INVESTIGATION OF A NEW COMPOUND, B.W.203, AND OF CHLORPROMAZINE IN THE TREATMENT OF PSYCHOSIS

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INTRODUCTION

THE discovery of chlorpromazine in the Rhône-Poulenc-Spécia laboratories in France, and the subsequent early clinical studies which were carried out in that country, for example in 1952 by Hamon *et al.* (5) and in 1953 by Delay and Deniker (1), eventually resulted in the enthusiastic and widespread application of this compound in the field of clinical psychiatry. Chemists and pharmacologists, in many countries, have been actively engaged during the ensuing years in the search for new compounds which might prove to be more potent therapeutic agents than chlorpromazine in the treatment of mental illness. One of the tangible manifestations of their labours is the present crop of "tranquillizers" which are being extensively used in the treatment of neurosis and psychosis. Whereas opinion may be divided with regard to the real or specific value of any one of these new drugs, few would disagree with the contention that none of them is ideal. Despite the considerable number and variety of phenothiazine derivatives and other new substances which have been developed as a result of extensive research, chlorpromazine has retained much of its original therapeutic reputation, in open competition with its rivals, down the years, and is still probably the most widely used tranquillizer today. This would seem to imply that no outstanding advance has been made since the early days of the new biochemical era in psychiatry. Valuable knowledge may have been obtained as a result of the application of scientific theory and empirical methods in this field, but in terms of effective therapeutic agents the results have been meagre, with the accent on quantity rather than quality. Nevertheless, a continued search is justifiable, and any new compound which holds forth promise must be put to a clinical test if final success is to be assured and if valuable therapeutic potential is not to be summarily dismissed or heedlessly cast aside.

In the light of these considerations we carried out a controlled trial of a new biochemical compound, B.W.203, (Burroughs Wellcome) in the treatment of psychosis. The chemical formula of this compound is as follows: unsymmetrical *n*-butyl-o-anisyl urea. Pharmacological investigations revealed that it is relatively non-toxic, and behaviour studies in cats suggested that "contentment and sociability" were increased, and "defensive hostility" was diminished, at dose levels of 20 and 40 mg./Kg. The trial, which forms the subject matter of this paper, enabled us to make direct comparisons between the effects associated with B.W.203, chlorpromazine, and a placebo. In this way the new

https://doi.org/10.1192/bjp.104.436.749 Published online by Cambridge University Press

compound might be compared with the original and most firmly established of the tranquillizers, and either might be measured against that time-honoured remedy the "placebo". The results we obtained are illuminating in certain respects, and, we hope, may be of some general interest.

METHOD

The patient material selected to test the psycho-trophic or "tranquillizing" properties of B.W.203, comprised 36 in-patient psychotics, of whom 34 were chronic schizophrenics, the remaining 2 being chronic manic-depressive psychotics. The sex distribution was, 25 males and 11 females. The over-all average age of the patients was 46·8 years, with an average duration of illness of 16·7 years. (Since 3 main and different wards were utilized in the trial, the following details relating to the patients in these wards may be relevant: Ward A—Average age 49·0, duration of illness 9·6; Ward B—Average age 47·8, duration of illness 17·5; Ward C—Average age 44·5, duration of illness 20·4). Approximately two-thirds of the trial patients were over-active, the remainder being under-active.

The trial was a comparative one, entailing the use of three different preparations, namely, B.W.203, chlorpromazine, and a placebo, so that the therapeutic efficacy of any one of these three preparations might be directly compared with that of either of the other two. The tablets, for oral administration, of the three preparations were identical in appearance, and were dispensed on a "blind" basis so that the pharmacist alone knew which preparation a particular patient was receiving at any time during the trial. Each patient acted as his, or her, own control, receiving by pre-determined design each of the three preparations consecutively.

The tablets of B.W.203 were 300 mg. in strength, and those of chlorpromazine were 25 mg. The duration of the trial was 12 weeks, divided up for each patient into 3 treatment periods during which the patient received each of the three preparations consecutively, in a pre-arranged sequence, as tabs. 1 b.i.d. for one week, followed by tabs. 2 b.i.d. for a further week, and tabs. 2 t.i.d. for the remaining two weeks of each 4-week period.

In this way each patient, in whichever 4-week period of the trial, received B.W.203 as 600 mg. daily for one week, 1,200 mg. daily during the ensuing week, followed by 1,800 mg. daily for two weeks; and chlorpromazine as 50 mg. daily for one week, 100 mg. daily during the next week, followed by 150 mg. daily for two weeks. Likewise, each patient during one of the three 4-week periods received placebo as tabs. 1 b.i.d. for one week, followed by tabs. 2 b.i.d. for a further week, and finally tabs. 2 t.i.d. for the remaining two weeks. This dosage regimen was considered to provide a reasonably comprehensive range of testing for Compound B.W. 203, and to reach a therapeutic level for chlorpromazine, if not necessarily the optimal one in each case, without reaching an upper level at which obvious side-effects such as gross pallor, hypotensive attacks, or Parkinsonian symptoms might be expected to appear and rob the trial thereby of its "blind" and, therefore, objective characteristic.

For purposes of comparing not only any differences in response of each of the 36 patients to the three treatments, but also to enable some judgment to be made with regard to whether a particular order or sequence of administration of these treatments was more, or less, effective than others, the patients were divided on a random basis into 6 sets comprising 6 patients per set. Each set

was assigned exclusively to one of the 6 possible sequences in which the three preparations might be administered:

	1st 4-week Period	2nd 4-week Period	3rd 4-week Period
(i)	Placebo	B.W.203	Chlorpromazine
(ii)	Placebo	Chlorpromazine	B.W.203
(iii)	B.W.203	Placebo	Chlorpromazine
(iv)	B.W.203	Chlorpromazine	Placebo
(v)	Chlorpromazine	Placebo	B.W.203
(vi)	Chlorpromazine	B.W.203	Placebo

From this arrangement it may be seen that in any one period of the trial, equal numbers of patients were receiving any one of the three preparations and, furthermore, comparable numbers of patients followed each of the six possible treatment sequences.

A dispenser's code was compiled, in advance, for the whole trial to conform to these fulfilments or requirements, and this code was subsequently divided into 3 parts so that the dispenser, at the outset, received only that part of the total code relevant to the first 4-week period. The second and third parts of the code were issued to the dispenser as and when they were required.

In advance each patient was assigned, upon a random basis, to one of the 6 treatment sequences to which he, or she, conformed throughout the trial. In no instance was there any deviation from the pre-arranged sequence, duration of treatment, or dosage, so that the initially adopted design of the trial was strictly adhered to throughout. Two patients were, however, withdrawn from the trial, one within the first week as a result of failure to co-operate in taking the tablets; the other due to the development, in the second 4-week period, of neutropenia (found to be associated with chlorpromazine).

The therapeutic efficacy of each preparation was to be judged in terms of the pre-selected forms of observations or measurements of clinical change, which were to be recorded during the trial. These consisted of: (*a*) weekly global assessments made on each patient, and representing the combined judgments of nursing staff and psychiatrist; (*b*) numerical scores derived from the application of a comprehensive 4-point 52-item psychiatric rating scale.

(*a*) All of the weekly global assessments were made by the same psychiatrist (B.G.F.), but a contribution to these was made by the nursing staff in the 3 main and different wards from which the patient material was selected.

(*b*) The rating-scale is one which was originally conceived by Dr. A. M. Spencer, and finally elaborated in its present form by the joint contributions of a number of his colleagues and staff. It will almost certainly be the subject of a published paper in due course, for which reason, together with the fact that the present writers were merely secondary contributors to it, details of the scale must, perforce, be omitted from the general description as given herewith. Suffice it to say, therefore, that it is a most comprehensive scale which, if skilfully applied, tests virtually the whole potential range of psychiatric abnormality as manifested by acute or chronic psychotic patients. The trial patients were individually rated on two separate occasions before the commencement of treatment. This dual rating was undertaken despite the considerable time factor involved, because the initial total score for each patient was to constitute the standard with which subsequent scores were to be compared, and it was considered that the mean of two initial total scores

would represent a more reliable permanent standard than a single total score recorded on one occasion for each patient. The product-moment correlation coefficient which was found to obtain between the two sets of initial rating scores was statistically significant at better than the 1 per cent. level of confidence:

$$r=0\cdot86,\ df.\ 34,\ P=<0\cdot01$$

At the end of each 4-week period the patients were re-rated, so that at the conclusion of the trial "improvement" scores, positive or negative, representing the difference between the initial mean total scores and the subsequent total scores, would be available for analysis.

The statistical techniques, by which the significance of the results was to be assessed, were to comprise the application of a chi-square test to the global assessments, and an analysis of variance to the rating scale scores. It was hoped that this latter analysis, besides indicating the significance of any differences between the mean improvement scores for the three preparations, might also provide some information concerning the individual efficacy of the sequences in which they were administered, and as to whether there was a significant difference between the response of the patients in the three different wards.

All specific methods of treatment, physical and medicinal, were withheld from all the trial patients for a period of some two weeks prior to the commencement of the trial. Throughout its subsequent duration the three test preparations were the only medical forms of therapy administered to any of the patients. (There was a single exception to this in the case of a manic-depressive woman who became so unmanageable, during the first four-week period of the trial, that a member of the medical staff deemed it imperative to administer E.C.T. to her on two consecutive days. She was retained in the trial, and final decoding revealed that she had been receiving B.W.203 at this unfortunate time.)

No deliberate attempt was made to study the side-effects of the preparations, as to do so, however interesting and valuable in itself, would have inevitably militated against the all-important "blindness" of the trial. Nevertheless, before the commencement of the trial, and following each four-week period, blood and urinary investigations were carried out, mainly as a precautionary measure. The patient who was withdrawn after six weeks was found to have developed a leucopenia (neutrophil count=48 per cent.), and it is felt that when a potentially agranulocytic drug such as chlorpromazine is being used in a therapeutic trial periodic white cell counts are imperative. The patient concerned, in this instance, was withdrawn before decoding, and her therapeutic responses for the six weeks during which she was in the trial cannot be included in the results of the 34 patients who completed the trial.

Results

The results are presented in summary form in Tables I–IV, which are appended, with the statistical interpretation expressed underneath each in the conventional manner. In terms of the rating-scale scores, recorded during the trial, the mean improvement scores associated with the three preparations were 5·73, 3·15, and 2·81 for the placebo, chlorpromazine, and B.W.203 respectively. However, the differences between these means, when subjected to an analysis of variance, are not statistically significant. Likewise, the differences between the mean improvement scores for the six different sequences of administration of the three treatments, and for the three main wards from which the trial patients were selected failed to reach a statistical level of significance.

TABLE I

Analysis of Variance

	Rating-scale Improvement Scores		
	df.	ss	Variance
Sequences	5	425·01	85·0
Wards	2	44·46	22·23
Treatments	2	176·80	88·40
Residual	92	6,990·31	75·98
Total	101	7,636·58	

Differences between treatments: F ratio = 1·16, df. 2 and 92, P = >0·05, not significant
Differences between sequences: F ratio = 1·12, df. 5 and 92, P = >0·05, not significant
Differences between wards: F ratio = 3·4, df. 2 and 92, P = >0·05, not significant

TABLE II

Analysis of Weekly Global Assessments for Whole Trial

Assessment	Placebo	B.W.203	Chlorpromazine	Total
Improvement ..	84	68	74	226
No change ..	39	37	44	120
Deterioration ..	13	31	18	62
Total ..	136	136	136	408

Differences between 3 treatments: $\chi^2 = 9·4$, df. 4, P = <0·06, significant at 5 per cent. level
Differences between Placebo and B.W.203: $\chi^2 = 8·06$, df. 2, P = <0·02, significant at 2 per cent. level
Differences between Placebo and Chlorpromazine: $\chi^2 = 1·24$, df. 2, P = >0·50, not significant
Differences between B.W.203 and Chlorpromazine: $\chi^2 = 3·56$, df. 2, P = >0·10, not significant

TABLE III

Analysis of Consistent *Improvements as Expressed by 4 Consecutive Positive Global Assessments in Any One 4-Week Period*

	Placebo		B.W.203		Chlorpromazine		Total	
Improved ..	10	(29·4)	7	(20·6)	8	(23·5)	25	(24·5)
Not improved ..	24	(70·6)	27	(79·4)	26	(76·5)	77	(75·5)
Total ..	34	(100)	34	(100)	34	(100)	102	(100)

(Percentages in brackets)

Differences between treatments: $\chi^2 = 0·32$, df. 2, P = >0·50, not significant

TABLE IV

Analysis of Consistent *Deterioration as Expressed by 4 Consecutive Negative Global Assessments in Any One 4-Week Period*

Placebo	B.W.203	Chlorpromazine
0 (0%)	4 (11·8)	0 (0%)

P value for a chance distribution of this order (0–0–4, 0–4–0, or 4–0–0) = <0·05
Differences between treatments are significant at the 5 per cent. level of confidence.

In terms of the global assessments, made each week on all 34 patients who completed the trial, there was a statistically significant difference in the results for the three treatments. The chi-square value for all of these assessments is within one decimal point of the required figure for significance at the 5 per cent. level of confidence, and, therefore, may be accepted at this level, and certainly at better than the 6 per cent. level of confidence. This would seem to justify

making direct comparisons between the three treatments in terms of the global assessments associated with each. When this is done a significant difference at better than the 5 per cent. level of confidence, in fact at the 2 per cent. level, is found to obtain between the results for the placebo and B.W.203 with the former quite clearly superior to the latter. The differences between the placebo and chlorpromazine, and between B.W.203 and chlorpromazine do not reach a significant level of confidence. The reason why a statistically significant difference was found between all three treatments and between the placebo and B.W.203, would appear to be due mainly, as may be seen from Table II, to the greater number of "deterioration" assessments associated with B.W.203.

In analysing the weekly global assessments it was found that some of the patients were consistently, that is for each and every week of a particular four-week period, recorded as being improved or deteriorated. The therapeutic performances of the three treatments in terms of this consistent response are presented in Tables III and IV. The percentages of patients who were consistently improved, and the particular preparation with which this improvement was associated, were as follows: 29·4 per cent., 23·6 per cent., and 20·6 per cent. for placebo, chlorpromazine, and B.W.203 respectively. The differences between these improvement proportions is not statistically significant. The percentages of patients who were recorded as being consistently deteriorated were: 0 per cent., 0 per cent., and 11·8 per cent. for placebo, chlorpromazine, and B.W.203 respectively. The differences between the three treatments, in terms of consistent deterioration, are significant at the 5 per cent. level of confidence, and reflect the poor record of B.W.203 in this respect.

Side-effects and toxic manifestations in general were remarkably few. Several patients became over-active, and some of these displayed mild euphoria, but decoding at the end of the trial revealed that these reactions were more or less equally associated with each of the three treatments. One patient developed a raised serum bilirubin level, of 1·55 mg. per cent., with B.W.203; and another patient developed an early depression of bone-marrow function as evidenced by a fall in the neutrophil count to 48 per cent., with chlorpromazine.

Discussion

To deal with limitations of the trial first. It might, with some reason, be argued that a period of four weeks was not sufficiently long to ensure that the full potential and optimal effects of chlorpromazine would become operative in each case. Again, it might be contended that the upper dosage level of chlorpromazine which was adopted, namely 150 mg. daily, was less than that which might have been required to achieve an effective biochemical reaction in every one of the trial patients. However, these objections might, to some extent at least, be discredited by the clinical findings of Elkes and Elkes (3) "that high dosages led to undesirable side-effects, and ultimately 150 mg. (two tablets t.d.s.) was found to be both safe and (in those cases in which response was noted) effective", with improvement manifesting itself "after three to six weeks". Furthermore, valid statements may be made about the therapeutic performance of chlorpromazine within the specified qualifications which were implicit in the design of the trial. The results are inevitably relative to the patient material; the nature of the observations recorded; the treatments which were used and contrasted; the various dose levels, and length of time for which they were administered. To determine the effects of a variation of any one, or more, of these factors would necessitate a new and different investigation.

The "blindness" of the trial was effectively preserved throughout. Neither pallor nor Parkinsonian symptoms emerged as identifiable characteristics of chlorpromazine. Three patients complained of "sleepiness" during the daytime, later found to be associated with chlorpromazine in two instances, and with B.W.203 in the third. The patient who complained of sore throat was immediately withdrawn from the trial because of her physically ill condition. Her neutrophil count was found, subsequently to be 48 per cent., and the drug she had been receiving was chlorpromazine. As she had been treated some time previously with a phenothiazine compound, it may be that she had become "sensitized" to chlorpromazine. Fatal cases of agranulocytosis due to phenothiazine compounds have been reported in the literature from time to time. Earle (2) in reporting upon a fatal case, due to promazine hydrochloride, concluded that "Since the dosage given was small, acute sensitization to the drug must be assumed". Feldman *et al.* (4) in commenting upon a fatal case of agranulocytosis during treatment with Pacatal, had the following to say: "Routine blood studies (monthly) were not effective in detecting the presence of agranulocytosis prior to the onset of the full-blown clinical picture. Such infrequent laboratory studies may be detrimental to the extent that they may lull the clinician into a false sense of security regarding this dreaded complication. If it is not feasible to consider routine blood studies as often as twice weekly (or oftener), such studies at infrequent intervals are of doubtful value". They emphasize the importance of the clinical aspects of a course of treatment with "less reliance upon infrequent laboratory data", and advocate that patients who exhibit any or all of the triad of symptoms, fever of undetermined origin, sore throat, or lesions of mucous membranes, "should be considered and treated as cases of agranulocytosis until proven otherwise". Immediate withdrawal of the drug at the slightest clinical or haematological suggestion of bone-marrow depression may well be the wisest course of action when using such drugs. To keep the patient on the compound whilst repeated white cell counts are carried out may render one wise when it is too late to alter the event.

There are certain inherent difficulties in a trial of this nature. When sets of patients have been devised in advance for different sequences of treatment, the withdrawal of a patient from the trial, for any reason, inevitably upsets the balance of the sets for the purposes of comparison. A further problem is that of resisting demands, from whatever source, for the administration of one of the physical methods of treatment to a trial patient who may have become more disturbed in his behaviour during the course of the investigation. A considerable degree of tact and vigilance are required if the trial, as a whole, is to be brought to a reasonably successful conclusion.

The therapeutic results are illuminating in many respects. The rating scale mean improvement scores for the 34 patients who received all three preparations consecutively were higher for the placebo than for either chlorpromazine or B.W.203, without, however, the results reaching statistical significance. A considerable number of "improvement" assessments were recorded for all three treatments, and those for the placebo exceeded the number recorded for either of the two "active" preparations. The differences between all of the recorded weekly global assessments just reached significance at the 5 per cent. level of confidence, and a glance at the relevant table would suggest that the major difference was as between the placebo and B.W.203, with chlorpromazine taking an intermediate position in the results. (A similar relationship may be seen to obtain for the 3 treatments in respect of the rating scale mean improvement scores.) When direct comparisons are made, and statistically analysed,

between any one preparation and either of the remaining two, the impression is confirmed that the major difference was between placebo and B.W.203, with the difference being significant at better than the 5 per cent. level of confidence ($P=0\cdot02$). This difference would seem to be a function of two separate factors: (*i*) the smaller number of improvement responses associated with B.W.203 as compared with the placebo; (*ii*) the greater number of deterioration responses associated with B.W.203 as compared with the placebo.

The most tenable interpretation of the results is, that although B.W.203 was associated with some therapeutic success in terms of improvement scores and clinical assessments, this was not due to any specific and beneficial effect of the drug, which may on the contrary have been exerting deleterious effects and so diminishing the overall potential "placebo" effect of the trial situation. Examination of individual patient responses, in retrospect, to some extent confirms this hypothesis, in that a small number of patients manifested an acute exacerbation of their psychotic symptoms during the period in which they were receiving B.W.203. Indeed, as may be seen from Table IV, all four of the patients who were consistently worse throughout a four-week period, were receiving B.W.203 at the coincidental time, and the differences between the three preparations in this respect is significant at the 5 per cent. level of confidence.

Each of the three treatments was associated with a positive mean improvement score, in terms of the rating scale, and likewise with a certain percentage of consistent improvement as expressed in global assessments. In the latter respect the placebo was associated with, approximately, a 30 per cent. improvement rate, whilst that for both chlorpromazine and B.W.203 was in excess of 20 per cent. This would seem to imply that the response of the patients, therapeutically, was a function of the investigation and investigators rather than the treatments themselves. On the other hand, consistent deterioration, in the small number of patients in which it may occur, would seem to be a direct function of a specific and undesirable effect of the preparation concerned. From this trial it may be reasonably deduced that a 20 per cent. improvement rate, in itself, is little or no criterion of the value of a drug unless the placebo response is seen to be significantly less than this. Furthermore, paradoxically, a 20 per cent. improvement rate may mask the positively detrimental effects of a compound such as B.W.203.

The therapeutic performance of chlorpromazine, in this trial, suggests that it was acting in a non-specific way. It was certainly not superior to the placebo which was used as a control. This would seem to confirm the negative results of Mitchell (6) who reported that, in a controlled experiment, using objective criteria of behaviour incidents, "chlorpromazine, even in a dosage of 300 mg. daily, made no significant difference in the aggressive psychomotor behaviour of chronic schizophrenic patients". On the debit side of its account, in our trial, must be weighed the single instance of polymorphonuclear leucopenia which was encountered. The "sleepiness" of which two chlorpromazine patients complained was so analogous to that of any sedative or hypnotic, e.g. a barbiturate, that one wonders how realistic, at the present time, is the qualitative differentiation which tends to be made between the so-called tranquillizers and the traditional group of sedatives and hypnotics.

The imperative need for placebo control in evaluating the effects of drugs which may be used in the psychiatric field has, once again, been illustrated.

SUMMARY

A blind "self" controlled comparative trial of 3 preparations, B.W.203, chlorpromazine, and a placebo, in the treatment of psychosis has been reported upon. Thirty-four in-patients received the three different treatments consecutively and in graded dosage for a period of four

weeks for each treatment. The therapeutic response of each patient was measured in terms of rating-scale scores and weekly clinical or global assessments. The design of the trial was such that direct comparisons might be made between the therapeutic performance of each of the three methods of treatment and to enable some judgments to be formed as to whether any one of the six possible sequences of administration was more effective than the others, and whether the response in any one of the three main wards was significantly greater than its counterparts.

Each of the three methods of treatment was associated with some degree of positive therapeutic success in terms of both the rating scale scores and global assessments. The mean improvement scores associated with the placebo exceeded that for either chlorpromazine or B.W.203, without the differences, however, being statistically significant. The differences between the effects of the three treatments in terms of global assessments were significant at the 5 per cent. level of confidence; and the difference between the placebo and B.W.203 was significant at the 2 per cent. level. Each treatment was associated with a consistent improvement rate, in global terms; 29 per cent., 24 per cent., and 21 per cent. for placebo, chlorpromazine, and B.W.203 respectively, without the differences being statistically significant. Of the three treatments, B.W.203 was the only one associated with consistent deterioration, and the proportion, in this respect, for this preparation was 12 per cent. and significant at the 5 per cent. level of confidence.

It is deduced, therefore, that in terms of the clinical assessments made upon the 34 psychotic in-patients included in this trial, and for the respective dosages and duration of administration of the three treatments applied, the placebo was superior in therapeutic effects to compound B.W.203, and that the effects of chlorpromazine ranged somewhere between the former and the latter, without, statistically speaking, differing significantly from either. A small but significant consistent deterioration rate was identified with the administration of B.W.203, but not with either the placebo or chlorpromazine.

From the results of the trial as a whole, it is concluded that there is a definite need for the disciplined evaluation of new, and perhaps already established drugs which may be used in the field of psychiatry.

Acknowledgments

We are indebted to the Wellcome Foundation Ltd., for generously sponsoring this piece of research. We are grateful to Dr. A. M. Spencer for providing the inspiration without which the work would not have been undertaken, and for permission for publication. We would like to thank Mrs. J. Randle for her diligent dispensing; the nursing staff for their conscientious co-operation; and, finally, Mrs. E. J. Sherwood for secretarial assistance.

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