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PLASMA CONCENTRATION OF PHENYLBUTAZONE AND ITS THERAPEUTIC EFFECT— STUDIES IN PATIENTS WITH RHEUMATOID ARTHRITIS

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1 Phenylbutazone in doses of 50, 100, 200 and 300 mg/day has been given for four periods of 3 weeks to seven patients with rheumatoid arthritis. The trial was double-blind and the order of administration of doses was arranged to eliminate order and carry-over effects.

2 Before the trial and at the end of each period, the patient's responses were assessed by measurement of the duration of morning stiffness, the pain score, paracetamol tablet count, grip strength, digital joint size and articular index.

3 The plasma phenylbutazone concentration was measured by gas-liquid chromatography and was also predicted by prior measurement of the phenazone half-life.

4 Compared with the pretreatment period, phenylbutazone had a significant therapeutic effect, as judged by morning stiffness, pain score and articular index, in a dose of 50 mg/day, but no statistically significant differences in effect were seen between the various doses of phenylbutazone.

5 There were no significant correlations between the plasma concentration of phenylbutazone and any of the clinical assessments.

6 The plasma phenylbutazone concentration agreed closely with that predicted at doses of 50 and 100 mg, but at higher doses the plasma concentration was significantly lower than predicted ($P < 0.05$). This may have been due to saturation of the protein binding sites at these doses.

Introduction

Phenylbutazone has been in use now as an anti-inflammatory drug for more than 20 years. However, its role in the treatment of rheumatoid arthritis is still a subject of discussion (Mills, 1974). Some patients with the disease respond better to phenylbutazone than other patients and there is no way of predicting those patients that will respond. Phenylbutazone is oxidized both in the side chain and in the phenyl ring (Burns, Rose, Chenkin, Goldman, Schulert & Brodie, 1953; Bakke, Draffan & Davies, 1974), the latter metabolite being oxyphenbutazone which has anti-inflammatory activity. There is a considerable inter-individual variation in the plasma half-life of phenylbutazone (from 1.2 to 7.3 days, Vessell & Page, 1968), and thus the steady state plasma concentration of phenylbutazone will vary among different individuals. In 1954, Bruck, Farnley, Meanock & Patley reported the results of a trial designed to relate the plasma concentration of phenylbutazone to its toxic and therapeutic effects. These authors found that toxic effects were more likely with higher plasma concentrations and that the optimum therapeutic effect was seen with plasma concentrations around 100 $\mu g\ ml^{-1}$ (10 mg 100 ml^{-1}). These studies were performed at a time when knowledge about the metabolism of phenylbutazone was relatively sparse. The method of analysis of plasma phenylbutazone concentrations utilized a spectrophotometric technique that may detect both

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phenylbutazone and its metabolites (Burns *et al.*, 1953). In addition, the measurement of the clinical response to anti-inflammatory agents has improved considerably in the last 20 years. We have undertaken a double blind study of the use of phenylbutazone in patients with rheumatoid arthritis in order to see if there is any relationship between the plasma concentration of phenylbutazone and its therapeutic effect.

Methods

Patients

Nine patients with classical or definite rheumatoid arthritis as defined by the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox & Jessar, 1959) were studied. Each patient had had the disease for at least six months and had never received systemic or intra-articular corticosteroid therapy, gold or immunosuppressive therapy. Seven patients were female and two were male and their ages ranged from 22 to 67 years. Their details are shown in Table 1. In the two months prior to the trial no other drugs were ingested by the patients except paracetamol.

Trial design

The patients were seen twice at three-weekly intervals prior to the trial. Phenylbutazone was then given to each patient in four different daily doses of 50 mg, 100 mg, 200 mg and 300 mg in random order using a randomized block design with order and carry over effects balanced for every four patients. Neither the patient nor the assessing physician knew which dose the patient was taking. Each dose of phenylbutazone was given as capsules of identical appearance. Each day's capsules were separately packed and each capsule contained phenylbutazone (50 mg), or placebo, so that six capsules were taken daily by every patient and the dose was taken as one single evening dose. Each dose was given for a three-week period at the end of which time the patients were seen for clinical assessment. All patients were also given a measured supply of paracetamol tablets (0.5 g) to be used for pain relief and at each clinic visit the number of tablets of paracetamol and phenylbutazone remaining, were counted. At the end of the 12 week double-blind part of the study the dose of phenylbutazone was increased to 400 mg daily in three patients, the patients and physician being aware of the change in dosage. This dose was continued for 3 weeks and the patients reassessed at the end of that time.

Clinical assessment

Subjective and objective assessments were made before starting the trial and after each treatment period by the same observer (P.J.L.H.). The degree of pain was measured on a vertical analogue scale and also by counting the number of paracetamol tablets consumed in each treatment period. Comparative global assessment (worse, unchanged, better, much better) was scored on a 4 point scale from 1-4. The duration of morning stiffness was recorded in minutes. Objective assessments were of grip strength (based on a mean of three measurements obtained from each hand with the bag inflated to 30 mmHg), the articular index of joint tenderness (Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieveson & Buchanan, 1968) and the proximal interphalangeal joint size (Boardman & Hart, 1967) giving the sum of all ten values. The values for the clinical assessment in the control period are given in Table 3. As can be seen from the value for the articular index, these patients did

Table 1 Clinical details of patients with rheumatoid arthritis used in the study

Patient	*Age (years)*	*Sex*	*Weight (kg)*	*Duration of disease (years)*	*Antipyrine* $T_{\frac{1}{2}}$ *(h)*	*Predicted phenylbutazone* $T_{\frac{1}{2}}$ *(h)*
1	30	F	54.1	3	9.6	65
2*	48	F	54.0	0.75	4.8	37
3	52	F	70.2	2	4.5	35
4	70	F	60.0	1	6.1	45
5	49	F	65.0	15	11.6	76
6	22	F	52.8	2	5.1	39
7	67	M	77.6	5	10.6	70
8	50	M	62.3	0.75	9.1	56
9*	58	F	56.0	0.8	–	–

* Not included in final analyses

not have very severe disease, since we felt it was unethical to leave a patient with more severe disease without treatment in the control period. At each visit to the clinic each patient was weighed and then questioned about any side effects experienced in the preceding 3 weeks. The clinic was held at the same time of day (midday) and blood was obtained by venepuncture at each visit for measurement of the plasma phenylbutazone concentration, the drug having been taken about 18 h before. During the last week of one three-week period each patient was seen on three successive days at midday and blood was taken for phenylbutazone analysis in order to be sure that steady state concentrations had been achieved.

Measurement of plasma concentration of phenylbutazone

Plasma phenylbutazone concentrations were measured by gas-liquid chromatography using a Varian 1400 gas chromatograph fitted with a flame ionization detector. The column was $3' \times \frac{1}{8}''$ i.d. coiled pyrex glass packed with 1% HI-EFF-8PB on gas chrom Q 100-120 mesh (Applied Science). The oven temperature was 215° C, detector temperature 280° C and injector temperature 230° C. The nitrogen flow was 40 ml min^{-1}, the hydrogen flow 20 ml min^{-1} and the air flow 300 ml min^{-1}. The plasma (1 ml), 3M HCl(0.5 ml) and hexane (10 ml) containing 1.5% isoamylacohol was added. After mixing for 60 s on a vortex mixer the organic phase was separated by centrifugation and 8 ml transferred to a dry test tube and evaporated to dryness on a vacuum line. The residue was reconstituted in 300 μl ethyl acetate containing 100 $\mu g\ ml^{-1}$ codeine. Portions (1 μl) were injected onto the gas chromatograph. The retention time of phenylbutazone was 3.2 min and of codeine 4.2 minutes. Linear calibrations of peak height ratio versus phenylbutazone concentration in plasma were obtained over the range 10 to 200 μg phenylbutazone/ml plasma. The recovery of phenylbutazone was 90 ± 4% and the reproducibility of each injection was ±1.4% (six injections).

Prediction of plasma phenylbutazone concentration

Prior to the trial a single dose of phenazone (antiyprine 600 mg) was given by mouth to each patient after an overnight fast and blood samples were taken at 4, 8, 12 and 24 h after dosing. Plasma phenazone was measured in each plasma sample by the method of Brodie, Axelrod, Soberman & Levy (1949) and a plasma phenazone half-life was calculated using the method of least squares. Davies & Thorgeirsson (1971) have shown that there is a linear relationship between the single dose half-life of phenazone and the multiple dose half-life of phenylbutazone. Steady state (C_{ss}) plasma phenylbutazone concentrations were predicted using phenazone half-lives to estimate the phenylbutazone half-lives and using the formula of Wagner, Northam, Alway & Carpenter (1965) where:

$$C_{ss} = \frac{1.44 \times F \times D \times T_{\frac{1}{2}}}{V_D \times \tau}$$

and where F = fraction of the dose (D) absorbed (assumed to be 1 here), V_D is the apparent volume of distribution and τ is the dosage interval. The apparent volume of distribution of phenylbutazone was taken to be 86.5 ml/kg body weight as found by Thorgeirsson (1972).

Statistical methods

Comparison of predicted plasma phenylbutazone concentrations and those observed in practice were analysed using a paired *t* test. The changes in each clinical assessment were correlated with the plasma phenylbutazone concentrations using linear regression analysis. The changes in the various clinical measurements were assessed for any order or dose effects by analysis of variance for a randomized block design. A trend in mean results from the smallest to the largest dose was tested by linear contrasts (Armitage, 1971).

Results

Seven patients completed the trial satisfactorily. One patient had completed three of the treatment periods with phenylbutazone but had to be withdrawn from the trial during the fourth period because of worsening of her arthritis which necessitated admission to hospital. One other patient dropped out of the trial during the second period for social reasons. Thus seven patients were available for analysis each of whom received phenylbutazone in four different dosages (twenty-eight treatment periods).

Plasma concentrations of phenylbutazone

The plasma phenazone half-lives in these patients varied between 4.5 and 11.6 h and the predicted phenylbutazone half-lives were between 35 and 76 h (Table 1).

In every patient, measurement of the plasma phenylbutazone concentration on three consecutive days at the end of one treatment period showed that steady state had been reached. The

variance of a single repeated plasma concentration estimation was less than 5% of the mean. The mean plasma phenylbutazone concentrations observed in the seven patients are shown in Table 2. There was a good agreement between the predicted and observed concentrations at the two lowest dose levels. However, with phenylbutazone (200 mg), the observed concentration of 82.5 ± 7.4 (mean ± s.e. mean) $\mu g\ ml^{-1}$ was significantly less than the predicted value of 117.6 ± 13.5 $\mu g\ ml^{-1}$ ($P < 0.02$). This disparity was even more marked with a dose of 300 mg day^{-1} (see Figure 1) with a predicted value of 176.3 ± 20.1 $\mu g\ ml^{-1}$ and an observed mean value 95.1 ± 7.0 $\mu g\ ml^{-1}$ ($P < 0.005$). In three patients given phenylbutazone (400 mg/day), the disparity between the predicted and observed concentrations was again noted (Table 2).

Therapeutic effects

Table 3 gives a summary of the results of the various clinical assessments. Compared to the pretreatment control there were significant improvements in the duration of morning stiffness, pain score and in the articular index ($P < 0.05$) with the lowest dose of phenylbutazone. There appears (from Table 3) to be an improvement both

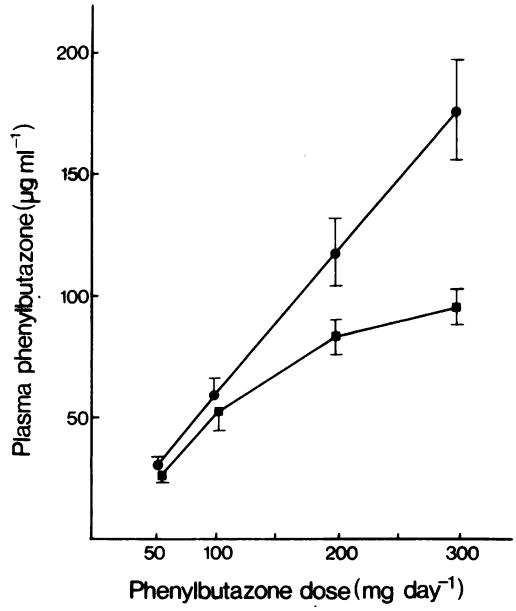

Figure 1 Predicted (•) and measured (▪) steady state plasma concentrations of phenylbutazone after different doses of the drug. The results are shown as mean ± s.e. mean, $n = 7$.

Table 2 Plasma phenylbutazone concentrations ($\mu g\ ml^{-1}$, mean ± s.e. mean)

Dose of phenylbutazone (mg)	n	*Predicted level*	*Observed level*	P
50	7	29.5 ± 3.4	25.3 ± 2.0	>0.1
100	7	58.8 ± 6.7	51.6 ± 7.4	>0.1
200	7	117.6 ± 13.5	82.5 ± 7.4	<0.02
300	7	176.3 ± 20.1	95.1 ± 7.0	<0.005
400	3	162.0 ± 20.8	98.6 ± 19.5	<0.05

Table 3 A summary of the clinical assessments. The results are expressed as mean ± s.e. mean

	Duration of morning stiffness (min)	*Pain score*	*Grip strength (mm/Hg)*	*Digital joint size (mm)*	*Articular index*	
Control data	*139.3 ± 16.7*	*11.2 ± 0.3*	*176.3 ± 13.9*	*574.3 ± 6.9*	*11.0 ± 0.7*	
Dose of phenylbutazone (mg)	*Improvement in morning stiffness (min)*	*Reduction in pain score*	*Improvement in grip strength (mm/Hg)*	*Change in digital joint size (mm)*	*Improvement in articular index*	*Number of paracetamol tablets consumed*
50	56.8 ± 23.1*	2.7 ± 0.9*	6.4 ± 38.8	−0.6 ± 5.8	3.3 ± 1.2*	124.0 ± 31.7
100	73.2 ± 22.3	2.5 ± 0.7	16.5 ± 27.0	−0.5 ± 5.9	3.3 ± 1.1	116.1 ± 30.3
200	71.1 ± 20.4	5.3 ± 1.4	35.2 ± 18.2	0.6 ± 7.5	4.3 ± 1.0	111.4 ± 26.3
300	93.2 ± 35.4	3.2 ± 1.2	35.9 ± 20.5	−1.1 ± 4.9	2.6 ± 1.2	118.1 ± 28.9

*$P < 0.05$ compared to control data.

in morning stiffness and in grip strength with increasing dose of phenylbutazone, however, the trend was not statistically significant. For each method of assessment there were significant between-patient differences ($F > 3.0$, $P < 0.05$). When the various treatment periods were compared, however, there were no significant order-related or dose-related differences among the various clinical assessments.

Individual clinical assessments

Pain score The mean pain score for the patients in the control period was 11.9 (maximum possible score 20) and this fell significantly during treatment with phenylbutazone (Table 3). There were however no significant differences in pain score between the treatment periods and there was no correlation between the pain score and the plasma phenylbutazone concentration.

Paracetamol tablet count There were no significant differences in the number of paracetamol tablets consumed in each treatment period (Table 3). There was no correlation between the number of paracetamol tablets consumed in any one period and the plasma phenylbutazone concentration in that period ($r = 0.34$, $P > 0.05$).

Duration of morning stiffness Compared to the control period there was a reduction in morning stiffness during treatment with phenylbutazone (Table 3). Although there was some improvement of morning stiffness with phenylbutazone (300 mg) compared to phenylbutazone (50 mg) there was no significant correlation between the improvement in morning stiffness (compared to control) and the plasma phenylbutazone concentration.

Grip strength There was no significant correlation between change in grip strength and plasma phenylbutazone concentration and it was only with phenylbutazone (200 mg/day) that the grip strength improved, compared to the control value (Table 3).

Digital joint size There was no significant change in digital joint size throughout the study and no correlation was seen between the plasma concentration of phenylbutazone and the change in digital joint size.

Articular index There was a slight improvement in the articular index during phenylbutazone therapy compared to control (Table 3) but no difference in the articular index between the various treatment periods and no correlation between the change in articular index and the plasma phenylbutazone concentration.

Comparative global assessment The patients commented that as a group they felt better during phenylbutazone treatment than during the control period but could detect no overall difference between the various treatment periods.

Side effects No side effects were noted during the trial either by comment from the patients or in reply to direct questioning. There were no significant changes in weight during the trial as compared to the control pretreatment period.

Discussion

This study has been unable to demonstrate any significant correlation between the therapeutic effects of phenylbutazone in rheumatoid arthritis and the plasma concentration of phenylbutazone. This is in contrast to the finding of Bruck *et al.* (1954). While the study was not designed to test the efficacy of phenylbutazone, we have been able to show a therapeutic effect of phenylbutazone compared to a pretreatment control period as judged by morning stiffness, pain score, and articular index. These three measures of therapeutic effect are felt to be the most sensitive available at the present time (Deodhar, Dick, Hodgkinson & Buchanan, 1973). Other measures including objective measures such as the technetium index (Oka, Rekonen, Ruotsi & Kuikka, 1973) are felt to be less sensitive. We have been unable to find any significant difference between the clinical effects of 50 mg and 300 mg daily of phenylbutazone. In Table 3 there is a progressive improvement in morning stiffness and grip strength with increasing dose of phenylbutazone, and there appears to be more pain relief with the higher doses of phenylbutazone than with the lower doses. These changes however do not reach statistical significance, perhaps due to the small number of patients in the trial.

It is possible that in these patients the disease process could show a spontaneous improvement during the 12-week period of the trial. All patients had had the disease for at least 6 months and at this stage spontaneous fluctuations are less likely than in the initial stages of the disease. The trial was also designed to try to mitigate any such spontaneous fluctuations by giving the doses of phenylbutazone in random order using a randomized block design and thus it would seem very unlikely that spontaneous fluctuations in the severity of the disease process have affected the results of this trial.

Phenylbutazone is an acidic drug, extensively bound to plasma proteins (about 99%) and has a small volume of distribution (less than 0.1 litre/kg body weight). It has a long half-life in plasma and our analyses showed that steady state plasma concentrations were achieved in each patient. Phenylbutazone is metabolized in the body to oxyphenbutazone which itself has anti-inflammatory and analgesic activity. Since our analytical method measures only phenylbutazone, this could explain the discrepancy of our results compared to those of Bruck *et al.* (1954) who may have measured both phenylbutazone and its metabolites. However, in our initial studies we compared this gas-liquid chromatographic method for phenylbutazone with the spectrophotometric assay and very similar results were achieved for both plasma phenylbutazone concentrations and half-lives in three volunteers given phenylbutazone (200 mg). This implies that oxyphenbutazone is not present in plasma to any great extent after administration of a single dose of phenylbutazone, or that the spectrophotometric assay does not measure significant amounts of oxyphenbutazone.

In our study the predicted phenylbutazone concentration agreed very well with that observed at the two lower dose levels and it thus seems unlikely that the apparent volume of distribution of phenylbutazone is different in patients with rheumatoid arthritis than in our normal volunteers (Thorgeirsson, 1972). However, at the two higher doses (200 and 300 mg day^{-1}) the observed plasma concentration was significantly lower than that predicted. Brodie, Lowman, Burns, Lee, Chenkin, Goldman, Weiner & Steele (1954) showed that the protein binding sites for phenylbutazone in plasma could be saturated with daily dosages of 400 to 600 mg and our observations suggest that this may occur with even lower doses. Under these conditions the proportion of phenylbutazone free in plasma would be greater and the apparent volume of distribution would be larger.

This would account for our finding of lower than predicted concentrations in plasma. In this context it is interesting that Eyberg, Moodley & Buchanan (1974) have reported saturation of the salicylate binding sites on plasma albumin at plasma concentrations at or above 40 mg 100 ml^{-1}. This concentration is close to the therapeutic range and salicylate and phenylbutazone being both acidic drugs, probably bind to the same sites on plasma albumin.

One other possible explanation for the observed plasma concentrations being lower than predicted is that phenylbutazone might have induced its own metabolism. Chen, Vrindten, Dayton & Burns (1962) have shown that phenylbutazone induced the metabolism of aminopyrine in man but only after initial doses of 10 mg kg^{-1}. Phenylbutazone has not been shown to induce its own metabolism in man, and Davies & Thorgeirsson (1971) have shown that in the doses used in this study, phenylbutazone does not induce antipyrine metabolism. It thus seems unlikely that enzyme induction can be an explanation of our findings.

We are unable to explain the disparity between our findings and those of Bruck *et al.* (1954) except that by using a specific assay for phenylbutazone we may not have measured the total anti-inflammatory activity in the plasma. It is interesting therefore that Brooks, Walker, Dick, Anderson & Fowler (1975) have been able to show a relationship between the plasma concentration of phenylbutazone (measured spectrophotometrically) and its therapeutic effect. Further studies on this subject are needed but elucidation of the problem will remain difficult because of the relative crudity of the methods of clinical assessment.

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