FLUPIRTINE: A HUMAN DRUG WITH POTENTIAL FOR USE IN THE VETERINARY FIELD

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ABSTRACT

Flupirtine is a nonopioid drug without antipyretic or antiphlogistic properties and with a favorable tolerability in humans. It constitutes a unique class within the group of nonsteroidal analgesics and displays a peculiar pharmacokinetic/dynamic profile that could have large potentialities of applications in the veterinary field. This review describes and evaluates the pharmacologic literature concerning flupirtine and addresses its potential in veterinary medicine.

Keywords: Animal Species, Painkiller Drug, Veterinary, Flupirtine

1. INTRODUCTION

The heterogenous group of nonopioid analgetic drugs can be divided into several classes according to their pharmacodynamic properties. Within this group, the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) constitute the largest drug family, followed by the coxibs. Increasingly, other drugs within the smaller classes are being used in pain therapy, often in combination with other drugs. Examples include the calcium channel antagonists, adrenoceptor agonists, gabapentin/pregabalin (these have structural homology with the neurotransmitter G-Aminobutyric Acid [GABA]), local anaesthetics, ligand-gated ion channel (TRPV1) agonists/antagonists and cannabinoid ligands (Hebbes and Lambert, 2011). Flupirtine (FL) belongs to the class of N-methyl-D-aspartate (NMDA) antagonists, although within this class it is considered atypical.

FL was initially synthesized by Degussa Pharma (Frankfurt/Main, Germany) and was first approved in the 1980s in Germany (Friedel and Fitton, 1993). Currently, it is marketed in several countries: Germany, Italy, Portugal, Russia, Slovakia, Estonia, Latvia, Lithuania, India, United States of America and Brazil.

1.1. Chemical Properties

FL is a derivative of triaminopyridine in the form of ethyl-N-[2-amino-6-(4-fluorophenylmethylamino) pyridin-3-yl] carbamate (Fig. 1). It is commercially available as the maleate salt because FL itself is poorly water-soluble. FL is a base, with a pKa of around 5.3; it is weakly lipophilic. A key structural feature of FL is the carbamate group, which can be cleaved under strong basic and acid conditions.

1.2. Pharmacodynamics

Initially it was assumed that FL exerted its effect via NMDA-antagonistic activity. This theory was supported by the results of various indirect studies (Perovic et al., 1994; Osborne et al., 1998). It was later determined that FL actually interacted with G-protein-regulated, Inwardly Rectifying K+ channels (GIRKs) (Jakob and Krieglstein, 1997). The GIRKs represent a newly recognised family of K+ channels distinct from the voltage-dependent ones. They are regulated by neurotransmitters, occur as different subtypes and are variously expressed in different parts of the brain (Klawe and Maschke, 2009). In essence, the FL activate GIRKs.
and stabilize the membrane resting potential. Therefore, FL inhibits the NMDA receptor indirectly, the Mg\(^{2+}\) block on the NMDA receptor remains unchanged. As the compound selectively interacts with neuronal K\(^{+}\), FL was offered as the prototype for a new class of drug, the “Selective Neuronal Potassium Channel Openers” (SNEPCO) (Kornhuber et al., 1999).

### 1.3. Pharmacokinetics

FL is rapidly absorbed from the gastrointestinal tract (Friedel and Fitton, 1993). Following oral administration of FL (100 mg), the maximum plasma drug concentration (C\(_{\text{max}}\)) was 0.77 mg L\(^{-1}\) in healthy volunteers, 1.12 mg L\(^{-1}\) in elderly patients and 0.72 mg L\(^{-1}\) in patients with renal impairment (Abrams et al., 1988). FL at 200 mg resulted in twice the C\(_{\text{max}}\) (1.98 mg L\(^{-1}\)) in healthy young volunteers. Rectal administration also produced a dose dependent C\(_{\text{max}}\) (Hlavica and Niebch, 1985). Absolute bioavailability for FL was 90.0 and 72.5% for oral and rectal administration, respectively (Hlavica and Niebch, 1985).

In healthy volunteers, the apparent volume of distribution for oral flupirtine 100 mg is 154 L. Renally impaired and elderly patients recorded higher volumes of distribution, 212 and 195 L, respectively (Abrams et al., 1988). Binding of FL to human plasma proteins is about 80%.

Flupirtine is bio-transformed in the liver into two primary metabolites, 4-fluoro-hippuric acid and the N-acetylated analogue D13223 (Fig. 1), which is pharmacologically active (about 30% of the analgesic potency of the parent drug) (Schuster et al., 1998; Methling et al., 2009). Following administration of oral FL (100 mg), the mean terminal plasma elimination half-life is about 6.5 h in healthy subjects, but this is increased in patients with mild renal impairment and in the elderly to 9.8 and 14.0 h, respectively (Abrams et al., 1988). The clearance of FL is similar in healthy and renal impaired patients (275 and 263 mL. min\(^{-1}\), respectively) but it decreases in elderly patients (161 mL. min\(^{-1}\)) (Abrams et al., 1988). FL is predominantly excreted via the urine (72%) (Hlavica and Niebch, 1985). FL does not undergo cytochrome P450 enzyme mediated metabolism to a significant extent (Methling et al., 2009) and human monoamine oxidase isoenzymes were considered unlikely to participate in \textit{in vivo} metabolism of the drug. In contrast, human myeloperoxidase and horse radish peroxidase enzymes produced rapid turnover of FL, suggesting that this drug was an excellent substrate for these enzyme pathways (Methling et al., 2009).

### 1.4. Safety and Tolerability

The most common adverse events occurring during FL therapy include drowsiness, dizziness, heartburn, headache, dry mouth, fatigue and nausea (Heusinger, 1987; Herrmann et al., 1993; 1987; McMahon et al., 1987). Such events have been reported as mild and transient, (McMahon et al., 1987) and are most likely to occur in the first 6 months of therapy (Herrmann et al., 1987). No clinically significant alterations in laboratory parameters or vital signs, including blood pressure, heart rate, ECG, renal function, haematologic and metabolic parameters, have been observed during FL therapy (Heusinger, 1987; Herrmann et al., 1993; 1987; McMahon et al., 1987). Rarely, an elevation of liver enzymes is induced and the urine may take on a greenish discoloration without any associated symptoms (Maiert et al., 2010).

Compared to other available analgesics, this active ingredient is better tolerated.

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 (Hirschowitz, 1994).
The tolerability profile of FL is also superior to that of opioids, which can cause constipation, nausea, vomiting, sedation, confusion, pruritus, urinary retention and respiratory depression and are associated with the development of tolerance and dependence (Schug et al., 1992). No signs of dependence or tolerance were observed with FL treatment for chronic pain.

1.5. Prospective in Veterinary Species

Nowadays, animals (especially pets) are treated as members of the family and pet owners demand the same level of care they expect for themselves. This change in attitude has resulted in a push for the development of more effective and innovative veterinary therapies (Giorgi et al., 2012a; Giorgi and Yun, 2012). Veterinary pharmacology still has a reduced drug armamentarium compared to human pharmacology; however, human drugs are increasingly being investigated for veterinary use in order to address this shortfall (Lavy et al., 2011; Rouini et al., 2012; Giorgi et al., 2012b). 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 paradigm, FL has wide potential, although no studies on veterinary species are present in the literature to date. Based on what has already been reported in humans, FL could be applicable for the treatment of many forms of pain. For pain control in humans, dosages between 100 and 200 mg t.i.d. are required (Klawe and Maschke, 2009). Given that 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 (Mueller-Schwefe, 2003; Luben et al., 1994; Li et al., 2008; Ringe et al., 2003; Worz et al., 1996) Furthermore, its effect as a muscle relaxant is of added value for pain associated with increased muscle tension (Worz, 1991; Worz et al., 1995). FL is also beneficial for short-term treatment of acute to moderate pain such as postoperative pain, trauma and dysmenorrhoea (Heusinger, 1987).

Chronic pain leads to nerve degeneration therefore an analgesic with neuroprotective, in addition to pain relief properties would be an advantage for the treatment of chronic pain. FL displays potent antioxidant properties in rat brain mitochondria and phaeochromocytoma 12 cell culture and administration of FL significantly inhibited free radical reactions (Gassen et al., 1998). Increasingly, veterinary patients are living longer and for this reason, there is likely to be a growing market for neuroprotective and antioxidant supplements.

Glutathione depletion is associated with a failure to maintain Reactive Oxygen Species (ROS) levels and it inevitably leads to cell death by apoptosis. FL maintains glutathione levels, a property that has prevented cell death in human RPE cells (Wood et al., 1998). This feature could be exploited in animal species that only have small amounts of this enzyme, such as cats and ferrets.

Several studies of pain-relief have made the comparison between FL and opioids. FL was shown to be significantly more effective in pain reduction compared to pentazocine, a lower adverse effect profile was reported also (Galasko et al., 1985; Scheef, 1987; Heusinger, 1987). When administration of 100 mg of FL and 60 mg of dihydrocodeine in post-surgical patients were compared, both drugs showed comparable pain-relieving properties (Moore et al., 1983). FL showed a efficacy profile superior to that of tramadol for cancer-associated pain (Luben et al., 1994). FL in combinational therapy with morphine, increased the antinociceptive activity of morphine 4-fold without increasing the adverse effects (Goodchild et al., 2008). Combinatorial therapy could be useful in animals when it is desirable to avoid moderately high regimens of opioids.

Other studies compared the efficacy of FL with NSAIDs. FL and diclofenac showed equal efficacy in orthopaedic post-operative pain (Mastronardi et al., 1988) and similar efficacy in musculoskeletal pain (Marczyk, 1992). FL’s reduction in pain associated with acute migraine was similar to that of paracetamol (Million et al., 1984) and patients affected by spinal root irritation reported a lower pain score with FL compared to aspirin (Sitzer, 1991).

Adverse Drug Reactions (ADR) may be dose-type A) or non-dose-dependent type B, Hypersensitivity Drug Reactions (HDR) (Rivier and Papich, 2009). HDR to NSAIDs reportedly occur at a prevalence of 0.5-2.5% in the general population (Baumer et al., 2006). FL could be an attractive alternative for patients with a history of HDR to NSAIDs (Treuiller et al., 2011). Furthermore, it does not induce the gastrointestinal side effects evoked by NSAIDs or the cardio-/cerebrovascular and renal side effects evoked with chronic therapy with coxib.

2. CONCLUSION

There is a substantial body of evidence on the efficacy of FL in humans however as yet, this is insufficient to recommend off-label use in veterinary clinical practice. The purpose of this manuscript is to highlight the attractiveness of FL’s pharmacology profile and its potential scope for use in veterinary medicine.
with the view to encourage scientists to perform studies on FL in the veterinary field.

3. REFERENCES


