of stimuli. This induces calcium entry into dorsal horn neurons (14), which activates nitric oxide (NO) syntheses and leads to NO synthesis. NO can affect nociceptor terminals and enhance the release of sensory neuropeptides(particularly substance P) from presynaptic neu-rons, which contributes to the development of hyperalgesia and the maintenance of central sensitization (14). The presence of several pain inhibitory and facilitatory centers in the brainstem is well recognized.The dorsolateral funiculus appears to be a preferred pathway for descending pain inhibitory systems.Disruption of one or more of the elements of the inhibitory system can result in the equivalent ofcentral sensitization (14).A variety of different mediators may play a role in the pain system. For example, increasing evidence has provided better understanding of the roles

of both immune and pro-inflammatory mediators such as the eicosanoids, bradykinins, serotonin,ATP/ADP, neurotrophins, cytokines, chemokines,and reactive oxygen species (17). These mediators are not exclusive to cells of immune/inflammatory origin, but they are also produced by Schwanncells and spinal glial cells, thereby potentially me-diating the mechanism of neuropathic pain. Mitogen-activated protein kinases (MAPKs) family are important for intracellular signal transduction and play critical roles in regulating neural plasticity and inflammatory responses. Accumulating evidence-shows that all MAPK pathways contribute to pain sensitization after tissue and nerve injury via distinct molecular and cellular mechanisms (18).

NSAIDs play a major role in the management of pain in acute and chronic rheumatic diseases, as well as post-surgical pain, considering the fact that these drugs, unlike paracetamol, are also able to relieve inflammation associated to these types of pain. The well known gastrointestinal-related side effects from NSAIDs can be reduced by careful attention to dose and duration of therapy, and may be prevented and treated by using appropriate therapy in combination with NSAIDs

However, ketoprofen is one of most used non-steroidal anti-inflammatory drugs because of speed and effectiveness of its activity. It is widely used in the management of inflammatory and musculoskeletal conditions, pain, and fever. Scientist are still looking for new uses of ketoprofen. In this study the authors attempt to describe the prospects of new uses of ketoprofen based on medical literature from 2015 onwards to 2021.

Gastrointestinal injury treatment and prevention: -

Ketoprofen lysine salt (KLS) is widely used due to its analgesic efficacy and tolerability. KLS have a higher solubility and a more rapid pharmacological activity, with an analgesic activity after oral administration compared to ketoprofen. Unlike the majority of NSAID's which are acid, KLS has neutral Ph. This feature may explain why manufacturers emphasize its gastroprotective properties.

Camino *et al.* published the result of their study that suggested the gastroprotective effect of KLS on gastric mucosa integrity in 2015. The researcher used monolayers of the human gastric epithelial cell line NCI-N87 and the ethanol gastric injury model. Cells were treated with ethanol 6%, and incubated cell with K or KLS or lysine for 24, 48, 72 hours. Accordingly , cells treated with ethanol presented an evident membrane damage resulting in the loss of tight junctions. Moreover, cells treated with ethanol and Ketoprofen appeared severely damaged with evident loss of tissue integrity, while cells treated with ethanol and KLS appeared preserved by ethanol injury.

The above study was confirmed by Brandling et al. on cell line NCI-N87, in 2018. They used the same approach as Camino *et al.* – the ethanol gastric injury model and incubated cells with K or KLS or lysine for 72 hours. As founded by Branding et al. the ethanol induced severe damage to the gastric mucosa layer at morphological level, while the KLS brought about an evident protection of the epithelium that was not observed with ketoprofen.

In the above-mentioned publications, the researchers attempted to understand the mechanism by which KLS improved the condition of damaged human gastric epithelial cells. The damage induced by ethanol could be attributed to the increase of reactive oxygen species (ROS). ROS plays a key role in the increase of lipid peroxidation products, including 4-hydroxy-2-nonenal(4-HNE) and malondialdehyde (MDA). L-lysine showed a marked antioxidant effect by counteracting ethanol-induced MDA increase in the gastric mucosa layer mode. KLS also counteracted the increase in 4-HNE protein adducts generated by ethanol treatment. The cap analysis showed a marked up-regulation of glutathione S-transferase P (GSTP), known to degrade 4-HNE by KLS.

Further research is needed to be able to use KLS in the presence of gastritis and gastric ulcers in humans. First, a test should be performed using laboratory animals with damaged gastric mucosa. During such an examination, not only the gastric mucosa be carefully examined, but other organs should also be assessed to determine the number of side effects of such KLS treatment. Currently, there is one laboratory animal study on the effect of KLS on damaged gastric mucosa in Wistar rats. Its results reduce the current optimism regarding the positive effects of KLS. In this study, Ketoprofen and KLS had a similar effect on the ethanol-damaged gastric mucosa.

Gemici *et al.* tested the chemo preventative potential of K and ATB-352. ATB-352 are a hydrogen sulfide (H2S)-releasing derivatives of K. The researchers evaluated the effects of K and ATB-352 in a model of precancerous colon cancer lesions in mice. They used 4 groups of 6-8 animals each. In the experiment, daily treatment for two weeks with K (10 mg/kg) or ATB-352 (in equimolar dose) significantly reduced the number of aberrant crypt foci by 40-50%. They also evaluated the chemo preventive effects of K and ATB-352 in Male Pac Min/+ mice- with a genetic defect that predisposes them to intestinal cancer.

Anti-allergic potential: -

The traditional form of K has no anti-allergic properties. Saunas et al. synthesized a novel binuclear μ-oxo diruthenium complex combined with K: [Ru2 O(K)2 (pie)6](PF6)2 where py = pyridine [15], and then used rat basophilic leukemia (RBL-2H3) cells to study mast cell degradation. According to the results of the study, allergens stimulated degradation of mast cells and the new drug inhibited mast cell activation and degradation. In

this study, pretreatment of IgE-sensitized RBL cells with the new drug at (25 µL, 50 µg/mL), followed by cell stimulation with allergen (DNPBSA), showed a strong inhibition of degranulation of mast cells. This RBL cells treatment with K alone (in equimolar dose) did not have this effect. The inhibitory potential of the [Ru2 O(K)2 (pie)6] (PF6)2 against mast cell stimulation suggests its promising application as a therapeutic agent for treating or preventing IgE-mediated allergic diseases. The results also suggest that this molecule shows no allergenic potential and can be safely used for other pharmacological applications besides anti-allergic, but further studies in vivo are needed.

Treatment of nonalcoholic fatty liver disease: -

Nonalcoholic fatty liver disease is due to the excessive fat stored in the liver without clear cause such as alcohol use. The main drugs for the treatment of NAFLD include lipid-lowering drugs, antioxidants, hepatic protectors, insulin sensitizers and anti-inflammatory drugs. Researchers have been investigating multi-targeted treatment NAFLD based on fat reduction, insulin sensitization and inflammation inhibition. For instance, Wang et al. developed a co-assembled nano system based on fenofibrate and ketoprofen and performed an NAFLD inhibition assay in vivo. In their study, they used mice that had been fed with a high-fat diet for 10 weeks (5 groups without information provided how many animals were in each group, of note, the article lacks data on the dose and duration of treatment by fenofibrate and the new drug). These researchers performed histopathological liver examinations using oil, red O, hematoxylin, and eosin staining for evaluation of hepatic lipid accumulation. They also determined the inflammatory factors (IL-1b, IL-6 and TNF-α) in the liver tissue fluid by applying a quantitative real-time polymerase chain reaction. The outcome of this work was that, compared to fenofibrate, the new drug had a better therapeutic effect on NAFLD by reducing hepatic lipid accumulation and inflammatory responses in the liver.

Wang et al. concluded that it could be an effective strategy for fenofibrate delivery and dual-targeted therapy of NAFLD, but clinical studies are needed.

Antidepressant and angiolytic effects: -

Epidemiological studies suggest links between pain, inflammatory response, and depression, and researchers have described a strong correlation between treatment resistant depression and increase in inflammatory cytokines in plasma and cerebrospinal fluid [20].From the first quarter of 2004 to the first quarter of 2017, Makunts et al. ran a retrospective data analysis of 430,783 individual Food and Drug Administration Adverse Event Reporting System (FAERS) and Adverse Event Reporting System (AERS) reports of patients treated for pain to identify potential antidepressant and anxiolytic effects of various anti-inflammatory. Patients treated for depression and patients taking any known antidepressants were excluded. The NSAID group contained 139 072 records and the non-NSAID group contained 291,711 records. Among the NSAID group were 1,534 records of patients who received K. Their work revealed that patients who received K had a decreased number of depression and suicidal behavior reports and a decreased number of anxiety reports [20]. More future prospective clinical trials, however, are needed to evaluate K in treatment of depression and anxiety caused by chronic or acute pain and inflammation. Research is also required to establish treatment and dosing guidelines for K to ensure proper management of pain and inflammation-related depression and anxiety.

Treatment of seizures: -

Many aspects of pathophysiology of epilepsy still remain unknown, but there is a relationship between epilepsy and inflammation. An increase in COX levels has been reported in neurodegenerative diseases such as epilepsy, Parkinson's disease and Alzheimer's disease. Neuronal loss is observed in these diseases and inflammation may be considered to have a significant role in its pathogenesis**.** Eras *et al.* investigated the effects of dexketoprofen in rat models of pentylenetetrazol (PTZ)-induced epilepsy accompanied by EEG records [19]. They used 24 male Sprague-Dawley rats for EEG recording (4 groups with 6 animals each) and 24 for behavioral studies (4 groups with 6 animals each). The Racine convulsion scale (RCS), first myoclonic jerk (FMJ) onset time, and spike percentages were evaluated. As an outcome of the work, the experimenters found that FMJ onset time values were significantly longer, while RCS and Spike percentage values were significantly lower in dexketoprofen given groups (once 20 mg/kg or 40 mg/ kg intraperitoneally). This study showed that dexketo-profen has an anti epileptic feature by increasing epileptic threshold and this effect increases as the dosage increases. Dexketo-profen can be preferred as an administered NSAID to epileptic patients, but clinical trials are needed. Dexketoprofen is the (S)-enantiomer of ketoprofen.

Use in transplantation: -

The micro encapsulation of cells and tissue appears as a promising strategy for the development of allotransplantation or xenotransplantation therapies. The main function of the encapsulation materials is to effect isolation from the host immune response and bidirectional diffusion of molecules essential for cell survival and metabolism. A semipermeable immobilization matrix has been found to offer protection cells against mechanical

stress and deteriorating environmental effects. These combined properties have the potential to enable transplantation of encapsulated nonhuman cells. In 2018, Noverraz et al. described the antifibrotic effect of K-grafted alginate micro capsules in the transplantation of insulin producing cells. The study was carried out on mice and had a follow-up period of 30 days. In the work, the researchers transplanted insulin producing cells in K-grafted alginate microcapsules to evaluated the ability of K to reduce inflammation at the implantation site and prevent pericapsular fibrotic overgrowth. In vitro quantification of K release indicated regular and sustained drug delivery over 14 days. The transplanted material demonstrated a clear reduction in the severity of pericapsular fibrotic overgrowth for microspheres functionalized with K and revealed the significant effect of K release to decrease fibrotic tissue formation. The present study provides a new approach to mitigate fibrotic response to microencapsulated cells transplantation.

Treatment of human lymphedema: -

Lymphedema is a consequence of relative lymphatic vascular insufficiency. In this disease, an imbalance of growth factors occurs due to the presence of persistent tissue inflammation. All forms of lymphedema are characterized by structural changes that include fibrosis of the lymphatic vasculature and surrounding tissues, increased interstitial tissue fluid content, adipose hypertrophy and inflammation. Preclinical investigations in vitro and in vivo strongly suggest that the therapeutic benefit of K in experimental lymphedema is specifically attributable to its inhibition of the 5-lipoxygenase (5-LO) pathway. In 2018, Rockson et al. published the results of a study of K efficacy in humans with lymphedema [18]. This was an open-label pilot study followed by a prospective, randomized, double blind, placebo-controlled exploratory study. Together, 21 patients were enrolled in the open-label trial, and 34 in the placebo-controlled study. Patients aged 18-90 years, with a history of lymphedema of >6 months duration met inclusion criteria. In both trials, the patients in research groups received 75 mg K per os 3 times a day for 4 months. Ketoprofen therapy was found to induce therapeutic architectural remodeling of the diseased skin. Participants in the K groups demonstrated reduced skin thickness, as well as improved composite measures of histopathology and decreased plasma granulocyte CSF (G-CSF) expression. The conclusion was that ketoprofen confers benefit in patients through its upstream inhibition of the 5-LO metabolite, LTB4. The improvement in skin thickness and histology in lymphedema following K treatment is a finding that paves the way for drug therapies of lymphedema, but further and larger clinical trials are needed.

Prospects for the use in oncology: -

In recent years, several studies have been published suggesting the chemo preventive potential of K [14,21-24]. In several diverse types of tumors, researchers found enhanced COX-2 expression. This suggests that COX-2 plays a role in carcinogenics. For this reason, COX inhibitors, including K are suggested for cancer prevention [14,21,22].Ravera et al., in 2019, synthesized a dual-action cis-platin-based Pt (IV) conjugate containing K, and tested this drug for its biological features on a panel of human cancer cell lines [21]. In the work they investigated cells of ovarian endometrioid adenocarcinoma A2780, lung adenocarcinoma A-549, biphasic malignant pleural mesothelioma MSTO-211H, colon carcinoma HCT 116, HT-29 and SW480. According to the outcome of the work, the Pt. (IV)-K complex (concentration 1-5 mM) showed higher antiproliferative activity on the cancer cell lines treated for 72h as compared to cisplatin (concentration 1 mM) and K (concentration 5 mm). In this study, K and the Pt (IV) conjugate containing K inhibited cell growth through a COX-independent mechanism. Most of the biological effects were related to the cisplatin metabolite. The Pt. (IV)-K complex increased the overall lipophilicity and the cellular accumulation of this drug, offered a little additive contribution in terms of gene NAG-1 activation (a member of the transforming growth factor beta (TGF-β) superfamily). The induced expression of NAG-1 correlates with the growth inhibition of cancer cells [21].In 2019, Çoban et al. developed a PEGylated nanocochleate formulation containing imatinib and dexketoprofen (IMA-DEX PEG COH) against □brosarcoma. They also synthesized three similar drugs that were not as effective [23]. In this study, a mouse □brosarcoma model was used and tumor size, histopathology and tyrosine kinase receptor inhibition were assessed after 14 days of treatment with the new drug. Herein, in vivo studies were performed on bro-sarcoma-bearing Blab-C male mice (5 groups of 5 animals each). The drug was designed for oral administration, and the doses were adjusted so that each animal received 4.8 mg imatinib and 0.09 mg dexketoprofen daily. In the IMA-DEX PEG COH group the researchers observed reduction of tumor volume and no neural cell division in the tumor stroma. Moreover, the percentage of healing at the cellular level was the highest compared to the other groups. No lymphocytic in□ltration and no necrotic area were found in the tissues. The IMA-DEX PEG COH group also demonstrated the greatest tyrosine kinase receptor inhibition [23]. More future studies are, however, needed to investigate chemo-therapy resistance and survival rates.Ferreira et al. synthesized a K-loaded pomegranate seed oil nanoemulsion stabilized by pullulan which is a selective antiglioma formulation for intravenous administration [24]. The research was conducted in vitro on the rat malignant glioma (C6) and broblasts cell line (3T3). The new drug presented 40% inhibition of cell growth C6 after 72 h of incubation at two different concentrations (50 and 100 μM) and did not exhibit cytotoxicity action against □broblast 3T3 in a non-transformed cells model. The study demonstrated that the nanostructures increased cell

membrane permeability and caused cell death by necrosis [24]. This is a promising alternative for the treatment of glioma, but further studies in vivo are needed.

Clinical Practices Of Ketoprofen: -

Ketoprofen In Chronic Rheumatic Disorder: -

Osteoarthritis: -

Osteoarthritis is a common disorder of the synovial joints. It is pathologically characterized by focal areas of damage of the articular cartilage,centred on load-bearing areas, associated with new bone formation at the joint margins (osteoporosis),changes in the subchondral bone, variable degree of mild synovitis, and thickening of the joint capsule (37-39). OA is strongly age-related, being less common before 40 years, but rising in frequency with age, such that most people older than 70 years have radio-logical evidence of osteoarthritis in some joints. The clinical problems associated with these pathological and radio graphic changes include joint pain related to use, short-lasting inactivity stiffness of joints, pain on movement with a restricted range, and cracking of joints (crepitus) (40-42). However, the severity of joint disease is only weakly related to that of the clinical problem. Re-cent evidence indicates that peripheral pain sensitization is a feature of the osteoarthritis joint, perhaps mediated by nerve growth factors or cytokines(38). In addition to peripheral pain sensitization,central pain sensitization at the spinal or cortical level can occur in OA (43). Finally, the experience of pain will be modulated by psychological, social, and other contextual factors. Pain in OA,therefore, could be due to local and central sensitization of pain pathways resulting in normal stimuli becoming painful (43). For these reasons all patients should be educated and treated with exercise, but if these measures fail, NSAIDs, physio-therapy, and the use of aids and appliances should be considered very early.In an open-label randomized trial conducted in 113patients with symptomatic hip osteoarthritis, a 4-week treatment with either oral ketoprofen or indomethacin showed a significant efficacy of these drugs in relieving osteoarticular pain, stiffness and in improving quality of life. It is worth noting that ketoprofen resulted in a much better safety profile compared to indomethacin with a lower number of patients with adverse reactions or that withdrew from the treatment (44). Efficacy of oral treatment with KLS has been demonstrated with a significant improvement of pain ($p<0.01$) in patients suffering from OA, with a favourable clinical outcome 67.6% of patients(45). Moreover, analgesic efficacy of acute oral administration of KLS has been shown to be greater than that of acetylsalicylic acid (ASA), with an in-creased circulating plasma levels of beta-endorphin and decreased levels of substance P. These data suggest that the rapidly acting and continuous analgesic activity in OA patients could be related to the effect on beta-endorphin and substance P levels in circulation (46).

Rheumatoid Arthritis: -

Rheumatoid arthritis (RA) is a chronic inflammatory disease that primarily affects the peripheral joints, tissue degradation and the destruction of bone and cartilage (47). It usually presents with pain, stiffness and symmetrical swelling of the small joints of the hands and feet,but may also involve other synovial joints. The incidence of RA is estimated at 4-13 per 100,000 for adult males and 13-36 per 100,000 for adult females. RA has a significant impact on a patient's physical, emotional and social functioning that often occurs very early in the disease. Current therapies target the inflammatory consequences of autoimmune activation with the use of disease modifying anti rheumatic drugs (DMARD) such as methotrexate (MTX) and biologic DMARD (47).The early use of effective DMARDs is a key point in patients at risk of developing persistent and erosive arthritis. Intensive treatment such as combi-nation DMARDs plus steroids or biological therapies can induce a high rate of remission, control of radiological progression and provide better out-come than DMARD mono therapy in early RA and should be considered in patients at risk (48, 49).Systemic glucocorticoids are effective in the short-term relief of pain and swelling and should be considered, but mainly as a temporary therapy as part of the DMARD strategy. Analgesics are used to manage pain in all stages of the disease, often in combination with other therapies to control the inflammatory process. NSAIDs have an immediate effect on pain and stiffness, without influencing the disease process. NSAIDs are more effective than simple analgesics in relieving the signs and symptoms of active dis-ease in established RA (50). These compounds should be used as supplementary therapy and for the shortest possible time. Among these drugs,KLS is a NSAID with favourable anti-inflammatory and analgesic properties and good penetration into joint space. In an open study of one week duration including twenty six patients with RA and persistent knee effusion, it was demonstrated that treatment with KLS and naproxen (NX) resulted in a significant improvement in tenderness and fair,but not significant, relief of the other clinical para-meters (51). Moreover, synovial prostaglandin 2(PGE-2) levels significantly decreased with bothdrugs, with a mild prevalence of KLS compared to NX (62.8% vs 51.7%). In another study involving 34 patients with rheumatic diseases (20 of which were suffering from RA), it was observed that oral treatment with KLS resulted in a significant improvement in pain,with a significant decrease in spontaneous pain($p<0.001$), tenderness, limitation of function and duration of morning stiffness over a 10-day treatment period in all the patients studied (45). More-over, in 10 patients with a persistent knee effusion,KLS was also observed to penetrate into the synovial fluid, causing a marked decrease in PGE-2levels in the rheumatoid knee effusion with a percentage of inhibition of about 73%. These results are

particularly important in elderly patients.

Ketoprofen In Acute Rheumatic And Traumatic Disorder: -

Acute rheumatic and traumatic diseases and soft tissue injuries are often characterized by pain,swelling and inflammation. They include sprains,strains to muscles and ligaments, tendonitis andbursitis, such as the common lateral epicondylitis(tennis elbow) and trochanteric bursitis, regional myofascial pain syndromes, with trigger points similar to those of fibromyalgia but in a localized distribution, low back pain and neurovascular entrapment, such as carpal tunnel syndrome and thoracic outlet syndrome.

Soft tissue injuries: -

The first treatment for most acute soft tissue in-juries (bruises, strains, sprains, tears) is to prevent,stop and reduce swelling (65, 66). For more serious overuse injuries, physical therapy, and complete rest associated with NSAIDs may be necessary. A randomized, double blind clinical trial of oral KLS (80mg/tid) versus placebo including 120 patients with soft tissue disease as tendinitis, bursitis and periarthritis, showed a significant improvement in pain, tenderness and functional limitation with a rapid and appreciable pain relief. Analgesic activity of KLS was already significant just 30 minutes after treatment. Moreover, no patient dropped out due to drug related adverse events and was observed to have an excellent safety profile that was identical to that of the placebo group. In conclusion, the study showed that oral KLS is efficacious and safe in patients with soft tissues diseases (68).Another comparative multi centre study was conducted with the main aim being to evaluate the efficacy and the tolerability of ketoprofen and diclofenac sodium in acute rheumatic and traumatic conditions. One hundred and eighty patients treat-ed with either ketoprofen or diclofenac for 15 days(initially by i.m. injection, then followed by oral ad-ministration) showed an improvement in pain symptoms; in particular, the overall complete pain relief of symptoms was observed in 25% of patients with ketoprofen versus 10% of patients with diclofenac. Ketoprofen was found to be more effective in providing analgesia in most of the conditions studied in the trial compared to diclofenac,with higher number of patients experiencing com-plete pain relief. The study also demonstrated a better tolerability profile of ketoprofen versus diclofenac, rated as excellent-good in a higher percentage of patients.

Low Back Pain: -

Low back pain is one of the most common conditions encountered in clinical practice and medications are the most commonly used type of treatment. Acute low back pain is usually defined as the duration of an episode of low back pain persisting for less than 6 weeks; sub-acute low back pain a slow back pain persisting between 6 and 12 weeks;and chronic low back pain as low back pain persisting for 12 weeks or more. For most patients with low back pain, regardless of the duration of symptoms, paracetamol (acetaminophen) and NSAIDs are the first-line choice for pain relief, as recommended by the APS/ACP and European guidelines (71-73). A systematic review of randomized trials found that NSAIDs were effective for short-term symptom relief, with an average improvement of about8 points (on a 0-100 scale) compared with placebo in patients with acute back pain and about 12points for chronic low back pain (74).Oral and intramuscular administration of ketoprofen have been studied in different clinical trials in patients suffering from lumbago. In a comparative 1-weektreatment study the efficacy and tolerability of intramuscular administration of ketoprofen and indomethacin were evaluated in 115 patients with acute low back pain. In this study ketoprofen was shown to significantly reduce global pain with a more sustained improvement compared to indomethacin. Moreover, it is worth noting that higher percentage of ketoprofen treated patients experienced pain relief in just 1 hour compared to the indomethacin group (61% vs 46.9%). An-other trial involving 155 patients with chronic lumbar pain showed that oral ketoprofen (150 mg/die)demonstrated higher improvement rates 1 week after administration when compared to diclofenac(75 mg/die), and thus, a faster onset of analgesic efficacy (71.4% of patients improved vs 62.36%, respectively).

Gout: -

Gout is an inflammatory arthritic condition affecting 1-2% of adults in the industrialized world that occurs when uric acid crystals accumulate in joints or other tissues (54-56). It is a common and increasingly significant cause of acute and chronic disability and impaired quality of life (57). Gout is frequently characterized by recurrent attacks of acute arthritis and sometimes it can lead to chronic arthropathy depositions, and renal disease. Gout is also associated with a broad range of comorbidity including cardiovascular disease,chronic kidney disease, metabolic syndrome (56).Standard management of acute attacks of gout involves treatment with glucorticoids, NSAIDs and colchicine, which remain the most widely recommended drugs to treat acute attacks (56, 58). These treatments should be started immediately to be most effective and in order to reduce the risk for acute gout flare (59). Several studies have evaluated the effects of ketoprofen in acute gout, showing that intramuscular or oral administration of ketoprofen for 1 week was effective in inducing a rapid and appreciable pain relief in patients with gouty arthritis. In a 7-day multi center double blind trial of oral ketoprofen versus indomethacin; including fifty-nine patients with acute gouty arthritis, more than 90% of the patients reported pain

relief within the 1st day of treatment.At the end of the study, most patients in both groups were rated as having a marked improvement both by both investigators and self-assessment. Moreover, this study concluded that ketoprofen can be expected to provide relief from pain of acute gouty arthritis within 24 hours with similar efficacy but less neurological side effects than the standard drug indomethacin.

Ketoprofen In The Postoperative Setting: -

Therapy with NSAIDs is widely used also in orthopedic clinical practice. They are prescribed in the treatment of osteomuscular pain in both the acute and the chronic phase and provide excellent support in postoperative analgesic therapy. However, the postoperative period in orthopedic surgery is not only characterized by the presence of pain, but also by a series of therapeutic interactions, complications of the bone and soft tissue and orthopedic and physiatric prescription with which these drugs may interact. Opioid drugs are probably recognized as the best drug available in pain management, since they are extremely effective due to their central analgesic action. However, these drugs do cause side effects that are important to be aware of (e.g., respiratory depression, urinary retention, tolerance /dependence, nausea, vomiting and pruritus) which may limit their use and that have led many researchers to seek a viable alternative. NSAIDs, supported by the safe paracetamol and enriched by the introduction of selective COX-2 inhibitors, are in part substituting opioid drugs or, if nothing else, are limiting their use when administered in combination. Among these, ketoprofen has been widely studied in the treatment of postoperative orthopedic pain in both the acute and the chronic phase. Results are presented with regard to the various possible ways of administration, whether intravenous, intramuscular or oral.

Intravenous administration: -

The analgesic efficacy of intravenous ketoprofen was investigated in a study by Castagnera et al.(1988) in 60 patients undergoing orthopaedics surgery detailed as follows: 16 of the spine (disc surgery, spinal stabilization), 15 of the hip (prosthesis and femoral nailing), 15 of the knee (prosthesis, osteotomies, ligament plastics), 14 of the foot and ankle (osteosynthesis or hallux valgus surgery). Patients were treated with ketoprofen (2.5mg /kg) injected at the onset of pain. Pain was measured by Visual Analogic Scale (VAS) and the Five-Item Verbal Rating Scale (VRS). Results showed a reduction in pain intensity greater than 50% after 15 minutes and 85% 2 and 3 hours after injection ($p<0.001$). Maximum analgesia obtained at 120 minutes in knee and hip surgery and 180 minutes in the spine and foot/ankle surgery. The duration of analgesic effect was similar between groups (8.5±1.5 hours). In conclusion, an analgesic effect was observed in 96.6% of cases, meaning that its analgesic activity combined with its anti-inflammatory effect make the intravenous administration of ketoprofen safe and effective in post-operative pain, reinforcing the consciousness that its antalgic effect is not only due to a peripheral action but also to a central effect.

II. Conclusion: -

Ketoprofen is a well-known and widely used substance and this indicates its safety and tolerance. The findings of the review confirm that K, its derivatives, and complexes have many newly discovered effects. This article has described K in the treatment and prevention of gastrointestinal injuries, its antiallergic potential, its possible use in the treatment of nonalcoholic fatty liver disease, human lymphedema and seizures, antidepressant and angiolytic effects, prospect use in oncology and prospects for the use of Ketoprofen in and transplant ology. It is likely that in the future K will have more indications than it is today, but further studies are needed. The studies described in the review are mainly preliminary observations. Each potential new use of K requires additional detailed research. We hope to see this come about in the near future. K is a substance with great potential in medicine.

Ketoprofen can be used safely in elastomeric combination without losing its effectiveness and its anti-inflammatory analgesic effect should not be forgotten, often useful in patients with osteomuscular disorders. Its effectiveness in preventing heterotopic calcification and osteopenia after immobilization has been demonstrated, decreasing in this way the rate of such complications that often delay the functional recovery of the patient. It has been proven to be a safe drug concerning its interaction with bone reparative process both in terms of the phenomena of bone regeneration and for the eventual integration of bone grafts that are often used in traumatology. Based on these clinical evidences, we can conclude that ketoprofen may be a valid treatment option for postoperative pain relief

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