COMPARISON OF EFFICACY OF AND TOLERANCE TO KETOPROFEN AND DICLOFENAC SODIUM IN THE TREATMENT OF RHEUMATOID ARTHRITIS

M L Boey, Sarah Rae, P H Feng

SYNOPSIS

Eighteen patients with rheumatoid arthritis were treated for 3 months with controlled release ketoprofen (Oruvail) 100 mgm once daily (9 patients) or diclofenac sodium (Voltaren) 25 mgm three times daily (9 patients). Patients were evaluated at the start of the study and at subsequent visits on days 28, 56 and 84. Clinical evaluation included assessment of severity and duration of morning stiffness and the severity of pain and joint tenderness. Patients were instructed not to take any other non- steroidal anti-inflammatory drug, although paracetamol tablets were provided for pain relief if required. Over the study period patients receiving ketoprofen showed a significant reduction in severity of pain, joint tenderness and morning stiffness. Patients receiving diclofenac sodium showed a significant decrease only in morning stiffness. No estimation of patient compliance or of consumption of paracetamol was made during the study. The incidence of side effects was similar with both drugs, and liver function tests, kidney function, electrolytes and haematology were not affected by drug treatment. Six patients withdrew from the study, three from each drug group. Both ketoprofen and diclofenac sodium were concluded to have beneficial therapeutic effects in patients with rheumatoid arthritis when administered at their minimum recommended dose levels.

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INTRODUCTION

Ethnic differences are known to exist in the metabolism and clearance of many drugs(1), although the relative contributions of environment and genetic factors to these differences are difficult to assess. Alcohol, cigarettes, caffeine and oral contraceptives, all more common in the western world, affect oxidative (phase I) metabolism by their induction of liver cytochrome P450(2). However, very little is known regarding the effects of environmental and genetic factors on conjugative (phase II) metabolism, by which route ketoprofen and diclofenac sodium are largely detoxified.

Ketoprofen (Oruvail, May & Baker) and diclofenac sodium (Voltaren, Ciba Geigy) have been used in the symptomatic treatment of rheumatoid arthritis in the UK for many years (3,4,5) and both drugs have been used in Singapore in similar doses.

This study attempts to examine the effects of controlled release ketoprofen 100 mgm once daily and diclofenac sodium 25 mgm three times daily (minimum recommended doses) in Asian patients.

Department of Medicine IV
Tan Tock Seng Hospital
Moulmein Road
Singapore 1130

M L Boey, MBBS, M MED, AM, Consultant

P H Feng, AM, MD, FRCP(G), FRCP(E),
Head and Senior Consultant

Present Address of Sarah Rae

Department of Rheumatology
King's College Hospital
Denmark Hall
London SE5 9KS
UK

PATIENTS AND METHODS

Thirty-three patients with rheumatoid arthritis were selected. Their age range was 20-75 years. They had no previous known intolerance to propionic acids and were not suffering from any disease in which non-steroidal anti-inflammatory drugs (NSAID) were contraindicated. Patients were not being treated with any other NSAIDs or receiving corticosteroid or immunosuppressive drugs. Pregnant women and nursing mothers were also excluded.

Thirty-three patients entered into the study, of whom fifteen were excluded because of protocol violations. Of the 18 remaining patients 16 were male and 2 female, with an age of 24-68 years (mean 42.7 + 11.3 SD). Nine received ketoprofen capsules 1 x 100 mg once daily and nine diclofenac sodium tablets 25 mg three times daily in an open randomised design, following a 1-week washout period, for a period of 3 months. In addition, patients were given paracetamol (0.5 gm) tablets as "rescue analgesics" during the 1-week washout and during the study period. These were to be taken for the relief of pain not adequately controlled by the study drugs. Only one patient in the ketoprofen group received concomitant medication (chlorpheniramine and tolbutamide) during the study.

Clinical assessments were carried out on days 0 (baseline), 28, 56 and 84. Patients were asked to record the duration of morning stiffness in minutes and its severity on a 5-point scale ranging from "very severe" to "very mild". Pain was estimated on the small scale. The Ritchie Articular Index was used to assess joint tenderness. This involved the summation of several quantitative evaluations of the pain experienced by each patient when various joints were subjected to firm pressure over the articular margin (or on movement of the cervical spine, hip, talocalcaneal and mid-tarsal joints). Pain was scored as: 0 = no pain; 1 = pain; 2 = pain and winces; 3 = pain, winces and withdraws.

Samples of blood and urine were analysed by routine methods for liver function, kidney function, haematology and electrolytes.

Statistical comparisons were by Chi-square and Van der Waerden distribution-free tests because of the categorical nature or skewed distribution of the data. Analysis of variance (F-test) was used to identify any significant treatment or time differences or treatment x time interaction. $p<0.05$ was taken as the level of significance.

RESULTS

The two patient groups were matched for all parameters measured except for age, the ketoprofen group being significantly older than the diclofenac sodium group (49.4 + 10.8 SD versus 35.9 + 7.1 SD years). This is unlikely to be of significance, since the duration of arthritis was similar in both groups.

Patient compliance and consumption of paracetamol were not assessed.

Clinical Assessments

The results are summarised in Tables 1 and 2.

Morning Stiffness

Morning stiffness was initially assessed as present or absent by the investigator at each visit. No significant difference was noted between treatments at any of the four visits. There was a trend towards a decrease in duration of morning stiffness after 3 months in both treatment groups, particularly in the ketoprofen group, although this failed to reach statistical significance.

The severity of morning stiffness was scored on a scale of 1-5 ranging from very 'mild' to 'severe'. Again, a decrease was observed, but the difference was not statistically significant, either between treatments or with time.

Incidence of pain

Almost all patients in both treatment groups suffered from some pain during the study. One patient in the ketoprofen group and one in the diclofenac sodium group improved from 'moderate pain' on Visit 1 to 'no pain' by Visit 3 or 4. One patient in the diclofenac sodium group reported 'no pain' on Visit 1 and 'moderate pain' on subsequent visits. Statistical analysis showed no significant difference between the two treatments when compared at each visit.

Severity of Pain

The severity of pain was graded as for severity of morning stiffness, on a scale of 1-5 from 'very mild' to 'severe'. There was a trend towards a decrease in pain severity with time for both treatments, especially with ketoprofen ($p = 0.04$).

Joint Tenderness

Although neither treatment group appeared to be severely affected at the initial clinical assessment, some reduction in joint tenderness was noted in both diclofenac sodium and ketoprofen patients. There was no statistically significant difference in joint tenderness with time when the treatments were considered together, but there was a significantly more marked improvement in patients receiving ketoprofen ($p = 0.05$) when the treatments were considered separately.

Side Effects

Side effects observed are summarised in Table 3. They include those reported by patients initially entered in the study but subsequently excluded because of protocol violations. Twelve of 33 patients reported at least one side effect, 4 from the ketoprofen group and 8 from the diclofenac sodium group. Of 4 reported side effects in the ketoprofen group, 3 were related to the gastrointestinal tract (indigestion, constipation and epigastric pain); the remainder (dizziness and irritability) was probably unrelated to treatment. No side effects were sufficiently severe to necessitate withdrawal from the trial.

In the diclofenac sodium group, 7 of 11 reported side effects were related to the gastrointestinal tract (epigastric pain or discomfort, indigestion and vomiting). Other probable treatment- related side effects were allergic rash and nausea. The allergic rash was sufficiently severe for the patient to be withdrawn from the study.

Treatment-related side effects reported by patients who were subsequently excluded from analysis included indigestion, nausea and vomiting (this patient was found to have a peptic ulcer) and epigastric pain. One patient with a previous history of asthma suffered a severe attack during the study.

Withdrawals

Six patients withdrew from the study over the 3-month treatment period, three from each treatment group. Two patients in the ketoprofen group withdrew due to lack of treatment effect; the third withdrew for reasons unrelated to treatment. Similarly, two patients receiving diclofenac sodium withdrew due to lack of effect, but the third developed an allergic rash. This patient developed a similar rash when being treated with naproxen, ketoprofen and meclofenamic acid.

Laboratory Tests

No significant differences between ketoprofen and diclofenac sodium groups were observed for any of the parameters measured, except serum creatinine (treatment effect, $p = 0.02$). In addition, there was no significant time effect over the 3-month treatment period, except for potassium (time effect, $p = 0.04$). Neither result was considered to be clinically important.

Several patients had trace amounts of blood, sugar and/or protein in the urine, but this was not considered to be treatment related.

Raised erythrocyte sedimentation rate (20 mm./h) and alkaline phosphatase levels (105 i.u/l) noted in both treatment groups throughout the study were considered to be indicative of active rheumatoid arthritis.

DISCUSSION AND CONCLUSIONS

This study compared the efficacy of two non-steroidal anti- inflammatory drugs, ketoprofen and diclofenac sodium, at the lowest active therapeutic dose, in patients with active rheumatoid arthritis. Patient tolerance to the two drugs over a 3-month treatment period was also assessed.

Although there were only 9 patients in each treatment group suitable for inclusion in the analysis, an improvement in their condition was observed with both ketoprofen and diclofenac sodium. Both treatments reduced the duration and severity of morning stiffness, severity of pain and

TABLE 1
RESULTS [MEAN (SD)] OF CLINICAL ASSESSMENTS PERFORMED ON PATIENTS IN THE TWO TREATMENT GROUPS AT INTERVALS DURING THE STUDY PERIOD

Assessment	Treatment Groups							
	Keroprofen (Visit No)				Diclofenac sodium (Visit No)			
	1	2	3	4	1	2	3	4
Incidence of morning stiffness								
Yes	8[a]	6[b]	5[c]	3[d]	91	6[a]	5[c]	3d
No	1	3	3	5	0	3	2	2
Duration of stiffness (min)	98 (64)	48 (38)	43 (53)	53 (59)	114 (124)	95 (77)	32 (18)	60 (0)
Severity of stiffness (scale 1–5)	3.4 (0.7)	2.5 (0.8)	2.2 (0.5)	2.3 (1.2)	2.9 (0.9)	2.8 (0.8)	2.2 (0.8)	2.3 (1.2)
Incidence of pain								
Yes	9[e]	9[f]	8[g]	7[h]	8[e]	9[f]	6[g]	5h
No	0	–	0	1	1	–	1	0
Severity of pain (scale 1–5)	3.6 (0.7)	2.3 (1.0)	1.5 (0.8)	1.7 (0.8)	3.1 (0.8)	2.7 (0.9)	2.7 (0.8)	2.6 (0.9)
joint tenderness (Ritchie)	11.8 (5.1)	6.9 (5.9)	4.9 (3.4)	4.1 (2.5)	12.0 (6.8)	12.4 (7.0)	11.1 (11.3)	9.8 (6.8)
Side effects								
Yes	1[j]	1[j]	0[h]			2[i]	1[j]	1h
No	8	7	8			7	6	4

Incidence of stiffness, pain and side effects anlysed by Chi-square. Results do not include patients excluded due to protocol violations.
Visit 1 = Day 0, Visit 2 + Day 28, Visit 3 + Day 56, Visit 4 + Day 84
[a]p = 0.2, [b]p = 1.0, [c]p = 0.7, [d]p = 0.8, [e]p = 1.0, [f]p = no value,
[g]p = 0.2, [h]p = 0.3, [i]p = 0.5, [j]p = 0.9, [k]p = 0.2

TABLE 2
STATISTICAL ANALYSIS OF RESULTS OF CLINICAL ASSESSMENTS PERFORMED DURING THE STUDY PERIOD

Assessment	Mean differences from Visit 1		Significance of difference using analysis of variance		
	Treatment groups		Treatment effect	Time (visit) effect	Treatment X time interaction
	Ketoprofen	Diclofenac			
Duration of morning stiffness (min)	−68.1 (n = 13)	−26.4 (n = 11)	F = 0.2 p = 0.7	F = 2.8 p = 0.13	F = 0.7 p = 0.5
Severity of morning stiffness (scale 1 5)	−0.3 (n = 14)	−0.4 (n = 14)	F = 3.2 p = 0.10	F = 2.4 p = 0.14	F = 0.3 p = 0.7
Severity of pain (scale 1–5)	−1.6 (n = 24)	0.4 (n = 17)	F = 3.2 p = 0.04*	F = 2.4 p = 0.1	F = 0.3 p = 0.4
Joint tenderness (Ritchie)	−6.6 (n = 25)	−0.05 (n = 21)	F = 4.3 p = 0.05*	F = 0.2 p = 0.8	F = 0.2 p = 0.8

Results do not include patients excluded due to protocol violations
n = number of values avilable for assessment
* = result significant at $p < 0.05$

TABLE 3

SIDE EFFECTS OBSERVED DURING 3 — MONTH TREATMENT PERIOD

A Patients receiving ketoprofen 100 mgm once daily

Patient no.	Visit	Day	Side effect
8	2	28	Gastric (? indigestion), constipation
8	3	56	Slight epigastric pain
24*	2	28	Dizziness, irritability
29*	3	56	Slight loss of appetite
32*	3	56	Epigastric discomfort

B Patients receiving diclofenac sodium 25 mgm three times daily

Patient no.	Visit	Day	Side effect
1	4	84	Pricking sensation (after medication), epigastric discomfort
9	2	28	Slight indigestion
9	3	56	Slight indigestion
11	2	28	Allergic rash (similar with naproxen, ketoprofen and meclofenamic acid) — withdrawn
21*	3	56	Hospitalised with asthma
22*	2	28	Indigestion (treated with antacids)
27*	2	28	Nausea and vomiting
30*	3	56	Chest tightness on speaking
34*	2	28	Mild epigastric pain

* denotes patients excluded from efficacy assessment due to protocol violations

joint tenderness, although these were more pronounced in patients receiving controlled release ketoprofen. There was a less significant decrease in the duration of morning stiffness in patients in both treatment groups.

Patient compliance and consumption of rescue analgesics were not assessed in this study, and it is therefore possible that patients in the ketoprofen group took more rescue analgesics for pain relief, or that diclofenac sodium patients were taking less frequently of the prescribed dose.

Of the adverse effects reported during the study period, most were related to the gastrointestinal tract and included epigastric pain, indigestion and vomiting. Other significant adverse reactions included an allergic rash and nausea in patients assigned to the diclofenac sodium group, although the patient with allergic rash showed similar symptoms when receiving other non-steroidal anti-inflammatory drugs. Only the patient with rash withdrew from the study because of adverse reaction. Other withdrawals were due to lack of treatment effect and to factors unrelated to treatment. Ketoprofen and diclofenac sodium therefore appear to be equally well tolerated in the 18 patients assessed.

Laboratory monitoring revealed no clinically significant changes in any of the parameters measured; raised ESR and alkaline phosphatase levels being indicative of active rheumatoid arthritis.

In conclusion, this relatively small study suggests that at their minimum recommended dose levels, both ketoprofen and diclofenac sodium have a beneficial effect in Asian patients with rheumatoid arthritis. Both treatments appear to be equally well tolerated over the 3-month study period.

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