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Review Article

Flupirtine: A Review on its Therapeutic Potency

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ABSTRACT

Flupirtine is a centrally acting non-opioid analgesic displaying indirect NDMA receptor antagonism and is the first representative of a pharmacological class of selective neuronal potassium channel openers. Clinical trials on large scale are missing but the data gathered so far by experimentation has proved flupirtine to reduce chronic musculoskeletal pain, migraine and other types of pain. Neuroprotective, antinociceptive and antioxidant properties have also been reported. This review paper is aimed to cover literature of flupirtine dating from 2003-2013. The objective was to cover the pharmacological applications of the drug studied so far and focus on the areas need to be explored more.

Keywords: Flupirtine, neuroprotective, antinociceptive, antioxidant.

INTRODUCTION

Drug discovery began from the origin of mankind.[1] Medicinal chemistry includes the sciences of chemistry, biochemistry, physiology, pharmacology, molecular modeling and is concerned with the discovery, development and interpretation of the action path of biologically active compounds at molecular level.[2] The synthetic compounds not only offer an opportunity to medicinal screening but also help design potent drugs and reduce drug toxicities.[3] Analgesics are referred to as drugs which relieve pain without consciousness loss.[4] They act on the central and peripheral nervous systems and cause pain relief by directly affecting pain related path ways without changing the underlying pathology. In pharmaceutical research, the investigation of compounds for treating both acute and chronic pain is a great challenge.[5] In 90% of diseases, from simple backache to varying types of cancer, pain is a common problem. The main classical therapies for pain use the non-steroidal anti-inflammatory drugs (NSAIDs) and opiates, whose main compounds (acetylsalicylic acid and morphine) were isolated in 19th century.[6] No internationally agreed upon classification is there of analgesics/antipyretics. Depending upon their efficacy, they are divided into two groups; Non-narcotic analgesics (for treating mild to moderate pain, some having antipyretic actions) and narcotic/opioid analgesics (for treating severe pain and may sometimes produce dependence). Many analgesics, being potent against inflammation, are used against arthritis and other inflammatory problems. Most show their effectiveness by prostaglandin synthesis inhibition. Being widely used, nonnarcotic analgesics are of major concern at the primary health-care level. The major classes of analgesics are: Paracetamol and NSAIDs, COX-2 inhibitors, Opiates and morphinomimetics, Flupirtine and some specific agents. Flupirtine works as an analgesic for severe chronic pain like migraines and gynaecology. Due to its muscle relaxant properties it is widely used for backache and other orthopaedic purposes. It has neuroprotective characteristics and has possible applications in multiple sclerosis, Batten disease, Alzeimer's disease and Creutzfeld- Jakob disease.[7-9] Liver toxicity and cardiac effects in patients are some of the side effects. It is free of addictive properties, psychological effects or effects on reproductive system.

Chemical nature and mechanism of action of Flupirtine

Flupirtine, being aminopyridine, functions as a selective neuronal potassium channel opener having NMDA receptor antagonist properties as well.[10] It is basically a non-opioid, non-NSAID and non-steroidal analgesic that acts centrally.
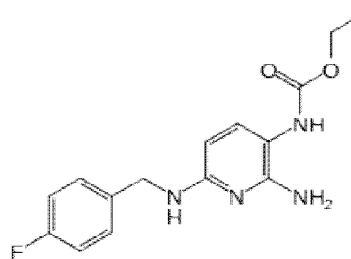

Figure 1: Structure of Flupirtine

Analgesic Effect

The role of flupirtine for postcraniotomy pain and its comparison with diclofenac sodium was carried out by randomized, double-blind, placebo-controlled study. The individuals (390 of either sex) undergoing elective craniotomy were divided into 3 groups comprising 130 individuals in each group. The control group was given placebo, whereas, the second and third group received diclofenac tablet and flupirtine capsule in the dosage of 50 mg and 100 mg, respectively. Level of sedation, side effects and Visual Analogue Scale score was observed.

After dropping 19 patients, the remaining patients showed significant reduction of Visual Analogue Scale Score in flupirtine and diclofenac as compared to control (p<0.0001). Pain relief was 69.8% for control and 90.2% and 90.5% for flupirtine and diclofenac, respectively. Side effects did not show any significant differences among the groups. Hence, oral flupirtine was proved to be equally effective as diclofenac.[11] Up till now, four triptans and flupirtine have been approved for the treatment of pedriatic acute migraine and TTH.[12] The efficacy of flupirtine maleate 100 mg thrice daily was compared to tramadol hydrochloriode 50 mg thrice daily in postoperative pain management for a period of 5 days by taking 113 volunteer patients. Out of them, 104 met the inclusion criteria and were further divided into two treatment groups. One group received flupirtine maleate orally whereas the other received tramadol hydrochloride orally. Significant reduction in pain score was found in the flupirtine group having equal efficacy to tramadol group but much less adverse effects were seen (7.4%). Hence, oral administration of both tramadol and flupirtine was found to be helpful in avoiding the adverse effects of opioids and NSAIDs.[13] In a rat model of prostate bone metastasis, both morphine (ED_{50} = 0.74 mg/kg) and flupirtine (ED_{50} = 3.32 mg/kg) caused dose-related anti-hyperalgesia at doses that did not cause sedation. Synergism was noted between flupirtine and morphine and addition of flupirtine to morphine improved morphine anti-hyperalgesia and reversed cancer-induced heat hyperalgesia. Hence, flupirtine in combination with low dose morphine was proved to manage pain caused by tumors growing in bone.[14] In another study, the analgesic efficacy of flupirtine MR 400 mg OD was found comparable to tramadol ER 200 mg OD but superior to that of placebo.[15] Flupirtine has been reported to be uninterrupting in the induction of inflammatory response, so animals are treated with flupirtine to relieve pain during colitis development.[16] In a postoperative case of right frontoparietal oligodendroglioma of a 22 year old, flupirtine completely subsided the neuropathic pain, after a number of trials with other drugs.[17] In patients suffering from sub-acute musculoskeletal pain, flupirtine was found to be superior to placebo at dosages of 100 - 400 mg/d. It was as active as the comparators used in study and showed a superior tolerability profile with lower treatment discontinuation rate.[18] Patients having chronic daily headache were divided into two groups. First group consisting of 16 patients was given katadolon (flupirtine) in dosage of 300 mg per day during 2 months. The second group comprising of 18 patients was given velafax (venlafaxine) in dose 75 mg per day. The second group patients experienced nausea, constipation, less appetite and impairment of attention. First group patients did not experience these symptoms except one patient.[19] The efficacy and tolerability of flupirtine in comparison with tramadol in moderate to acute low back pain (LBP) was analyzed by randomized, double-blind, parallel-group trial by taking 209 patients (18-65 yrs age). They were orally given flupirtine 100 mg (n = 105) vs. tramadol 50 mg (n = 104), both three times daily for a period of 5-7 days. Flupirtine proved to be more efficient in pain relieve as compared to tramadol. Mean LBP intensity dropped from 6.8 (95% CI: 6.5-7.0) to 2.8 (95% CI: 2.3-3.1) for flupirtine and from 6.9 (95% CI: 6.6-7.1) to 3.0 (95% CI: 2.6-3.4) for tramadol, hence, pain relief rates of 57% (95% CI: 51-63%) and 56% (95% CI: 50-62%) respectively (p = 0.796) were found indicating superiority of flupirtine.[20] The efficacy of flupirtine in the treatment of cancer-related neuropathic pain was assessed by an 8 day, open-label study of 10 palliative care patients despite opioid treatment. The patients were given initially 100 mg flupirtine orally four times daily (QID) that could be titrated. There was no statistically significant change in overall opioid use but 8/10 patients had some reduction in opioid use and three of those required substantially reduced doses of opioid when flupirtine was added to their treatment regime, hence, suggesting that flupirtine may be useful in the treatment of neuropathic pain when used in combination with opioids.[21] In a rat model of diabetic neuropathic pain, Leconotide (0.02 mg/kg) and flupirtine (5 mg/kg) caused 25.3 +/- 7.6 and -6 +/- 9.5% reversal of hyperalgesia, respectively when given alone. In combination 84.1 +/- 7.2% reversal of hyperalgesia was observed (P < 0.01; one-way anova).[22] In 30 patients with backache, the two-week treatment with flupirtine improved all measured muscle-specific indicators: pain pressure threshold (+48%), pain pressure tolerance (+27%) and depth of penetration in the muscle (+18%) significantly, hence, proving flupirtine retard as an effective option for chronic back pain treatmenet.[23]

Antinociceptive Effect

Flupirtine, being a KCNQ2-3 potassium channel opener, was tested in rats in an observer-blinded fashion for treating pain states characterized by central sensitization with flupirtine alone and in combination with morphine. Complete reversal of carrageenan-induced hyperalgesia was caused by 10 mg/kg flupirtine with 0.4 mg/kg morphine. In the diabetic neuropathy model, morphine (1.6 mg/kg) with flupirtine (10 mg/kg) caused highly significant antinociceptive effects resulting in complete reversal of hyperalgesia due to diabetic neuropathy.[24] Flupirtine has been proved to enhance, in a synergistic manner, the acute antinociceptive effects exerted by opioids like morphine and tramadol and has been found to increase paw withdrawal threshold in musculoskeletal pain up to a dosage of 20 mg/kg.[25,26]

Neuroprotective Effect

In guinea pig gall bladder smoothnmuscle, flupirtine inhibited the contractility and increased outward currents in dispersed bladder SMC. It further hyperpolarized the cell memebrane at the concentration of 20 µM.[27] In immature rat substantia gelatinosa, flupirtine (30 µM) along with retigabine (10 and 30 µM), had a depressant effect on 4-AP-induced excitation in SG.[28] Flupirtine up to the dosage of 3-30 µM shortened the relative refractory period and increased superexcitability in human

myelinated axons in vitro. When given orally, without placebo, the refractory period of motoneurons to APB was reduced by 2 hours in healthy subjects. Flupirtine (20 mg p.o.) was found to reduce ectopic axonal activity induced by 10 min of lower arm ischemia and visual analogue ratings of sensations were reduced.[29] Effect of flupirtine in two types of motor neuron-like cells were examined. Decrease in the amplitude of delayed rectifier $K(+)$ current $(I(K(DR)))$ with a concomitant raise in current inactivation in NSC-34 neuronal cells was observed with a dissociation constant of 9.8 µM and its inactivation curve was shifted towards hyperpolarized potential. Linopirdine, NMDA and gabazine at concentration of 10 µM, 30 µM and 10 µM, respectively, could not reverse these changes. In the presence of flupirtine, cumulative inactivation of $I(K(DR))$ was elevated. The amplitude of M-type $K(+)$ current $(I(K(M)))$ was increased with a leftward shift in the activation curve of $(K(M))$. In NG108-15 neuronal cells, flupirtine reduced $I(K(DR))$ amplitude and the inactivation rate of $I(K(DR))$ was enhanced. Hence, it was shown that flupirtine acts as an open-channel blocker of delayed-rectifier $K(+)$ channels in motor neurons.[30] The effect of KCNQ openers (retigabine and flupirtine) in preventing myotonia caused by anthracene-9-carboxylic acid was investigated by using an animal model elicited in murine skeletal muscle by 9-AC treatment. Retigabine and flupirtine inhibited the increased twitch amplitude (0.1 Hz stimulation) along with prolonged twitch duration of skeletal muscle and reduced the tetanic fade (20 Hz stimulations) observed in the presence of 9-AC., hence, suggesting these KCNQ openers as preventive in myotonia induction by 9-AC by enhancing potassium conductance in skeletal muscle.[31] Flupirtine has been found to imply its analgesic action by acting on both GABA(A) receptors and K(V)7 channels and has been found to inhibit calcitonin-gene related peptide release from rat brainstem in vitro.[32,33] The acute and chronic effects of K(V)7.2-7.5 channel openers i.e. retigabine, flupirtine on the severity of L-DOPA-induced dyskinesias (LID) and parkinsonian signs were examined in a rat model of LID taking glutamate receptor antagonist amantadine as positive control. Retigabine up to 2.5, 5 mg/kg i.p. and flupirtine up to 5, 10 mg/kg i.p. reduced the severity of abnormal involuntary movements (AIM) to a comparable extent as amantadine given up to 20, 40 mg/kg s.c.[34] Function of Kv7 (KCNQ) voltage-activated potassium channels in guinea pig and human airway smooth muscle cells (ASMCs) was explored. The bronchoconstrictor agonists methacholine (100 nM) or histamine (30 µM) suppressed Kv7 currents, but, were restored by Kv7 channel activator, flupirtine (10 µM). Constriction of airways, in precision-cut human lung slices, by histamine was also significantly reduced in the presence of flupirtine.[35] The efficacy of flupirtine in repetitive febrile seizures (RFS) Sprague-Dawley (SD) rat models was tested. RFS was induced at postnatal day 10 in a warm water bath for consecutive 8 days with or without the pre-administration of flupirtine or phenobarbital. Latency was increased and rate of febrile

seizures was decreased, the result being more significant in case of flupirtine treated group.[36] The effect of flupirtine on the electrical excitability of myelinated axons in isolated segments of rat sural nerve was examined in vitro. Low concentrations of the drug resulted in an increase in threhold current, a reduction of refractoriness and an increase in post-spike superexcitability, therefore, proving its effects on measures of excitability that are altered in the myelinated axons of patients with peripheral nerve disorders.[37] The effect of flupirtine on pulmonary hypertension (PAH) in two independent mouse models i.e. PAH induced by hypoxia and spontaneous PAH in mice over-expressing the 5-HT transporter (SERT(+) mice) was investigated. Development of chronic hypoxia-induced PAH in mice was attenuated and established PAH in SERT(+) mice was reversed via K(v)7 channel activation. This result provided evidence that drugs activating K(v)7 channels can be of benefit in the treatment of PAH.[38] Flupirtine is considered as an interesting candidate for evaluation of its neuroprotective potential in MS.[39] Flupirtine has been proved to slow down cognitive decline and has also been shown to have anticonvulsant action in patients of encephalitis at dosage of 20 mg/kg i.p.[40,41] In one investigation, the AVP-sensitive I(Kv) being resistant to 4-aminopyridine, iberiotoxin and glibenclamide was inhibited completely by the selective KCNQ channel blockers linopirdine (10 microM) and XE-991 (10 microM) but enhanced by the KCNQ channel activator flupirtine (10 microM).[42] Pronounced antidystonic activity of flupirtine was found in the dt sz mutant making it liable to help improve these disorders.[43] Neuroprotective effect of retigabine and flupirtine was studied in rat organotypic hippocampal slice cultures (OHSCs) exposed to N-methyl-D-aspartate (NMDA), oxygen and glucose deprivation along with reoxygenation (OGD) or serum withdrawal (SW). The most probable susceptible region to NMDA and OGD-induced neurodegeneration was CA1 and selective cell death in the dentate gyrus (DG) was due to OHSCs exposure to SW. Retigabine (0.01-10 µM) and flupirtine (0.01-10 µM) prevented DG neuronal death induced by SW, their with IC50 s being 0.4 microM and 0.7 µM, respectively, whereas, NMDA antagonist MK-801 (10-30 microM) failed to do so. Moreover, both retigabine and flupirtine (0.1-10 µM) reduced SW-induced ROS production in the DG with IC50 s of approximately 1 µM.[44] In a living human brain slice culture system TRAIL-mediated death of total CNS cells and neurons was found to be prevented by flupirtine-maleate.[45] Flupirtine was found to have protective effective on cognitive functions in patients with CJD.[46]

Effect on subacute sclerosing panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a disease with symptoms of slow measles virus infection, apoptotic cell death and volume reduction in frontotemporal cortex in patients at early stages of disease. Flupirtine being an anti apoptotic agent and used in Alzheimer disease, prion diseases and neuronal ceroid lipofuscinosis has been

hypothesized to be a remedy for the disease in combination with antiviral therapy.[47]

Antioxidant Effect

Antioxidant properties of flupirtine in relation to oxidant-induced damage to retinal photoreceptors were investigated. Initially in vitro studies on brain membranes revealed flupirtine to be approximately 20 times more efficient than trolox (vitamin E analogue) and 8 times more effective than metipranolol at attenuating lipid peroxidation caused by sodium nitroprusside (SNP). Following an intraocular injection of SNP, retinal photoreceptors were the only retinal cell types that were clearly affected. Co-injecting flupirtine significantly blunted the effects to the retina caused by SNP on retinal proteins and mRNAs, hence, proving flupirtine to be a powerful antioxidant attenuatimg the detrimental influence of SNP to retinal photoreceptors.[48]

Effect on tinnitus perception

The effect of flupirtine on tinnitus perception was investigated by taking 24 patients. Loudness visual analogue scale (VAS) and tinnitus questionnaire (TQ) was used to assess the burden of tinnitus. The patients were treated with a 2 x 100 mg daily dosage of oral flupirtine for a period of 3 weeks in an open prospective design. No positive effect on VAS and TQ was shown except one patient showed some positive signs up to 4.2% but due to amnesia and concentration disorders discontinued the treatment.[49]

CONCLUSION

Flupirtine is an analgesic with many potential therapeutic benefits that has proved and may prove useful in the treatment of many diseases and ailments. In the past decade considerable work has been done on the analgesic and neuroprotective effects of the drug but flupirtine should be explored as an adjunct analgesic also with opioids for the management of pain states involving central sensitization. Studies need to be increased in the field of neurodegenerative disorders and its effect on tinnitus perception needs to be cleared. Exploring its therapeutic potency in many other medical applications will prove miracle in pharmacology.

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