Lornoxicam: a Newer NSAID

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Abstract

Pain relieving drugs are one of the most commonly used drugs worldwide either through prescription or as over the counter medication. 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. Certain NSAIDs, for example, rofecoxib and nimesulide have been banned because of their adverse effects. Lornoxicam (chlortenoxicam) 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 post operative pain and rheumatoid arthritis (RA). The present review provides an overview of lornoxicam.

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Abbreviations used: COX-Cyclooxygenase, NSAID-Non Steroidal Anti-inflammatory Drug, PG-Prostaglandins, TNF-Tumor Necrosis Factor, IL-Interleukin, NO-Nitric oxide, cGMP-Cyclic Guanosine Monophosphate, PDGF-Platelet Derived Growth Factor, TOTPAR- Total Pain Relief Score, C_{max}-Maximum Concentration, AUC-Area Under Curve

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 > or = 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] Recently, an experimental study in mice has demonstrated its protective effects against herpetic stromal keratitis (HSK), presumably through the down-regulation of nuclear factor kappa B (NF-kappa B) activation. Lornoxicam treatment significantly decreased the incidence of recurrent HSK, attenuated the corneal opacity scores, and also effectively suppressed both NF-kappaB activation and TNF-alpha expression in biological analysis.[4] Other potential indications of lornoxicam are being investigated.

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.[5]

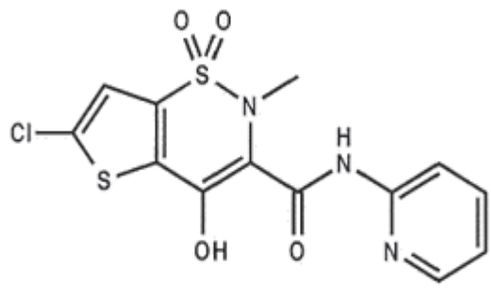

FIG. 1. Chemical structure of lornoxicam ($C_{13}H_{10}ClN_3O_4S_2$).

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.[6] It might produce the peripheral analgesic effects by NO-cGMP pathway and the opening of K^+ channels.[7,8] It also acts by inhibition of spinal nociceptive processings, elevation of plasma levels of dynorphin and ß 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-1â.[9]

Pharmacokinetics

Lornoxicam is absorbed rapidly and almost completely from the gastro-intestinal tract. Peak plasma concentration is attained with in 2.5 hrs. On repeated administration, C_{max} is increased in dose related manner. No evidence of drug accumulation on repeated drug administration has been reported. Food reduces the absorption of the drug. The absolute bioavailability of lornoxicam is 90-100%. Almost 99% is protein bound exclusively to albumin. No first-pass effect has been observed. Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite. The hydroxylated metabolite exhibits no pharmacological activity.[5,10] CYP2C9 has been shown to be the primary enzyme responsible for the biotransformation of the lornoxicam to its major metabolite, 5'-hydroxylor noxicam.[11] Approximately 2/3 is eliminated via the liver and 1/3 via the kidneys as inactive substance. Unlike other oxicams, it has a relatively short plasma half-life (3 to 5 hours). It is eliminated following biotransformation to 5'-hydroxy-lornoxicam, which does not undergo enterohepatic recirculation. Glucuroconjugated metabolites are excreted in urine and faeces with a half-life of about 11 hours. Lornoxicam and its metabolites bind extensively to plasma albumin. It readily penetrates into synovial fluid, the proposed site of action in chronic inflammatory arthropathies. Lornoxicam synovial fluid: plasma AUC ratio is 0.5, after administration of 4 mg twice daily.[12]

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.[13] 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 lornoxican 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.[13-15]

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.[16,17] Anti inflammatory and antipyretic effects of lornoxicam include prevention of the degenerative bone loss seen in chronic inflammation by inhibiting polymorphornuclear 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.[18]

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.[3]

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 NF-kappa B activation and TNF-alpha expression in biological analysis.[4]

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.[19]

Dosage and Route

It is available in oral and parenteral formulations. Its oral dose is 4mg thrice daily or 8mg twice daily.[20]

Safety Pharmacology & Toxicological studies

Prostaglandins play an important role in gastrointestinal mucosal protection by strengthening the mucosal barrier for acid and in inhibiting gastric acid secretion. Thus the adverse effects of the acidic NSAIDs are mainly because of inhibition of prostaglandin production. The gastric side effects range from mild dyspepsia and heartburn to ulceration and hemorrhage. Lornoxicam does not increase the serum pepsinogen levels (a marker of morphological and functional state of gastric mucosa in contrast to other NSAIDs e.g. indomethacin, ibuprofen which increase the serum pepsinogen levels). Risk factors for NSAIDs induced gastropathy include smokers, old age, history of peptic ulcer and those receiving oral corticosteroids and oral anticoagulants. Clinical investigations done so far have suggested its improved gastrointestinal toxicity profile. This is probably due to the short half-life of lornoxicam as compared to the other oxicams. [21-23] Renal side effects can range from acute and chronic renal failure to edema and electrolyte imbalance which play only a minor role in normal person. And when the renal function is compromised drug side effects are pronounced to a greater extent. Lornoxicam because of its short half-life is less liable to nephrotoxicity on repeated drug administration. No evidence of nephrotoxicity on administration of doses upto 8 mg twice daily, have been found in either in healthy volunteers or patients with mild to moderate renal impairment.[20,24,25] Hematological effects of lornoxicam include interference with platelet aggregation leading to prolonged bleeding time.[24] The preclinical studies for its chronic oral toxicity and carcinogenic potential suggested that the drug-related toxicity mainly comprised mortality, reduced body weight gain, clinico-pathological changes indicative of anaemia resulting from blood loss, and renal damage, renal papillary necrosis and gastrointestinal mucosal lesions. The kidney-associated changes were not completely reversible during the recovery period. Toxicokinetic investigations demonstrated a dose-linear absorption of the drug. In female rats, the terminal half-life was about twice that in males which led to a higher exposure of this gender to lornoxicam. A dose of 0.01 mg/kg/day was established as no-observed-effect level. In a 104-wk carcinogenicity study, lornoxicam was administered by oral gavage to male and female rats. Drug-related changes were similar to those in the chronic studies and consistent with the anticipated side-effects of NSAIDs. No carcinogenic potential was revealed.[26]

Drug Interaction

Like other NSAIDs, it appears to interact with warfarin, sulphonylureas, digoxin and furosemide. It is not affected by the co-administration of ranitidine, aluminium, magnesium and calcium containing antacids. Cimetidine co-administration inhibits elimination of lornoxicam resulting in significant increase in steady state C_{max} and AUC (area under curve) values and a reduction in apparent plasma clearance.[27] Lornoxicam displaces glibenclamide from its protein binding site leading to enhanced glibenclamide effect.[28] It increases the concentration of warfarin leading to increased coagulation time. Lornoxicam decreases the plasma digoxin clearance and increases methotrexate concentration.[29]

Clinical Studies

Clinical investigations focusing on efficacy and tolerability of lornoxicam have been carried out. Comparison of lornoxicam and rofecoxib in patients with activated osteoarthritis (COLOR Study) was carried out in 2520 patients for over 25 days on average. Before and after treatment patients documented their individual scores for pain on movement, at rest and during the night, and their

individual duration of morning stiffness as well as the consequent grade of restriction. Pain on movement (-45.3%), at rest (-42.0%) and at night (-42.5%) was reduced by rofecoxib, whereas improvements after treatment with lornoxicam exceeded those effects significantly (-55.8%, -55.8% and -59.9%, respectively). Shortening of the duration of morning stiffness was significantly ($p < 0.001$) more pronounced with lornoxicam (-66.6%) than with rofecoxib (-50.2%). Adverse events were reported in 5.4% of all lornoxicam patients compared with 12.0% of the rofecoxib recipients ($p < 0.001$). GI symptoms showed a slight trend of being less frequent following rofecoxib therapy. All improvements in each efficacy parameter were clinically relevant in each treatment group and significantly superior ($p < 0.001$) in the lornoxicam group. The results of this study confirmed that both lornoxicam and rofecoxib are effective in the treatment of patients with activated osteoarthritis; the analgesic and anti-inflammatory effects of lornoxicam are significantly superior to those of rofecoxib without inferiority in tolerability.[30]

In another randomized, double blind clinical study; lornoxicam was investigated as a treatment for RA versus naproxen. Lornoxicam (4 mg t.i.d. and 8 mg bi.d.) and naproxen (500 mg b.i.d.) were given to 225 patients for 12 weeks. Grip strength and scores on the Ritchie Articular Index improved similarly in all the treatment groups.[17] In a further multicenter, double blind clinical trial, lornoxicam was as potent as diclofenac sodium with comparable tolerability.[31]

Conclusion

The data available from clinical studies have demonstrated that lornoxicam has advantageous profile in moderate to severe pain in combination with an anti inflammatory efficacy comparable to other NSAIDs. In addition, it may be an alternative to other NSAIDs for the treatment of painful arthritic and inflammatory diseases. Furthermore, it possesses superior gastrointestinal safety profile as compared to other NSAIDs.

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