DRUG MONOGRAPH

AN OVERVIEW OF ISOXICAM: A NEW NONSTEROIDAL ANTI-INFLAMMATORY DRUG

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SYNOPSIS

Isoxicam is effective and well tolerated in all the major rheumatic diseases. It has been shown to be more efficacious than most currently available NSAIDs, and at least as well tolerated. Its elimination half-life of 31 hours suits it ideally for once daily administration, and also allows occasional omission of a dose without loss of therapeutic control. The pharmacokinetic disposition of isoxicam is comparable in young and elderly subjects, as well as in patients with renal or hepatic impairment. This *isokinetic* profile allows a standard dosing regimen to be employed across all age groups (except children) and also in patients with major organ dysfunction. No unusual drug interactions have been noted, and the frequency of side-effects is low. Isoxicam is as well tolerated by elderly patients as by younger age groups, reflecting the constancy of the pharmacokinetic disposition with age.

INTRODUCTION

Isoxicam (Maxicam®) is the product of an independent drug discovery program, set up in 1966 by Warner-Lambert, to search for novel non-steroidal anti-inflammatory drugs (NSAIDs) of the non-carboxylic acid type. Isoxicam is an enolic acid and a benzothiazine derivative of the oxicam class of drugs, other members of which are piroxicam, tenoxicam and sudoxicam. Its full chemical name is [4-hydroxy-2-methyl-n-(5-methyl-3-isoxolyl)-2H-1, 2-benzothiazine-3-carboximide 1,1-dioxide](1). The structural formula is shown in Fig. I.

PHARMACOLOGY

In standard animal models, isoxicam has shown anti-inflammatory, analgesic and antipyretic activity. In particular, it has been demonstrated to produce long-lasting inhibition of carrageenan-induced paw oedema, and also of adjuvant-induced arthritis, both in prophlactic and in therapeutic studies(2). In addition, isoxicam was also effective in inhibiting collagen-induced arthritis(3). In comparison with other NSAIDs, isoxicam is only a week inhibitor of cyclo-oxygenase, and demonstrates no inhibitory activity against 5-lipoxygenase(4).

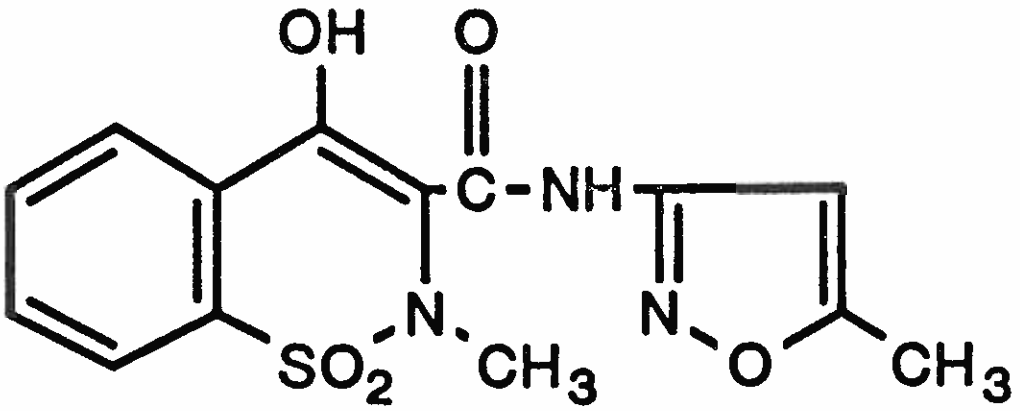

Figure 1. The structure of isoxicam.

PHARMACOKINETICS

Following oral administration, peak plasma levels occur within 4-8 hours. The drug is virtually 100 percent bioavailable, and demonstrates linear pharmacokinetics over the recommended therapeutic dosage range. Like other NSAIDs, isoxicam is highly bound to plasma proteins (98 percent at normal dosing levels). It is extensively metabolised in the liver, with only approximately 2 percent of parent drug appearing unchanged in the urine. In common with other drugs of the oxicam class, isoxicam has a low total body clearance resulting in a long elimination half-life(2). The mean value is 31 hours, based on single and repeated dose studies making isoxicam ideally suited for once daily administration. In patients with hepatic disease, there is some reduction in plasma protein binding resulting in slightly more *rapid* elimination(5). Even in patients with severe impairment of renal function, there is no excessive accumulation of isoxicam with repeated dosing(6). This is undoubtedly a reflection of the extensive metabolism to polar metabolites, which are readily excreted even in patients with severe impairment of renal function.

There has been a growing awareness, in recent years, that the elderly may constitute a distinct subgroup of the population in respect to the pharmacodynamic expression and pharmacokinetic disposition of drugs. A number of well-recognised age-related physiological changes may significantly alter the biological handling and effects of drugs in the elderly subject(7). The pharmacokinetics of isoxicam have been intensively investigated in a series of single and repeated dose pharmacokinetic studies in healthy young and elderly subjects as well as elderly patients with rheumatoid arthritis. Results from these studies have indicated that the pharmacokinetic disposition of isoxicam does not alter, with age. Table I shows results obtained from a 21-day repeated dose study of 200mg isoxicam given once daily to young and elderly subjects(8). There were no significant differences between the two age groups in any of the pharmacokinetic variables. This constancy of the kinetic disposition of isoxicam has been termed the *"isokinetic"* phenomenon, and indicates that no dosage modification is necessary in the treatment of the elderly patient. The relatively slow elimination of isoxicam allows maintenance of the plasma level at 65 percent of the steady state value, even if a dose is missed(9). In a clinical study in patients with rheumatoid arthritis, substitution of placebo for active isoxicam did not result in worsening of the patients' pain for 48 hours, further indicating maintenance of adequate plasma (and tissue) levels of isoxicam when one or even two doses of isoxicam are omitted (10).

TABLE 1

	Age	
Pharmacokinetic Variable	**18-64 (years) n = 34**	**65-88 (years) n = 15**
Elimination half-life (hours)	31.4	31.2
Maximum concentration (ug/Ml)	40.8	43.6
Area under plasma concentration/ time curve (ug. hours. ml^{-1})	663.7	714.3

Pharmacokinetic variables following 21 day repeated dosing with isoxicam 200mg once daily (mean values)

The long duration of action of isoxicam is complemented by a rapid onset of action of analgesia. Significant pain reduction, based on patient self-rating pan scales, was observed 3 hours after the first 200mg isoxicam dose in patients with rheumatoid arthritis(11), and as early as 2 hours after a single 400mg dose in patients with acute gouty arthritis(12). This rapid onset of pain relief is likely to enhance patient confidence in the drug and also promote compliance.

In order to reduce the frequency of dosing of short half-life drugs, it is common pharmaceutical practice to reformulate such agents in a "slow-release" or "retard" preparation. However, the release characteristics of such preparations may be altered by changes in the gastrointestinal milieu, resulting in erratic or incomplete liberation of active drug substance. In a double-blind comparative study, isoxicam (200mg once daily) was compared with diclofenac retard (100mg once daily) in patients with rheumatoid arthritis. Both drugs produced rapid relief to the cardinal symptoms of pain and joint tenderness following the first dose. However, at the pre-dose assessments after 2 and 4 weeks, the scores for pain and joint tenderness were not significantly different from baseline (pre-treatment) in the patients on diclofenac retard. On the other hand, significant reductions in these clinical variables were maintained at the pre-dose assessments in the patients receiving isoxicam. The results are summarized in Table 2. These data indicate that the once-daily administration of the retard formulation of diclofenac does not provide 24-hour relief of symptoms or signs at the recommended dosage, and supports the contention that round-the-clock relief with a once-a-day dosing regimen can only be relief upon by using a drug with an intrinsic long half-life, such as isoxicam (13).

DRUG INTERACTIONS

Many patients receiving NSAIDs are often taking additional medication for concomitant diseases. Under such circumstances, the potential for drug-drug interactions requires to be assessed. In an extensive investigational program using a variety of pharmacodynamic and pharmacokinetic designs, no clinically significant interactions have been noted with antacids, cimetidine(16), digoxin, propranolol, glibenclamide(17), phenytoin or alcohol(18). On the other hand, isoxicam did potentiate the anticoagulant effect of warfarin(16), a phenomenon common to other NSAIDs. Furthermore, the isoxicam plasma level was reduced in the presence of anti-inflammatory doses of aspirin(19). This also happens with other NSAIDs, but is of dubious clinical significance.

CLINICAL TRIAL PROGRAM

OPEN-LABEL STUDIES

Studies conducted in the open-label format are primarily designed to provide information about long-term safety, rather than efficacy. However, the latter may be inferred by the fact that patients choose to remain on trial medication for months or even years. In the case of isoxicam more than 1500 patients entered long-term open-label studies, and to date over 300 have been on the drug for longer than 3 years for the treatment of rheumatoid arthritis or osteoarthritis.

COMPARATIVE STUDIES

Studies comparing isoxicam with other commonly-used NSAIDs have been carried out in the clinical indications of

TABLE 2

	Diclofenac Retard			Isoxicam		
Clinical Variable	**Base-line**	**2 weeks**	**4 weeks**	**Base-line**	**2 weeks**	**4 weeks**
Pain Scale	14.30	10.44	10.89	11.18	5.91	5.91
p*		NS	NS		<0.05	<0.05
Joint Tenderness	19.30	13.67	14.56	14.55	5.64	5.64
p		NS	NS		<0.001	<0.001

Results of clinical variables immediately prior to dosing at baseline, and after 2 and 4 weeks treatment with diclofenac retard (100mg once daily) or isoxicam (200mg once daily).

*p = significance level compared with baseline (Wilcoxon matched pairs signed ranks test)
NS = not significant ($p<0.05$

CLINICAL PHARMACOLOGY

In a four week study using chromium-tagged red cells, occult gastrointestinal blood loss during isoxicam administration ranged between 0.6 and 1.1 ml daily, values comparable with those obtained following naproxen administration(14).

In a further four week study of renal function, isoxicam administration resulted in a significant *increase* in creatinine clearance after two and four weeks of therapy, as well as significant reduction in serum uric acid levels(15).

rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute musculoskeletal disorders. With the exception of one single-blind trial in musculoskeletal disease, all studies were conducted on a double-blind basis, utilizing, where necessary, the double-dummy technique. Most of the studies were of the parallel group format, but several employed a cross-over design.

Rheumatoid Arthritis

The dose of isoxicam in this indication was 200mg adminis-

tered as a single daily dose. Isoxicam was shown to be superior in efficacy *and* tolerance to aspirin in a dose of 900mg four times daily. This is the first drug even shown in clinical trials to be superior to aspirin(20). Furthermore, isoxicam was shown to be superior in efficacy to full doses of naproxen (500mg twice daily), and also to indomethacin (25mg three times daily) and piroxicam (20mg once daily) (21). The tolerance of isoxicam was at least as good as the comparative agents.

Osteoarthritis

In this indication, the daily dose of isoxicam was again 200mg, usually administered as a single daily dose. Statistically significant superiority was noted for isoxicam in comparison with ibuprofen (400mg three times daily), full doses of naproxen (500mg twice daily) and diclofenac (50mg three times daily), as well as piroxican (20mg once daily)(22). Furthermore, isoxicam was as efficacious as full doses of indomethacin (50mg three times daily) but significantly better tolerated(23).

Ankylosing Spondylitis

In a twelve-week study of 97 patients, isoxicam (200mg once daily) was compared with indomethacin (25mg three times daily). Isoxicam was statistically significantly superior to indomethacin in 11 of the 13 clinical variables assessed, and even in the two remaining indices, the trends favoured isoxicam. In addition, significantly more subjects dropped out of study for lack of efficacy of indomethacin(20).

Musculoskeletal Disorders

In the treatment of acute soft tissue rheumatism, post-traumatic or post-operative inflammatory disorders, the dose of isoxicam is increased to 300mg daily. Clinical studies in these indications have shown isoxicam to be superior to diclofenac retard (100mg once daily)(24) and as effective as indomethacin (75mg daily) and oxyphenbutazone (100mg three times daily).

ADVERSE REACTIONS

The main site of adverse reactions to isoxicam, as might be expected, is the gastrointestinal tract. The incidence, however, in clinical trials was relatively low, and certainly comparable with that of other commonly-used NSAIDs. In particular, the incidence of peptic ulceration determind from double-blind and long-term open label studies is less than 0.5 percent, a remarkably low figure for a drug of this therapeutic class.

It is generally assumed that the elderly are more prone to develop side-effects from drugs. Consequently, adverse reaction data have been analysed from all patients who received the usual recommended dose of 200mg isoxicam daily, and broken down by age, using 75 years and older as the stringent definition of "old age". Table 3 shows the percentage incidence of gastrointestinal side-effects categorised by age. The data clearly demonstrate that isoxicam is at least as well tolerated by the elderly as it is by the younger age groups. Similarly in other body systems, e.g., the nervous system, skin and appendages, etc., the frequency of adverse reactions was low, and comparable in both age groups. These results are summarised in Table 4. The similarity in the frequency of adverse reactions in the two age groups is probably a reflection of the isokinetic disposition of isoxicam (25).

TABLE 3

Symptom	Under 75 years	75 years and older
Abdominal Pain	5.2	1.2
Dyspepsia	5.5	1.2
Nausea/Vomiting	4.7	2.4
Stomatitis	0.6	0.0
Diarrhoea	2.2	0.6
Peptic Ulcer	0.3	0.0
Constipation	0.7	0.3
Gastritis	1.0	0.3
G.I. Bleeding	0.3	1.2

Percentage incidence of gastrointestinal adverse reactions in patients receiving 200mg isoxicam daily.

TABLE 4

Body System	Adverse Reaction	Under 75 years	75 years and older
Skin	Rash	1.5	1.2
	Pruritus	0.8	0.9
	Dermatitis	0.2	0.0
Nervous System	Dizziness	1.2	0.6
	Vertigo	0.6	0.9
	Somnolence	0.4	0.8
Other	Oedema	2.3	2.4
	Weight Increase	0.3	0.0
	Fatigue	0.6	0.3
	Headache	0.9	0.0

Percentage incidence of non-gastrointestinal adverse reactions in patients receiving 200mg isoxicam daily.

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