The Role of Lornoxicam in Pain and Inflammation: A Review
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ABSTRACT
Non-steroidal anti-inflammatory drugs usually abbreviated as NSAIDs, are the drugs with analgesic, antipyretic and, in higher doses, with anti-inflammatory effects. NSAIDs inhibit cyclooxygenase (COX) 1 and 2. So, most of the side effects develop as a result of cyclooxygenase inhibitory activity. Lornoxicam is a strong analgesic and anti-inflammatory NSAID of the oxicam class with better tolerability profile when compared to other NSAIDs. Its analgesic activity is comparable to that of opioids. It has been shown to be effective in the treatment of postoperative pain and rheumatoid arthritis (RA). The present review provides an overview of lornoxicam.

Keywords: Lornoxicam, NSAIDs, Rheumatoid arthritis, oxicam

1. INTRODUCTION
Lornoxicam, a congener of tenoxicam, is a new NSAID belonging to the oxicam class. It is a strong analgesic and anti-inflammatory NSAID as compared to other NSAIDs. Its analgesic activity is comparable to that of opioids. Studies have shown that it is more effective than 10 mg morphine when used at doses ≥ 8 mg to control pain after oral surgery. Lornoxicam combines the high therapeutic potency of oxicams with an improved gastrointestinal toxicity profile as compared to naproxen which is probably due to the short half-life of lornoxicam as compared to the other oxicams. Clinical investigations have established it as a potent analgesic with excellent anti-inflammatory properties in a range of painful and/or inflammatory conditions, including postoperative pain and RA.1,2 Lornoxicam has shown protective effects on the development of myocardial infarction in rats under conditions of ischemia and ischemia-reperfusion.3

Lornoxicam inhibits the COX-1/COX-2 system, the production of interleukin-6, and the inducible NO synthase.4 It may be applied by the intramuscular or intravenous route; its bioavailability after oral application is approximately 90%. Although its elimination half-life is only about four hours.5 The duration of effect is approximately eight hours, analogous to other acidic antipyretic analgesics.

Chemistry
The active drug substance is 6-chloro-4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno-[2,3-e]-1,2-thiazine-3-carboxamide-1, 1-dioxide (Fig.1). It is a yellow crystalline solid with a pKa of 4.7. It is highly ionized at physiological pH and has relatively low lipophilicity thereby preventing distribution to fatty tissues. It has a molecular weight of 371.82 Da.
Figure 1: Chemical structure of lornoxicam (C₁₃H₁₀CN₃O₄S₂).

Pharmacology of Lornoxicam

Pharmacodynamics

Lornoxicam is an active substance from the group of acidic anti-pyretic analgesics. The accumulation of acidic analgesics in the inflamed tissue is considered to be a significant aspect of their anti-inflammatory effect. In cases of painful inflammatory reactions, the capillaries in the inflamed tissue are damaged and plasma proteins along with bound pharmaceutical substances are discharged into the extravascular space. On account of the reduced pH value in inflamed tissue, analgesic acids are able to move from the extracellular space and enter the cells more easily. This also explains why the duration of action of acidic substances is generally longer than one would expect in consideration of their plasma half-life. The inflamed tissue probably behaves like a deep compartment whose filling and depletion adjust to the plasma concentrations with substantial delay.

Pharmacokinetics

The bioavailability of lornoxicam after oral application is more than 90%. Maximum plasma concentrations are achieved after about two hours. Given normal liver and kidney function, the plasma half-life is about four hours (see Figure 3). In elderly patients the clearance of lornoxicam is reduced by about 30% to 40%; thus the half-life is somewhat longer. Even in the presence of impaired kidney and liver function, no major differences in pharmacokinetics have been observed. On account of its short half-life, no accumulation is likely to occur even in cases of repeated administration – in contrast to NSAID with a longer half-life. Like other oxicams and diclofenac, lornoxicam is metabolised via cytochrome P450 (CYP-2C9). Due to a genetic polymorphism some individuals may metabolise slowly and therefore have elevated levels of lornoxicam.

Mechanism of action

Like all NSAIDs, it acts by inhibiting the metabolites of COX branch of arachidonic acid pathway. It inhibits both isoforms in the same concentration range i.e. COX-1/COX-2 = 1. Thus, a perfectly balanced inhibition of COX-1 and COX-2 is achieved. COX-1 is a constitutive enzyme expressed in many cells as a house keeping enzyme and provides homeostatic prostaglandins. COX-2 is an inducible enzyme, which is expressed at the onset of inflammation in many cell types involved in inflammatory responses. It differs from other oxicam compounds in its potent inhibition of prostaglandin biosynthesis, a property that explains the particularly pronounced efficacy of the drug. Prostaglandins are involved in all phases of inflammatory events including fever, pain reactions and physiological functions like intestinal motility, vascular tone, renal function, gastric acid secretion etc. The inducing events include phorbol esters, cytokines and endotoxins.

It might produce the peripheral analgesic effects by NOcGMP pathway and the opening of K+ channels. It also acts by inhibition of spinal nociceptive processings, elevation of plasma levels of dynorphin and β endorphin following IV administration. In vitro tests have shown that lornoxicam also inhibited the formation of nitric oxide. It has also shown marked inhibitory activity on endotoxin induced IL-6 formation in THP 1 monocytes with less activity on TNF alpha and IL-1α.

Interactions

Plasma concentrations of lornoxicam and many other NSAID are increased by cimetidine but not by ranitidine. Lornoxicam reduces the renal clearance of digoxin. Lornoxicam may also increase serum concentrations of methotrexate and cyclosporine. Interactions with CYP-2C9 inducers (e.g., rifampicin) may also occur.

Tolerability

In large studies 16% of patients experienced gastrointestinal intolerance. Thus, lornoxicam is well within the range of many non-selective NSAID. The other side effects of lornoxicam are mild. In general lornoxicam is a NSAID with a typical side effect profile. With regard to disturbances of renal and hepatic function,lornoxicam compares well with other NSAID. No major increases in kidney or liver data have been observed with lornoxicam.Nevertheless, caution should be exercised when using NSAID and also lornoxicam to treat patients with impaired liver or kidney function. The short half-life of lornoxicam is an advantage in patients with impaired renal function because it offers recovery phases for the kidney between the individual doses. In clinical practice the increase in the volume of extracellular fluid secondary
to NSAID is significant because it may lead to cardiac problems in predisposed patients

**Therapeutic uses**

**Analgesia: Acute and Chronic Pain**

Lornoxicam has been shown to produce dose related analgesia. 16 mg and 32 mg were significantly superior to 4 mg with respect to pain relief. The total pain relief score after 6 hours of intake of lornoxicam are highest at 32 mg. Hence it is a useful agent in the treatment of postoperative pain and other acute traumatic painful conditions such as fractures. In pain following oral surgery and post thyroidectomy; lornoxicam in a dose of 8 mg gives better pain relief than aspirin 650 mg, has higher response rate, faster onset of action and longer duration of action. The duration of analgesic effect of lornoxicam is approx 4.5 hrs with maximum pain relief occurring at approximately 2 hrs. The analgesic effects of parenteral lornoxicam is not immediate as some time is required to inhibit the arachidonic acid pathway, thus pre operative administration may be more appropriate for those requiring procedures under 2 hrs.

Lornoxicam is found effective in acute sciatica, lumbosciatica and chronic low back pain. Lornoxicam can decrease the opioid requirement when used as an adjunctive analgesic in patients with cancer pain. Lornoxicam decreases the number of headache episodes and also reduces the analgesic intake in migraine attacks.

**Anti Inflammation**

In osteoarthritis, 8mg twice daily improves pain and functional disability. Other area where lornoxicam is found useful is ankylosing spondylitis and Rheumatoid arthritis. Anti inflammatory and antipyretic effects of lornoxicam include prevention of the degenerative bone loss seen in chronic inflammation by inhibiting polymorphonuclear leucocyte migration (for this effect an additional dose of 0.1 mg/kg is required). Antipyretic effect is observed at a dose 10 fold higher than that required for inflammation.

**Reduction of myocardial infarction volume**

Activation of inflammation and enzyme cyclooxygenase with formation of proinflammatory prostaglandins is a key element of development of myocardial infarction in patients with acute coronary syndrome. Lornoxicam has shown protective effects on the development of myocardial infarction in rats under conditions of ischemia and ischemia-reperfusion.

**Herpetic Stromal Keratitis**

An experimental study in mice has demonstrated its protective effects against herpetic stromal keratitis (HSK), presumably through the down-regulation of NF-kappa B activation. Lornoxicam treatment significantly decreased the incidence of recurrent HSK, attenuated the corneal opacity scores, and also effectively suppressed both NFkappa B activation and TNF-alpha expression in biological analysis. Other effects of lornoxicam include inhibition of release of superoxide from polymorphs and inhibition of the release of platelet derived growth factor (PDGF) from the platelets, both of which are involved in the pathogenesis of RA. Thus lornoxicam can have protective effects in the management of RA. Lornoxicam also stimulates proteoglycan synthesis suggesting possible reparative effects in RA.

**REFERENCES**


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