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A REVIEW ON FLUPIRTINE MALEATE & ITS THERAPEUTIC POTENCY

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Abstract: Flupirtine is the first member of a pharmaceutical family of selective neuronal potassium channel openers. It acts centrally, is non-opioid, and has indirect NDMA receptor antagonistic properties. Flupirtine has been shown to lessen chronic musculoskeletal pain, migraines, and other forms of pain, according to research data that hasn't been subjected to large-scale clinical studies.Additional reports include antioxidant, antinociceptive, and neuroprotective effects. The literature on flupirtine that was published between 2003 and 2013 is the focus of this review. The goal was to go through the pharmacological uses of the medicine that had been previously investigated and to concentrate on the areas that still need more investigation.

Keywords **- : Flupirtine, neuroprotective, antinociceptive, antioxidant**

INTRODUCTION-

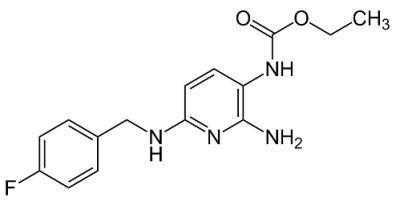
Drugs have been around since the beginning of recorded history. Discovering, developing, and interpreting the molecular action r oute of chemically active substances for physiological purposes is the focus of medical chemistry.The fields of chemistry, bioche mistry, physiology, pharmacology, and molecular modelling are all included.

Synthetic chemicals help create potent treatments and reduce drug toxicity in addition to offering a possibility formedical testing. Analgesics are medications that reduce pain without compromising consciousness.

Without altering the underlying illness, they directly modify pain-related pathways by acting on the central and peripheral nerve systems to relieve pain. The examination of substances for treating both acute and chronic pain is a major challenge in pharmaceutical development. Analgesics and antipyretics do not have a universally recognised categorization. They are separated into two types based on how well they work: non-narcotic analgesics (for treating mild to moderate pain; some also have antipyretic effects), and narcotic/opioid analgesics (for treating severe pain; occasionally may cause dependency). Numerous analgesics are used to treat arthritis and other inflammatory conditions because of their significant anti-inflammatory properties. Most are effective by inhibiting prostaglandin production. Nonnarcotic analgesics, which are often utilised, are extremely problematic at the basic healthcare level. The main categories of analgesics are as follows: COX-2 inhibitors, opiates and morphinomimetics, flupirtine, and certain specialised drugs. For severe chronic pain, such as migraines and gynaecological discomfort, flupirtine acts as an analgesic. It is frequently used for backaches and other orthopaedic conditions because of its muscle relaxant effects. It exhibits neuroprotective properties and may be used to treat conditions including multiple sclerosis, Batten disease, Alzeimer's disease, and Creutzfeld-Jakob disease. One of the negative effects is liver toxicity, which can also have cardiac repercussions on individuals. There are no psychological or reproductive side effects, or any addictive qualities.

Chemical nature and mechanism of action of Flupirtine-

Flupirtine, an aminopyridine, has NMDA receptor antagonist and selective neuronal potassium channel opening characteristics. 10 It primarily functions as a centrally acting non-opioid, non NSAID, and non steroidal analgesic.



Analgesic Effect-

A randomised, double-blind, placebo-controlled research was used to examine flupirtine's effectiveness for treating postcraniotomy pain and compare it to diclofenac sodium. The 390 people (of either sex) having elective craniotomies were split into 3 groups with 130 people each. A placebo was supplied to the control group, while flupirtine capsules and diclofenac tablets, each at dosages of 50 mg and 100 mg, respectively, were administered to the second and third groups. Sedation level, adverse effects, and Visual Analogue Scale score were noted. As 19 patients were dropped, the remaining patients' Visual Analogue Scale Scores for flupirtine

and diclofenac significantly decreased when compared to the control group (p 0.0001). For control, pain alleviation was 69.8%; for flupirtine and diclofenac, it was 90.2% and 90.5%, respectively. There were no discernible differences between the groups in side effects. Consequently, it was discovered that oral flupirtine was just as effective as diclofenac. For the treatment of pedriatic acute migraine and TTH, four triptans and flupirtine have so far received approval. A 5-day study with 113 volunteer patients evaluated the effectiveness of flupirtine maleate 100 mg three times per day and tramadol hydrochloride 50 mg three times per day in the treatment of postoperative pain. . There were 104 of them who satisfied the inclusion criteria and who were then split into two treatment groups. Orally administered tramadol hydrochloride was given to one group, while flupirtine maleate was given to the other. In the flupirtine group, which had effectiveness comparable to that of the tramadol group but far fewer side effects, there was a significant decrease in pain scores (7.4 percent). Thus, it has been discovered that taking both tramadol and flupirtine by mouth can help prevent the negative effects of NSAIDs and opioids. Both morphine (ED50 = 0.74 mg/kg) and flupirtine (ED50 = 3.32 mg/kg) produced dose-related antihyperalgesia at levels that did not result in sedation in a rat model of prostate bone metastases.

There is a synergistic relationship between flupirtine and morphine, and adding flupirtine to morphine enhances its anti-hyperalgesic effects and reverses heat hyperalgesia brought on by cancer. Thus, it was discovered that flupirtine combined with low-dose morphine effectively treated the pain brought on by bone tumours. 4 In a different trial, it was discovered that flupirtine MR 400 mg OD had analgesic effectiveness that was superior to placebo but equivalent to tramadol ER 200 mg OD. Animals are given flupirtine to reduce discomfort while colitis develops because it has been found to be uninterruptive in the onset of inflammatory response. Flupirtine totally reduced the neuropathic pain in a 22-year-old patient's right frontoparietal oligodendroglioma after several unsuccessful attempts with other medications. 17
Flupirtine, at doses of 100 to 400 mg/d, was shown to be more effective than a placebo in treating individuals with subacute musculoskeletal pain. It had a higher tolerability profile with a reduced rate of treatment termination, was as active as the study's comparator drugs, and was as effective. Eight patients were split into two groups, each with a chronic daily headache.
First group of 16 patients received katadolon (flupirtine) at a dose of 300 mg daily for two months.
Velafax (venlafaxine) 75 mg/day was administered to the second group, which consisted of 18 individuals. Patients in the second group reported feeling nauseous, constipated, less hungry, and having trouble paying attention. Patients in the first group, with the exception of one, did not have these symptoms. 209 participants participated in a randomised, double-blind, parallel-group experiment to compare the effectiveness and acceptability of flupirtine and tramadol for the treatment of mild to acute low back pain (LBP) (18-65 yrs age).

Flupirtine 100 mg was administered orally (n = 105) as opposed to. both three times daily over a period of 5-7 days while taking tramadol 50 mg (n = 104). Compared to tramado, flupirtine was shown to be more effective in relieving pain. Mean LBP intensity decreased for flupirtine from 6.8 (95 percent CI: 6.5-7.0) to 2.8 (95 percent CI: 2.3-3.1) and for tramadol from 6.9 (95 percent CI: 6.6-7.1) to 3.0 (95 percent CI: 2.6-3.4), respectively. As a result, pain relief rates of 57 percent (95 percent CI: 51-63 percent) and 56 percent (95 percent CI: 50-62 percent) were discovered, 2. An 8-day, open-label research with 10 palliative care patients who were receiving opioid medication was conducted to evaluate the effectiveness of flupirtine in the treatment of cancer-related neuropathic pain. As a starting dose that may be increased over time, the patients were given 100 mg of flupirtine orally four times per day (QID). Despite the fact that there was no statistically significant change in the overall opioid use, 8 out of 10 patients had some reduction in opioid use, and three of them needed significantly lower doses of opioid when flupirtine was added to their treatment plan, suggesting that flupirtine may be helpful in the treatment of neuropathic pain when used in conjunction with opioids. When administered alone, Leconotide (0.02 mg/kg) and flupirtine (5 mg/kg) reversed hyperalgesia in a rat model of diabetic neuropathic pain by 25.3 +/- 7.6 and -6 +/- 9.5 percent, respectively. Combining the two led to an 84.1 +/- 7.2 percent reversal of hyperalgesia (P 0.01; one-way anova). The two-week flupirtine treatment significantly increased all muscle-specific indicators measured in 30 backache patients, including pain pressure threshold (+48%), pain pressure tolerance (+27%), and depth of penetration in the muscle (+18%), demonstrating flupirtine retard's efficacy as a treatment option for chronic back pain.

Antinociceptive Effect-
Flupirtine, a KCNQ2-3 potassium channel opener, was investigated in rat models under observer blinding for the treatment of pain states characterised by central sensitization both by itself and in conjunction with morphine. The combination of 10 mg/kg flupirtine and 0.4 mg/kg morphine completely reversed the hyperalgesia generated by carrageenan. In the diabetic neuropathy model, morphine (1.6 mg/kg) and flupirtine (10 mg/kg) had extremely substantial antinociceptive effects, completely reversing the hyperalgesia brought on by diabetic neuropathy. Up to a dosage of 20 mg/kg, flupirtine has been reported to raise the paw withdrawal threshold in musculoskeletal pain and has been shown to synergistically improve the immediate antinociceptive effects of opioids like morphine and tramadol.

Europrotective Effect-
Flupirtine decreased contractility and boosted outward currents in scattered bladder smooth muscle in guinea pig gall bladder smooth muscle. When present in a concentration of 20 M, it further hyperpolarized the cell memebrane. 27 Flupirtine (30 M) and retigabine (10 and 30 M), when administered to juvenile rat substantia gelatinosa, exhibited a depressive impact on 4-AP-induced excitement in SG. induced myelinated axons. The motoneurons' refractory time to APB was shortened by two hours in healthy participants when administered APB orally and without a placebo. Flupirtine (20 mg orally) was discovered to lessen the ectopic axonal activity brought on by lower arm ischemia for 10 minutes, as well as the visual analogue evaluations of feelings. It was investigated how flupirtine affected two different kinds of motor neuron-like cells. With a dissociation constant of 9.8 M, NSC-34 neuronal cells showed a decrease in the amplitude of delayed rectifier K(+) current (I(K(DR)) with a concurrent increase in current inactivation, and the inactivation curve was moved towards hyperpolarized potential. The effects of gabazine, NMDA, and linopirdine at concentrations of 10 M, 30 M, and 10 M, respectively, could not be reversed. Cumulative inactivation of I (K(DR)) was increased in the presence of flupirtine. A shift to the left in the activation curve of (K(M)) led to an increase in the amplitude of M-type K(+) current (I(K(M))). Flupirtine decreased I(K(DR)) amplitude and increased I(K(DR)) inactivation rate in NG108-15 neuronal cells.

Thus, it was established that flupirtine inhibits delayed-rectifier K(+) channels in motor neurons by acting as an open-channel blocker. Using an animal model generated in mouse skeletal muscle by 9-AC therapy, the effectiveness of KCNQ openers (retigabine and flupirtine) in mitigating myotonia produced by anthracene-9-carboxylic acid was examined. Retigabine and flupirtine decreased the tetanic fading (20 Hz stimulations) seen in the presence of 9-AC and suppressed the extended twitch length and enhanced twitch amplitude (0.1 Hz stimulation) of skeletal muscle. Therefore, through improving potassium conductance in skeletal muscle, it is suggested that these KCNQ openers may act as a preventative in myotonia induced by 9-AC. 31 According to research, flupirtine inhibits the release of a peptide linked to the calcitonin gene from the rat brainstem in vitro by acting on both GABA(A) receptors and K(V)7 channels. 32,33 K(V)7.2-7.5 channel openers' immediate and long-term effects, such as Retigabine and flupirtine were tested in a rat model of LID using glutamate receptor antagonist amantadine as a positive control to determine their effects on the severity of L-DOPA-induced dyskinesias (LID) and parkinsonian symptoms. Retigabine up to 2.5, 5 mg/kg intravenously and flupirtine up to 5, 10 mg/kg intravenously both lessened the severity of abnormal involuntary movements (AIM) to a degree equivalent to amantadine up to 20, 40 mg/kg intravenously. 34 In guinea pig and human airway smooth muscle cells (ASMCs), the role of Kv7 (KCNQ) voltage-activated potassium channels was investigated. Methacholine (100 nM) or histamine (30 M), bronchoconstrictor agonists, decreased Kv7 currents, while flupirtine (10 M), a Kv7 channel activator, restored them. In carefully sliced human lung slices, histamine-induced airway constriction was dramatically reduced in the presence of flupirtine. 5 Flupirtine's effectiveness in Sprague-Dawley (SD) rat models for recurrent febrile seizures (RFS) was examined. The induction of RFS took place on postnatal day 10 in a warm water bath for eight consecutive days, either with or without the pre-administration of flupirtine or phenobarbital. The rate of febrile seizures reduced and latency rose, with the latter finding being more significant in the group receiving flupirtine. In vitro testing was done to see how flupirtine affected the electrical excitability of myelinated axons in isolated rat sural nerve segments. Low drug concentrations increased threshold current, decreased refractoriness, and increased post-spike superexcitability, demonstrating the drug's effects on excitability parameters that are changed in myelinated axons of individuals with peripheral nerve diseases. Flupirtine's impact on pulmonary hypertension (PAH) in two distinct mouse models was studied, including spontaneous PAH in mice over-expressing the 5-HT transporter (SERT(+) mice) and PAH brought on by hypoxia. An established PAH in SERT(+) mice was reversed by activating the K(v)7 channel, which also decreased the development of chronic hypoxia-induced PAH in mice. This outcome demonstrated that PAH therapy may benefit from using medicines that activate K(v)7 channels. 8 The neuroprotective potential of flupirtine in MS is being investigated as an intriguing possibility. 39 When administered 20 mg/kg i.p. to encephalitis patients, flupirtine has been demonstrated to both reduce cognitive deterioration and have anticonvulsant effects. AVP-sensitive I(Kv), which was resistant to 4-aminopyridine, iberiotoxin, and glibenclamide, was totally reduced by the selective KCNQ channel blockers linopirdine (10 microM) and XE-991 (10 microM), but was boosted by the KCNQ channel activator flupirtine (10 microM). Flupirtine was reported to have a strong antidystonic effect in the dt sz mutant, suggesting that it may be able to treat these illnesses. Retigabine and flupirtine's neuroprotective effects were investigated in rat organotypic hippocampal slice cultures (OHSCs) that had been subjected to N-methylD-aspartate (NMDA), oxygen and glucose deprivation followed by reoxygenation (OGD), or serum withdrawal (SW). The most likely location to experience neurodegeneration brought on by NMDA and OGD was CA1, and exposure to SW by OHSCs caused selective cell death in the dentate gyrus (DG). Retigabine (IC50: 0.4 microM) and flupirtine (IC50: 0.7 microM) stopped DG neuronal mortality brought on by SW, although NMDA antagonist MK-801 (IC50: 10-30 microM) failed to do so. Additionally, retigabine and flupirtine (0.1–10 M) also had IC50 values of about 1 M for reducing SW-induced ROS generation in the DG. 44

Flupirtine-maleate was discovered to be able to stop the TRAIL-mediated death of total CNS cells and neurons in a live human brain slice culture system.
45 In CJD patients, flupirtine was proven to be beneficial at protecting cognitive skills.

Effect on subacute sclerosing panencephalitis-
Subacute sclerosing panencephalitis (SSPE) is a condition that manifests in patients as a frontotemporal cortex volume loss, delayed measles virus infection, and apoptotic cell death. Combining antiviral medication with the anti-apoptotic drug flupirtine, which is used to treat prion illnesses, Alzheimer's disease, and neuronal ceroid lipofuscinosis, has been proposed as a treatment for the illness.

Antioxidant Effect-
Investigated were the antioxidant capabilities of flupirtine in relation to oxidant-induced damage to retinal photoreceptors. Attenuating lipid peroxidation brought on by sodium nitroprusside was the focus of early in vitro research on brain membranes, which showed flupirtine to be around 20 times more effective than trolox (a vitamin E analogue) and 8 times more effective than metipranolol (SNP). The only retinal cell types that were visibly impacted by an intraocular injection of SNP were the retinal photoreceptors. Flupirtine was shown to be a potent antioxidant that dramatically attenuated the negative effects of SNP on retinal proteins and mRNAs, demonstrating its effectiveness in treating retinal photoreceptor damage.
Effect on tinnitus perception-
Flupirtine was found to be an efficient antioxidant that significantly reduced the detrimental effects of SNP on retinal proteins and mRNAs, supporting its use in the treatment of retinal photoreceptor damage. An open prospective design was used to administer oral flupirtine at a dose of 2 x 100 mg daily to the participants for 3 weeks. The only patient who shown some good indicators up to 4.2 percent but stopped therapy owing to forgetfulness and attention issues did not exhibit a beneficial effect on VAS or TQ.

CONCLUSION-
Analgesic flupirtine has shown to be effective in the treatment of a wide range of illnesses and conditions and may continue to do so. Flupirtine should be investigated as an adjunct analgesic with opioids for the therapy of pain states including central sensitization. Over the past ten years, much research has been done on the drug's analgesic and neuroprotective benefits. The impact of neurodegenerative illnesses on tinnitus perception has to be clarified, and research in this area needs to be expanded. Pharmacology will experience a miracle by investigating its therapeutic potential in several different medicinal applications.

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