

Clinical evaluation of tolmetin

Peter M. Brooks, M.B., M.R.A.C.P.,
Caroline F. Watkins,
Roger D. Sturrock, M.B., M.R.C.P.,
and
Peter Lee, M.B., M.R.A.C.P.

*The Centre for Rheumatic Diseases,
and University Department of Medicine,
Royal Infirmary, Glasgow, Scotland*

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Summary

A clinical therapeutic trial of tolmetin in daily doses of 1200 and 1600 mg. is reported in 16 patients with rheumatoid arthritis. The drug was given for a period of 2 weeks at both dose levels. Significant improvement was noted with both dose levels in pain relief, articular tenderness and grip strength, but no significant differences were noted between the two dosages. An anti-inflammatory effect could not be demonstrated. Five of the 16 patients had to discontinue therapy at the lower dose due to gastric intolerance.

Key words: Arthritis, rheumatoid – tolmetin – anti-inflammatory agents

Introduction

The vast majority of patients with rheumatoid arthritis are managed throughout the course of their illness by their own general practitioner and most of these patients are receiving non-steroidal, anti-inflammatory drugs. Despite the consensus of opinion amongst rheumatologists that aspirin is the optimum drug in this class there are indications that this opinion is shared neither by the patients nor by their family doctor.⁶

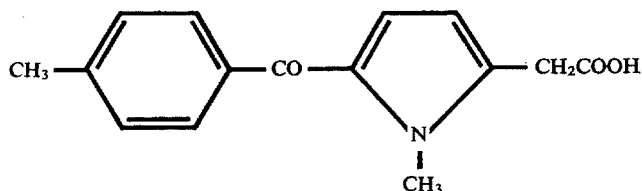
It is possible that this discrepancy in opinion reflects a combination of the unpleasant side-effects of aspirin and the obvious failure of that drug to alter radically the natural history of the disease. Whatever the precise reasons for this, it seems reasonable to pursue the quest for a drug which will influence the course of rheumatoid arthritis and which will be more acceptable to patients.

Tolmetin (sodium tolmetin dihydrate)† is a proposed new anti-rheumatic drug which is related chemically to indomethacin (Figure 1). In the usual exhaustive animal studies¹¹ in numerous experimental models of inflammation, which are of doubtful relevance to human arthritis, this compound has proved to possess anti-inflammatory activity with therapeutic ratios of side-effects to effects substantially less than indomethacin or aspirin.

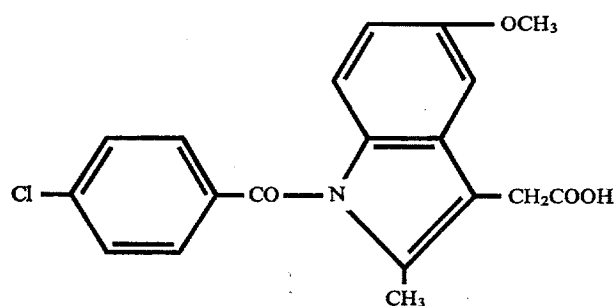
Reprint requests: Dr. Peter M. Brooks, Centre for Rheumatic Diseases, 35, Baird Street, Glasgow, G40EH, Scotland.

†'Tolectin' trade mark Ortho Pharmaceutical Ltd.

Figure 1. Structural formulae of tolmetin and indomethacin



Tolmetin



Indomethacin

In man, peak blood levels are reached at 30 minutes after oral administration and the plasma half-life is of the order of 2 hours. Protein binding, however, may result in a prolongation in terms of biological activity. The drug appears to be excreted in the urine and elimination seems to be in accord with first order kinetics.³

In studies on patients with rheumatoid arthritis in the U.S.A.,² the optimum dose would appear to be of the order of 800 to 1600 mg./day (average 1200 mg./day) in divided doses, and although symptomatic improvement was noted within a few days maximal therapeutic effect was not always achieved within 60 days of administration; a finding somewhat at variance with the short half-life of the drug.

Side-effects encountered in man have been principally gastro-intestinal and dermatological, a low incidence of dyspepsia and of skin rashes having been observed. The relative paucity of central nervous system side-effects encountered in comparison with indomethacin in early studies³ may be related to the absence in tolmetin of a serotonin-like ring.

A major problem in assessing the effects of drugs in patients with rheumatoid arthritis lies in the propensity for these patients to be subjectively improved over brief periods of time by any drug, even a placebo.¹

The purpose of the present study was to establish in a fully documented group of patients with rheumatoid arthritis, employing standardised methodology, whether or not this drug had anti-rheumatic activity and, if so, whether this was related to the dose of tolmetin administered.

Method and materials

Patients studied

Sixteen patients (mean age $53 \pm$ S.E.M. 3.4 years) of whom 5 were male freely consented to participate in this study with full knowledge of its contents and implications. All of these patients were suffering from 'classical' rheumatoid arthritis by the criteria of the American Rheumatism Association, and the mean duration of their disease was 6 years (\pm S.E.M. 2.4 years). None had received either corticosteroid or cytotoxic drugs or chrysotherapy. All these patients had synovial hypertrophy on clinical examination, erosions on joint X-ray, and a positive test for rheumatoid factor; 6 had subcutaneous nodules, but none had either Sjögren's syndrome or evidence of vasculitis. The mean articular index⁹ at entry into this study was 18.5 score units (\pm S.E.M. 3.0 units) denoting moderate activity. The scale of this parameter lies between 0 and +78 score units. None of these patients gave a past history of hypersensitivity or idiosyncratic reactions to indomethacin, or to any other drug; and no patient had evidence of disease of any other major system.

Experimental design

This study was conducted on an out-patient basis. Each patient refrained from taking any antirheumatic drug for 48 hours, and thereafter received first 1200 mg. tolmetin per day for 14 days and then 1600 mg. per day for a further 14 days. No other drugs were prescribed and the patients were encouraged to volunteer information of coincident drug intake. Each patient continued their pre-trial daily habits of diet, work, rest and physiotherapy. Neither the patients nor the assessors were aware of the identity of the trial tablets.

Assessments

Each patient was assessed at the beginning and at the end of each period of treatment. The methods of assessment were those which are routinely employed to document change in disease activity in patients at the Centre for Rheumatic Diseases, Glasgow.^{4,8} The routine assessments including patient preference, pain and articular index, grip strength, 'ring sizes' and radioactive technetium ^{99m}Tc joint uptake⁵ are all performed by a single trained observer (C.W.) whose inter- and intra-observer errors for each of these tests has been documented. The order of testing was standardised in each assessment, the subjective indices being conducted before the objective. The pain index employed was based on the patient's assessment of the severity of pain expressed upon the scale 0=absent, 1=mild, 2=moderate, and 3=severe. The articular index is a summation index of joint tender-

ness. Grip strength was measured in both right and left hands, using a modified sphygmomanometer cuff and a mean of three readings was recorded from a baseline of 30 mm.⁷

The circumference of each proximal interphalangeal joint was measured with the Geigy gauge and recorded in millimetres.¹⁰ Radioactive technetium uptake was measured by external directional counting 15 minutes following the intravenous injection of approximately 200 μ c: (10,000 counts per minute at 16 cm. from the detector) of ^{99m}Tc with the detector placed at 2.5 cm. from each joint. The results are expressed as the percentage of the injected dose of the count rates over both knee and wrist joints.

The haematological and biochemical parameters were determined in the relevant routine laboratory tests and a specimen of urine was tested upon each occasion for protein content and blood.

Comparison of the results in each patient at the three assessments was by a paired Student 't' test.

Results

Of the 16 patients who commenced the trial, only 10 completed the two treatment periods. The 6 patients who defaulted did so because of gastric side-effects, i.e. abdominal pain and nausea.

The results of the trial are summarised in Table I and the statistical analysis is shown in Table II. The results show that tolmetin in daily doses of 1200 and 1600 mg. per day produces significant improvement in pain, articular index of joint tenderness and grip strength, but not in digital joint circumference or in ^{99m}Tc

Table I. Clinical and laboratory data (mean values \pm S.E.M.) on two dosage regimes of tometin

Measurement	No treatment	Tolmetin	
		1200 mg./day	1600 mg./day
Pain index	2.4 \pm 0.26	1.9 \pm 0.23	1.6 \pm 0.22
Articular index	18.5 \pm 3.0	13.3 \pm 2.37	13.6 \pm 2.6
Grip strength (mm.Hg.)			
Right hand	106 \pm 7.39	130 \pm 9.06	133 \pm 12.1
Left hand	103 \pm 4.9	118 \pm 9.3	126 \pm 8.4
Digital joint circumference (mm.)			
Right	290 \pm 8.05	292 \pm 8.9	288 \pm 8.8
Left	281 \pm 7.6	281 \pm 7.0	279 \pm 7.2
^{99m} Tc uptake (%)			
Right knee	28.81 \pm 2.29	27.25 \pm 2.4	26.74 \pm 1.5
Left knee	27.84 \pm 2.07	21.79 \pm 1.2	23.86 \pm 1.8
Right wrist	20.55 \pm 1.31	24.34 \pm 3.33	19.0 \pm 1.8
Left wrist	18.03 \pm 1.58	19.49 \pm 1.95	18.5 \pm 1.8

Table II. Results of statistical analyses (p values)

Measurement	No treatment vs 1200 mg/day	No treatment vs 1600 mg./day	1200 mg./day vs 1600 mg./day
Pain index	0.05	0.01	N.S.
Articular index	0.0025	0.01	N.S.
Grip strength (mm.Hg.)			
Right	0.01	0.01	N.S.
Left	0.05	0.0025	0.025
Digital joint circumference (mm.)			
Right	N.S.	N.S.	N.S.
Left	N.S.	N.S.	N.S.

N.S. =not significant

joint uptake measurements. Although there was slight improvement in pain, grip strength, digital joint circumference and ^{99m}Tc joint uptake (with the exception of the left knee) with 1600 mg. tolmetin compared to 1200 mg. the differences did not reach statistical significance.

Discussion

This trial was designed with the simple aim of determining whether tolmetin in doses of 1200 mg. and 1600 mg. per day had analgesic and anti-inflammatory action in rheumatoid arthritis. The results show clearly that 2-week's treatment with both dose levels of the drug significantly reduce pain, joint tenderness, and grip strength. This clearly indicates that the drug has an antirheumatic effect at both dose levels. No statistical difference, however, could be demonstrated between the two dose levels in clinical effect. This suggests that further clinical trials of the drug probably would best be carried out with 1200 mg. per day rather than with the larger dose.

Although tolmetin undoubtedly has analgesic action it has not been possible in the present study to demonstrate anti-inflammatory effect by reduction in either digital joint circumference or ^{99m}Tc joint uptake measurements. This, of course, does not exclude the fact that the drug has anti-inflammatory effects in man; it is just that we have been unable to demonstrate them. Swelling of the small joints of the fingers in rheumatoid arthritis can be due to causes other than soft-tissue swelling, and it may not always be possible to demonstrate reduction in joint circumference with known anti-inflammatory drugs. Patients are selected for a clinical trial on the basis of persistent joint pain and not on the ability to demonstrate reduction of digital joint circumference. Likewise, reduction in ^{99m}Tc joint uptake requires reversible inflammation in the joints studied, and not all inflammation in joints of patients with chronic rheumatoid arthritis can be reduced with short courses of non-steroidal, anti-inflammatory drugs. Clearly, further studies are required to determine whether tolmetin has anti-inflammatory action in man.

A high incidence of gastric side-effects was noted in the present study. This is at variance with previous studies, and this aspect of tolmetin clearly requires further study.³

In summary, this study has demonstrated that tolmetin in a daily dose of 1200 mg. per day has analgesic effect in rheumatoid arthritis. Higher doses of the drug, 1600 mg. per day, gave no more pain relief. An anti-inflammatory effect of the drug could not be demonstrated. Gastric intolerance necessitated withdrawal of the drug when given in a daily dose of 1200 mg. in 5 of 16 patients studied.

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