PHENYLBUTAZONE: A CLINICO-PHARMACOLOGICAL STUDY IN RHEUMATOID ARTHRITIS

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- 1 A clinical trial of phenylbutazone in high dose (300 mg daily) and low dose (50 mg daily) is presented.
- 2 By analysis of the data by different methods, significant differences in clinical efficacy were shown between the two therapeutic regimens.
- 3 A relationship between the clinical effect and plasma level of phenylbutazone was demonstrated.
- 4 Some problems in the interpretation of plasma level-clinical effect correlates are discussed.

Introduction

Phenylbutazone was introduced in 1952 and has established itself as an efficacious anti-inflammatory agent for the treatment of rheumatoid arthritis (Currie, Peebles-Brown & Will, 1953; Mason, Barnardo, Fox & Weatherall, 1967; Lewis-Faning & Fowler, 1971). Currie *et al.* (1953) and Brodie, Lowman, Burns, Lee, Chenkin, Goldman, Weiner & Steele (1954) noted a relationship between plasma level and clinical effect but recently Davies, Orme, Williams, Hughes & Holt (1973) failed to demonstrate this relationship conclusively.

With the improvement in clinical methods of assessing anti-inflammatory activity and the suggested relationship between plasma level and toxic effect of phenylbutazone (Cunningham, Leyland, Delamore & Price-Evans, 1974) we thought it important to study the effect of phenylbutazone prescribed in a high dose (300 mg daily in two divided doses) and a low dose (50 mg daily in two divided doses) in patients with rheumatoid arthritis.

Methods

Ninety patients with sero-positive rheumatoid arthritis agreed to participate in the trial. They were asked to stop their usual therapy and take the trial drug for a period of two weeks, and

return for clinical assessment and a blood test on the last day of the two week treatment period. The patients were all given a pain self-assessment chart (Lee, Webb, Anderson & Buchanan, 1973) and asked to note each night on retiring the severity of their pain during the day on a scale of nil, mild, moderate, severe or very severe.

At the end of the trial patients were asked to rate the drug according to five global scores of satisfaction, namely, totally ineffective, ineffective, moderately effective, effective and highly effective. A separate questionnaire was provided for completion if the patients withdrew prematurely from the trial and the number of days withdrawn was noted in each case. For statistical analysis, the five grades of pain were allocated the numerical scores of one to five, where nil = 1, mild = 2, moderate = 3, severe = 4, and very severe = 5. Similarly the five global grades of satisfaction were scored from one to five, where totally ineffective = 1, ineffective = 2, moderately effective = 3, effective = 4, and highly effective = 5.

The clinical assessments were made by a single observer who was unaware of the treatment regime and who performed an articular index of joint tenderness according to the method of Ritchie, Boyle, McInnes, Jasani, Dalakos, Grievson & Buchanan (1968) and who noted the pain score of the patient at the time of blood sampling. Patients were asked to take their tablet at 08.00 h before

attending for assessment and the time that blood was withdrawn was noted.

In twenty-nine of the patients clinical assessments were made before and after therapy, again by a single observer. Statistical analysis of these results was carried out by a Student's *t*-test for paired values. Statistical analysis of the clinical parameters at the time of blood sampling was carried out using a Student's '*t*' for unpaired values.

Blood was collected in lithium-heparin tubes, centrifuged for 15 min at 2000 rev/min and the supernatant stored at -4°C until analysis was performed.

Phenylbutazone was measured by the spectrophotometric method of Burns, Rose, Chenkin, Goldman, Schulert & Brodie (1953). The method shows a high degree of reproducibility and standard serum samples containing phenylbutazone (10 mg/100 ml of plasma) were measured with each set of determinations.

Statistical method

The three variables which summarize the patient's response to treatment are the patient's assessment of his satisfaction with therapy administered, the number (if any) of days withdrawn from the trial and the average treated pain rating (ATPR). The last observation is the average of the daily pain ratings, ignoring the missing values.

Comparisons of the different treatment groups was made by analysis of variance and co-variance, using the initial observations on the patients as concomitant variables (Cochran & Cox, 1957). Since patients with rheumatoid arthritis at the

beginning of a trial will vary considerably in disease activity, adjustments are made to correct for initial differences between patient groups. As previously reported (Lee *et al.*, 1973) the inclusion of the initial pain rating (IPR) as a co-variate significantly increases the precision of the analysis of between treatment differences in ATPR. Lee *et al.* (1973) have shown that after allowing for the IPR, the effects of other pre-treatment observations (concomitant variables) on the analysis are not significant. It is therefore possible to adjust the raw ATPR means to give a mean ATPR at a specific IPR level.

Results

Forty-five patients were given phenylbutazone (300 mg daily) in two divided doses, two patients failed to return and three patients dropped out of the trial due to increasing pain (2) and nausea (1). Blood samples were taken from thirty-five of the patients.

Forty-five patients were given phenylbutazone (50 mg daily) in two divided doses, five failed to return and fifteen dropped out of the study because of increasing pain and stiffness. Blood samples were taken from thirty patients in this group. The two patient groups were matched for age, sex and duration of rheumatoid arthritis (Table 1).

Blood was taken for estimation of phenylbutazone level and simultaneous articular index and pain score measurements made in sixty-seven of the patients. These results are summarized in Table 2. On analysis of these results by Student's

Table 1 Clinical details of the patients studied. Age and duration of disease expressed as mean $\pm$ s.e. mean

Daily phenylbutazone dose	Age (years)	Duration of disease (years)	Sex
300 mg	50.8 $\pm$ 1.6	9.2 $\pm$ 1.0	33 ♀ 12 ♂
50 mg	54.2 $\pm$ 1.5	11.2 $\pm$ 1.7	30 ♀ 15 ♂

Table 2 A comparison of the clinical indices (mean $\pm$ s.e. mean) at the end of the treatment period.

Daily phenylbutazone dose	Articular index	Pain score	Satisfaction score
300 mg	11.8 $\pm$ 1.5	2.3 $\pm$ 0.1	3.7 $\pm$ 0.02
50 mg	17.5 $\pm$ 2.8	3.8 $\pm$ 0.6	2.4 $\pm$ 0.05
<i>n</i> = 67	1.812	2.528	5.658
<i>P</i>	0.05	0.01	0.005

t-test for unpaired variants, there was a statistically significant difference between the articular index, the pain score and the mean satisfaction score at the two dose levels of phenylbutazone, all three parameters being significantly lower in the group treated with high dose phenylbutazone.

Table 3 summarizes the results of the patients studied in both treatment groups before and at the end of therapy. It can be seen that there was no significant difference between the initial pain score and articular index of joint tenderness in either group. Phenylbutazone in a dose of 300 mg/day significantly reduced the articular index of joint tenderness in the patients studied but though it reduced the pain score it did not do so to a statistically significant degree. Low dose treatment with phenylbutazone (50 mg daily) did not reduce the clinical parameters at all.

Tables 4, 5 and 6 show the results of the analysis of co-variance of the Lee pain charts. The mean IPRs in the two groups are very similar (phenylbutazone 300 mg daily 2.8, and phenylbutazone 50 mg daily 3.0) indicating a good randomization (Table 4). The difference in the mean ATPR adjusted for IPR is significant at the 1% level (*F* test in the analysis of variance). The mean number of days withdrawn is also

Figure 1 The relationship between the phenylbutazone plasma level and the two dose regimes, ○ 300 mg/day and ■ 50 mg/day.

Table 3 A comparison of clinical indices (mean $\pm$ s.e. mean) in each treatment group before and after therapy.

		Pre-treatment	Post-treatment	t	P
Phenylbutazone (300 mg daily) <i>n</i> = 17	Articular index	12.5 $\pm$ 1.9	6.9 $\pm$ 1.2	4.804	0.0005
	Pain score	2.5 $\pm$ 0.1	2.3 $\pm$ 0.2	0.790	NS
Phenylbutazone (50 mg daily) <i>n</i> = 12	Articular index	13.4 $\pm$ 2.5	15.5 $\pm$ 3.5	1.008	NS
	Pain score	2.8 $\pm$ 0.3	2.9 $\pm$ 0.3	0	NS

Table 4 Number of patients treated with each drug, the initial pain rating (IPR), the average treated pain rating (ATPR) and the latter adjusted for IPR. The results are expressed as mean $\pm$ s.e. mean.

Daily dose of phenylbutazone	n	IPR	ATPR	ATPR adjusted for IPR
300 mg	43	2.8 $\pm$ 0.12	2.7 $\pm$ 0.11	2.8 $\pm$ 0.15
50 mg	40	3.0 $\pm$ 0.13	3.3 $\pm$ 0.12	3.3 $\pm$ 0.16

Table 5 The number of patients prematurely withdrawn from the trial. The results are expressed as mean $\pm$ s.e. mean.

Daily dose of phenylbutazone	n	Days withdrawn
300 mg	3	0.5 $\pm$ 0.6
50 mg	15	3.5 $\pm$ 0.6

Table 6 Satisfaction scores. The results are expressed as mean $\pm$ s.e. mean.

Daily dose of phenylbutazone	Satisfaction score
300 mg	3.6 $\pm$ 0.16
50 mg	2.5 $\pm$ 0.16

Figure 2 Phenylbutazone plasma level and articular index of joint tenderness.

Figure 3 Phenylbutazone plasma level and pain score.

statistically significant at the 1% level (Table 5). The mean satisfaction rating (Table 6) was 3.6 (phenylbutazone 300 mg) and 2.5 (phenylbutazone 50 mg), a result which is also significant.

Figure 1 shows the relationship between the level of phenylbutazone and the two dose regimes. It can be seen that there is no overlap of plasma levels between the two dose schedules but within each dose schedule there is a considerable variation in plasma level achieved.

Figures 2 and 3 show the plot of plasma level of phenylbutazone against the articular index and against pain score at the time of blood sampling. It can be seen that there is little correlation between the plasma phenylbutazone level and the clinical indices in these patients, the correlation coefficients being $r = 0.29$ and $r = 0.34$ respectively.

Discussion

Though phenylbutazone has been used as an anti-inflammatory drug for 20 years there is little data on the ideal dosage to be prescribed. It was because of this lack of knowledge and the fact that Davies *et al.* (1973) had failed to conclusively demonstrate a relationship between clinical effect and plasma level using daily doses of phenylbutazone ranging from 50-300 mg daily, that we decided to study the effect of high dose phenylbutazone (300 mg per day) and low dose (50 mg per day) in patients with sero-positive rheumatoid arthritis.

In our experience the method used in this trial has proved useful in assessing the efficacy of

anti-rheumatic drugs. Deodhar, Dick, Hodgkinson & Buchanan (1973) have shown that the most sensitive criteria in clinical trials of anti-rheumatic drugs have been the patient's assessment of joint pain and the articular index of joint tenderness, and the least sensitive indices have been objective measurements such as isotope 'uptake' in the joint and ring sizes. The method shows a high degree of reproducibility (Lee, Anderson, Miller, Webb & Buchanan, 1975). Huskisson (1974) has recently shown that pain relief score (the inverse of the above method) taken at hourly intervals for a 6 h period following the administration of analgesic or placebo tablets, is a valid and useful method of assessing analgesics in patients with rheumatoid arthritis. We know of no evidence to suggest that a two week study adequately reflects the long term efficacy of a drug but feel that differences between treatments can be demonstrated using this method providing one recognizes these limitations.

The results show clearly by the conventional before and after study, and by the novel Lee pain chart method, that phenylbutazone in a dose of 300 mg/day is statistically significantly better than phenylbutazone 50 mg/day.

The ATPR adjusted for IPR is almost equal to the IPR in the high dose group and greater than the IPR for the low dose group. This suggested that the patients' previous therapy was better than low dose phenylbutazone and equal to the high dose phenylbutazone. This appears to be at variance with the smaller internal before and after study where phenylbutazone (300 mg/day) significantly reduces the articular index of joint

Figure 4 The inflammostat, showing the variation in clinical state of rheumatoid patients around a fixed plasma drug level.

tenderness and does reduce the mean pain score but not to a significant degree. This variance has arisen because the larger group studied by the Lee method (Lee *et al.*, 1973) included patients not returning, having dropped out of the trial on account of increasing joint pain. This selection of patients will tend to produce lower treated pain scores and articular indices in the group studied before and after therapy than when the groups are considered as a whole by the Lee method (Lee *et al.*, 1973).

The plasma levels of phenylbutazone show a remarkable relationship as a group to the dose administered (there being no overlap of plasma levels between the two groups), but show a marked variation in individual level on the same dose. This is consistent with the known variation in metabolism of phenylbutazone as a result of genetic control (Whittaker & Price-Evans, 1970).

Phenylbutazone is absorbed rapidly from the gastro-intestinal tract and though plasma levels increase progressively during the initial three or four days of therapy a plateau is then reached with little variation within the individual (Burns *et al.*, 1953). We can assume that our single plasma determinations of the phenylbutazone level do reflect a fairly constant level of the drug as therapy had been continued for a period of 14 days.

From Figure 1 it can be seen that there is a significant difference between the phenylbutazone levels achieved on the two therapeutic regimes. If one relates that fact to the data already presented on the significant differences in the two groups clinically then one is led to the assumption that there is a direct relationship between the level of phenylbutazone and degree of pain. However when one looks at Figures 2 and 3 it can be seen

that there is in fact no correlation between the clinical state of the patient and the plasma phenylbutazone level.

The explanation of this anomaly is difficult. It may be that our techniques for measuring pain were too crude to be compared with a highly accurate chemical method for measuring drug concentrations, or it may be that there was a time lag between maximum therapeutic effect and plasma concentration (Brooks, Bell, Lee, Rooney & Dick, 1974). This latter reason is unlikely to occur with a long half-life drug such as phenylbutazone (72 h) when a steady state has been reached.

What is probably happening is that the clinical indices are continuing to vary quite markedly within a certain range but by altering the steady rate plasma level we are moving the range either up or down the scale but not altering the variation to any marked degree. We may in fact just be altering the 'inflammostat' (Figure 4) to a degree which will give a correlation between the means of groups of drug level and clinical index but will not reflect any correlation when individual figures are compared.

Koch-Weser (1972) emphasizes the value of monitoring plasma drug levels in an attempt to improve safety and efficacy of drug therapy, and Turner (1974) points out the importance of relating pharmacokinetic studies and clinical effects.

These results indicate certain problems in the correlation of clinical effect and plasma phenylbutazone concentrations which may also pertain to other so called 'steady state' situations with long half-life drugs producing relatively constant plasma levels.

In this study we have shown that phenyl-

butazone in a dose of 300 mg/day was significantly better than phenylbutazone 50 mg/day in the relief of pain in patients with rheumatoid arthritis. However because of the potential side effect of bone marrow depression in patients treated with this drug, it is desirable to weight the clinical efficacy against toxicity in a quantitative way. Though this is obviously beyond the scope of this study, we hope to have added another small part to the information required to make a rational decision on the prescribing of phenylbutazone.

This study highlights some of the problems involved in bringing the spectrophotometer to the bedside but does indicate that simultaneous measurements of clinical state and plasma drug

level are useful in assessing the efficacy of treatment in rheumatoid arthritis. It goes part of the way towards explaining the anomalies in correlating these plasma levels with clinical effect in individuals and in larger groups. The authors do not claim it is the whole or even the right explanation but merely indicate that it is worth consideration as an explanation.

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