Drug Therapy

Nimesulide

K. Rajeshwari
A.P. Dubey

Nimesulide is a newer non-steroidal anti-infalmmatory 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 sulfonilide class and is chemically 4 nitro 2 phenoxy methanesulfonnilide. 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.

From the Department of Pediatrics, Hindu Rao Hospital, Delhi 110 007 and Lok Nayak Hospital, New Delhi 1 10 002.

Reprint requests: Dr. A.P. Dubey, Professor of Pediatrics, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi 110 002.

Nimesulide demonstrates anti-inflammatory activity at a dose far lower than that associated with gastro-intestinal toxicity(l). 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 hydroxy 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-nimuselide 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 glucuronic acid conjugation. 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, otorhinolaryngological inflammation, dysmenorrhea and thrombophlebitis. The drug is contraindicated with a history of prior hyper sensitivity and in gastric ulcer or hemorrhage. The recommended dose in children is 5 mg/kg per day in 2 or 3 divided doses for 7-10 days. This duration of therapy is effective in controlling the inflammatory process in upper airway disorders like rhinitis, rhinosinusitis, 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 cyclo-oxygenase 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 naproxan 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 cyclo-oxygenase inhibition is not seen with nimesulide as it does not increase 5 lipoxygenase products(21).

Side Effe cts

At presen t there are no large long term studi es to adequa tely assess the overal l incidence of side effects with nimesulide. Heart burn, excessive perspira tion, flush- ing, hyperexc itability and skin rash are the occasional side effects rep orted(22). The in- cidence of adverse events usually ranging between 0 to 10% increase with a longer duration of therapy.

Preparations

Nimesul ide is available as tablets (100 and 200 mg), susp ension (50 mg/5ml) and transgel form for local ap plication.

Con clusion

Although the studies on antipyretic effi- cacy of nimesu lide in chi ldren are limited in number, where comparative agents have been used, this drug has prov en to be at least as efficacious (and in many cases more effective). With its convenient dosage schedule of twice daily administra tion and almos t the same cost, nimesu lide appear s to offer a useful alternative to other NSAIDs in the symptomatic treatment of children with inflammatory conditions and/or pain and fever states. However, ad- ditional long term data is desirabl e to reaf- firm its general safety in children especially for prolonged use.

REFERENCES

1. Magni E. The effect of nimesulide on prostagla ndin formation. Drugs 1993; 46 (Suppl 1): 10-14.
2. Capsoni F, Venegoni E, Minonzio F, *et al.* Inhibition of neutrophil metabolism by nimesulide. Agents Actions 1987; 21: 121- 129.
3. Butler JM, Chan SC, Stevens SR, *et al.* In creased leucoc yte histamine release with elevated cyclic AMP phosphodiesterase activity in atopic dermatitis. J Allergy Clin Immun 1983; 71: 490-497.
4. Bevilacqua M, Vago T, Ber etta A, *et al.* Nimesulide as an inhibitor of superoxi de anion production by human polymorpho- nuclear leucocytes. Pain Reproduction 1988; 31: 265-272.
5. Bevilacqua M, Magni E. Recent contribu- tions to knowle dge of the mechanism of action of nimesulide. Drugs 1993; 46 (Suppl 1): 40-47.
6. Ceserani R, Carboni L, Germini M, *et al.* Antipyretic and platelet antiaggreVating effects of nimesu lide. Drugs 199 3; 46 (Suppl 1): 48-51.
7. Swingle KF, Moo re GGI. Preclinical pharmocol ogical studies with nimesulide. Drugs Exp Clin Res 1984; 10: 587-597.
8. Velo GP. The anti-inflamm atory, analge sic and antipyretic activity of nimesulide in experimental models. Drugs Invest 1991; 3 (Suppl 2): 10-13.
9. Cunietti E, Monti M, Vigand A, *et al.* Stud ies clinico in doppio cieco sull 'efficacia e sicur ezza della nimesuli de in confonto a paracetamolo nel trattamento della iperpiressia nell anziano. Arzneimittal Forschung 1993; 43:160-162.
10. Barberi I, Maccaia A, Spata N, *et al.* Efficacia e sicurezza della nimesulide valuta ta in doppio cieco nel trattamento della affezioni respiratorie acute in terapia pediatri ca. Gazzetta Medica 199 3; 152: 49-55.
11. Pulkki nen V, Vue nto M. Dist ribution of oral nimesulide in female genital tissues. Biopharm Drug Disp 1991; 12:113-117.
12. Ugazio AG, Guarnaccia S, Beradi M, Renzetti M. Clinical and pharmocokinet ic study of nimesulide in children. Drugs 1993; 46 (Suppl 1): 215-218.
13. Perruca E. Drug interactions with nimesul ide. Drugs 1993; 46 (Suppl 1): 79- 82.
14. Steinhaustin F, Munafo A, Buchin T, *et al*. Renal effects of nimesulide in furosemide treated subjects. Drugs 1993; 46 (Suppl 1): 257-262.

15. Nouri EM. Nimesulide for treatment of acute inflammation of the upper respira tory tract. Clin Ther 1984; 6:142-150.

16. Leconte L, Monli T. Antipyretic effects of nimesulide in pediatric practice: A double blind study. Curr Med Res Opin 1991; 12: 296-303.

17. Polidori G, Tilli G, Peiragostine A, *el al.* A comparison of nimesulide and paracetamol in the treatment of fever due to inflammatory diseases of the upper respiratory tract in children. Drugs 1993 ; 46 (Suppl 1): 231-233.

18. Salzberg R, Giambonini S, Maurizio M, *et al. A* double blind comparison o f nimesulide and mefenamic acid in the treatme nt of acute upper respiratory tract infection in children. Drugs 1 993; 46 (Suppl 1): 208-211.

19. Cappella L, Guerra A, Laudizi L, Cavazutti GB. Efficacy and tolerability of nimesulid e and lysine acetylsalicylate in the treatment of pediatric acute upper respirator y tract inflam mation. Drug s 1993; 46(Suppl 1): 222-225.

20. Salmon Rodriguez LE, Arista Viver os HA, Liyan ME. Assessment of the efficacy and safety of nimesulid e vs naproxen in pediatric patients with respirato ry tract infections. Drugs 1993; 46 (Suppl 1): 226-230.

21. Rufer C. Mode of action of anti-inflammatory methansulphonalides. Biochem Pharmacol 1982; 31: 3591-3596.

22. Ward A, Brogden RN. Nimesulide. A preliminary review of its pharmecolo gical properties and therapeutic efficacy in inflamm ation and pain stat es. Drug s 1988; 36: 732-753.