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Concise review: Therapeutic potential of flupirtine maleate

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ABSTRACT

Flupirtine is a non-opioid analgesic without antipyretic or antiphlogistic properties. Flupirtine is a centrally acting analgesic but the analgesic action of flupirtine does not depend on any central opioid effect. The fact behind this statement is that the pain-relieving property of flupirtine is not reduced by the opioid antagonistic drug naloxone. Flupirtine has been reported for its neuro-protective properties and possess a selective neuronal potassium channel opener that also has NMDA receptor antagonist properties. Flupertine is transformed into two primary derivatives, 4-fluoro-hippuric acid and the Nacetylated analogue D13223. Both derivatives of are flupirtine pharmacologically active with 30% of the analgesic potency of the parent drug and further oxidized and then conjugated with glycine to form inactive metabolites, Recently, Flupirtine maleate has been introduced in Indian market in oral, intravenous and rectal dosage forms. 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. There is plenty of literature available on the effect of Flupirtine maleate on chronic and acute pain management. These preliminary finding require confirmation in further comparative studies.

Keywords: Flupirtine maleate, Naloxone, Opioid, NMDA

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INTRODUCTION

Flupirtine maleate is an aminopyridine , clinically use as a nonopioid analgesic and belongs to the class of N-methyl-D-aspartate (NMDA) antagonists[1]. In Europe, Flupirtine is in use for the last 25 years for the management of pain due to surgery, pain associated with muscle spasm, degenerative joint diseases, trauma, cancer, dental extraction and other conditions such as headache and dysmenorrhoea[2]. It has been proved that flupirtine is effective at least as the non-steroidal anti-inflammatory agents as suprofen, diclofenac and ketoprofen, as well as the dihydrocodeine and pentazocine and opiate analgesics codeine, dipyrone and paracetamol[3]. According to the AHCPR Clinical Practice Guidelines "Unrelieved pain has negative physical and psychological consequences. Aggressive pain prevention and control that occurs before, during, and after surgery can yield both short-term and long-term benefits[4]. There are a number of medications available for the treatment of pain such as non-steroidal anti-inflammatory drugs (NSAID), opioids, and their derivatives[5]. In pharmaceutical research, the investigation of compound for the treatment of both acute and chronic pain is a great challenge. Pain is a specific enteroceptive sensation; it can be perceived as arising from a particular portion of the body, its temporal properties can be detailed, it can be differentiated qualitatively (for example, as stinging, pricking, burning, throbbing, dull or aching), and it involves dedicated subsets of peripheral and central neurons[6]. Flupirtine has been reported for its neuro-protective properties and possess a selective neuronal potassium channel opener that also has NMDA receptor antagonist properties[7]. Flupirtine used as an analgesic for chronic pain like migraines and gynaecology. In addition, flupirtine has muscle relaxant properties thus it is 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[8]. In 1984, it was firstly authorised in the European Union (EU) as the non-steroidal anti-inflammatory drugs (NSAIDs) and an alternative analgesic to opioids for the pain treatment. At Present, it is authorized for

the treatment of acute pain in adults as an alternative when other analgesic treatment is contraindicated[9]. Liver toxicity and cardiac effects in patients are some of the side effects[10].

CHEMISTRY OF FLUPIRTINE MALEATE

Chemical structure of flupirtine is-2-amino-3-ethoxy-carbonylamino-6-4-fluorobenzylamino- Pyridine[11]. It is a weak lipophilic, alkaline in nature with 5.3 pKa value (Fig.1). The carbamate group is a key feature of flupirtine and it can be cleaved under strong acid and basic conditions[12].

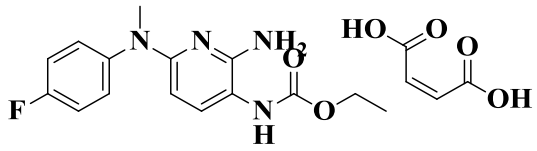


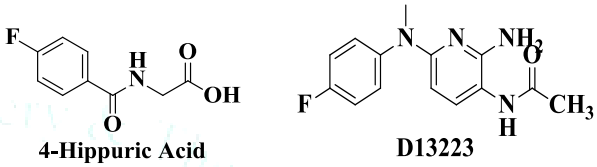
Fig. 1 Chemical structure of flupirtine maleate.

PHARMOCODYNAMICS

Flupirtine is a centrally acting analgesic but the analgesic action of flupirtine does not depend on any central opioid effect. The fact behind this statement is that the pain-relieving property of flupirtine is not reduced by the opioid antagonistic drug naloxone[13,14]. It was later determined that flupirtine interacted with G-protein regulators and secretly react with K^+ channels (GIRKs) which is a recognised family of K+ channels distinct from the voltage-dependent[14]. GIRKs are regulated by neurotransmitters, occur as different subtypes and are variously expressed in different parts of the brain[15]. By the activation of K^+ channel hyperpolarisation occurs in neuronal membrane and neurons become less excitable and resting neuronal membrane is stabilized[16]. This channel of drug activation is known as selective neuronal potassium channel openers (SNEPCO) and flupirtine is the prototype[17]. Osborne and collgue, investigated that flupirtine might suppress channel opening by acting as an oxidizing agent at the redox site of the NMDA receptor which leads to inhibition of the transmission of nociceptive impulses during neuronal excitation[18]. A group of neuronal channels has been characterized and classified as Kv7.2–Kv7, as a result of good efficiency SENCO homology with a cardiac channel which is in the pathogenesis of the long QT syndrome (Kv7.1) [19,20]. These channels provide the basis of the neuron-specific M-current, a voltage-dependent, non-inactivating, and slowly activating/ deactivating K+ current, which contributes to setting the resting membrane potential, limits the action potential frequency and participates in spike-frequency adaptation[21-26]. The efficacy of flupirtine in migraine was determined when a group of 20 patients suffering were treated with 100mg with paracetamol 1000mg, each taken up to 4 times daily for 5 days. Similar number of doses was taken in both groups (6.65 *vs* 6.85, respectively) .results shown the equal effect of both groups and there is no significant difference in the number of days of work missed, the number of patients confined to bed or those patients experiencing nausea[27].

PHARMACOKINETICS

Flupertine is transformed into two primary derivatives, 4-fluoro-hippuric acid and the Nacetylated analogue D13223 shown in Fig. 2. The effect of flupirtine is parallel in healthy and renal impaired patients with 275 and 263 ml/min, respectively, but it is decreases about 161 ml/min in old age patients[28,29]. In a pharmacokinetic study of flupirtine in patients with moderate renal impairment and in healthy elderly subjects, oral administration of 100mg, it was found that elimination half-life of flupirtine was higher in elderly patients than in younger normal subjects, and this was associated with an increased maximum serum concentration and reduced clearance. There was no correlation between observed elimination half-life and degree of renal impairment, but the creatinine clearance of most patients fell in a narrow range between 43 and 60 ml/min. The mean half-life in patients with renal impairment was higher than in normal subjects. Flupirtine is mainly isolated from urine (72%)[29,30]. Flupirtine is a hydrophilic in nature. It is rapidly absorbed from gastrointestinal tract within 15-30 minutes with bioavailability of 90% by oral route and 70% by rectal route and reaching a peak plasma concentration of approximately 0.8 mg/l at 1.6 to 2 hours after 100mg oral dose[29-31]. In a rectal dose of l50mg, a similar peak plasma concentration is reached in 5.7 hours. Binding of flupirtine to human plasma protein in vitro is about 80% and has an apparent volume of distribution for oral flupirtine 100 mg is 154 l in healthy volunteers[30]. At 200 mg flupirtine, plasma drug concentration (Cmax) becomes double i.e., 1.98 mg/l. Rectal administration also showed the dose dependent plasma drug concentration. Steady-state concentration is achieved at oral dose of 75mg flupirtine in healthy volunteers 12hrs. Both derivatives of are flupirtine pharmacologically active with 30% of the analgesic potency of the parent drug and further oxidized and then conjugated with glycine to form inactive metabolites[31-33].



4-Hippuric Acid **D13223**

Figure 2: Derivatives of flupiritine maleate

TOLERABILITY OF FLUPIRTINE

The tolerability profile of flupirtine is higher to facilitate the opioids, which may be cause dizziness and tiredness, constipation, vomiting, Headaches sedation, pruritus, urinary retention and respiratory depression[34-36]. Allergic reactions such as urticaria are also denoted. Occasionally, an increase in liver enzymes is induced and the urine may take on a greenish discoloration without any associated symptoms[37]. According to the data filed in ASTA Medica, a clinical study done with 8478 patients and observed results revealed the volume of adverse effect of flupirtine such as, fatigue/somnolence (13.4%), dizziness/vertigo (7%), nausea (5.7%), headache (2.7%), dry mouth (2.1%), dyspepsia (1.7%), sweating (1.3%) and vomiting (1.3%). In the first 6 month treatment of flupirtine such actions have been reported as mild and transient[36]. There is no clinically significant alterations have been observed in flupirtine in laborator parameters or vital signs, including blood pressure, heart rate, ECG, renal function, haematologic and metabolic parameters. Adverse reactions are dose dependent and usually subside in the course of treatment or soon after discontinuation. There are no medically pertinent interactions. In comparative study of flupirtine with dihydrocodeine depressed mood were statistically more frequent, but the latter was associated with a significantly higher incidence of drowsiness[38-40]. The use of NSAIDs is limited by gastrointestinal adverse events, including dyspepsia, which has been reported to occur in up to 40% of NSAID recipients[41]. Anxiety were not observed in the dose of 400 to 500 mg/day orally or 600 to 750 mg/day rectally for 2 to 3 days[42]. In hepatic dysfunction, there is a limited data present on the adverse effect of flupirtine in elderly patients where as in a single-dose study of elderly healthy volunteers, in 5 of II subjects shown adverse reactions, consisting of transient faintness, dizziness or lethargy, but there were no clinically significant changes in heart rate or blood pressure[29]. Similarly, at 100mg dose of flupirtine 4 times daily for two weeks there is slight increase in leukocyte. This slight change is not clinically important. During the last month of treatment; there is increase in

thrombocyte count, noted in 10 of the 55 patients. There is no change in Blood glucose, triglyceride and cholesterol values. In contrast, systolic blood pressure was decreased in first 3 month treatment from average value of 160 to 150mm Hg while diastolic blood pressure and heart rate was unchanged[43]. The efficiency 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. The 104 meet the insertion criteria and were further divided into two treatment groups. One group received flupirtine maleate orally and 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 [44].

DRUG INTERACTION

There is no evidence for short term (three weeks) oral administration to determined the hepatic enzyme induction by flupirtine at 100mg dose (3 times daily), while although at double time period (6 month),a slight degree of enzyme induction has been reported. It was also reported that flupirtine delay the diuretic response to furosemide without affecting the magnitude of the response.There is no information related to link between flupirtine and other hepatically metabolised drugs, also it is unclear that flupirtine represent pharmacokinetic or pharmacodynamic interaction between two drugs[43-45]. A single dose of flupirtine maleate, did not provoke significantly the diuretic action of frusemide when compared with indomethacin and placebo in normal human beings[46]. Flupirtine increased the hepatotoxic potential of paracetamol so that hepatic transaminases levels should be monitored when both the drugs are given concomitantly. Coadministration with carbamazepine is not advisable as carbamazepine induces hepatic enzymes. There is no information related to link between flupirtine and other hepatically metabolised drugs, also it is unclear that flupirtine represent pharmacokinetic or pharmacodynamic interaction between two drugs[47].

THERAPEUTIC USES

Musculoskeletal Pain

From a previous marketing observation of flupirtine 200-300 mg/day for 1 week has shown improvement in response rate as assessed by visual analogue pain scale[48]. Flupirtine has been compared with placebo and diclofenac sodium (a standard analgesic), observation showed that the response rate of flupirtine in acute, sub-acute and chronic pain in patients was 94%, 89.4%, and 85.9%, respectively. 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. A random study revealed that flupirtine 300 mg/day was as effective as tramadol 150 mg/day in reducing sub- acute low back pain[49-51].

Headache

Flupirtine showed significant response for chronic tension headache in those patients who had had insufficient response to conventional analgesics. In comparative study of flupirtine 100mg and placebo in chronic headache, flupirtine shown significant reduction in three time daily while placebo shown reduction in pain intensity in 2 weeks. Flupirtine 100 mg has shown better efficacy in terms of pain relief in acute migraine effect restriction in working ability with less adverse effects when compared to paracetamol 1 gm orally [49,50].

Neurogenic Pain

A study shown that 380mg/day dose of flupirtine is more effective in comparison to aspirin 1800 mg/day in in reducing lumbar and cervical spinal root pain. The study also revealed that 25% of flupirtine-treated patients reported no pain and 46% reported improvement, but in those who received aspirin only 35% reported an improvement. An early study of utilised a heat stimulation test to evaluate the ability of flupirtine, pentazocine and placebo, administered orally and intravenously, to increase the pain threshold in 6 healthy volunteers. Over a period of 60 minutes after doses of both analgesics, the pain threshold rose steadily, the level achieved being higher for flupirtine than for pentazocine. Feingold et al. (1982) also demonstrated an increase in pain threshold in 20 healthy males after a single oral dose of flupirtine 50mg, using both an electrical stimulation test and a tourniquet technique to elicit ischaemic pain. The potency of flupirtine, measured on a visual analogue scale, was less than that of tramadol 50mg but greater than that of dipyrone 500mg[52-54]. Thermic stimulation of the tooth pulp was used to measure pain threshold before and up to 60 minutes after a single oral dose of tlupirtine or placebo in 2 groups of 15 healthy volunteers. Flupirtine was statistically superior to placebo, producing a rise in pain threshold within 15 minutes which lasted up to 45 minutes postdose[55]. Preclinical observations backed up the hypothetical neuroprotective effect of flupirtine derived from knowledge of its pharmacodynamic properties. In optic neuritis in the context of experimental autoimmune encephalomyelitis, flupirtine exerted neuroprotective effects both in the presence and absence of interferon (IFN)-β. Flupirtine and retigabine exerted neuroprotective actions in organotypic hippocampal cultures exposed to NMDA, oxygen, and glucose deprivation followed by reoxygenation or serum withdrawa[56,57]. In *in-vitro* studies on primary neurons, flupirtine significantly reduced the apoptotic effect displayed by A-beta 25 – 35, a fragment of the amyloid beta-protein, and prevented the toxic effect of PrP, the aetiological agent of CJD. Despite these results, no larger clinical trials with flupirtine for the treatment of Alzheimer's disease have been performed so far [58].

Cancer Pain

According to the studies, flupirtine is more effective in reduction of cancer pain in comparison with tramadol and pentazocine. In addition, pentazocine showed a higher side effect incidence in central nervous system (CNS) although the adverse reaction profile was similar in both flupirtine and tramadol. In a study of cancer patients with metastatic involvement of myofascial or neural structures for whom opioid analgesics are contraindicated on account of their spasmogenic effects flupirtine offer a non sedating alternative to the benzodiazepines. Flupirtine has analgesic and muscle relaxant effects, thus expected to be particular benefit in relieving musculoskeletal and myofascial pain of the type frequently associated with non-inflammatory degenerative disease such as non-articular rheumatism, and sub acute and chronic spinal syndromes[59-61].

Fibromyalgia

Flupirtine has shown more efficiency to reduced pain of fibromyalgia more than the available drugs. A Pharmaceutical company ADEONA was granted permission by US FDA to conduct randomized, double blind, placebo-controlled phase II clinical trial of flupirtine in Fibromyalgia syndrome[60,62].

Postoperative pain

Flupirtine is more significant in analgesic effect with minimal side effects in pain during postoperative period when compared to standard drugs. Flupirtine showed 69%

reduction in pain score 6 h after administration when compared to placebo which had only 26% reduction in post-episiotomy. Flupirtine also had greater efficacy in post episiotomy pain reduction when compared to suprofen and paracetamol[62,63].

Other effects

An *in vivo* study revealed that flupirtine has an anti-diuretic property[64]. On the other hand, a single oral administration of flupirtine 200mg in healthy volunteers did not show any evidence of significant anti-diuretic action of (frusemide)[48]. An ocular toxicity study of flupirtine at 7 days oral administration of 200 to 400 mg/day in healthy volunteers showed no change in visual function. Studies showed that flupirtine produces only weak mydriasis and has no local anaesthetic activity in mice, but has a a weak local anaesthetic effect on the rabbit cornea[64-66]. In contrast, on topical application to the nasal mucosa of healthy volunteers, flupirtine (12 to 30mg) has a local anaesthetic effect, as reflected in a significant decrease in the amplitude of pain-related chemo-somatosensory evoked potentials[44]. Veterinary pharmacology still has a reduced drug facilities compared to human pharmacology; however, human drugs are increasingly being investigated for veterinary use in order to address this shortfall. This has stimulated pharmaceutical companies to market drugs developed specifically for animal use as well as academia to perform experimental studies in veterinary species with human drugs. In this consequence, FL shown wide potential in veterinary pharmacology, it effects as a muscle relaxant is of added value for pain associated with increased muscle tension[65-69]. In addition, its mechanism of action promotes neuronal rest; it has proven useful in conditions involving neuronal hyperexcitability such as chronic pain (non-malignant and malignant), migraine and neurogenic pain[70,71].

CONCLUSION

In the past decade significant researches has been done on the neuroprotective analgesic and 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. It is an analgesic with many potential therapeutic benefits that has proved useful in the treatment of many diseases and diseases. Flupirtine can be used as an alternate analgesic because there is no seen of serious upper gastrointestinal side effects including bleeding, perforation, and obstruction associated in ulcer treatment, like other NSAIDs

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

REFERENCES

1. Tatch W. U.S. Patent Application No. 14/097,317, 2015.
2. Harish S, Bhuvana K, Bengalorkar GM, Kumar TN. Flupirtine: clinical pharmacology. Journal of Anaesthesiology, Clinical Pharmacology2012; 28(2):172-178.
3. Friedel HA, Fitton A. Flupirtine. Drugs 1993; 45(4):548-569.
4. Max MB, Donovan M, Miaskowski CA, Ward SE, Gordon D, Bookbinder M, Janjan N. Quality improvement guidelines for the treatment of acute pain and cancer pain. Jama 1995; 274(23):1874-1880.
5. Ramachandran S, Maheswari VU. Synthesis, analgesic and ulcerogenic evaluation of some novel Schiff and mannich bases of isatin derivatives. International Journal of Pharma and Bbio Sciences 2011; 2:251-260.
6. Craig AD, Sorkin LS. Pain and analgesia. Encyclopedia of Life Sciences 2001; 1-8
7. Kornhuber J, Bleich S, Wiltfang J, Maler M, Parsons CG. Flupirtine shows functional NMDA receptor antagonism by enhancing Mg 2+ block via activation of voltage independent potassium channels. Journal of Neural Transmission 1999; 106(9-10):857-867.
8. Klawe C, Maschke M. Flupirtine: pharmacology and clinical applications of a nonopioid analgesic and potentially neuroprotective compound. Expert Opinion on Pharmacotherapy 2009; 10(9):1495-1500.
9. Swedberg MD, Shannon HE, Nickel B, Goldberg SR. Pharmacological mechanisms of action of flupirtine: a novel, centrally acting, nonopioid analgesic evaluated by its discriminative effects in the rat. Journal of Pharmacology and Experimental Therapeutics1988; 246(3):1067-1074.
10. Dhar S, Bitting RL, Rylova SN, Jansen PJ, Lockhart E, Koeberl DD, Boustany RMN. Flupirtine blocks apoptosis in batten patient lymphoblasts and in human postmitotic CLN3-and CLN2-deficient neurons. Annals of Neurology 2002; 51(4):448-466.
11. Kathirvel S, Sujatha R, Pandit MR, Suneetha A. Stress degradation studies on flupirtine maleate using stability-indicating RP-HPLC method. Chromatography Research International 2013; 1-6.
12. Devulder J. Flupirtine in pain management. CNS drugs 2010; 24(10):867-881.
13. Giorgi M, Owen H. Flupirtine: a human drug with potential for use in the veterinary field. American Journal of Animal and Veterinary Sciences 2012; 7(4):213-218.
14. Nickel B, Herz A, Jakovlev V, Tibes U. Mechanism of action of the analgesic flupirtine. Arzneimittel-Forschung 1985; 35(9):1402-1409.
15. Nickel B. The antinociceptive activity of flupirtine: a structurally new analgesic. Postgraduate Medical Journal 1987; 63:19-28.
16. Jakob R, Krieglstein J. Influence of flupirtine on a G-protein coupled inwardly rectifying potassium current in hippocampal neurones. British Journal of Pharmacology 1997; 122(7): 1333-1338.
17. Klawe C, Maschke M. Flupirtine: pharmacology and clinical applications of a nonopioid analgesic and potentially neuroprotective compound. Expert Opinion on Pharmacotherapy 2009; 10(9):1495-1500.
18. Jakob R, Krieglstein J. Influence of flupirtine on a G-protein coupled inwardly rectifying potassium current in hippocampal neurones. British Journal of Pharmacology 1997; 122(7):1333-1338.
19. Gribkoff VK. The therapeutic potential of neuronal KCNQ channel modulators. Expert Opinion on Therapeutic Targets 2003; 7(6):737-748.
20. Sättler MB, Williams SK, Neusch C, Otto M, Pehlke JR, Bähr M, Diem R. Flupirtine as neuroprotective add-on therapy in autoimmune optic neuritis. The American Journal of Pathology 2008; 173(5):1496-1507.
21. Brown DA, Passmore GM. Neural KCNQ (kv7) channels. British Journal of Pharmacology 2009; 156(8):1185-1195.
22. Martire M, Castaldo P, D'Amico M, Preziosi P, Annunziato L, Taglialatela M. M channels containing KCNQ2 subunits modulate norepinephrine, aspartate, and GABA release from hippocampal nerve terminals. Journal of Neuroscience 2004; 24(3):592-597.
23. Mackie AR, Brueggemann LI, Henderson KK, Shiels AJ, Cribbs LL, Scrogin KE, Byron KL. Vascular KCNQ potassium channels as novel targets for the control of mesenteric artery constriction by vasopressin, based on studies in single cells, pressurized arteries, and in vivo measurements of mesenteric vascular resistance. Journal of Pharmacology and Experimental Therapeutics 2008; 325(2):475-483.
24. Wladyka CL, Kunze DL. KCNQ/M-currents contribute to the resting membrane potential in rat visceral sensory neurons. The Journal of Physiology 2006; 575(1):175-189.
25. Yeung SYM, Pucovský V, Moffatt JD, Saldanha L, Schwake M, Ohya S, Greenwood IA. Molecular expression and pharmacological identification of a role for Kv7 channels in murine vascular reactivity. British Journal of Pharmacology 2007; 151(6): 758-770.
26. Million R, Finlay BR, Whittington IR. Clinical trial of flupirtine maleate in patients with migraine. Current Medical Research and Opinion 1984; 9(3):204-212.
27. Friedel HA, Fitton A. Flupirtine. Drugs 1993; 45(4):548-569.
28. Giorgi M, Owen H. Flupirtine: a human drug with potential for use in the veterinary field. American Journal of Animal and Veterinary Sciences 2012; 7(4):213-218.

29. Hlavica P, Niebch G. Pharmacokinetics and biotransformation of the analgesic flupirtine in humans. Arzneimittel-Forschung 1985; 35(1):67-74.
30. Keshri UP, Sharma J. Flupirtine: a mini review. Journal of Drug Delivery and Therapeutics 2013; 3(6):113-116.
31. Schuster KC, Urlaub E, Gapes JR. Single-cell analysis of bacteria by Raman microscopy: spectral information on the chemical composition of cells and on the heterogeneity in a culture. Journal of Microbiological Methods 2000; 42(1):29-38.
32. Methling K, Reszka P, Lalk M, Vrana O, Scheuch E, Siegmund W, Bednarski PJ. Investigation of the in vitro metabolism of the analgesic flupirtine. Drug Metabolism and Disposition 2009; 37(3):479-93.
33. Heusinger JH. Efficacy and tolerance of flupirtine and pentazocine in two multicentre trials. Postgraduate Medical Journal 1987; 63:71-79.
34. Herrmann WM, Kern U, Aigner M. On the adverse reactions and efficacy of long-term treatment with flupirtine: Preliminary results of an ongoing twelve-month study with 200 patients suffering from chronic pain states in arthrosis or arthritis. Postgraduate Medical Journal 1987; 63:87-103.
35. Schug SA, Zech D, Grond S. Adverse effects of systemic opioid analgesics. Drug Safety 1992; 7(3):200-213.
36. Maier A, Liu Y, Scholze A, Westhoff TH, Tepel M. Green urine following exposure to flupirtine. American Journal of Kidney Diseases 2010; 56:1014-1015.
37. Galasko CSB, Courtenay PM, Jane M, Stamp TCB. Trial of oral flupirtine maleate in the treatment of pain after orthopaedic surgery. Current Medical Research and Opinion 1985; 9(9):594-601.
38. Million RR. Management of head and neck cancer. International Journal of Radiation Oncology, Biology, Physics 1984; 10: 58.
39. Moore RA, Bullingham RES, Simpson S, O'sullivan G, Evans PJD, McQuay HJ, Lloyd JW.Comparison of flupirtine maleate and dihydrocodeine in patients following surgery. BJA: British Journal of Anaesthesia 1983; 55(5):429-432.
40. Hirschowitz BI. Clinical course of nonsurgically treated Zollinger-Ellison syndrome. In Endocrine tumors of the pancreas. Karger Publishers 1994; 360-371.
41. Johnston A, Warrington SJ, Turner P, Riethmuller-Winzen H. Comparison of flupirtine and indomethacin on frusemide-induced diuresis. Postgraduate Medical Journal 1987; 63(745):959-961.
42. Kobal G, Hummel T. Effects of flupirtine on the pain-related evoked potential and the spontaneous EEG. Agents and Actions 1988; 23(1-2):117-119.
43. Naser SM, Sarkar N, Biswas A, Kamal F, Prakash R, Rahaman QM, Das AK. Efficacy and safety of flupirtine maleate and tramadol hydrochloride in postoperative pain management--a prospective randomised double blinded study. Journal of the Indian Medical Association 2012; 110(3):158-160.
44. Narang A, Konopka A, Ramkrishna D. Dynamic analysis of the cybernetic model for diauxic growth. Chemical Engineering Science 1997; 52(15):2567-2578.
45. Hedges LV. How hard is hard science, how soft is soft science? The empirical cumulativeness of research. American Psychologist 1987; 42(5):443.
46. Johnston A, Warrington SJ, Turner P, Riethmuller-Winzen H. Comparison of flupirtine and indomethacin on frusemide-induced diuresis. Postgraduate Medical Journal 1987; 63(745):959-961
47. Ueberall MA, Mueller-Schwefe GH, Terhaag B. Efficacy and tolerability of flupirtine in subacute/chronic musculoskeletal pain-results of a patient level, pooled re-analysis of randomized, double-blind, controlled trials. International Journal of Clinical Pharmacology and Therapeutics 2011; 49(11):637-647.
48. Treudler R, Pohle K, Simon JC. Flupirtine is a safe alternative drug in patients with hypersensitivity to NSAIDs. European Journal of Clinical Pharmacology 2011; 67(9):961-963.
49. Mueller-Schwefe G. Flupirtine in acute and chronic pain associated with muscle tenseness: results of a postmarket surveillance study. Fortschr Med Orig 2003; 121:11.
50. Li C, Ni J, Wang Z, Li M, Gasparic M, Terhaag B, Überall MA. Analgesic efficacy and tolerability of flupirtine vs. tramadol in patients with subacute low back pain: a double-blind multicentre trial. Current Medical Research and Opinion 2008; 24(12):3523-3530.
51. Million RR. Management of head and neck cancer. International Journal of Radiation Oncology Biology Physics 1984; 10: 58.
52. Feingold E, Classen W, Tille C, Netter P. Comparison of analgesics on different pain stimuli. In Arzneimittel-Forschung/ Drug Research 1982; 32 (8):901-909.
53. Gatto R, Frontespezi S. Study on the analgesic activity of flupirtine in dentistry. Quadeni di Odontostomatologia 1986; 3: 71-82.
54. Sättler MB, Williams SK, Neusch C, Otto M, Pehlke JR, Bähr M, Diem R. Flupirtine as neuroprotective add-on therapy in autoimmune optic neuritis. The American Journal of Pathology 2008; 173(5):1496-1507.
55. Boscia F, Annunziato L, Taglialatela M. Retigabine and flupirtine exert neuro protective actions in organo typic hippo campal cultures. Neuropharmacology 2006; 51(2):283-294.
56. Schwarz M, Nolden-Koch M, Purr J, Pergande G, Block F. Antiparkinsonian effect of flupirtine in monoamine-depleted rats. Journal of Neural Transmission 1986; 103(5):581-590.
57. Schmidt WJ, Schuster G, Wacker E, Pergande G. Antiparkinsonian and other motor effects of flupirtine alone and in combination with dopaminergic drugs. European Journal of Pharmacology 1997; 327(1):1-9.
58. Scheef W. Analgesic efficacy and safety of oral flupirtine in the treatment of cancer pain. Postgraduate Medical Journal 1987; 63: 67-70.
59. Twycross R. Schmerzbehandlung bei Karzinompatienten. Der Schmerz 1990; 4(2):65-74.
60. Khair-ul-Bariyah S, Shahid MT. Flupirtine: A Review on its Therapeutic Potency. Int. J. Pharm. Sci. Rev. Res 2013; 22(1):231-235.
61. Fleckenstein J, Sittl R, Averbeck B, Lang PM, Irnich D, Carr RW. Activation of axonal Kv7 channels in human peripheral nerve by flupirtine but not placebo-therapeutic potential for peripheral neuropathies: results of a randomised controlled trial. Journal of Translational Medicine 2013; 11(1):34.
62. Riethmüller-Winzen H. Flupirtine in the treatment of post-operative pain. Postgraduate Medical Journal 1987; 63:61-65.
63. Jakovlev V, Achterrath-Tuckermann U, Schlichtegroll AV, Stroman F, Thiemer K. Allgemeine pharmakologische untersuchungen mit dem analgetikum flupirtin. Arzneimittel-Forschung1985; 35(1):44-55.
64. Darius H, Schrör K. The action of flupirtine on prostaglandin formation and platelet aggregation in vitro. Arzneimittel-Forschung1985; 35(1):55-59.
65. Lavy E, Prise U, Soldani G, Neri D, Brandriss N, Chaim AB, Giorgi M. Pharmacokinetics of methylphenidate after oral administration of immediate and sustained-release preparations in Beagle dogs. The Veterinary Journal 2011; 189(3): 336-340.
66. Rouini MR, Lavasani H, Sheikholeslami B, Nikoui V, Bakhtiarian A, Sgorbini M, Giorgi M. Pharmacokinetics of mirtazapine and its main metabolites after single oral administration in fasting/Fed horses. Journal of Equine Veterinary Science 2013; 33(6):410-414.
67. Giorgi M, Saccomanni G, Del Carlo S, Manera C, Lavy E. Pharmacokinetics of intravenous and intramuscular parecoxib in healthy Beagles. The Veterinary Journal 2012; 193(1):246-250.
68. Wörz R. Flupirtine in chronic myofacial pain conditions. Fortschritte Der Medizin 1991; 109(6):158-160.
69. Wörz R, Lobisch M, Schwittmann B, Gessler M, Grotemeyer KH, Langohr HD, Schabet M. Effectiveness of flupirtine in chronic tension headache. Results of a double-blind study versus placebo. Fortschritte Der Medizin 1995; 113(32):463.
70. Wörz R, Bolten W, Heller B, Krainick JU, Pergande G. Flupirtine in comparison with chlormezanone in chronic musculoskeletal back pain. Results of a multicenter randomized double-blind study. Fortschritte Der Medizin 1996; 114(35-36):500-504.
71. Ringe JD, Miethe D, Pittrow D, Wegscheider K. Analgesic efficacy of flupirtine in primary care of patients with osteoporosis related pain. Arzneimittelforschung 2003; 53(07):496-502.