Nimesulide

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Nimesulide is a newer non-steroidal anti-inflammatory agent with additional anti-pyretic and analgesic activity. For many years the principal non-steroidal anti-inflammatory drugs (NSAIDs) in use have been inhibitors of prostaglandin synthesis like ibuprofen. The therapeutic efficacy of these drugs usually correlates with the reduction in prostaglandin levels. However, this effect is also responsible for the inhibition of gastroprotective prostaglandins leading to gastrointestinal intolerance. The development of new NSAIDs has focussed on the discovery of potent anti-inflammatory compounds that display alternative modes of action. Nimesulide is a non-steroidal anti-inflammatory analgesic drug of the sulfonamide class and is chemically 4-nitro-2-phenoxymethanesulfonyl. It differs from conventional NSAIDs both in structure and pharmacological profile.

Mechanism of Action

Nimesulide produces irreversible inhibition of prostaglandin synthetase equally inhibiting formation of PGE2 and PGF2.

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Nimesulide demonstrates anti-inflammatory activity at a dose far lower than that associated with gastro-intestinal toxicity(1). At doses that inhibit acute inflammation, nimesulide has no effect on the arachidonic acid metabolism in organs such as stomach, kidneys and lungs normally affected by other NSAIDs. Moreover, the effect of nimesulide is more at inflammatory sites. Nimesulide also acts by various other non-prostaglandin mechanisms which include free radical scavenging, effect on histamine release and activity, effect on neutrophil peroxidase, cartilage degradation and metalloprotease synthesis, phosphodiesterase type IV inhibition, platelet aggregation and synthesis of platelet activating factor(2-6). Nimesulide also exerts an anti-inflammatory effect by inhibiting the release of tumor necrosis factor and thereby decreasing cytokine release. An antipyretic effect of nimesulide was first demonstrated in experimental animals(7,8). The therapeutic antipyretic effectiveness of nimesulide has now been proven clinically in various double blind studies both in adults and children(9,10).

Pharmacokinetics

After oral administration, the drug is completely absorbed. It is extensively bound to serum proteins (99%) and is distributed throughout the tissues(11). It undergoes rapid and extensive biotransformation via several mechanisms. The principal metabolite is its hydroxyl derivative (OH-Nimesulide) conjugated with glucuronic acid which is excreted in urine. It is more rapidly and extensively absorbed in children compared to adults. The terminal half life is shorter in children (2.36 hours) than in adults (3.02 hours)(12). In patients
with moderate renal failure, the terminal elimination half life of hydroxy-nimesulide is increased leading to its accumulation. This accumulation appears to have little clinical significance. However, in patients with severe renal failure it is better to withhold the drug till the risks of accumulation of the metabolite are well studied. Patients with liver disease should not receive the drug because of its elimination after glucuronidation. As a result of its extensive plasma protein binding, nimesulide may be displaced from binding sites by concurrently administered drugs like fenifibrate, salicylic acid and tolbutamide. No other major drug interactions of any clinical significance have been described(13). Nimesulide may reduce the natriuretic response to furosemide and potentiate the reduction in glomerular filtration and renal blood flow. Caution is to be exercised when prescribing nimesulide in combination with drugs known to adversely affect renal function(14). Few patients have shown an increase in anti-coagulant effect with warfarin when given concomitantly with nimesulide.

**Therapeutic Uses**

Studies to date suggest that nimesulide is an effective anti-inflammatory and analgesic agent in the treatment of osteoarthritis, rheumatoid arthritis, acute and chronic respiratory tract inflammation, otitiss, laryngeal and pharyngitis and secretory otitis media(15). It is capable of modulating the inflammatory process by scavenging the free radicals which cause tissue damage and produce rapid recovery of the important functions of the respiratory mucosa. This may prevent development of complications such as chronic sinusitis or bronchopulmonary disorders(16). In patients with suspected bacterial infection, antibiotic therapy should also be prescribed to facilitate full recovery. In addition, some studies indicate that nimesulide has greater anti-inflammatory effects than other NSAIDs which are due at least in part to the ability of nimesulide not only to inhibit cyclooxygenase pathways but also to act as scavenger of free oxygen radicals.

In a study in children, treatment with nimesulide resulted in normalization of body temperature more rapidly which was also longer lasting in comparison to paracetamol(17). During treatment, normal body temperature was achieved after an average of 2.8 doses of nimesulide and 4.7 doses of paracetamol (p <0.01)(12). The combined antipyretic and anti-inflammatory effects of nimesulide were associated with a more pronounced and rapid improvement in the general condition of patients than was observed with paracetamol. Antipyretic effects of nimesulide were documented to be better than mafenamic acid, aspirin and naproxen and definitive fever resolution was achieved with fewer doses(18-20).

At therapeutic concentration nimesulide inhibits superoxide anion production and has an inhibitory effect on phosphodiesterase type IV. Inhibition of this enzyme is responsible for suppressing histamine release from basophils and hence it is useful in the treatment of chronic asthma. Broncho-constriction because of cyclooxygenase inhibition is not seen with nimesulide as it does not increase 5 lipoxygenase products(21).
Side Effects

At present there are no large long term studies to adequately assess the overall incidence of side effects with nimesulide. Heart burn, excessive perspiration, flushing, hyperexcitability and skin rash are the occasional side effects reported(22). The incidence of adverse events usually ranging between 0 to 10% increase with a longer duration of therapy.

Preparations

Nimesulide is available as tablets (100 and 200 mg), suspension (50 mg/5ml) and transgel form for local application.

Conclusion

Although the studies on antipyretic efficacy of nimesulide in children are limited in number, where comparative agents have been used, this drug has proven to be at least as efficacious (and in many cases more effective). With its convenient dosage schedule of twice daily administration and almost the same cost, nimesulide appears to offer a useful alternative to other NSAIDs in the symptomatic treatment of children with inflammatory conditions and/or pain and fever states. However, additional long term data is desirable to reaffirm its general safety in children especially for prolonged use.

REFERENCES


