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Psychotropic Actions of BW 234U in the Treatment of Inpatient Schizophrenics: A Dose-Range Study

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ABSTRACT

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In a 28-day, dose-range study, 11 chronic schizophrenic inpatients newly admitted to the hospital with acute exacerbations were administered a new antipsychotic, BW 234U, in daily doses ranging from 100 to 400 mg/day on a fixed/flexible schedule to determine therapeutic dose range, safety, and psychotropic activity with special regard to possible antiaggressive action. The results of weekly assessments with standard psychiatric rating instruments indicate that BW 234U has dual psychotropic action—an antipsychotic and an activating effect—that may have potential value in the treatment of depressive illness. The drug appears to be relatively free from neurologic, cardiovascular, anticholinergic, and CNS-depressant side effects.

Key words: atypical antipsychotic drug, schizophrenia, psychotropic actions, dose range

INTRODUCTION

The dopamine hypothesis states that the therapeutic action of an antipsychotic agent results from the inhibition of dopaminergic neuronal systems in the mesolimbic area of the brain, while undesirable extrapyramidal side effects result from inhibition of nigrostriatal dopaminergic systems. Most currently used neuroleptics; e.g., chlorpromazine and haloperidol, are known to inhibit both mesolimbic and nigrostriatal dopaminergic systems nonselectively.

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The present study is one part of a multicenter trial to determine the effective dose range, therapeutic potential, and safety of a novel drug, BW 234U, in chronic schizophrenic inpatients with acute exacerbation of their illnesses. In preclinical studies, BW 234U, a substituted carbazole (Fig. 1), has been known to block an important response associated with stimulation of postsynaptic dopaminergic receptors in mesolimbic areas (aggressive behavior) and to do so without blocking responses associated with apomorphine-induced stimulation of postsynaptic dopaminergic receptors in striatal areas (stereotyped behavior) [McKenzie, 1971]. Biochemical studies have also shown that BW 234U has no effect on dopamine synthesis and does not inhibit in vitro dopamine receptor binding [Ferris et al., 1982]. These effects suggest that BW 234U has a specific but indirect effect on dopaminergic activity in the limbic area. The absence of direct or indirect dopaminergic activity in striatal areas by BW 234U make it unlikely that the drug will induce extrapyramidal symptoms. The aggregate animal data, as well as the phase I human volunteer data, suggest that BW 234U is a novel agent which may have utility in the treatment of psychotic states, especially those with an aggressive component, and that it is relatively free from neurologic, cardiovascular, anticholinergic and CNS-depressant side effects [Clinical Investigator's Manual, 1978].

METHODS

The study design was a 28-day open trial in which, following signed informed consent, BW 234U was administered to 11 hospitalized patients on a fixed/flexible schedule (bid) in doses ranging from 100 to 400 mg/day. After a maximum 7-day washout period, patients between 18 and 55 yr of age had to meet DSM-III criteria for chronic schizophrenia with acute exacerbation and have no significant physical illness or history of continuous alcohol/drug abuse, organic brain syndrome, or mental retardation. In addition, only surgically sterile female patients were admitted to the study. Assessment procedures were scheduled at baseline and weekly thereafter and consisted of the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions (CGI), Nurses' Observation Scale for Inpatient Evaluation (NOSIE), Abnormal Involuntary Movement Scale (AIMS), and Simpson-Angus Extrapyramidal Scale (SAES) [Guy, 1976]. The complete Inpatient Multidimensional Psychiatric Scale (IMPS) was administered at baseline and termination while an abbreviated 16-item IMPS was administered weekly specifically to assess effects on aggressive behavior. In addition, pre/post physical, neurological, and EEG examinations, weekly EKG, clinical laboratory tests, and vital signs were performed. Plasma levels of BW 234U were obtained at baseline, week 2 and termination for subsequent analyses.

RESULTS

Demographic Data

Demographic data for the study sample is presented in Table 1. Eleven newly hospitalized patients (nine males, two females) ranging in age from 18 to 50 yr (mean = 33 yr) were

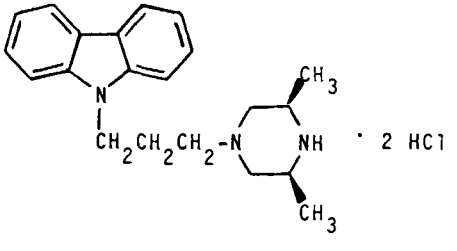


Fig. 1. BW 234U: *cis*-9-[3-(3,5-Dimethyl-1-piperazinyl)propyl]carbazole dihydrochloride.

TABLE 1. Demographic Data and Clinical Status

Patient age/sex	Educational level	DSM-III schizophrenic subtype[a]	Approximate length of illness (yr)	Initial severity	Days in study	Level of improvement	Reason for termination
18/M	Part HS	Disorganized	2	Severe	28	Much imp	Per protocol
23/M	HS grad	Paranoid	2	Severe	14	Unchanged	Ineffectiveness
31/M	Part college	Paranoid	4	Severe	28	Minimal imp	Per protocol
37/F	Part HS	Undifferentiated	10	Severe	28	Much imp	Per protocol
25/M	Part HS	Undifferentiated	10	Severe	7	Much worse	Ineffectiveness
37/M	Part HS	Undifferentiated	4	Severe	16	Minimal imp	Ineffectiveness
39/M	HS grad	Undifferentiated	6	Mod severe	28	Very much imp	Per protocol
33/M	Part HS	Undifferentiated	12	Mod severe	28	Minimal imp	Per protocol
32/M	Part HS	Undifferentiated	11	Severe	10	Much worse	Ineffectiveness
50/M	Part HS	Undifferentiated	21	Severe	28	Much imp	Per protocol
42/F	Part HS	Undifferentiated	19	Mod severe	6	Much worse	Ineffectiveness

[a]Course for all patients = chronic with acute exacerbation.

entered into the study. Predominantly diagnosed as the undifferentiated subtype, all patients—save one—had histories of multiple hospitalizations. Length of illness as estimated by age at first hospitalization ranged from 2 to 21 yr with a mean length of approximately 9 yr. For one patient, the present hospitalization was the first—length of illness being estimated by relatives' statements as approximately 2 yr.

Nine of the eleven patients were judged to be "Severely Ill" on the CGI at baseline; i.e., 6 on a 7-point scale. Six patients completed the full 28 days of the study and were judged on the CGI to be improved—five of the six being "Much" or "Very Much" improved. All five noncompleters were terminated because of ineffectiveness of treatment. Three of these noncompleters were rated as "Very Much Worse"; i.e., to have deteriorated. Nine of the patients received the maximum permissible daily dose of BW 234U (400 mg), while one patient received a maximum of 300 mg/day and another—200 mg/day.

Efficacy Data

Statistical analyses utilizing a cohort of ten patients consisted of analysis of variance-repeated measures model including baseline, week 2 and week 4 ratings and a similar analysis using only the baseline and termination ratings of each patient. In the first analyses, terminal ratings were substituted for those patients without a week 4 rating. Three of the five BPRS factors—Anxiety-Somatization, Anergia, Thought Disturbance—as well as Total Score exhibited significant improvement from baseline ($P < 0.05$) at both week 2 and week 4 (Fig. 2). In contrast to the usual decrements obtained with neuroleptic treatment, the factor of Activation showed a sharp increase in severity at week 2, followed by a decrease at week 4—a decrease which, nevertheless, remained above the pretreatment level of severity. Hostile-Suspiciousness remained essentially unchanged across time. In neither instance did the changes reach statistical significance.

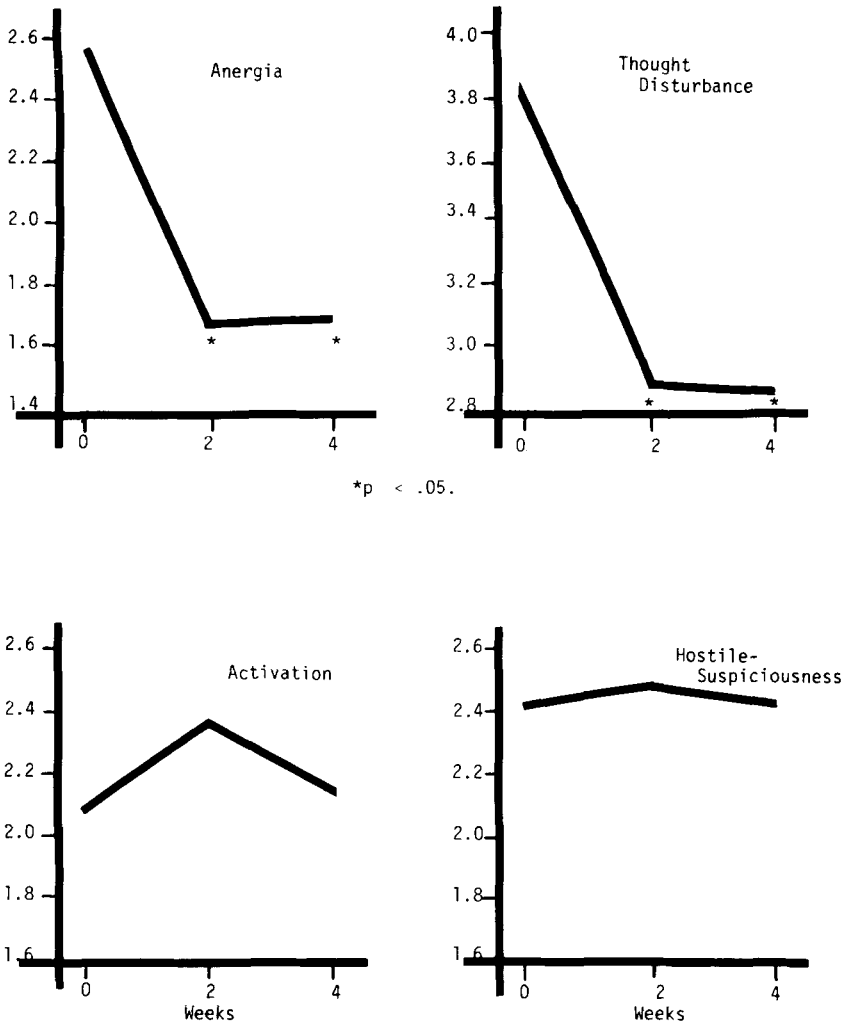
Pre/post analyses of variance of the NOSIE produced no statistically significant differences on the majority of factors or on the Total Assets. On the factor of Irritability, however, a statistically significant difference ($P < 0.05$) reflecting increased severity at termination was obtained, which may be consistent with the increased activation noted on the BPRS.

As previously mentioned, a modified version of the IMPS was included in the assessment battery to evaluate the effect of BW 234U on aggressive or hostile behavior. In Figure 3, the time course of BPRS Total Scores is compared to those of the abbreviated IMPS Scores. BPRS Total Score differences at weeks 2 and 4 are statistically significant ($P < 0.01$) and reflect improvement over the baseline level. In contrast, abbreviated IMPS score differences at weeks 2 and 4, while not statistically significant, reflect increased aggression over the baseline level. An analysis of variance using the baseline and termination ratings of the complete IMPS reflects improvement for the sample just below the magical "0.05 level" ($P < 0.059$).

Safety Data

Table 2 presents the occurrences of treatment emergent symptoms (TES), which are defined as those not reported by or observed in the patient at pretreatment but cited subsequently under drug treatment. Four patients were asymptomatic throughout the medication period. Of the seven patients who exhibited TES, five displayed symptoms which can be classified as behavioral in type and characterized as activating in quality, i.e., as symptoms suggesting arousal. These are also the TES which required remedial medication (chloral hydrate, flurazepam). Three of the patients who were therapeutic failures also reported these symptoms.

The results obtained on both the AIMS and the SAES were highly consistent and tend to support the claim that BW 234U is unlikely to produce extrapyramidal side effects. Eight of the 11 patients were rated essentially asymptomatic, i.e., total scores of 2 or less, throughout the trial on both instruments. One patient exhibited mild abnormal leg movements at week 1. The two patients with low symptomatic pretreatment scores remained essentially unchanged



*p < .05.

Fig. 2. Mean BPRS factor scores across time.

on the AIMS and exhibited decreased scores at termination on the SAES. One patient, a 37-year-old female, exhibited neck pain in association with a headache on the final day of the study while receiving 400 mg/day of BW 234U—a questionable dystonic reaction.

DISCUSSION

Given the small sample sizes used as well as the meager knowledge of the drug's effects in patients at this stage of development, early phase 2 trials are most often evaluated on an idiosyncratic rather than a nomothetic level. This is entirely appropriate since it is imperative that clinical experience concerning the drug's positive and negative effects in patients be

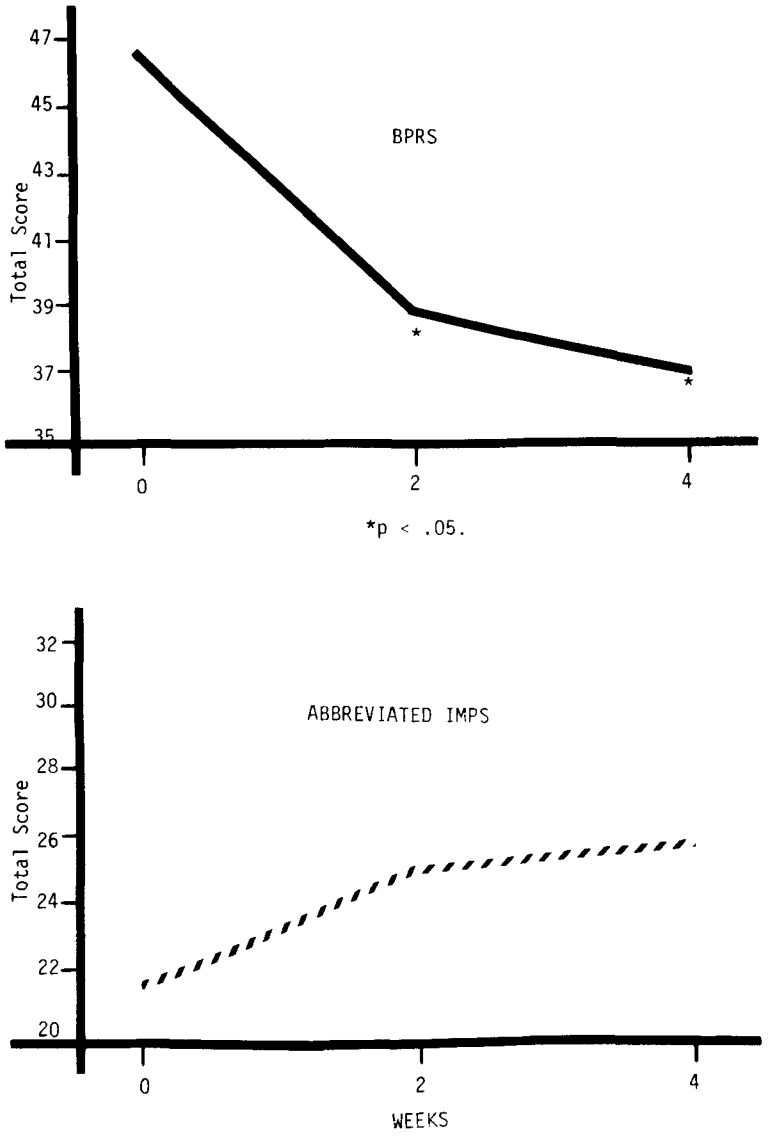


Fig. 3. Mean total scores across time for the BPRS and abbreviated IMPS.

obtained as quickly as possible [Wittenborn, 1977]. More often than not, early clinical findings tend to confirm what has been hypothesized on the basis of animal data. Occasionally, however, an early phase 2 trial may reveal significant clinical effects which were either not anticipated or were regarded as minor or secondary effects. This would appear to be the case in this study.

The evaluation of efficacy seems to have produced a bimodal picture in which approximately half of the patients improved and completed the study; while the remainder were unimproved and were prematurely terminated. The positive changes on BPRS Total Score and three of the factors strongly suggest that BW 234U has antipsychotic properties. All of the

TABLE 2. Treatment Emergent Symptoms

Patient	Symptom	Day of citation	Daily dose (mg) at citation
18M	Euphoria	21	300
31M	Diarrhea	7	200
	Diarrhea	14	300
	Fatigue	17	400
	Drowsiness	21	400
37F	Euphoria	17	400
	Euphoria	21	400
	Euphoria	28	400
	Neck pain/headache	28	400
25M	Inappropriate aggression	7	400
	Palpitations	7	400
33M	Rash	7	200
32M	Irresponsible behavior	3	100
	Inappropriate aggression	3	100
	Inappropriate aggression	10	400
	Increased libido	10	400
	Irresponsible behavior	12	400
	Inappropriate aggression	12	400
42F	Confused	7	400
	Inappropriate aggression	7	400
	Increased libido	7	400

patients judged to be "Much Worse" on CGI-Improvement, and, consequently, terminated within 10 days, were characterized as exhibiting inappropriate aggression and/or irresponsible behavior; i.e., characteristics of activation or increased arousal. Despite this outcome and limited duration of treatment, these early terminators, nevertheless, showed reduction of symptomatology on the factor of Thought Disturbance. It should be noted that, in subsequent treatment these early terminators required a lengthy course of standard neuroleptic medication before adequate response was obtained. Treatment completers, on the other hand, were successfully switched to standard medications and discharged to outpatient follow-up. Additionally, two patients who improved under BW 234U were also characterized as "euphoric," although their behavior was not considered disruptive. Based on the admittedly small sample, BW 234U appears to have two psychotropic actions—an antipsychotic and an activating one—both of which can be observed in varying degrees within the same patient. It might be speculated, then, that BW 234U possesses stimulating properties which might be of value in the treatment of depressive illness—particularly those with psychotic features. In support of this speculation, animal data suggest that BW 234U may have a possible antidepressant effect since it potentiates d-amphetamine-induced locomotor activity and weakly inhibits dopamine reuptake [Ferris et al., 1982]. However, unlike desmethylimipramine, it does not confer protection in rats against the behavioral depressant effects of tetrabenazine.

An alternate explanation of this secondary activating effect has been suggested by Singh [Singh, 1976; Singh and Kay, 1979] who has shown that there is a subgroup of nonparanoid unclear schizophrenics with poor prognoses who develop a dysphoric state, characterized by anxiety, depression, and accusatoriness, early in the course of neuroleptic treatment. This state—resembling the agitated state of involutional melancholia—tends to be accompanied by an increase in autonomic arousal as reflected in resting pulse rate and foreshadows poor short-term and long-term therapeutic outcome. While the present sample can be categorized as a

poor-prognosis, nonparanoid one, the observed affective state cannot be described as depressive in quality—rather the opposite was true. Similarly, in the majority of patients, resting pulse rate decreased and/or remained essentially unchanged as treatment proceeded. Only two patients exhibited increased pulse rates, and they were both therapeutic responders. The affective changes observed in this small sample, therefore, do not appear to parallel those obtained in the previously cited studies.

In summary, BW 234U does appear to possess antipsychotic activity at 300–400 mg/day dose levels. Evidence from this study, however, does not indicate antiaggressive properties. To the contrary, BW 234U exhibits activating effects which may presage its usefulness as an antidepressant. Finally, behavioral effects aside, the drug evokes a minimum of neurologic, cardiovascular, or anticholinergic side effects.

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