Night medication in rheumatoid arthritis

T. R. L. BAYLEY, M.B., Ch.B.
Vocational trainee
IAN HASLOCK, M.D.
Consultant rheumatologist
The Department of Rheumatology, South Tees Health District

SUMMARY. The efficacy of indomethacin 100 mg, diazepam 10 mg, and placebo in producing sleep, relieving night pain, and reducing the severity of morning stiffness, was compared in 18 patients in hospital with active classical or definite rheumatoid arthritis.

There was no statistically significant difference in the preference of patients or sleep score among the three forms of treatment. Both indomethacin and diazepam were more effective than placebo in relieving night pain. Indomethacin decreased, but diazepam increased, morning stiffness in comparison to placebo. Neither active therapy produced significant side-effects.

Introduction

Early morning stiffness and sleep which is disturbed by pain are two of the most distressing symptoms experienced by patients with rheumatoid arthritis. Indomethacin capsules given at bedtime have been shown to be effective in alleviating morning stiffness (Huskisson *et al.*, 1970; Huskisson and Hart, 1972), and to be more effective than amylobarbitone at inducing sleep (Huskisson and Grayson, 1974). This comparison with a barbiturate is, however, of decreasing relevance in the context of diminishing use of barbiturates as hypnotics.

A pharmacological group of first choice now is the benzodiazepines. Of these, diazepam appears to be unique in having significant muscle relaxant as well as sedative and psychotropic properties. It has been our practice for some years to give diazepam 10 mg at night under the clinical impression that as well as inducing sleep, the skeletal muscle relaxant property was of value in alleviating morning stiffness.

Aims

This study was designed to test this hypothesis and to compare the efficacy of diazepam and indomethacin.

Method

Eighteen in-patients with classical or definite rheumatoid arthritis (Ropes *et al.*, 1959) were included in the trial. Informed consent was obtained from each patient at the beginning of the study and all 18 completed the full trial protocol. All the patients had been in hospital in order to control active joint disease. No patient taking corticosteroids or more than indomethacin 75 mg daily was included, and patients with known hypersensitivity to either drug being used in the trial were excluded.

Each patient was given either indomethacin capsules 100 mg, diazepam tablets 10 mg, or a placebo, on each of three consecutive nights, the treatment order being randomised. The double-blind nature of the experiment was ensured by using appropriate dummies and individual packaged doses.

The trial medication was given in place of any other prescribed analgesic or hypnotic at the night medicine round (2200 hours). The short duration of the study was used in order to minimise fluctuation in disease activity, and was selected in the knowledge that single-night studies are as accurate as longer trials in predicting the response of patients with rheumatoid arthritis to night-time medication of this type (Huskisson, 1976).

The quality of the night's sleep was recorded using the self-administered questionnaire devised by Wolff (1974). Night pain was recorded using a ten centimetre visual analogue scale completed on waking. The duration of morning stiffness was recorded in minutes. Side-effects

© *Journal of the Royal College of General Practitioners*, 1976, **26**, 591–594

were elicited using the direct question " Has the treatment upset you in any way? " and on the last morning the patient's preference was recorded.

Results

Three male and 15 female patients participated in the trial; 15 had classical and three definite rheumatoid arthritis and 16 were seropositive. The age of the patients and duration of their disease is shown in table 1.

TABLE 1
AGE OF PATIENTS AND DURATION OF DISEASE

	Range	*Mean*	*Standard deviation*
Age (years)	18–75	43·7	±16·6
Duration of disease (years)	½–25	6·2	±9·0

Six patients expressed a preference for indomethacin at night, five for diazepam, and four for placebo. Two patients were unable to state any clear preference.

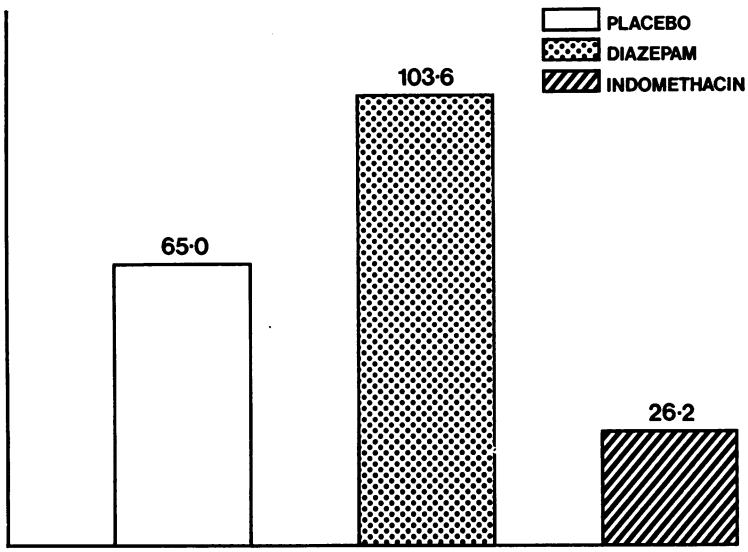

Figure 1
Mean duration of morning stiffness (minutes)

TABLE 2
SIGNIFICANCE OF COMPARISONS

	Indomethacin v *placebo*	*Diazepam* v *placebo*	*Indomethacin* v *diazepam*
Patient preference	Not significant	Not significant	Not significant
Morning stiffness	$p<0·05$	Not significant	$p<0·01$
Night pain	$p<0·05$	$p<0·05$	Not significant
Sleep score	Not significant	Not significant	Not significant

The effect on morning stiffness is shown in figure 1. Indomethacin was significantly better than diazepam and placebo, but there was no significant difference between the last two therapies (table 2). Figure 2 shows the degree of pain recorded by the patient expressed as centimetres

from the ' no-pain ' line on the visual analogue scale. Both indomethacin and diazepam produced significantly more pain relief than placebo (table 2). The sleep score is shown in figure 3, high scores indicating improved sleep. There is no significant difference between any of the results. The individual questions were analysed separately, and in no case was any significant difference found among the three groups.

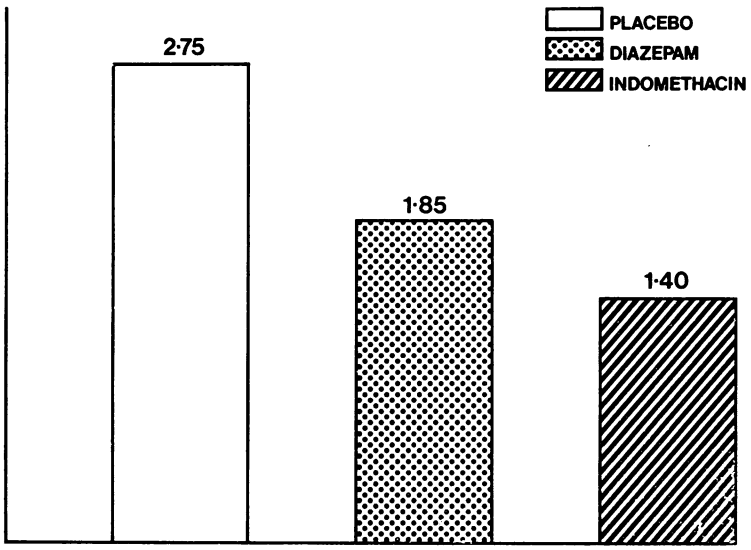

Figure 2
Mean pain scores (see text)

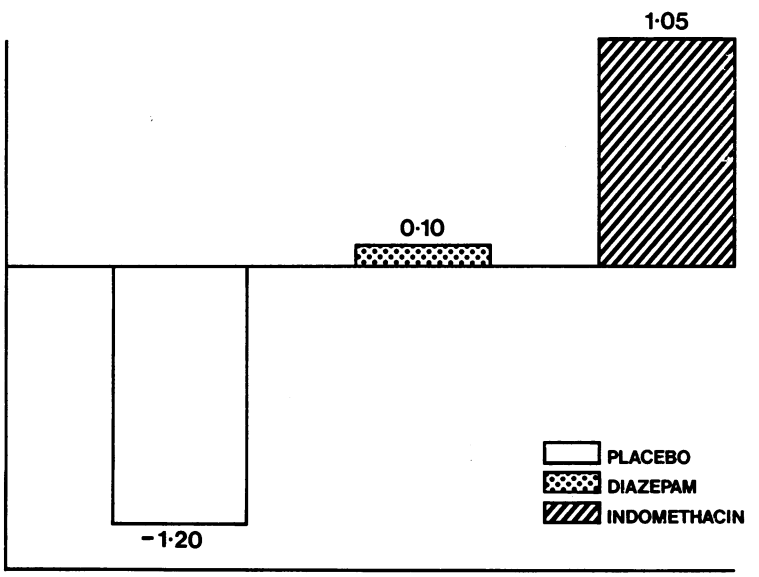

Figure 3
Mean sleep score (see text)

No patient developed serious side-effects during the course of the study. Minor side-effects occurred on 15 of the 54 patient-nights of trial and are shown in table 3.

TABLE 3
SIDE-EFFECTS DURING TRIAL (PATIENT NIGHTS)

	Indomethacin	*Diazepam*	*Placebo*
No side-effects	15	13	11
Headache	0	3	5
Sedation	1	2	1
Nausea	2	0	1
Nocturia	1	0	0
Tinnitus	1	0	0
Nightmares	0	0	1

Two side-effects were noted during two nights on indomethacin and one night on placebo.

Discussion

The reduction of night pain and morning stiffness by indomethacin was anticipated from the results of previous studies. In contrast, the effect of diazepam was unexpected. Analgesia may be explained by the psychotropic effect of the drug, but the significant increase in morning stiffness in comparison to placebo is less easily accounted for, especially as diazepam in large doses has been shown to abolish the daytime stiffness of rheumatoid arthritis measured objectively on the knee arthrograph (Haslock and Wright, 1972). It is possible that the combination of these sedative and muscle relaxant effects produces such still sleep that a single position is maintained for a long period, thus exacerbating stiffness. We are continuing to study this effect.

A further finding anticipated from previous work was the low incidence of side-effects produced by the large night-time dose of indomethacin (Haslock, 1976). No severe side-effects were encountered in any patient, but minor side-effects were more common in the placebo group. It may be suggested that the tension of insomnia or restless sleep contributed towards the headaches suffered by five placebo-treated patients on waking.

The inability of the sleep questionnaire to distinguish between active drugs and placebo is disappointing, although a trend does emerge. It will be interesting to see if significant changes are found during the further study currently in progress, or whether this method of sleep assessment is inapplicable to this form of trial.

Acknowledgements

We should like to thank Dr A. R. Rhymer of Merck, Sharp and Dohme for supplies of indomethacin and for help with the organisation of the trial and Dr J. F. Hort of Berk Pharmaceuticals for supplies of diazepam and placebo; Dr D. R. L. Newton for allowing us to study patients under his care; Sister Cook, Sister Mulloy and the nursing staff of Ward 5, West Lane Hospital for their help with drug administration and Mrs D. L. Woodburn for typing the manuscript.

REFERENCES

Haslock, D. I. (1976). *Indomethacin in the treatment of rheumatoid arthritis.* Proceedings of the European Symposium on inflammatory arthropathies. *Exerpta Medica.* In press.

Haslock, D. I. & Wright, V. (1972). *Medicine*, **1**, 18.

Huskisson, E. C. (1976). Chronopharmacology. Proceedings of the European Symposium on inflammatory arthropathies. *Exerpta Medica.* In press.

Huskisson, E. C. & Grayson, M. F. (1974). *British Journal of Clinical Pharmacology*, **1**, 151.

Huskisson, E. C. & Hart, F. D. (1972). *Practitioner*, **208**, 248–251.

Huskisson, E. C., Taylor, R. T., Burston, D., Chuter, P. J. & Hart, F. D. (1970). *Annals of the Rheumatic Diseases*, **29**, 393–396.

Ropes, M. W., Bennett, G. A., Cobb, S., Jacob, R. & Jessar, R. A. (1959). *Annals of the Rheumatic Diseases*, **18**, 49.

Wolff, B. B. (1974). *Clinical Pharmacology and Therapeutics*, **115**, 130–140.