is 5%. An advantage of this method is that the risk of making errors of this kind is stated (Bross, 1952).

In both of the methods described the number of patients needed to decide the outcome was less than would be needed, on the average, with the equivalent fixed-sample-size test. This economy in cases is a valuable feature of sequential methods. The small numbers were also determined by the comparatively high proportion of preferences required for the new drug before we were willing to recommend it.

Because the procedure is so simple both methods are well suited to the trial of new drugs in a busy out-patient clinic or admission ward. Suitable patients are observed as they occur in the course of the daily work; the data are analysed without any computation or only one computation with the sequential t-test; and the psychiatrist is only required to assess carefully one crucial clinical characteristic of each patient. The last consideration, however, also imposes a restriction which may limit their application: improvement in the mental state of psychiatric patients must often be assessed on a number of aspects of behaviour. It should be possible to overcome this difficulty by setting up sequential tests for two or three essential clinical features to run concurrently. In our trial, for example, we might have begun by proposing that it would be decided in favour of prochlorperazine only if and when the path in both the sequential test of the patients' preferences and the sequential t-test of the measure of their anxiety crossed the upper boundary, and the decision "no important difference" be made only when the middle and lower boundaries are crossed. Should the upper boundary be crossed on one characteristic and another boundary on the other the result would be inconclusive concerning which treatment is therapeutically superior; but the information obtained would presumably still be a valuable guide to that aspect of behaviour on which the drug's activity is effective.

Conclusions and Summary

In psychiatry there is a need for rapid and reliable methods for the clinical assay of the many new compounds of potential therapeutic value now being manufactured. The method of sequential analysis was considered for this purpose. A trial was therefore undertaken to compare the effectiveness of a new tranquillizer, prochlorperazine, and a placebo in the treatment of anxious psychoneurotics.

After each patient had received each treatment for a week he stated which was preferred. No important difference at the 5% level of significance was found between the treatments when 20 patients had entered the trial.

Each patient also completed an anxiety questionnaire at the end of each week. A sequential t-test was undertaken and no significant difference was found between the decrease in anxiety scores with each treatment after 13 patients had entered.

It is concluded that in certain circumstances sequential methods are well suited to the early evaluation of new psychiatric drugs. They are easier to administer, more economical, and give a more precise decision than conventional tests.

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AN APPRAISAL OF PHENYLBUTAZONE SUPPOSITORIES

BY

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The patient with both rheumatoid arthritis and a peptic ulcer presents a difficult therapeutic problem. Drug therapy for the joint condition, whether with salicylates, phenylbutazone ("butazolidin") and its analogues, or adrenocorticosteroids, may have harmful effects upon the upper gastro-intestinal tract. Aspirin in high or low dosage can cause gastric irritation and probably bleeding (Douthwaite and Lintott, 1938; Muir and Cossar, 1955). Corticosteroids may produce peptic ulcers (Sandweiss, 1954). Similarly, a risk of phenylbutazone is peptic ulceration (Raffensperger, 1953), which can be fatal from perforation (Shield *et al.*, 1953; Beutler and Bergenstal, 1954) or from haemorrhage (Stephens *et al.*, 1952; Benstead, 1953). Phenylbutazone has other complications, such as depression of the bone-marrow and agranulocytosis (Dilling, 1953; Leonard, 1953), skin rashes (Cudkowicz and Jacobs, 1953), stomatitis (Freeland *et al.*, 1953); visceral lesions (MacCarthy and Jackson, 1955), and water retention (Wilkinson and Brown, 1953), which may precipitate cardiac failure in the elderly. However, the toxicity of any drug must be weighed against the benefits conferred by it, and we believe that its use is justified in carefully selected cases of the painful and crippling rheumatic disorders. The avoidance of gastric irritation has been a particular interest, and we report a small clinical trial where phenylbutazone has been given as a suppository rather than as a tablet or by injection.

Material and Methods

There were 26 patients. Nineteen suffered from rheumatoid arthritis; 11 of these also had a duodenal ulcer, two a gastric ulcer, two a hiatus hernia, two had a dyspepsia of unknown origin which made oral therapy impossible, and two developed a dyspepsia on phenylbutazone tablets. Two patients had ankylosing

spondylitis; one with a duodenal ulcer and one developed phenylbutazone dyspepsia. There were five cases of osteoarthritis: two with dyspepsia following phenylbutazone tablets, one with dyspepsia of unknown origin, and two volunteered to have the suppositories, though oral therapy had not been tried. The diagnosis of ulcer had in every case been proved radiologically, and three had previously perforated.

Oral therapy was not abandoned because of dyspepsia unless it was certain that the patient had taken the drug after meals, as this probably lessens the chance of gastric disturbance. A suppository containing 250 mg. of phenylbutazone was inserted into the rectum each night, and occasionally two were used in the 24 hours. Serum phenylbutazone estimations were carried out to assess absorption of the drug from the rectal mucosa. It was found by Currie *et al.* (1953) in a clinical trial involving 424 cases that a serum level of 8–11 mg./100 ml. was optimal for the suppression of symptoms, but that a remission could be maintained at concentrations between 4.6 and 8 mg./100 ml. Bruck *et al.* (1954) claimed that no further clinical improvement is likely if attempts are made to increase the serum level above 10 mg./100 ml., but that there is a rapid increase in toxic side-effects above that figure. The difference in the number of patients with toxic symptoms above and below 10 mg./100 ml. was statistically significant. As a routine we estimate the serum level of phenylbutazone of patients receiving the drug orally and adjust the dose according to the blood levels.

The technique for estimating phenylbutazone was a modification of Pulver's (1950) method. 1 ml. of serum or plasma is added to 10 ml. of acetone, shaken, and allowed to stand for 30 minutes. The acetone extract is then filtered into a 50-ml. conical flask and the precipitate washed twice with 5-ml. portions of acetone. This is carefully evaporated on a sandbath until the solution becomes turbid. 2 ml. of 20% *p*-toluene sulphonic acid is added to the test, to a "reagent blank" containing 1 ml. of water, and to the standards. It is only necessary, in practice, to prepare one standard, of 10 mg./100 ml. 1 ml. of this is equivalent to 0.1 mg. of phenylbutazone actually used in the estimation. The acid mixtures are heated in an oven at approximately 100° C. for not less than three hours. Then 4 ml. of water is added to each and heating continues for another three hours. Either of these heating periods can be extended and the specimens left in the oven overnight, if necessary, without detriment to the result. 20 ml. of water is added to the dry residue and filtered (Whatman No. 42), repeating if necessary until the filtrate is clear. To a 5-ml. aliquot of the filtrate is added 1 ml. of 0.1% sodium nitrite, with shaking; allow to stand for three minutes. Next add 1 ml. of 0.5% ammonium sulphamate, with shaking. Wait two minutes. Finally add 1 ml. of 0.1% naphthyl-ethylenediamine dihydrochloride, mix, and allow to stand for two minutes. The resulting coloured solutions are read within five minutes in a photoelectric colorimeter, using an Ilford 605 filter. The result is calculated as follows (RT is the reading of unknown and RS the reading of standard):

$$\text{Phenylbutazone} = \frac{RT}{RS} \times 0.1 \times \frac{100}{1} \text{ or } \frac{RT}{RS} \times 10 \text{ mg./100 ml.}$$

Analyses were routinely carried out in duplicate and the mean value was reported. The average deviation from the mean occurring in 20 consecutive specimens

was $\pm 4.25\%$. It is essential to put up a phenylbutazone standard with each batch of estimations rather than to rely on results read off from a prepared table or graph, as colour development varies with the freshness of the reagents. It also has to be remembered that sulphonamides will interfere with the colour development and give erroneously high results. The method needs no special apparatus, and can be carried out in any clinical laboratory.

Results

Phenylbutazone is rapidly absorbed from the rectum, as shown when serum levels are estimated at intervals of two, four, and six hours after a suppository containing 250 mg. (Fig. 1). The actual height of these initial readings can be discounted, as there is a progressive increase in the serum levels over the first few days until a plateau level is reached at the end of 7 or 10 days. Readings after this period are fairly constant for the individual and probably depend upon individual differences in the rate of metabolism of the drug rather than varying rates of excretion in the urine (Burns *et al.*, 1953). The serum levels obtained with rectal phenylbutazone are comparable to those from the oral route (Fig. 2).

When the 26 patients were maintained on a single suppository daily, it was found that 12 had a serum phenylbutazone level above 8 mg./100 ml.; 10 kept a level above 4.6 mg./100 ml., and most of these had satisfactory relief from pain; increase to two suppositories daily raised the serum level to a more

FIG. 1.—Showing rapid absorption of phenylbutazone after administration of one suppository daily.

FIG. 2.—Serum phenylbutazone levels estimated on 100 patients receiving the tablets and on 26 treated by suppositories.

effective therapeutic range. Four patients had low levels between 1 and 4 mg./100 ml.; two of these were raised satisfactorily by doubling the suppositories, but the other two still maintained too low a level. This last fact is a well-known problem, and occurs in spite of massive oral or intramuscular doses. It is not due to an increased excretion in the urine or deposition in the tissues, but, more likely, results from a greater rate of metabolism of the drug in certain subjects (Burns *et al.*, 1953).

Six patients received the suppositories for periods of one year or longer, 12 for six months or longer, and eight for short periods of six months or less. Once the plateau level of phenylbutazone is obtained, the serum level remains constant, and only slowly declines over a period of 14 days when the drug is discontinued. Thus only one dose is necessary in the 24 hours. This is the same with the rectal route, and was confirmed by means of diurnal variations of the serum level in three patients. Von Rechenberg (1953) used phenylbutazone suppositories for short periods in five patients and obtained serum levels similar to our figures.

There was no practical difficulty in insertion of the suppositories except in patients with severe deformity of the hands; then a nurse or relative could do this instead. Local effects from the suppositories were noted in two cases; one had a transient pruritus, which disappeared though the drug was continued; the other developed diarrhoea, but there was no recurrence of this when the suppositories were begun again later. Sigmoidoscopy was performed in six patients who had received suppositories for periods longer than three months, and the rectal mucosa appeared normal. Rectal biopsy was done in four, the histology being also normal.

Phenylbutazone dyspepsia disappeared when the suppositories were substituted for the tablets, and none of the 13 patients with proved peptic ulcers had any activation of their symptoms, though four received the drug for longer than one year continuously. The purpose of this trial was to demonstrate that phenylbutazone can be given effectively by the rectal route rather than to assess the therapeutic effectiveness, which has been done previously on large series; pain relief is claimed in approximately 80% of cases (McMahon, 1957; Kelly, 1954). Rectal administration has perhaps been neglected. It is preferable to intramuscular injection of the drug, which is painful and particularly difficult for these patients with their wasted muscles and deformed hands.

In our series, pain relief correlated moderately well with serum level, though some patients have adequate serum levels with no clinical effect, a fact that is unexplained. Systemic toxic effects are to be expected with the same frequency whether phenylbutazone is given orally, parenterally, or rectally. This occurred in one patient, a woman with rheumatic heart disease in whom early cardiac failure was precipitated owing to salt and water retention but disappeared rapidly after withdrawal of the drug. Slight oedema of the ankles of no serious significance occurred in two others, but was controlled by a low-salt diet. No patient showed any depression of the white blood cells, a complication which is probably no more common than with gold therapy.

Discussion

The pathogenesis of dyspepsia following oral phenylbutazone therapy is not completely known. A direct irritant effect upon the gastric mucosa is probably

the sole cause in many cases, giving a picture of multiple superficial gastric erosions (Raffensperger, 1953). The aggravation of existing peptic ulcers, which is a striking lethal complication of oral therapy, probably occurs through increase of the basal gastric secretion (Kirsner and Ford, 1955). The drug usually increases hydrochloric acid production when given orally, and may to a less extent do the same after intramuscular injection. This latter fact would explain the occasional instances where parenteral phenylbutazone has caused haematemesis (de Sèze, 1953) and this could obviously occur with rectal administration. Fortunately it has not yet happened in our experience. We regard the suppository as a useful route of administration in cases where gastric symptoms or peptic ulcers make oral administration either dangerous or impossible.

Summary

Phenylbutazone suppositories can be used as the sole therapy where oral administration is contraindicated.

Absorption of phenylbutazone from the rectum is adequate, as shown by serum levels of the drug.

This work was carried out at the Highfield Hospital, Droitwich, and appreciation is given to the nursing staff for their careful co-operation. Grateful acknowledgments are made to Mrs. P. K. Limerick, Miss E. M. Skyme, and Miss P. A. Goodyear for technical assistance; also to Geigy Pharmaceutical Company Ltd. for supplying the pure phenylbutazone from which the analytical standard was prepared. The technique for estimating phenylbutazone was a modification of that of Pulver (1950) developed by Dr. Ena Bruck (West London Hospital, 1953).

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The 14th Congress of the Scandinavian Neurological Association was held in Helsingfors last year at the invitation of the Finnish Neuro-Psychiatric Society, and its proceedings have now been published. The main subject of the Congress was the late sequelae of traumatic brain injuries, and delegates were taken to visit special homes for veterans injured in this way. It was decided that the next Congress should be held in Denmark in 1960. (*Acta Psychiatrica et Neurologica Scandinavica, Supplementum 137, Volume 34, 1959.*)