Discussion

The British comparative thromboplastin or its routine counterpart the Manchester comparative reagent is used in almost all hospitals in Britain. The BCT is also used throughout the world as a reference material. Hitherto the lower limits of the therapeutic range have been defined by clinical experience and correlation with other monitoring systems used in Britain and overseas. Our study allows an objective evaluation of the effectiveness of oral anticoagulant dosage monitored by the BCT to be made. The DVT incidence in untreated patients (23%) agrees with other series. It is similar to that in the study of Ballard *et al*[4] in gynaecological patients (29%) and to that in the multicentre trial study[8] of mixed surgical patients (24%). The incidence in patients treated with low-dose heparin (our positive control group) approximates to that reported by Ballard *et al*,[4] who studied a similar group of patients using the same dosage regimen.

In contrast, the incidence in our oral anticoagulant group (6%) differs greatly from that found by Vroonhoven[5] using the Thrombotest method of anticoagulant control. In Vroonhoven's study[2] oral anticoagulants were, however, started on the first postoperative evening, and nine patients (18%) developed DVT. In eight of these patients this occurred during the first three days after operation when anticoagulation could not have reached a fully effective level. Our patients were started on oral anticoagulants at least five days preoperatively to achieve prolongation of both intrinsic and extrinsic clotting. This may explain the better protection attained with oral anticoagulants, which was equal to that of low-dose heparin. The three patients who developed DVT in the oral anticoagulant group had preoperative prothrombin ratios below 2·0, the recommended lower limit of the therapeutic range with the BCT. These results therefore confirm that this doubling of the normal prothrombin time is needed to achieve prophylaxis with our method of laboratory control. In all three cases, however, the preoperative PTT seemed adequately prolonged, which suggests that intrinsic clotting tests alone may not be a reliable guide to protection by oral anticoagulants in patients undergoing surgery.

The incidence of haemorrhagic complications was not significantly increased in patients on oral anticoagulants. Hence our study confirms the view that it is safe to operate when patients are anticoagulated at levels within the therapeutic range. Other experience, however, on the effectiveness of prophylaxis and haemorrhagic side effects has been based on trials in which anticoagulant dosage was determined by extrinsic clotting tests alone—that is, Quick prothrombin time test or Thrombotest. Our results also show the interesting and important finding that surgery is safe when intrinsic clotting is depressed, as judged by a prolongation of PTT, provided that this is not excessive.

For moderate-risk patients, the necessary preoperative stabilisation period for oral anticoagulants makes this type of prophylaxis unnecessarily troublesome. For these patients the present study endorses the effectiveness of the fixed low-dose heparin regimen. If, however, a patient is already stabilised on oral anticoagulants, it is apparently not worth changing to low-dose heparin for the operative period, as has recently been suggested.[9] The incidence of DVT and excessive haemorrhage is similar with both forms of prophylaxis, and stopping oral anticoagulants abruptly to change to heparin may well produce hypercoagulability.[10]

Morris and Mitchell[1] have shown that oral anticoagulants are effective in patients with hip trauma when low-dose heparin in a fixed dosage regimen is not. High-risk patients were, however, largely excluded from our study, and in moderate-risk patients the two treatments were equally beneficial. Further study is needed to see whether monitoring the low-dose heparin dosage will improve prophylaxis in high-risk patients, or whether oral anticoagulants are preferable.

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References

1 Morris, G K, and Mitchell, R A, *Lancet*, 1976, **2**, 869.
2 Vroonhoven, T J M V, van Ziijl, J, and Müller, H, *Lancet*, 1974, **1**, 375.
3 Baertschi, U, *et al*, *Geburtshilfe und Frauenheilkunde*, 1975, **35**, 754.
4 Ballard, R M, *et al*, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1973, **80**, 469.
5 Poller, L, Thomson, J M, and Palmer, M K, *Lancet*, 1976, **2**, 842.
6 Blackburn, E K, *Prescribers' Journal*, 1977, **17**, 73.
7 Kakkar, V V, *et al*, *Lancet*, 1970, **1**, 540.
8 International Multicentre Trial, *Lancet*, 1975, **2**, 45.
9 Brozovic, M, and Mibishan, R S P, in *Recent Advances in Surgery*, ed S Taylor. Edinburgh, Churchill Livingstone, 1977.
10 Poller, L, and Thomson, J M, *Lancet*, 1964, **11**, 62.

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Indoprofen and naproxen in the treatment of rheumatoid arthritis: a clinical trial

H BERRY, L FERNANDES, A K CLARKE, E B D HAMILTON, JOAN DAVIES, A ST J DIXON

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Summary and conclusions

Thirty-six patients suffering from rheumatoid arthritis took part in a double-blind crossover trial, in which they received either indoprofen 800 mg/day, naproxen 500 mg/day, or a matching placebo. Indoprofen was shown to be significantly superior as an analgesic and in improving grip strength and the patients preferred it. Adverse effects were comparable, although indigestion was seen slightly more often during indoprofen treatment.

Indoprofen is therefore at least as effective as existing anti-inflammatory drugs in rheumatoid arthritis and seems to be better tolerated.

Department of Rheumatology, King's College Hospital, London
H BERRY, DM, MRCP, consultant physician in rheumatology and rehabilitation
L FERNANDES, MRCP, senior registrar
A K CLARKE, MRCP, senior registrar
E B D HAMILTON, MA, FRCP, consultant physician

Royal National Hospital for Rheumatic Diseases, Bath
JOAN DAVIES, MB, DPH, medical assistant
A ST J DIXON, MD, FRCP, consultant physician

Introduction

Aspirin has been the standard treatment for rheumatoid arthritis and remains so in many centres. In some patients, however, aspirin causes adverse effects severe enough to prevent them

TABLE I—*Mean values for pain relief, articular index, early morning stiffness, ring size, grip strength, and analgesic consumption, and statistical comparison*

	Pain (Visual analogue scale)	Articular index	Early morning stiffness (min)	Ring size (mm)	Grip strength (mm)	Analgesic consumption (No of tablets)
Treatment:						
Before treatment	50·5	22·5	93·7	569·9	242·7	
Indoprofen	33·2	17·5	56·1	567	267·2	17·5
Naproxen	43·7	19·3	66·0	570·4	252·5	22
Placebo	57·9	23·2	176·8	569·2	243·0	34·6
Statistical comparisons:						
Indoprofen *v* naproxen	$t=1·78$; $0·1>P>0·05$	$t=0·60$; NS	$t=0·57$; NS	$t=0·35$; NS	$t=0·48$; NS	$t=0·82$; NS
Indoprofen *v* placebo	$t=4·09$; $P<0·001$	$t=1·91$; $P=0·05$	$t=2·52$; $P=0·02$	$t=0·22$; NS	$t=0·78$; NS	$t=2·88$; $P<0·01$
Naproxen *v* placebo	$t=2·39$; $P=0·02$	$t=1·23$; NS	$t=2·32$; $P=0·02$	$t=0·12$; NS	$t=0·31$; NS	$t=1·98$; $P=0·05$

NS = Not significant.

TABLE II—*Mean haemoglobin concentration and ESR*

	Before treatment	Indoprofen	Naproxen	Placebo
Haemoglobin (g/dl)	12·9	12·4	12·5	12·7
ESR (mm in 1 h)	33·1	40·8	37·8	38·8

from taking an anti-inflammatory dose of the drug (4 g/day), although in a recent study half the patients were able to tolerate aspirin in anti-inflammatory doses for six months.[1] Because of the toxicity of aspirin in some patients, drugs of at least comparable efficacy and without its adverse effects have been developed. Of these, fenoprofen and naproxen are the most active, but naproxen was preferred by more patients because of its low incidence of adverse effects.[2]

Indoprofen (α-(4-oxo-2-isoindolinyl)phenyl) propionic acid) has been shown to have analgesic, anti-inflammatory, and antipyretic properties in animals.[3] In man it is rapidly absorbed from the gastrointestinal tract and reaches peak blood concentrations one to two hours after ingestion.[4] Absorption of tablets is not impaired if the drug is taken with food, although peak values are slightly delayed.[5 6] Radioactive tracer studies[4] have shown that 96% is excreted in the urine as the glucuronide, only 4% being excreted in the faeces. Clinical trials have shown that the drug has an analgesic effect in osteoarthritis[7] and also in cancer.[8] Indoprofen also causes less gastrointestinal bleeding than aspirin.[9]

Our study was carried out to determine whether indoprofen has analgesic and anti-inflammatory properties in rheumatoid arthritis and to compare it with naproxen for efficacy and toxicity.

Methods

Outpatients of both sexes who were aged 20 years or more and had classical or definite rheumatoid arthritis[10] were included in the study. They were attending either King's College Hospital, London, or the Royal National Hospital for Rheumatic Diseases, Bath. Patients with peptic ulceration or liver or renal disease and those who had received gold, penicillamine, or immunosuppressive agents in the preceding three months were excluded. Women of child-bearing age were admitted to the study if they were taking suitable contraceptive measures.

The trial compared indoprofen 200 mg four times a day with placebo and naproxen 250 mg twice a day by the double dummy technique. The trial was double blind. Patients were randomly allocated to treatment and a six-line block system was used to minimise the effect of carry over.

Each treatment period lasted two weeks and patients took each treatment on a crossover basis. Before the first period there was a 48-hour run-in period during which only paracetamol was given.

Every fortnight the patients were supplied with 84 500-mg paracetamol tablets to be taken two at a time up to a maximum of six a day. At each outpatient attendance (every two weeks) a return tablet count was made.

At the start of the study and after two, four, and six weeks the following indices were measured: pain, using the visual analogue scale[11]; duration of morning stiffness; grip strength; articular index[12]; ring size; and haemoglobin concentration and erythrocyte sedimentation rate (ESR). Adverse effects were also sought at each assessment by asking: "Has the treatment upset you in any way?" We did not use a check list.

At four and six weeks the patients were asked which of the two treatments received in the previous four weeks they had preferred.

Results

Thirty-six patients were admitted to the study, 30 at King's College Hospital, London, and six at the Royal National Hospital for Rheumatic Diseases, Bath. One patient suffered a flare of disease activity that was severe enough to warrant her withdrawal from the trial before she had completed the first treatment period. She had received placebo. All the other patients completed the study.

Pain relief, articular index, and the duration of morning stiffness improved on both indoprofen and naproxen; the improvement was greater but not significantly so (Student's *t* test) on indoprofen (table I). Similar trends were shown for ring size, grip strength, and analgesic consumption. Haemoglobin concentrations fell slightly on both active drugs, but the ESR showed no significant change on either of the drugs or placebo (table II). Comparing the two drugs with paired *t* tests instead of Student's *t* tests (table III) showed that indoprofen produced significantly greater improvements in pain relief and grip strength than naproxen.

Patients preferred indoprofen to naproxen, and both drugs were preferred to placebo, using the χ^2 test (table IV).

Adverse effects—Fifty-two adverse effects were recorded (table V). There were no differences in the incidence of adverse effects during any treatment, although symptoms affecting the alimentary system were reported more often during indoprofen treatment. No patient reported a rash.

Discussion

The plethora of non-steroidal anti-inflammatory drugs currently available suggests that no one agent has great advantage

TABLE III—*Indoprofen compared with naproxen, using paired t tests*

	Pain	Grip strength	Articular index	Morning stiffness	Ring size
t	2·45	1·99	1·8	0·90	0·96
P value	0·02	0·05	0·07	NS	NS

TABLE IV—*Patient preferences**

Drugs compared:	No who preferred: Naproxen	Indoprofen	Placebo	Significance χ^2	P
Naproxen and placebo	14		2	5·20	<0·05
Indoprofen and placebo		17	2	5·98	<0·05
Naproxen and indoprofen	3	13		4·72	<0·05

*Some patients expressed no preferences.

TABLE V—*Adverse effects reported by patients*

	Indoprofen	Naproxen	Placebo
Alimentary system:			
Indigestion	7	3	2
Nausea	3	3	3
Constipation	2	2	1
Diarrhoea	1	1	2
Dry mouth	0	1	1
Wind	1	0	0
Central nervous system:			
Faintness	0	1	0
Headache	3	0	2
Dizziness	0	0	1
Fatigue	0	0	1
Sleeplessness	0	1	0
Depression	1	0	2
Skin:			
Itching	0	0	1
Rash	0	0	0
Other:			
Difficulty in micturition	1	0	0
Frequency of micturition	1	0	0
Arthritis worse	0	0	4
Total	20	12	20

over the others. Huskisson *et al*[2] has suggested that any one non-steroidal drug is effective in some of the population treated, so the existing "best" drug will by no means be suitable for all patients. Conversely, the "worst" drug in this group will be effective in some patients. There is no way of predicting which patients will respond best to which treatment. This suggests that there is still room for a new effective anti-inflammatory analgesic of low toxicity and high acceptability.

Animal experiments have shown that indoprofen appears to have anti-inflammatory effects at least equivalent to those of phenylbutazone and indomethacin.[3] In man the analgesic properties have been well demonstrated in comparison with ibuprofen in the treatment of osteoarthritis[13] and in comparison with indomethacin and placebo.[6] The combination of this analgesic effect in man and the finding of anti-inflammatory effects in the animal experiments led us to conclude that the drug should be studied in rheumatoid arthritis.

Patient preference is considered to be an important test of a new anti-inflammatory analgesic agent. Previous studies have shown that naproxen (500 mg/day) is the most preferred anti-inflammatory analgesic agent,[2] but our patients found indoprofen 800 mg/day significantly better than naproxen 500 mg/day. Indoprofen also relieved pain and improved grip strength better than naproxen.

In all the other values studied, although both naproxen and indoprofen were effective and better than placebo, the trend was in favour of indoprofen. Both indoprofen and naproxen treatments were associated with a slight but insignificant fall in haemoglobin, but the ESR fell on neither. In terms of toxicity there were a few more cases of indigestion with indoprofen than with naproxen, but these were mild and did not cause any patient to stop treatment.

Our results therefore suggest that indoprofen is at least as effective as existing anti-inflammatory analgesic treatment in rheumatoid arthritis and that it might be better tolerated.

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References

1 Huskisson, E C, *et al*, *British Medical Journal*, 1974, **1**, 176.
2 Huskisson, E C, *et al*, *British Medical Journal*, 1976, **1**, 1048.
3 Buttinoni, A, *et al*, *Arzneimittel-Forschung*, 1973, **23**, 1100.
4 Fuccella, L M, *et al*, *European Journal of Clinical Pharmacology*, 1973, **6**, 256.
5 Tammassia, V, *et al*, paper presented at VII International Symposium on Clinical Pharmacology, Pavia, 1976.
6 Tammassia, V, *et al*, *European Journal of Clinical Pharmacology*, 1976, **19**, 257.
7 Marcolongo, R, *et al*, *Journal of Clinical Pharmacology*, 1977, **17**, 48.
8 Ventafridda, *et al*, *Clinical Pharmacology and Therapeutics*, 1974, **17**, 284.
9 Porro, G, *et al*, *Journal of International Medical Research*, 1977, **5**, 155.
10 Ropes, M, *et al*, *Annals of Rheumatic Diseases*, 1959, **18**, 49.
11 Berry, H, and Huskisson, E C, *Journal of Clinical Trials*, 1971, **13**, 1100.
12 Ritchie, D M, *et al*, *Quarterly Journal of Medicine*, 1968, **37**, 393.
13 Peruzza, M, *et al*, *International Journal of Clinical Pharmacology*, 1976, **14**, 81.

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Bronchopulmonary infection due to Branhamella catarrhalis: 11 cases assessed by transtracheal puncture

G NINANE, J JOLY, M KRAYTMAN

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Summary and conclusions

Transtracheal punctures were performed in 193 miners of anthracosilicotic coal who presented with an acute exacerbation of chronic bronchitis. The transtracheal aspirates were bacteriologically positive in 104 patients. Branhamella catarrhalis was isolated in 15 patients; 10 of these responded to chemotherapy, as shown by the resolution of all symptoms and the disappearance of the organism on a repeat transtracheal puncture performed 48 hours after the end of treatment. One ampicillin-treated patient, whose bronchial secretions yielded a beta-lactamase-producing B catarrhalis, showed no improvement. But subsequent treatment with cefuroxime was followed by clinical and bacteriological recovery.

B catarrhalis probably acted as an opportunistic respiratory pathogen in these patients, who were probably compromised hosts in view of their clinical history. B catarrhalis normally responds to the penicillins commonly used for respiratory infections, but if treatment fails a transtracheal puncture is essential to identify the strain and determine an appropriate antibiotic.

Centre Médico-technique, Fonds des Maladies Professionnelles, Morlanwelz, Belgium
G NINANE, MD
J JOLY, MD
Hôpital Universitaire Brugmann, Université Libre de Bruxelles
M KRAYTMAN, MD

Introduction

Branhamella catarrhalis is classically considered to be non-pathogenic for the respiratory tract. Nevertheless, a case of