

Flupirtine: Clinical pharmacology

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Abstract

Flupirtine is neither an opioid nor a non steroidal anti-inflammatory drug (NSAID) producing its analgesic action through blockade of glutamate N-methyl-D-aspartate receptor. It is devoid of adverse effects of routinely used analgesic drugs, but is equally efficacious in reducing pain sensation. It has a distinctive mechanism of action, exerting a dual therapeutic effect with both analgesic and muscle relaxant properties that has utility in the treatment of pain, including that associated with muscle tension.

Key words: Flupirtine, N-methyl-D-aspartate receptor, non-steroidal anti-inflammatory drug, opioids

Introduction

Pain is the most miserable symptom of disease presentation. Treatment of this noxious sensation is a challenge for clinicians. There are a number of medications available for the treatment of pain such as non-steroidal anti-inflammatory drugs (NSAID), opioids, and their derivatives. Flupirtine is in use for the last 25 years for the management of pain following surgery, trauma, dental extraction, pain associated with muscle spasm, cancer, degenerative joint diseases, and conditions such as headache and dysmenorrhoea in Europe. It is a nonopioid, non-NSAID analgesic, and is devoid of common adverse effects seen with NSAIDs and opioids. Additional effects identified include muscle relaxation, neuroprotection, and antiapoptotic action. Although it is not yet approved by United States Food and Drug Administration (US FDA), it is still used in many countries including India. Recently, US FDA granted permission to carry out phase II clinical trial with flupirtine for the treatment of fibromyalgia.

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Chemistry

Flupirtine is a triaminopyridine derivative having a chemical structure - 2-amino-3-ethoxy-carbonylamino-6-(4-fluorobenzylamino)-pyridine [Figure 1]. The basic molecule used for synthesis of flupirtine was 2, 6-dichloro 3-nitropyridine.^[1] It was first synthesized in 1980s in Germany and was marketed by Degussa Pharma.^[2]

Pharmacodynamics

Analgesic action

Flupirtine was introduced as an alternative analgesic to opioids and NSAIDs. Subsequently, multiple other actions such as muscle relaxation and neuroprotective activity were identified. Flupirtine acts indirectly as N-methyl-D-aspartate (NMDA) receptor antagonist by activation of K⁺ channels.^[3] Flupirtine causes a dose-dependent reduction of NMDA receptor mediated glutamate induced rise in intracellular Ca⁺⁺ concentration.^[4] It binds to and activates G- protein coupled inwardly rectifying K⁺ channels. Activation of this channel leads to hyperpolarization of neuronal membrane and the neuron becomes less excitable; thus, there is stabilization of resting neuronal membrane.^[5] The drugs activating this

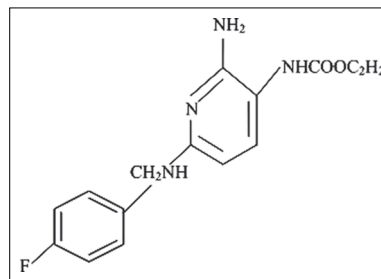


Figure 1: Structure of flupirtine

channel are called as selective neuronal potassium channel openers (SNEPCO) and flupirtine is the prototype.^[3] Experimental evidence suggests that flupirtine might suppress channel opening by acting as an oxidizing agent at the redox site of the NMDA receptor.^[6] This action inhibits the transmission of nociceptive impulses during neuronal excitation.

Muscle relaxant action

The muscle relaxation is due to inhibition of both mono- and polysynaptic reflexes. The spinal polysynaptic flexor reflex, mediated by NMDA receptors, was depressed by flupirtine, whereas the monosynaptic Hoffmann reflex (H-reflex), mediated by non-NMDA receptors, was not influenced.^[7] Healthy human subjects responded with a significant reduction of both the early phase of the electrically elicited polysynaptic flexor reflex of pretibial muscles and the medium latency response of the toe-up paradigm after 2 h of 200 mg of flupirtine. Flupirtine possesses analgesic as well as muscle-relaxing effect in same dose ranges; thus, it can be used in the treatment of painful diseases of the motor system presenting with spasticity and chronic musculoskeletal pain.^[8]

Neuroprotective action

Apoptosis, a programmed cell death, is caused by increased intracellular Ca^{++} levels, mitochondrial dysfunction, cell membrane disruption, and finally, nucleolysis. *In vitro* studies with primary cortical neurons from rat embryos have shown that lead acetate, prions like PrP^{sc}, HIV coat protein gp120, and β amyloid peptide will cause apoptotic cell death. But if preincubated with flupirtine, it completely protects apoptotic cell death caused by above agents in the neurons.^[2] It has been found that flupirtine also antagonizes both glutamate and NMDA induced increase in intracellular levels of Ca^{++} , as observed in *in vitro* cultures of cortical and hippocampal neurons.^[9]

The expression of Bcl-2, an antiapoptotic agent, and glutathione, a scavenger of reactive oxygen, are reduced during glutamate or NMDA-induced apoptosis in cells. Flupirtine is found to increase the levels of Bcl-2 and glutathione in glutamate or NMDA-induced apoptosis of human Ntera/D₁ (hNT) neurons as well as cultured retinal pigment cells.^[2,5] Flupirtine reduced the expression of oncogenes and formation of reactive oxygen radicals in experimental models which explains its action of preventing ischemia-induced apoptosis. This explains the role of flupirtine in future for treatment of neuroinfections such as immune deficiency syndrome (AIDS), prion diseases, and neurodegenerative disease such as Alzheimer's.^[3]

Antiparkinsonian action

Flupirtine has an NMDA receptor antagonistic action and

hence it was studied for its antiparkinsonian effect as an adjuvant to L-3,4-dihydroxyphenylalanine (L-DOPA). Akinesia and muscular rigidity were produced in rats by giving reserpine and α methyl p-tyrosine. Flupirtine was given alone and in combination with L-DOPA, it strongly reduced muscle rigidity and increased the ability of L-DOPA to reverse akinesia.^[10]

In haloperidol-induced catalepsy, which is considered as a model of Parkinson's disease, flupirtine alone and in combination with L-DOPA exerted a potent anticataleptic effect.^[7,10] However, human studies are not available till date to support this evidence. If studies are done to prove effectiveness in Parkinson's disease, it can be combined with L-DOPA.

Pharmacokinetics

Absorption

Flupirtine is a hydrophilic compound. It is completely absorbed from gastrointestinal tract with a bioavailability of 90% by oral route and 70% by rectal route.^[11] 100 mg of oral flupirtine in normal healthy volunteers reached a peak plasma concentration of 773 μ g/L at 1.6 h and rectal administration 890 μ g/L. Steady-state concentrations were achieved after 2 days in four healthy volunteers who received 75 mg of flupirtine orally at 12 h intervals.^[12]

Distribution

Flupirtine has large volume of distribution (Vd) and gets equally distributed into both extra and intravascular compartments. Vd of 100 mg flupirtine is 154 L, 212 L, and 195 L in healthy volunteers, patients with renal impairment, and elderly patients, respectively.^[2,11] Flupirtine is 80–84% bound to human albumin. Concentration in CSF is same as that in plasma and higher concentration was observed in liver and exocrine glands, whereas lower concentration was observed in the kidney.^[12] The half-life of flupirtine on oral, intravenous, and rectal administration with 100 mg is 6.5, 8.5, and 10.7 h, respectively, in healthy volunteers. The clearance of 100 mg of flupirtine after oral administration is 275, 263, and 161 ml/min in healthy volunteers, renal impairment patients, and elderly people, respectively.^[2,11]

Metabolism and elimination

Flupirtine is metabolized in liver to 4-Fluorhippuric and N-acetylated analogue D13223 by peroxidase enzymes [human myeloperoxidase and horse radish peroxide (HRP)]. The N-acetylated metabolite D13223 retains 20–30% of activity of its parent compound. The two metabolites are further oxidized and then conjugated with glycine to form inactive metabolites.^[1,13] 72% of the total dose administered appears in urine as parent drug and its metabolites, whereas 18% is excreted in feces.^[14]

Dosage and formulation

Flupirtine can be administered by oral and rectal routes. It is available as 50 and 100 mg for oral administration. Adult dose is 300–400 mg per day and can be increased to 600 mg per day. Dose in children is 150–200 mg per day in 3–4 divided doses.^[1,2,15] Rectal suppositories are administered in the dose range of 450–600 mg per day in adults and 150–250 mg per day in children.^[15] In India, it is being marketed under the trade name KETADOL as 100 mg tablet (Lupin Pharmaceuticals). Drug Controller General of India (DCGI) has approved flupirtine maleate 100 mg for treatment of acute and chronic pain, i.e., for painful increased muscle tone of the posture and motor muscles, primary headache, tumor pain, dysmenorrhea, and pain after trauma/orthopedic operations and injuries.^[16]

Special group

Safety of flupirtine in pregnant, lactating women, and children less than 6 years is not established. If indicated in lactating women, breastfeeding should be stopped. Dose of flupirtine should be reduced to 50% in elderly patients and those with renal and hepatic impairment.^[1,15]

Drug interactions

Flupirtine has shown to increase warfarin toxicity but the mechanism is not clear; hence, patients on oral anticoagulant therapy should be monitored for prothrombin time. It also increases hepatotoxic potential of paracetamol; thus, hepatic transaminases levels should be monitored when both the drugs are given concomitantly. Alcohol and other sedatives including benzodiazepines potentiate tiredness and dizziness due to flupirtine.^[15] Coadministration with carbamazepine is not advisable as carbamazepine induces hepatic enzymes. Not much information is available regarding interaction with other drugs.

Contraindications

Flupirtine is avoided in patients with history of hypersensitivity to flupirtine, hepatic encephalopathy, cholestasis, myasthenia gravis, chronic alcoholism, primary biliary cirrhosis, and liver disease.

Uses

Musculoskeletal pain

Flupirtine has been compared with placebo and standard analgesics to determine the analgesic efficacy and tolerability. A post marketing surveillance of flupirtine 200–300 mg/day for 1 week has shown improvement in response rate as assessed by visual analogue pain scale. It was observed that the response rates were 94%, 89.4%, and 85.9% for patients with acute, subacute, and chronic pain, respectively.^[1,17] A randomized, double blind study revealed that flupirtine 300 mg/day was as

effective as tramadol 150 mg/day in reducing subacute low-back pain.^[18] Comparative studies with diclofenac 150 mg/day has also shown that flupirtine 300 mg/day significantly reduced postoperative pain equally. The pain reduction was significant after 60 min of oral administration of both the drugs.

Headache

Patients who had insufficient response to conventional analgesics for chronic tension headache showed better response to flupirtine.^[17] Comparative studies of flupirtine 100 mg three times daily with that of placebo in chronic headache of 2 weeks have shown significant reduction in pain intensity.^[1,17] In acute migraine attacks, flupirtine 100 mg has shown better efficacy in terms of pain relief, restriction in working ability with less adverse effects when compared to paracetamol 1 gm orally.

Neurogenic pain

Flupirtine 380 mg/day was found to be effective in reducing lumbar and cervical spinal root pain in comparison with aspirin 1800 mg/day. The study also showed that 25% of flupirtine-treated patients reported no pain and 46% reported improvement, but in those who received aspirin only 35% reported an improvement.^[1,19]

Cancer pain

Studies have shown that flupirtine reduced cancer pain more effectively than tramadol and pentazocine. Also, the adverse reaction profile was similar in both flupirtine and tramadol treated patients.^[20] But, with an increased incidence of central nervous system (CNS) side effects to pentazocine when compared with flupirtine.^[21]

Fibromyalgia

Flupirtine has been found to reduce the pain of fibromyalgia better than other available drugs. ADEONA, a pharmaceutical company, was granted permission by US FDA to conduct randomized, double blind, placebo-controlled phase II clinical trial of flupirtine in Fibromyalgia syndrome.^[21]

Postoperative pain

Pain during postoperative period is most distressing to the patient. Flupirtine is found to have better analgesic effect with minimal side effects compared to standard drugs. In postepiostomy pain, flupirtine showed 69% reduction in pain score 6 h after administration when compared to placebo which had only 26% reduction. Flupirtine also had greater efficacy in postepiostomy pain reduction when compared to suprofen and paracetamol.^[22]

A parallel group control study comparing flupirtine with diclofenac was done in 40 orthopedic patients to evaluate the

Table 1: Comparison of flupirtine with opioids and NSAIDs

	Flupirtine	Opioids	NSAIDs
Mechanism of action	Activates inwardly rectifying K ⁺ channels. A selective neuronal potassium channel opener (SNEPCO). ^[3]	Morphine is a agonist at μ , κ , and δ receptors. All are G-protein coupled receptors, inhibit adenylyl cyclase, and decrease cyclic AMP and decrease the phosphorylation of ion channels. ^[28]	Aspirin by inhibiting COX -1 and COX -2 enzymes, thereby inhibiting prostaglandin synthesis. ^[29]
Uses	Musculoskeletal pain Headache Neurogenic pain Cancer pain Postoperative pain	Musculoskeletal pain Flupirtine 300 mg/day was equally as effective as tramadol 150 mg/day in reducing subacute low back pain. ^[18] Neurogenic pain Flupirtine was effective as an add on therapy to opioids in reducing cancer-related neuropathic pain. ^[1] Cancer pain Flupirtine reduced cancer pain more effectively than tramadol and pentazocine. Also, the adverse reaction profile was similar in both flupirtine and tramadol treated patients. ^[21] Postoperative pain Flupirtine 100 mg and dihydrocodeine 60 mg were equally effective in reducing postoperative pain in hysterectomized women when given orally for a period of 3 days. ^[24] Other uses Myocardial infarction ^[30] Preanesthetic medication ^[31] Balanced anesthesia ^[31] Acute left ventricular failure ^[31] Cough ^[31]	Musculoskeletal pain Flupirtine 100 mg showed significant reduction in musculoskeletal pain compared to diclofenac 50 mg given twice daily. ^[1] Neurogenic pain Flupirtine 380 mg/day was found to be effective in reducing lumbar and cervical spinal root pain in comparison with aspirin 1800 mg/day. ^[1,19] Headache Acute migraine attacks, flupirtine 100 mg has shown better efficacy in terms of pain relief, restriction in working ability with less adverse effects when compared to oral paracetamol 1 gm. ^[1,19] Postoperative pain Flupirtine and diclofenac were equally effective in reducing postoperative pain in 40 patients who underwent orthopedic surgery. ^[24] Other uses Dysmenorrhea ^[32] Fever ^[33] Coronary artery diseases ^[34]
Adverse effects	Dose-dependent side effects include dizziness, drowsiness, pruritus, dry mouth, gastric fullness, nausea, tremors, heart burn, vomiting, sedation, headache, fatigue, and mood elevation. ^[26] When 100 and 200 mg were administered, an insignificant increase in systolic blood pressure with not much alteration in heart rate was observed. ^[12,27]	Common side effects are sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression. Less common include delayed gastric emptying, hyperalgesia, hormonal dysfunction, muscle rigidity, and myoclonus. ^[33]	Common side effects are gastritis and epigastric pain. Serious side effects are hemorrhage and perforation. ^[35] Others are tinnitus, Reye's syndrome, and angioedema. ^[35]

efficacy in reducing postoperative pain. This study concluded that flupirtine and diclofenac were equally effective in reducing postoperative pain.^[23] Flupirtine was also equally effective as that of pentazocine in reducing postoperative pain but with less adverse effects.^[24] In a double blind parallel group study, 50 women who underwent abdominal hysterectomy were given 100 mg of flupirtine and 60 mg of dihydrocodeine for 3 days. Both the drugs produced equal efficacy in reducing postoperative pain.^[25]

Adverse effects

In long-term trials done for rheumatic disease, majority of adverse reactions occurred within 6 months of treatment, among which most common were dizziness (11%), drowsiness (9%), pruritis (9%), dry mouth and gastric fullness (5%), nausea, and muscle tremor (2%).^[26] Other side effects were heart burn, vomiting, disturbed sleep, sedation, headache,

fatigue, and mood elevation. All these effects were dose dependent. A dose of 100 and 200 mg caused an insignificant increase in systolic blood pressure with not much alteration in heart rate and other hematological parameters.^[27] Rare and serious side effects were increased transaminases levels, drug-induced hepatitis, ataxia, tremors, restlessness, and nervousness.

In elderly healthy individuals, it was reported to cause transient faintness, dizziness, and lethargy, whereas in patients with renal dysfunction, it has produced transient light headedness and headache. But in liver disease patients, it produced serious adverse effects such as encephalopathy due to increased plasma concentration of the drug; so, the drug was discontinued.^[12]

Advantages over NSAIDs

NSAIDs is frequently associated with symptoms of

dyspepsia, heartburn, and epigastric pain leading to reduced compliance especially among patients on long-term treatment. A randomized open label study has shown that flupirtine was better tolerated and had better patient compliance compared to diclofenac.^[23] It has been documented that NSAIDs are associated with endoscopically diagnosed ulcers, serious upper gastrointestinal side effects including bleeding, perforation, and obstruction. In contrast, these are not seen with flupirtine; hence, it can be used as an alternate analgesic.

Advantages over OPIOIDS

Long-term use of opioids for treatment of pain leads to constipation, nausea, sedation, confusion, pruritis, urinary retention, tolerance, and dependence. These adverse effects were not seen with flupirtine when given daily for 12 months in chronic pain. Comparative studies of flupirtine with tramadol and pentazocine showed that it is equally efficacious but without adverse effects as that of opioids. Hence, flupirtine could be a better alternate to opioids. Comparison of flupirtine with opioids and NSAID s is enumerated in Table 1.

Conclusion

Studies suggest flupirtine as an effective analgesic for treatment of acute pain states such as postoperative pain, traumatic injury, headache, and migraine, as well as chronic pain such as musculoskeletal pain. It is effective and better tolerated for treatment of cancer pain. It has been observed to be equally effective like pentazocine, diclofenac, naproxen, ketoprofen, and paracetamol. It lacks anti-inflammatory effect which limits its use in inflammatory conditions such as rheumatism, rheumatic fever, and osteoarthritis. Its antiapoptotic, cytoprotective, and antioxidant properties can be used in treatment of neurodegenerative diseases. It is well tolerated with mild and infrequent adverse effects. No effects on respiration, lack of tolerance, or physical dependence are added advantage over opioids. Evidence of flupirtine's efficacy from clinical trials and well-established use in European countries for more than 2 decades suggests that it has a unique and important place in pain management.

Many drugs which were effective in clinical practice like analgin, spiramycin, qing hao (artemisinin) were not popular worldwide for a long time because it was not approved by US FDA; flupirtine is one among them. It is in use in European countries for the last two decades. It is presently under phase II clinical trials for fibromyalgia.^[21]

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