Does the addition of ketotifen to non-steroidal anti-inflammatory drugs confer any additional benefit in rheumatoid arthritis?

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1 Ketotifen (benzocycloheptathiophene) was evaluated in a double-blind study of patients with active rheumatoid arthritis.

2 Sixty patients were randomly allocated to receive active or matching placebo drug and reviewed 6 weekly for 24 weeks. Conventional NSAIDs were continued throughout.

3 Disease activity was assessed clinically and biochemically at weeks 0, 12 and 24.

4 Nineteen patients remained on active drug for 24 weeks and 11 on placebo. Significant improvement in articular index was seen in both groups but no objective improvement was noted in either group. No undue toxicity was encountered in either group.

5 Use of a drug considered to have selective LTC₄ and LTD₄ antagonism in combination with conventional cyclo-oxygenase inhibitors did not confer any additional benefit in rheumatoid arthritis.

Keywords ketotifen arthritis non-steroidal anti-inflammatory drugs

Introduction

Clinicians who manage patients with rheumatoid arthritis (RA) are confronted with a surfeit of similar symptom-relieving non steroidal anti-inflammatory drugs (NSAIDs), but have few 'disease modifying' or 'second line' treatments available. The drugs in the latter category such as gold, penicillamine or levamisole tend to be toxic and relatively few patients remain on any one drug for prolonged periods. Therefore the search for less toxic second line drugs continues. The development of an entirely new drug is expensive and fraught with hazards. The potential market for such a drug is small compared with an NSAID which may be used for other forms of arthritis and soft tissue rheumatism. The currently used disease modifying drugs were in use for other conditions, and serendipity or co-incidence led to studies in RA.

Ketotifen (benzocycloheptathiophene) has a different immunopharmacological profile from available anti-inflammatory and immunosuppressive agents (Borel, 1980). It is currently used in the prophylaxis of bronchial asthma, and very

few toxic effects have been reported (Radielovic & Greenwood, unpublished data). It acts on both basophils and neutrophils inhibiting release of histamine and SRS-A (Kumagai, 1978), a mixture of leukotrienes, LTC₄ and LTD₄; products of the lipoxygenase pathway of arachidonic acid metabolism (Austen, 1978; Orning *et al.*, 1980). These agents act synergistically with other local inflammatory mediators and modify the inflammatory response (Goetzl, 1980).

The extent to which modifications of these factors may benefit rheumatoid patients is unknown, but a controlled trial of this relatively non-toxic medication was considered worthwhile.

Methods

Sixty patients with definite or classical RA whose disease activity was not controlled by NSAIDs were selected. No patient was receiving corticosteroids. Most had received previous second

line therapy, either gold, penicillamine or levamisole which had been withdrawn because of side effects (at least 3 months before study). Informed consent was obtained from each patient prior to entry into the study.

The trial was a double-blind comparative assessment with two parallel groups. Patients were randomly allocated to either active drug-ketotifen 2 × 2 mg tablets or matched placebo twice daily. Treatment was continued for 6 months and NSAIDs were kept constant as far as possible.

In the absence of toxicity, patients were encouraged to continue for 24 weeks but if severe symptoms persisted alternative second line therapy was considered.

All patients were given written details about potential side effects, particularly drowsiness.

Clinical assessments

Each patient was seen at 6 weekly intervals by both a metrologist and doctor: assessments included:

- Duration of morning stiffness in minutes.
- Richie articular index.
- Grip strength (a mean of three measurements with each hand using a sphygmomanometer and adapted cuff).
- Pain score.

Laboratory assessments were made at weeks 0, 12, 24 and included FBC, platelets, ESR, rheumatoid factor (Rose Waaler) titre, albumin, globulin.

Results

There was no significant difference in the age, duration of rheumatoid arthritis and initial ESR

in the two groups (Mann Whitney II sample tests, Table 1).

Thirty patients completed the 24 week study period. Of these, 19 were on active drug and 11 on placebo. In both groups there was significant improvement in articular index but this was not reflected in other clinical assessments namely grip strength and pain score, nor in laboratory parameters, i.e. haemoglobin, platelet count or ESR.

Reasons for withdrawal

Twenty-one patients were withdrawn due to progressive disease, seven in the active and 14 in the placebo group. One patient on active drug dropped out before 6 weeks for unrelated reasons. Eight patients developed toxic effects, three on active drug and five on placebo. Table 2 shows the nature of these side effects. Sedation occurred in two patients on active ketotifen and one on placebo.

In one patient with pre-existing inflammatory bowel disease, recrudescence of bowel symptoms was noted. This patient was receiving active ketotifen but the deterioration was not considered to be due to the drug. All the side effects resolved on withdrawal of either ketotifen or placebo. Monitoring of urine, haematology and biochemistry showed no change over the 24 week period in either group.

Discussion

In this study a drug presumed to produce selective antagonism in the lipoxigenase products, LTC₄ and LTD₄, did not confer any additional symptomatic benefit in RA, nor was a disease modifying effect achieved. It is of interest that more patients remained on active therapy than

Table 1 Characteristics of patients at start of study

	Placebo n = 30		Ketotifen n = 30	
	Median	Range	Median	Range
Age (years)	58	37–75	60	39–72
Duration RA (years)	11	2–28	8.5	2–42
Rheu factor (+/-)		18:12		12:18
AMS (min)	105	0–1440	60	0–1440
Pain score	2	1–4	3	1–4
Grip strength—R	80	34–180	86	48–180
—L	70	34–138	83	46–180
Articular index	23	2–50	20	4–60
ESR (mm/h)	51	10–108	65	11–124
Hb (g/100 ml)	11.4	9.3–16.2	12	9.4–16.5
Platelets	404	173–708	403.5	216–999

Table 2 Side effects necessitating withdrawal

Adverse reaction	Placebo	Ketotifen
Drowsiness	1	2
Nausea/vomiting	2	1
Diarrhoea/vomiting	1	0
Rash	1	0
Total	5	3

placebo. This could be due to a sedative effect of ketotifen rather than a direct anti-inflammatory action.

The roles of the individual arachidonic acid products in the perpetuation of rheumatoid synovitis is not known. Conventional cyclooxygenase inhibitors inhibit synthesis of prostaglandins and afford considerable symptomatic relief (Vane, 1971). However, NSAIDs may also enhance the accumulation of leucocytes and inflammatory exudates (Adams *et al.*, 1977; Eakins *et al.*, 1980a, b).

In rheumatoid arthritis it is possible that continued lipoxigenase pathway activity may allow

leucocyte lysosomal mediated tissue degradation to proceed unchecked. There is thus a theoretical reason to assess the possible benefit of a drug which acts on the lipoxigenase pathway.

The recommended maximum dose of ketotifen (in asthma) is 4 mg daily which was the dose used in this study; it is possible that the site and greater degree of inflammation in rheumatoid arthritis would require a higher dose to achieve a therapeutic effect. As lipoxigenase products are local inflammatory mediators measurement of these agents was not feasible and we cannot be certain that the expected pharmacological effect was achieved. Whether specific pharmacological manipulation of other leukotrienes, in particular LTB₄ which is more chemotactic, would be beneficial in patients with rheumatoid arthritis remains to be clarified.

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