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Role of Flupirtine in the Treatment of Pain - Chemistry and its Effects

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PREFACE

The pain shares its etymological origin with the words punishment and penalty. For the perception of pain to serve its evolutionarily adaptive function, thermal, mechanical, and chemical stimuli need to be recognized. Pain is a universally understood signal of disease and it is the most common symptom that brings the patient to physician's attention. The function of the pain in sensory system is to protect the body and to maintain the homeostasis.

The choice of analgesics for acute pain depends on the efficacy, side - effects, complications, pharmacokinetics and its cost-effectiveness. Flupirtine is a centrally-acting, non-opioid analgesic with N-methyl-D-aspartate (NMDA) receptor antagonist property which has been shown to be effective in the management of post-operative pain. It is also effective in other painful conditions in which the primary requirement for analgesia is without sedation or anti-inflammatory effects.

Flupirtine is a non-opioid analgesic without antipyretic or antiphlogistic properties. It constitutes a unique class within the group of WHO-I analgesics and was first approved in Germany on a national level in 1989. This selective neuronal potassium channel opener evolved rapidly into one of the most preferred analgesics for the treatment of musculoskeletal pain in some European countries. However, its use outside Europe was limited due to a discrepancy between the empirical application of the drug and supporting evidence. As a consequence, the German Pain Society commissioned an independent research institute to

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perform a pooled re-analysis of all the available data from randomized controlled trials (including some trial not yet published) (1). ❑

CHEMISTRY

Flupirtine is a derivative of triaminopyridine with a chemical formula of ethyl-N-{2-amino-6-(4-fluorophenylmethylamino) pyridine-3 yl} cabamate. It is available as the maleate salt because flupirtine is itself poorly water soluble. Flupirtine is a base and is weakly lipophilic.

Pharmacodynamic Effects

The spectrum of action of flupirtine includes analgesia, muscle relaxation and neuroprotection. The analgesic effect of flupirtine does not appear to be associated with any central opioid effect. Flupirtine does not appear to act on the usual binding sites of the NMDA receptor such as glycine site or polyamine site or the magnesium site. There is evidence to show that flupirtine may suppress the opening of the NMDA channel by acting as an oxidizing agent at the redox site of the NMDA receptor. Jacob and Kriegelstein found an activation of G protein-regulated inwardly rectifying K^+ channels (GIRKs) by flupirtine in therapeutically relevant concentration ranges (2).

Absorption and Plasma Concentration

Flupirtine maleate is freely soluble in water and undergoes rapid gastric absorption. After administration of single oral dose of flupirtine 100 or 200 mg to healthy volunteers, it appeared in the plasma within 15-30 minutes resulting in peak plasma concentrations (C_{max}) of approximately 0.8 and 2.0 mg/L at 1.6 to 2 hours (T_{max}) post dose. Plasma flupirtine concentrations were linearly related to dose over the range of 50 to 300 mg. Rectal administration of flupirtine maleate 150 mg resulted in a C_{max} of 0.89 mg/L at 5.7 hours post dose. Bioavailability in comparison with an intravenous dose of flupirtine tartrate 80 mg was 100% for the oral dose and 72.5% for the rectal dose. Plasma flupirtine concentrations reached steady-state after 2 days in 54 healthy volunteers receiving flupirtine 75 or 150 mg at 12 hours intervals; plasma drug accumulation was not observed after oral administration of flupirtine 100 mg times daily for 28 day (3).

Distribution

The apparent volume of distribution of flupirtine in healthy volunteers was 154 L.3 or 1.15 or 1.16 L/kg for the intravenous. Other routes for administration are oral and rectal.2 Over a plasma concentration range of 0.05 to 2.0 mg/L, flupirtine was 94% bound to plasma proteins in the rat and 0 to 84 % reversibly bound to human albumin (4).

Elimination

Flupirtine whether administered orally or rectally, undergoes biotransformation in the liver. The apparent clearance of flupirtine in healthy volunteers following an oral dose was 16.5 L/h.4,5 Of the total dose administered, 72% was excreted in the urine, and with the parent compound plus the two identified metabolites accounting for 54 to 67% of urinary radioactivity, and 18% was excreted in the faeces (2).

The half life of flupirtine following intravenous administration was 1.8 hours, while the plasma elimination half life in healthy young volunteers following single dose administration of flupirtine by the intravenous, oral and rectal routes was 8.5, 9.6 and 10.7 hours respectively (2).

Tolerability Profile

In short term trials flupirtine has been well tolerated. Although adverse reactions were common, they were not severe, and necessitated to withdraw in few patients (6-8). Adverse events commonly reported were nausea, vomiting, colic/wind, gastric and abdominal discomfort, diarrhea, constipation and heartburn. Symptoms attributable to a central system effect included drowsiness, dizziness, headache, depression, disorientation and hallucinations. The tolerability profile of flupirtine on long term therapy is essentially similar to that described in short terms trials and does not appear to be modified by age.

Slight increases in liver enzymes, bilirubin, blood urea nitrogen and creatinine were reported in a few patients, as were slight increases in leucocyte counts, but none of these changes were clinically important. ❑

DRUG INTERACTIONS

Although there was no evidence of hepatic enzyme induction following short term (3-weeks) oral administration of flupirtine 100 mg, 3 times daily to healthy volunteers (Hedges et al. 1987), a slight degree of enzyme induction has been described on long term (6 -months) administration to epileptic patients. There is a possible potentiation of anticoagulant effects of co-administration of flupirtine with oral anticoagulants and the need for regular monitoring of blood coagulation times during treatment. The possible occurrence of other drug interactions of this nature should be borne in mind. ❑

CLINICAL STUDY

A clinical trial was carried out in 66 patients to compare the effectiveness of oral flupirtine maleate (100 to 200 mg) and oral pentazocine (50 to 100 mg) in the treatment of pain after hip replacement surgery. The trial analgesics were used as sole analgesia from the second to the fifth post-operative day. Similar numbers of patients were withdrawn from the trial in each group (flupirtine 6, pentazocine 5) because of poor efficacy or the appearance of symptoms, the relationship to treatment of which was uncertain. Indices of the quality, speed and degree of pain relief were similar in both groups on all days of the study, no significant differences being seen (6).

A retrospective pooled analysis of the individual patient data from 8 randomized controlled Phase III-IV clinical trials was carried out which included patients with sub-acute and chronic musculoskeletal pain. The efficacy and tolerability of flupirtine at dosages of 100-400 mg/d were compared to placebo and/or active comparators. Data were pooled by treatment and by subject. The primary endpoint was the average change in pain intensity for the overall maintenance period (1). A total of 1,046 patients was evaluated for efficacy and 1,095 patients for safety. Based on 3,337 pain assessments, treatment with flupirtine and active comparators resulted in significant reductions in pain intensity compared to baseline beginning from Day 4 (flupirtine) and Day 5 (comparators) and continuing up to the end of the study period as well as during the overall maintenance period (all $p < 0.001$). Flupirtine proved to be non-inferior to the active comparators ($p < 0.001$) but showed a superior tolerability profile with a significantly lower number of patients reporting treatment emergent adverse events (28.6 vs. 39.1%, $p < 0.001$) and a significantly lower percentage of patients who prematurely discontinued study medication due to these adverse events (7.1 vs. 11.7%, $p = 0.013$). **Limitations:** The limitations in the study were confined to those inherent in the retrospective and pooled analysis design. On the basis of this pooled analysis of individual data from 8 controlled clinical trials involving patients suffering from sub-acute/chronic musculoskeletal pain, the efficacy of flupirtine was superior to placebo across its effective and approved dosage range (1). ❑

DOSAGE AND ADMINISTRATION

Flupirtine maleate is available in 50 and 100 mg oral capsules and 75 and 150 mg rectal suppositories. The usual adult dosage is one 100 mg capsule or one 150 mg suppository 3 to 4 times daily, to a maximum of 6 doses daily. For more severe pain, single 200 mg oral doses may be taken up to 3 times daily. The duration of treatment should not exceed 8 days without review by a medical practitioner, or 4 weeks on repeated prescription. Monitoring of transaminases is recommended on prolonged administration in elderly patients or those with mild to moderate renal impairment, therapy should be initiated with the lowest dose which will achieve pain relief.

Summary - Flupirtine maleate is a non-opioid drug without antipyretic and anti-inflammatory properties which is approved by EMA for acute and chronic pain, especially of musculoskeletal origin. It has a unique pharmacologic profile via the activation of GIRKs and represents a new class of drug called selective neuronal potassium channel openers.

Flupirtine is as effective as opioids to settle the pain in post-surgical cases, cancer related, neuropathic and myofascial in origin. The clinical use of flupirtine will be more acceptable as it lacks the typical side effects of the opioid drugs.

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