INDOMETHACIN OR AMYLOBARBITONE SODIUM FOR SLEEP IN RHEUMATOID ARTHRITIS, WITH SOME OBSERVATIONS ON THE USE OF SEQUENTIAL ANALYSIS

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- 1 A double blind crossover trial in patients with rheumatoid arthritis showed that indomethacin given at night was superior to a hypnotic in providing sleep and relieving morning stiffness.
- 2 In a second trial, the combination of a hypnotic with indomethacin was not superior to indomethacin alone as judged by patients' preference, but further analysis suggested that the combination improved sleep without affecting morning stiffness.
- 3 It is argued that the use of a small closed sequential design produced too small a sample in the first trial. In the second trial, the sample was relatively large but the result was inconclusive; measurement of the response in terms of preference alone obscured the effect of treatment on one aspect of the symptomatology studied.

Introduction

Pain at night, loss of sleep and morning stiffness are important components of the symptom complex in rheumatoid arthritis (Hart, Taylor & Huskisson, 1970). Indomethacin in a large single dose of 100 mg taken as a suppository, has been shown to give effective relief (Holt & Hawkins, 1965). Huskisson, Taylor, Burston, Chuter & Hart (1970) showed that capsules were at least as effective as the same dose in suppository form. Huskisson & Hart (1972) showed that oral indomethacin was more effective than either a long-acting salicylate or a placebo. Pain from chronic musculoskeletal disorders has been described as the biggest single indication for hypnotics in general practice (Johnson & Clift, 1968).

The present study was designed to test the value of an anti-inflammatory and analgesic drug or a hypnotic in giving patients with rheumatoid arthritis a settled night. The second part of the study was later undertaken to see whether the addition of a hypnotic drug gave increased benefit to that provided by an anti-inflammatory and analgesic drug alone.

Methods

Forty patients in hospital with definite or classical rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox

& Jessar, 1959) took part in the study. All had active disease with pain at night and morning stiffness. Both parts of the trial were double blind, using the double placebo technique so that all patients always received four yellow capsules plus one white tablet at bedtime. A randomized single dose crossover design was used, and each patient received the two comparative treatments on consecutive nights. Regular daytime treatment was maintained unchanged, but no other nocturnal medication was given. Patients receiving steroids were excluded. Administration was supervised by the nursing staff.

Trial 1

The eight patients in this part of the study received either indomethacin 100 mg or amylobarbitone sodium 200 mg orally at 22.00 h on the first day; on the second day they crossed over to the other medication.

Trial 2

Thirty-two patients received either indomethacin 100 mg plus amylobarbitone sodium 200 mg or indomethacin 100 mg plus placebo on the first day, crossing over on the second day.

On the morning after each treatment, all

Fig. 1 Sequential analysis of preference in Trial 1. (2α , 0.05; $(1-\beta)$, 0.95; θ , 0.85; (n) , 27. The sample is perhaps too small. Horizontal scale, number of preferences.

Fig. 2 Sequential analysis of preference in Trial 2. (2α , 0.05; $(1-\beta)$, 0.95; θ , 0.85; (n) , 27. The sample is perhaps unnecessarily large and the 'not statistically significant' result misleading in view of the trend. Horizontal scale, number of preferences.

patients recorded an assessment of the quality of their night's sleep and also of how they felt on waking, using a nine point verbal scale of change: as well as ever (1), much better (2), moderately better (3), slightly better (4), as usual (5), slightly worse (6), moderately worse (7), much worse (8), and as bad as ever (9), measuring changes from before the start of the trial. The duration of morning stiffness was also noted. Finally, on the second morning, all patients were asked to provide an overall preference for the treatment on one or other night, or to state that there was no difference.

The preferences were analysed sequentially

using a small closed design in which $2\alpha = 0.05$, $1-\beta = 0.95$, $\theta = 0.85$ and $n = 27$ (Armitage, 1960). The other assessments were analysed separately for interest at the end of each part of the study.

Results

The sequential analyses are shown in Figures 1 and 2.

Trial 1 showed a statistically significant result at the 5% level in favour of indomethacin against amylobarbitone sodium. The trial ended when eight patients had completed the comparison. One

Table 1 Mean sleep and waking scores, expressed on a verbal two-way, nine-point scale where 5 = as usual, 1 = full improvement and 9 = full deterioration, and mean duration of morning stiffness

Treatment		Sleep score	Waking score	Duration of morning stiffness (min)
Trial 1 (8 patients)	Indomethacin	3.3	3.0	33.0*
	Amylobarbitone sodium	6.5	6.6	75.7*
Trial 2 (30 patients)	Indomethacin plus amylobarbitone sodium	3.8	4.2	46.1
	Indomethacin plus placebo	5.9	4.6	51.9

* Means are from the first seven patients only, because patient no. 8 provided figures of 5 h for indomethacin and 12 h for amylobarbitone sodium, which if included would skew the means. The means for all eight patients are in fact 66.4 and 156.3 min respectively.

of these recorded no difference between the treatments and does not appear on the graph. All of the other seven recorded a preference for indomethacin.

Trial 2 showed no statistically significant difference between the combination of indomethacin and amylobarbitone sodium and indomethacin alone. Twenty-seven of the patients recorded preferences which were charted on the graph; three noted no difference between the two treatments, and the other two were excluded from the study (one took the wrong tablets, the other had an intercurrent illness).

The mean results of the other assessments are shown in Table 1. No statistical analysis of these results was performed because the sequential design determined the end point of each trial and the samples would therefore have been biased. From the means alone, it is clear that in Trial 1 indomethacin was better than amylobarbitone sodium during sleep, on waking and in reducing morning stiffness. In Trial 2, there is an apparent advantage for indomethacin plus the hypnotic in the sleep score but the means are almost the same on both regimes for the waking score and the duration of morning stiffness.

Side effects

During Trial 1, one patient felt hazy and dizzy after indomethacin, and one felt unwell and another had pain and noises in the head after amylobarbitone sodium. In Trial 2, nine patients experienced the following symptoms: sleepiness (3), headache (3), nausea (3), dizziness (2), deafness and echoing sensation, 'hangover', nasty taste. One of these patients had symptoms after indomethacin alone, two after the combined drugs alone, and the others noted symptoms on both nights.

Discussion

Strict interpretation of the results of these trials using only the sequential analysis shows that indomethacin given at night was superior to amylobarbitone sodium in patients with active rheumatoid arthritis and that the difference between a combination of indomethacin with amylobarbitone sodium and indomethacin alone was not statistically significant. This provides experimental confirmation of the well-known therapeutic principle that conditions characterized by pain at night should be treated with anti-inflammatory and analgesic drugs rather than hypnotics.

The data shown in the table represent an

analysis of some of the components on which the patients' preference is likely to be based. They suggest that indomethacin, by relieving pain, improves sleep as well as relieving morning stiffness. The combination of indomethacin and amylobarbitone sodium was superior to indomethacin alone in improving sleep and it is worth noting that the addition of a hypnotic did not worsen morning stiffness, which has been suggested as a possible adverse effect of deep sleep in rheumatoid arthritis (Hart *et al.*, 1970).

The use of sequential analysis in these experiments prompted some observations on the method. The advantages of sequential analysis, particularly using closed designs, include restriction of the size of sample required to answer a particular question to a specified level of precision, with consequent ethical and economic benefits. It may be argued of Trial 1 that a study conducted on eight patients (one of whom did not even contribute to the final result) fails to inspire confidence. Such a small sample may be unrepresentative of the population studied in many ways, for example by tending to consist only of those suitable patients most readily to hand at the start of the trial who are often the most severely affected. On the other hand, the closed sequential design chosen allows for a sample as small as seven pairs or as large as 27, and by the acceptance of sequential analysis one must presumably accept the possibility that experimentation using a small design will end with a small sample. Neither ethical nor financial considerations here demanded sequential analysis, which may therefore have been inappropriate. In Trial 2, 30 patients were tested and the graph extended to its maximum number of 27 pairs, so that economy was not achieved.

Although the trials were analysed on the basis of preference, three separate components of the drug response were also assessed; effects on sleep and after waking, and duration of morning stiffness. A larger number of patients would have been desirable for this purpose, at least in Trial 1. It must be seldom that clinical trials do not attempt to provide some information additional to the specific objective of the experiment. Few therapeutic responses are sufficiently simple to be measured only by preference.

This is borne out by the tabulated results of Trial 2. The means show that the combination of indomethacin and amylobarbitone sodium was strikingly better than indomethacin alone in improving the quality of sleep, although no such advantage was evident in the waking score or in the duration of morning stiffness. This is interesting from the clinical point of view, and it may reflect the component of the response which contributed to the obvious trend, seen in Fig. 2,

for the graph to move towards the boundary showing a significant advantage for the combined drugs. Nevertheless, the graph ended at the boundary indicating no statistically significant difference between the treatments, and it is theoretically incorrect to attempt to deduce any 'trends' from the shape of the graph alone. Thus some valuable information was lost by using the sequential test alone.

It was interesting that in Trial 2 it was left to the last patient to provide the overall decision of a 'significant' or 'not significant' difference between the treatments. It would be tempting to try to assign a significance value to the point reached on the inner boundary, but it is theoretically preferable not to do this on the basis of the sequential experiment (Armitage, personal communication). Clearly the significance value here cannot be much greater than $P = 0.05$, and the standard non-sequential tests might provide a more useful statement of the result than that produced by sequential analysis. It is suggested that a statement of the result, and whatever significance value is reached, can be indicating possibly important

trends be more satisfactory than adhering rigidly to the arbitrary value of $P = 0.05$.

Another component of the overall preference decision was the presence or severity of side effects. In more than one patient, a disturbing side effect on one or other night prejudged the preference for that patient, whereas other components of the response would have indicated the opposite preference. This may be clinically important for the individual patient concerned but it cannot truly represent a means of deciding differences in therapeutic benefit for extrapolation to a population.

Sequential analysis appears to be becoming rarer in clinical trials and it may be that Mantel (1971) was right in stating that 'there are probably comparatively few situations in which sequential procedures can be valid and useful'.

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