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Pipothiazine Palmitate in the Management of Aggressive Mentally Handicapped Patients

D. M. LYNCH, C. L. S. ELIATAMBY and A. A. ANDERSON

Summary: The efficacy of intramuscular pipothiazine palmitate (PP) in the management of aggressive mentally handicapped patients was examined in a double-blind, placebo-controlled, cross-over study, in which 30 patients received each treatment for 13 weeks. A target symptom scale of aggressiveness (TSA) and a clinical global impression scale of efficacy were rated at monthly intervals, and an extra-pyramidal side-effects scale weekly. The patients showed marked improvement during treatment with PP, which was assessed as superior to placebo. Individual and total TSA scores were also reduced compared to placebo.

There have been relatively few reports of the effects of major tranquillisers in the field of mental handicap, although their beneficial actions are well established, particularly in the disturbed child (Badham, *et al,* 1963; Hunter & Stephenson, 1963; Ucer & Kreger, 1969; Karland & Goldberg, 1970; Reid, 1972). Aggressive behaviour is also well controlled by this group of drugs (Itil & Wadud, 1975). However, the treatment of profound and severely mentally handicapped patients who present with overt aggressiveness remains a considerable problem. Drug treatment is usually required on a long-term basis, when difficulties of patient compliance may be overcome by the use of a depot neuroleptic.

Pipothiazine palmitate is a piperidine derivative of the phenothiazine group, which when administered intramuscularly has a mean duration of action of four weeks (Ayd, 1983). It has been shown to be effective in chronic psychosis, especially schizophrenia (Brown-Thomsen, 1973; Schlosberg & Shadmi, 1978; Singh & Saxena, 1979; Albert *et al,* 1980) and clinical experience suggests a lower incidence of extrapyramidal symptoms than has been observed for the piperazine phenothiazines (Ayd, 1983).

The object of the present study was to investigate whether the ability of pipothiazine palmitate to control aggressive symptoms in schizophrenics could be reproduced in aggressive mentally handicapped patients, in a double-blind comparison against placebo. Consequently, the level of aggressiveness was considered as a major factor in the overall assessment of efficacy. The scale of aggressiveness chosen for this study has previously been shown to be sensitive to the action of drugs which can reduce aggressive behaviour (Albert *et al,* 1977).

Method

Thirty mentally handicapped in-patients of both sexes (21 male, nine female) were selected for the study on the basis of being aggressive or difficult to manage. The exclusion criteria were: symptoms or signs of schizophrenia, psychomotor epilepsy, renal dysfunction or heart disease, as well as pregnancy or the likelihood of becoming so (in females). Patients were aged between 19 and 62 years (mean 37.1 years, s.d. = 12.1).

The study was conducted in four phases. The initial screening period (phase I) commenced with a complete medical and psychiatric evaluation, including laboratory tests (full blood count, urea, and electrolytes), urinalysis, and electrocardiogram. During this two-week period, the existing oral neuroleptic therapy was maintained. Phase I was followed by a drug-free four-week wash-out period (phase II), to provide a base-line for the subsequent psychiatric assessments.

After this standardisation period, patients received, in random order, the experimental drugs in phases III and IV, each of which lasted for 13 weeks. There was no wash-out period between phases III and IV, on ethical grounds.

At the commencement of phase III, each patient was given a test dose (0.5 ml) of drug A (either pipothiazine palmitate 25 mg or matching placebo) by deep intramuscular injection into the buttock. In the absence of any deleterious effect, the test dose was followed one week later by a 1 ml injection (pipothiazine palmitate 50 mg or placebo). Two further injections were given at four-weekly intervals. On entry to phase IV, an identical procedure was followed using drug B.

In the event of extremely disruptive or aggressive behaviour, oral thioridazine was available as an emergency drug. In addition, oral orphenadrine was authorised to be used in the event of extra-pyramidal side-effects.

Clinical assessment of the patients' condition was obtained weekly during phases I and II and at monthly intervals in phases III and IV, using the Clinical Global Impressions scale (CGI) of the US National Institute of Mental Health (Guy, 1976) and a target symptom scale of aggressiveness (TSA) (Albert *et al,* 1977), which is a modified version of a scale described by Rajotte *et al,* 1966. The 11 symptoms of aggressiveness were scored on a four-point rating of severity, ranging from 'none' to 'extremely marked'. The CGI consists of three global scales. Two of the items, 'severity of illness' and 'global improvement', are rated on a seven-point scale, while the third, 'efficacy index', requires a rating of the interaction

of therapeutic effectiveness and side-effects (performed during phases III and IV only).

Patients were assessed on a multi-disciplinary basis. In addition to daily observations by the nurses, weekly assessments were made by the nurses and, independently, by the doctor. The final assessment was a consensus, agreed upon by all involved, at weekly meetings in phases I and II, and at monthly meetings in phases III and IV.

Clinical assessment of side-effects was carried out at weekly intervals throughout the study, using an extra-pyramidal side-effect (EPS) scale, which rated the degree of akinesia, akathisia, Parkinsonism, and dystonia as a five-point scale. The laboratory tests were repeated at the end of phases III and IV.

Demographic data for the two treatment order groups were compared, using the Chi-square and Van der Waerden distribution-free statistical tests. Base-line comparability of the clinical assessments over the four-week wash-out period (phase II) was examined using analysis of variance.

Since there was no cross-over wash-out period, and in an effort to exclude any carry-over effects of the first treatment, only data collected at the end of each 13-week treatment period (weeks 19 and 32) were included in the statistical analysis of the cross-over design. The assumption made is that the effects of the drug received in period A do not persevere to the end of period B. The cross-over data were analysed for treatment, period, and interaction effects, using analysis of variance following normalisation of the data, using a Van der Waerden ranking procedure (Conover, 1980).

Results

Twenty-eight patients completed the study. Two were classified as withdrawals: one of these was diagnosed as suffering from a hiatus hernia with chronic peptic oesophagitis, which was not considered to be related to the trial medication; the second was withdrawn during pipothiazine treatment because of urinary retention—a documented side-effect of phenothiazine therapy which has been attributed to the atropine-like activity of these drugs. Twelve of the patients received concomitant anti-convulsant medication (in some cases in combination with a tranquillising agent) during the study; one received an oral contraceptive. Details are given in the Table. The doses of all drugs were maintained at a constant level throughout the study; thioridazine was not required as an emergency drug.

The two treatment order groups were similar for age, height, weight, gender, concurrent medication, and for haematology and biochemistry measures. During the wash-out period (phase II), the most obvious effect was a

TABLE

Concomitant medication

Medication	*Number of patients*
Phenobarbitone	5
Beclamide	4
Primidone	2
Sodium Valproate	2
Ethosuximide	1
Nitrazepam	3
Diazepam	2
Norethisterone/ethinyloestradiol	1

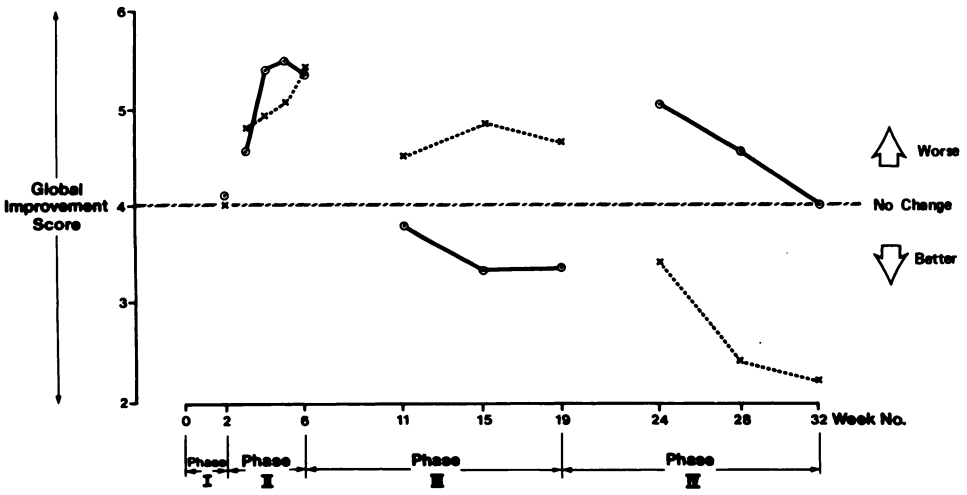

FIG 1. Change in global improvement scores during phases I–IV

Points are the mean scores for the physicians' assessment of patients' change in condition, relative to their condition at the end of week 1 for each treatment order group (2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse). Treatment group 1 (○——○) received pipothiazine palmitate in phase III followed by placebo treatment in phase IV whereas treatment group 2 (X - - - - X) received placebo in phase III and pipothiazine palmitate in phase IV.

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gradual worsening of the patients' condition during weeks two to six following withdrawal of active medication. This is illustrated in Fig.1 for 'global improvement'. The TSA score also increased during this period (increased aggressiveness).

In the cross-over analysis, none of the measures showed any statistically significant ($P > 0.1$) interaction effects of 'treatment × period', which would have invalidated any further analysis based on a cross-over design.

The CGI scales showed highly significant treatment effects in favour of pipothiazine for severity of illness, global improvement, and efficacy index. The superiority of pipothiazine treatment over placebo treatment was reinforced by the highly significant treatment effect for the overall TSA score. The TSA scores during phases III and IV are illustrated graphically in Fig. 2 for each treatment order group. It should be remembered, however that the cross-over analysis is based on intra-subject changes during the two phases. The individual items of the TSA scale showed varying degrees of statistically significant treatment effects in favour of pipothiazine, the exceptions being 'auto-mutilator' and 'sexual aggressivity', which showed no significant treatment effects. This is not surprising in view of the fact that these symptoms were only reported in four and five patients respectively during the active treatment periods.

Fig.1 shows the overall pattern of global improvement for each treatment order group during the study, compared with patients' previous treatment, and confirms the effectiveness of pipothiazine when compared with placebo treatment. When account is taken of any drug side-effects by expression of the efficacy index, a superior score is still observed for pipothiazine treatment during phases III and IV (Fig. 3). In fact, extra-pyramidal side-effects were only recorded for seven of the patients overall. Two of these patients developed moderately severe akathisia and Parkinsonism during placebo treatment; orphenadrine (50 mg orally) provided symptomaticwere only recorded for seven of the patients overall. Two of these patients developed moderately severe akathisia and Parkinsonism during placebo treatment; orphenadrine (50 mg orally) provided symptomatic relief, and was maintained for the duration of the study. Orphenadrine (50 or 100 mg orally) also relieved similar symptoms, which were recorded for three patients whilst receiving pipothiazine treatment. The remaining two experienced more severe akathisia and Parkinsonism with akinesia during pipothiazine treatment, and administration of benztropine (2 mg i.m.) was required to adequately control their symptoms. No other adverse events were reported by the nursing staff. The patients were too severely handicapped to be expected to offer spontaneous reports of side-effects.

There was a statistically significant ($P < 0.05$) elevation of the plasma urea concentration during pipothiazine treatment (compared with the placebo period). However,

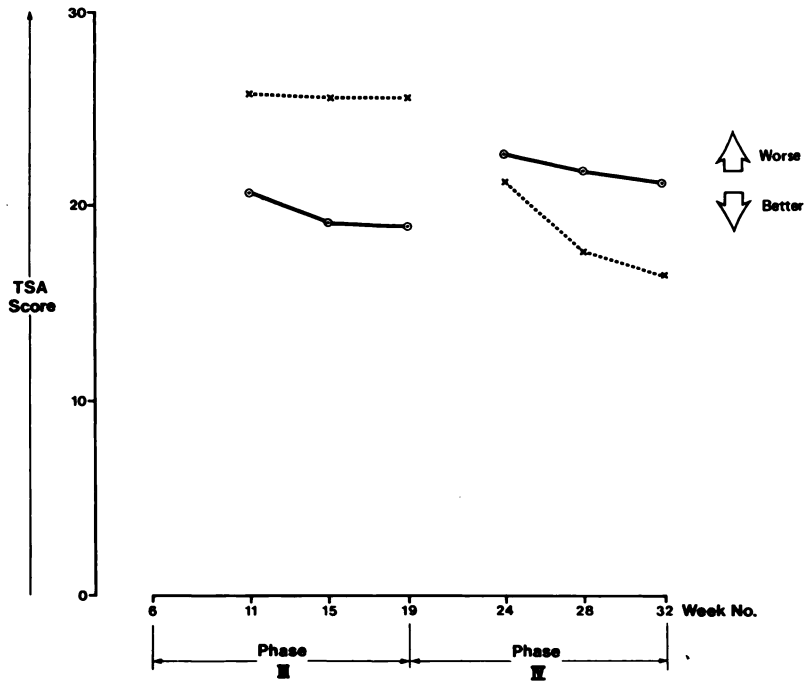

FIG 2. Target Symptom Aggressiveness scores during cross-over

Points are the mean total TSA scores for each treatment order group during phases III and IV. Treatment group 1 (○——○) received pipothiazine palmitate in phase III followed by placebo treatment in phase IV whereas treatment group 2 (X - - - - X) received placebo in phase III and pipothiazine palmitate in phase IV.

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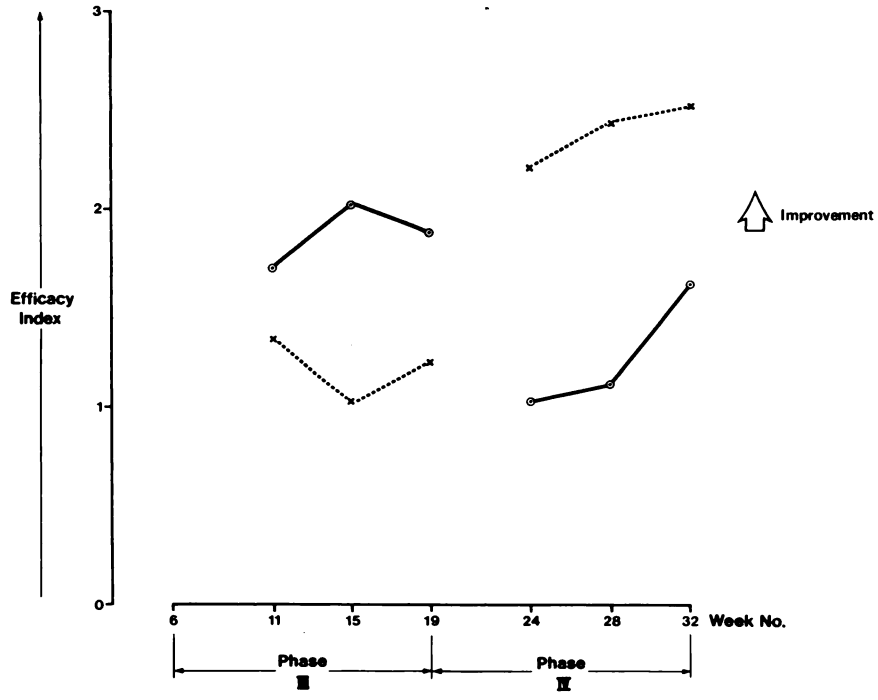

FIG 3. Efficacy Index Scores during cross-over
Points are the mean scores for efficacy index (a joint rating of efficacy and side-effects) during phases III and IV. Treatment group 1 (○—○) received pipothiazine palmitate in phase III follwed by placebo treatment in phase IV whereas treatment group 2 (X - - - - X) received placebo in phase III and pipothiazine palmitate in phase IV.

individual values for urea were all within the laboratory normal range, as were values for haemoglobin, red and white blood cell counts, haematocrit, glucose, alkaline phosphatase, SGOT, and total bilirubin.

Discussion

Hills & Armitage (1979) have discussed the advantages and disadvantages of the cross-over design in clinical trials. While a comparison of treatments on the same patient may be more precise than an inter-subject comparison, the presence of carry-over effects from the previous treatment can make interpretation extremely difficult. In this study, none of the measures showed any significant interaction effects of treatment with period, thus supporting the assumption made regarding carry-over effects. There have been reports that depot phenothiazines are effective in the management of aggressive and 'difficult' behaviour (Kinnell, 1977; Perinpanayagam & Haig, 1977), but one study of fluphenazine decanoate in mentally-handicapped patients (Craft & Schiff, 1980) has been criticised by Macdonald (1981) on the grounds that it did not attempt to minimise sources of bias.

The present double-blind, placebo-controlled study has provided strong evidence of the efficacy of pipothiazine palmitate in reducing the level of difficult and violent behaviour in the mentally handicapped.

The significant decrease in the severity of the individual target symptoms which comprise the scale of aggressiveness was further supported by the results of the physicians' global evaluation scales, which showed a highly significant reduction of the severity of the illness, an improved efficacy index, and a consequent global improvement in the patients' condition. Pipothiazine palmitate was well tolerated by the patients, with only one withdrawal as a result of treatment. Extra-pyramidal symptoms, which were reported for five patients during treatment, were well controlled by drug intervention. Laboratory tests were all within normal limits. The results suggest that once-monthly injections of 50 mg pipothiazine palmitate can provide reliable control of mentally-handicapped patients with behavioural problems, reducing their level of difficult and disruptive behaviour.

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D. M. Lynch, FRCPsych. *Consultant Psychiatrist, Turner Village Hospital, Colchester, Essex CO4 5JP*

C. L. S. Eliatamby, MB. BS(Ceylon). DipPsych(Lond). *Locum Consultant Psychiatrist, Essex Hall Hospital, Colchester, Essex CO1 1XE*

A. A. Anderson, BSc. PhD. *Clinical Trials Co-ordinator, Department of Clinical Research, May & Baker Ltd., Dagenham, Essex RM10 7XS*

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