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MINI REVIEW ARTICLE

FLUPIRTINE: A MINI REVIEW

[1]Kumar Raj*, [2]Keshri Umashanker Prasad, [3]Sharma Janardan

[1]PG student, Department of Pharmacology, Rajendra Institute of Medical Sciences, Ranchi, India- 834009

[2]Associate professor, Department of Pharmacology, Rajendra Institute of Medical Sciences, Ranchi, India- 834009

[3]Professor, Department of Pharmacology, Rajendra Institute of Medical Sciences, Ranchi, India- 834009

**Corresponding Author's Email: drraj11081983@gmail.com, Phone: 9693696139*

ABSTRACT

Pain is the oldest medical problem of human, yet it has been little understood in physiology until very recently. Persistent, unremitting pain may adversely affect the body's endocrine, cardiovascular, immune, neurologic and musculo-skeletal systems and require aggressive treatment of the pain as well as its complications. It can significantly interfere with a person's quality of life and general functioning. So, treatment of this sensation is a challenge for clinicians. Flupirtine is a novel, centrally acting, non-opioid and non NSAID analgesic agent, and is devoid of common adverse effects seen with NSAIDs and opioids. It was first synthesized and used in Europe although it is not yet approved by United States Food and Drug Administration (USFDA). It acts as a selective neuronal potassium channel opener and has indirect N-methyl-d-aspartate (NMDA) receptor antagonist properties. In addition to analgesic action, it has also muscle relaxant, antioxidant, neuroprotective and antiparkinsonian effects. It is presently under phase II clinical trials for fibromyalgia. Evidence of flupirtine's efficacy from clinical trials and well-established use in European countries for more than 25 years suggests that it has a unique and important place in pain management. Despite its broad spectrum action, it is among such drugs which were not popular worldwide for a long time because they were not approved by USFDA.

Key Words: Pain, Flupirtine, Selective neuronal potassium channel openers, Neuroprotective, Antioxidant.

INTRODUCTION

Pain is one of the commonest symptoms in clinical practice. Nearly, half of all patients who visit a physician have a primary complain of any type of pain. Person who is experiencing the pain can only describe it properly. It is a very subjective experience.

Pain is a part of the body's defence system which protect our body from the painful stimulus and avoid that harmful situation in the future.[1] It is an important part of human life and vital to healthy survival. People with congenital insensitivity to pain have reduced life expectancy.[2] Most pain resolves promptly once the painful stimulus is removed and the body has healed, but sometimes pain persists despite removal of the stimulus and apparent healing of the body; and sometimes pain arises in the absence of any detectable stimulus, damage or disease.[3]

Humans have always tried to understand why they experience pain and how that pain comes about. While pain was previously thought to be the work of evil spirits, it is now understood to be a neurological signal. However, the perception of pain is not absolute and can be impacted by various factors including surrounding painful stimulus, the visual perception of the stimulus and an individual's personal history with pain.

Pain may significantly impair the ability to perform normal daily activities, such as dressing oneself comfortably as well as sleeping comfortably. This impairment must be taken into account when designing treatment programs for our patient. The psychological effect of these impairments on patient can be of great significance. A person with chronic pain can suffer from depression, anxiety, anger or loss of self esteem. Social consequences are also important to consider as a result of change in physical functioning. The suffering that a person experiences; relationship with family and friends; intimacy, including sexual activity, all will often become worse. People feel isolated and this isolation also contributes to the impact of chronic pain on patient. Finally, from societal point of view, it is important to recognize that chronic pain disables more people and contributes more to healthcare costs than cancer and heart disease combined. So, control and management of pain is essential for smooth and easy going life.

Analgesics are drugs that selectively relieve pain without blocking the conduction of nerve impulses, markedly altering sensory perception, or affecting consciousness.[4] These drugs act in various ways on peripheral and central nervous systems. In selecting analgesics, type and severity of pain, and response to other medication determines the choice of agent. In pharmaceutical research, the investigation of compounds for treating both acute and chronic pain is a great challenge.[5] Depending on 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). Other modalities of pain management include tricyclic antidepressants and anticonvulsants, interventional procedures, physical therapy, physical exercise, application of ice and/or heat, and psychological measures, such as biofeedback and cognitive behavioral therapy.

Flupirtine is the prototype of a new class of drug: the selective neuronal potassium channel opener (SNEPCO) which is used as an analgesic for acute and chronic pain,

in moderate to severe cases.[6] It is unique as a non-opioid, non-NSAID and non-steroidal analgesic. However, it lacks anti-inflammatory effect which limits its use in inflammatory conditions such as rheumatism, rheumatic fever and osteoarthritis.

The portions of the nervous system responsible for the sensation and perception of pain may be divided into three areas:[7,8]

1. Afferent pathways

2. CNS

3. Efferent pathways

Afferent pathways terminate in the dorsal horn of the spinal cord (1st afferent neuron). 2nd afferent neuron creates spinal part of afferent system. The portion of CNS involved in the interpretation of the pain signals are the limbic system, reticular formation, thalamus, hypothalamus and cortex.

The efferent pathways, composed of the fibers connecting the reticular formation, midbrain, and substantia gelatinosa, are responsible for modulating pain sensation.

There are four basic processes involved in pain sensation.[9] These are:

1. Transduction
2. Transmission
3. Perception
4. Modulation

There are three categories of noxious stimuli:

A. Mechanical (pressure, swelling, abscess, incision, tumour growth)
B. Thermal (burn, scald)
C. Chemical (excitatory neurotransmitter, toxic substance, ischaemia, infection)

These noxious stimuli cause a release of chemical mediators from the damaged cells including:

- Prostaglandin
- Bradykinin
- Serotonin
- Substance P
- Potassium
- Histamine

These chemical mediators activate and/or sensitise the nociceptors to the noxious stimuli. In order for a pain impulse to be generated, an exchange of sodium and potassium ions (de-polarisation and re-polarisation) occurs at the cell membranes. This results in an action potential and generation of a pain impulse. The pain impulse is then transmitted from the spinal cord to the brain stem and thalamus via two main nociceptive ascending pathways. These are the spinothalamic pathway and the spinoparabrachial pathway.

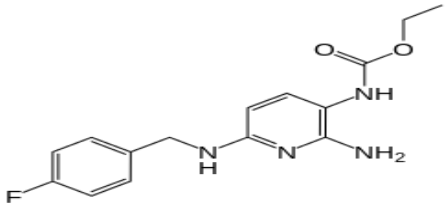
Perception of pain is the end result of the neuronal activity of pain transmission and where pain becomes a conscious multidimensional experience. The multidimensional experience of pain has affective-motivational, sensory-discriminative, emotional and behavioural components.

The multiple and complex pathways involved in the modulation of pain are referred to as the descending modulatory pain pathways (DMPP) and these can lead to either an increase in the transmission of pain impulses (excitatory) or a decrease in transmission (inhibition).

The exact mechanisms involved in the pathophysiology of chronic pain are complex and remain unclear. It is believed that following injury, rapid and long-term changes occur in parts of the CNS that are involved in the transmission and modulation of pain.[10]

CHEMICAL STRUCTURE-

Flupirtine is an aminopyridine which systematic (IUPAC) name is ethyl {2-amino-6-[(4-fluorobenzyl)amino]pyridin-3-yl}carbamate. Its synthesis is a four-step process starting from 2,6-dichloro-3-nitro-pyridine.[11] Its Formula is $C_{15}H_{17}FN_4O_2$ and molecular mass is 304.32 g/mol.



Structure of Flupirtine

HISTORY

Flupirtine (as flupirtine maleate) was first synthesized by Homburg, Degussa Pharma Group of Frankfurt, Germany in 1981.[12] It was approved for the treatment of pain in 1984 in Europe. However, it has never been approved by USFDA for any clinical use. Currently, flupirtine is sold under various brand name (Pruf & Vasfree by Intas Pharma, Lupirtin by Lupin Laboratories Ltd, etc) in India.

In 2010, the chemically related drug (the difference being that the pyridine group in flupirtine is replaced with a phenyl group) retigabine was approved by the FDA as an anticonvulsant for the treatment of partial seizures.

PHARMACODYNAMICS

Flupirtine is a nonopioid drug without antipyretic or antiphlogistic properties and has a favorable tolerability. The action of flupirtine does not depend on any central opioid effect because pain-relieving property of flupirtine is not reduced by naloxone, it does not induce any dependence or there is no need for a constant increase of the dose to maintain the clinical effect and it shows no relevant affinity to any of the known opiate receptors. Also, serotonin receptor antagonists do not inhibit the pain-relieving effect of flupirtine. There are no relevant affinities for α1- or α2-adrenoreceptors.[13]

Analgesic action: It is a selective neuronal potassium channel opener that also has indirect N-methyl-d-aspartate (NMDA) receptor antagonist properties.[14] The drug activates G-protein-coupled receptors that stimulate K+ channels of neuronal cells. Flupirtine inhibits neuronal excitability and reduce calcium Ca2+ influx into the cells. The mechanism is vital for neuronal transmission of pain

signals to motor neurons. Activation of this channel leads to hyperpolarization of neuronal membrane and the neuron becomes less excitable; thus, there is stabilization of resting neuronal membrane.[15] This action inhibits the transmission of nociceptive impulses during neuronal excitation.

Muscle relaxant action: The muscle relaxant action of flupirtine is due to inhibition of both mono- and polysynaptic reflexes. It possesses analgesic as well as muscle-relaxing effect in same dose ranges; thus, can be used in the treatment of painful diseases of the motor system presenting with spasticity and chronic musculoskeletal pain.[16]

Neuroprotective action: Flupirtine protects from apoptosis of neuronal cells which is caused by increased intracellular Ca ++ levels, mitochondrial dysfunction, cell membrane disruption and nucleolysis.[17] It also increases the levels of Bcl-2 and glutathione in glutamate or NMDA-induced apoptosis of human neurons as well as cultured retinal pigment cells.[15,17] It reduces the expression of oncogenes and formation of reactive oxygen radicals in experimental models which explains its action of preventing ischemia-induced apoptosis. This explains that flupirtine has role treatment of neuroinfections such as immune deficiency syndrome (AIDS), prion diseases, and neurodegenerative disease such as Alzheimer's.[6]
Antiparkinsonian action: Flupirtine reduces muscular rigidity and increased the ability of L-DOPA to reverse akinesia.[18] It, alone and in combination with L-DOPA exerts a potent anticataleptic effect when used in haloperidol-induced catalepsy.[19]

PHARMACOKINETICS

Flupirtine is a water soluble compound and almost completely absorbed from gastrointestinal tract with a bioavailability of 90% by oral route and 70% by rectal route.[20] It has large volume of distribution (Vd) and gets equally distributed into both extra and intravascular compartments. It 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.[21] The half-life of flupirtine on oral, intravenous and rectal administration with 100 mg is 6.5, 8.5 and 10.7 hr, respectively, in healthy volunteers. Biotransformation of flupirtine takes place in the liver. It is converted to two primary metabolites, p-fluoro-hippuric acid and an acetylated metabolite.[22] The two metabolites are formed by oxidative degradation and acetylation of a hydrolysis product, respectively. The two metabolites are further oxidized and then conjugated with glycine to form inactive metabolites.[23] Most of the total dose administered appears in urine whereas 18% is excreted in feces.

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 in 3-4 divided dose and can be administered up to 600 mg per day. Dose in children is 150-200 mg per day in 3-4 divided doses.[23,24] Rectal suppositories are administered in the dose range of 450-600 mg per day in adults and 150-250 mg per day in children.[24]

USES

Flupirtine works as an analgesic for various types of acute and chronic pain like headache, trauma, migraine and gynaecology. Due to its muscle relaxant properties it is widely used for backache and other orthopaedic pain. Due to its neuroprotective action, it has possible applications in multiple sclerosis, Batten disease, Alzeimer's disease and Creutzfeld- Jakob disease.[25,26] It is very useful in reducing pain of fibromyalgia.[27] It is also very effective in cancer and post operative pain. It is used in Parkinson's disease as anticataleptic agent and also reverses muscle rigidity and akinesia.

DRUG INTERACTIONS

Flupirtine increases warfarin toxicity by unknown mechanism and 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.[24] Carbamazepine induces hepatic enzymes so should not be given together.

SIDE EFFECTS

Flupirtine is a safe drug and has high tolerability. Drug tolerance does not develop in most cases.[28] Its side effects are dose dependant and divided into two categories.[29,30]

Peripheral Side Effects: Dryness of mouth, nausea, vomiting, constipation, blurring of vision, abdominal discomfort, heartburn, pruritus, hypotension, arrhythmias, atrial fibrillation, left bundle branch block, thrombocytosis, elevated liver enzymes, elevated blood urea nitrogen and serum creatinine.

CNS Side Effects: Fatigue, headache, insomnia, weakness, sedation, tremor, anxiety, hallucination, disorientation, depression, etc.

SAFETY PROFILE

Flupirtine is notably devoid of any addictive properties, negative psychological or motor function effects, or effects on reproductive function. Drug tolerance does not develop in most cases.[28] It can also be safely administered in diabetic and renal patients. Common side effects of flupirtine are dizziness, drowsiness, heartburn, dry mouth, nausea, elevated mood, fatigue, weakness, etc. which are mild and transient. Slight decreases in systolic blood pressure, elevation in liver enzymes, blood urea nitrogen and serum creatinine have been observed in some patients treated with flupirtine, although it is unclear if these effects were drug-related.[29]

Safety of flupirtine in pregnant, lactating women and children less than 6 years is not clear. If indicated in lactating women, breastfeeding should be stopped. Dose should be reduced in severe renal failure and elderly patient.[23]

Contraindications: Flupirtine should be avoided in patients with history of hypersensitivity to flupirtine, hepatic encephalopathy, cholestasis, myasthenia gravis, chronic alcoholism, primary biliary cirrhosis and other liver diseases.

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Advantages over NSAIDs and OPIOIDs: NSAIDs and Opioids are conventional analgesic drugs and are widely used for various pain management, but they are well known to produce worrisome adverse effects such as respiratory depression, tolerance and dependence that are typical of opioids,[31] and gastrointestinal (epigastric pain, bleeding, perforation, obstruction, etc) and renal problems[32] (nephropathy, interstitial nephritis, acute tubular necrosis, etc) associated with NSAIDS.

CONCLUSION

Many diseases present with symptom of pain as presenting complaint, so proper treatment of this symptom is of great significance. Flupirtine is effective analgesic for treatment of acute and chronic, mild to moderate pain states such as postoperative pain, traumatic injury, headache, migraine, musculoskeletal pain, cancer pain, orthopaedic and gynecological problems. It is equally effective but better tolerated than commonly used agents for these conditions. Its additional antiapoptotic, cytoprotective and antioxidant properties has usefulness in treatment of neurodegenerative diseases like Multiple sclerosis, Batten disease, Alzeimer's disease, Creutzfeld- Jakob disease and Parkinson disease. It is well tolerated with mild and infrequent adverse effects. Minimal effects on gastrointestinal and renal system, respiration, and lack of tolerance or physical dependence, are added advantage over NSAIDs opioids.

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