A COMPARATIVE STUDY OF PIPOTHIAZINE PALMITATE AND FLUPHENAZINE DECANOATE IN THE MAINTENANCE OF REMISSION OF SCHIZOPHRENIA

O K Leong, K E Wong, W K Tay, R C Gill

ABSTRACT

This paper reports a randomized, controlled, partially-blinded, flexible dose, parallel group, comparative study of the efficacy and tolerance of pipothiazine palmitate and fluphenazine decanoate in patients in remission from Schizophrenia over a 28 week period. The results show that pipothiazine palmitate is at least as efficacious and well-tolerated as fluphenazine decanoate in preventing relapses from maintained Schizophrenia.

Keywords: pipothiazine palmitate, fluphenazine decanoate, Schizophrenia.

SING MED J. 1989; NO 30: 436 – 440

INTRODUCTION

Pipothiazine palmitate has been indicated in the management of chronic psychoses, especially schizophrenia (1-3). In comparative trials it has been shown to be more effective than fluphenazine enanthate against a wide range of symptoms (1, 4) and to have a faster onset of action (4). Pipothiazine palmitate has been shown to be at least as effective as fluphenazine decanoate in controlling the symptoms of schizophrenia (5-7), the balance of side-effects and efficacy favouring pipothiazine palmitate.

Thus, with the proven efficacy of pipothiazine palmitate in controlling a wide range of psychotic symptoms, a study to evaluate its efficacy in preventing the relapse of patients in remission from schizophrenia was undertaken.

SUBJECTS, MATERIALS & METHODS

Study Population

Sixty out-patients who were attending the Lim Ah Pin Psychiatric Clinic in Singapore (27 male, 33 female) aged between 18 and 65 years (mean, 37.8 years, standard error, 1.87 years) and who had been in the remission phase of schizophrenia (ICD 295,—) for at least three months were recruited. The criterion for inclusion in the study was that the patient required medication to maintain remission from schizophrenia. Patients with severe concomitant illness, who had pathological laboratory variables which precluded prescription of the study treatments or who refused to give informed consent to participate in the study were excluded.

Woodbridge Hospital
Jalan Woodbridge
Singapore 1954

O K Leong, MBBS, DPM, MRCPsych,
Consultant Psychiatrist
K E Wong, MBBS, DPM, MRCPsych,
Senior Registrar
W K Tay, MBBS, DPM,
Senior Registrar

Clinical Research Department
May & Baker
Dagenham
Essex
England

R C Gill

Correspondence to: Dr Leong

Study Design

This was a partially-blinded randomised, flexible dose, parallel group, comparative study of the efficacy and tolerance of pipothiazine palmitate and fluphenazine decanoate in patients in remission from schizophrenia. On admission, the patients were assigned the next available study number in numerical sequence and allocated to receive either pipothiazine palmitate or fluphenazine decanoate for a period of 28 weeks. The administration of the study medications was open to the person giving the injections but the patients' symptoms and side-effects, recorded after each four week period of treatment, were assessed by one of the investigators who had no knowledge of which study medication had been prescribed.

Medication

Patients were initially prescribed 25 – 50 mg of pipothiazine palmitate ('Piportil Depot', May & Baker Ltd., United Kingdom) calculated, where appropriate, as twice the mg dose of fluphenazine decanoate previously prescribed, or 12.5 – 50 mg of fluphenazine decanoate. The drugs were administered, according to the manufacturers' instructions, by deep intramuscular injection in the gluteal region. Subsequent dosages of prescribed neuroleptic were reviewed at each of the 4-weekly visits for repeat drug administration.

If the patients required anti-parkinsonian therapy for extrapyramidal side-effects, benzhexol hydrochloride was to be prescribed. For sleep disturbance, diazepam was to be prescribed. Neuroleptic treatment other than the study medications was excluded.

Clinical Evaluation of Patients

Pre-treatment Evaluation

At the initial visit, the patient's date of birth, sex, diagnosis, duration of disease, current therapy and its duration, together with any specific somatic disease, were recorded.

Treatment Period Evaluation

At the initial visit and at the seven subsequent four-weekly visits, the dose of the study treatment given to the patient was recorded. The reasons for any change of dose of the study medications were documented together with details of any concomitant medication.

At each visit the patients were assessed by the Brief Psychiatric Rating Scale (BPRS), by a Side-effects Checklist, by an Extrapyramidal Side-effects (EPS) Rating Scale and by a Clinical Global Impressions (CGI) Scale. All adverse events and the data and reasons for withdrawal were also recorded at each visit.

Statistical Methods

For all but the data for which analyses of variance were considered suitable, chi-squared tests for n by 2 tables were used in reviewing the results.

For the BPRS and the Side-effects Checklist, analysis of variance (BMDP8V) (8) was used.

The EPS and the CGI scored only four and three questions respectively. Thus, these questionnaires were reported upon by category of response and chi-squared tests used to review any differences.

RESULTS

Pre-treatment Evaluation

Thirty patients were randomly allocated to receive each of the study medications. The duration of their schizophrenic illness ranged from two to twenty five years.

All but five of the patients (two of the pipothiazine palmitate treatment group and three of the fluphenazine decanoate treatment group) were recorded as having been receiving fluphenazine decanoate, alone or in combination with other drugs, in doses ranging from 6.25 mg every six weeks to 50 mg a month. The pipothiazine palmitate treatment group had been receiving an average of 19.1 mg a month (standard error 1.6 mg) and the fluphenazine decanoate treatment group an average of 19.5 mg a month (standard error 1.8 mg).

On admission to the study, the patient population had a mean BPRS score of 2.40 ranging from 0 to 12. The pipothiazine palmitate treatment group had a mean score of 2.70, ranging from 0 to 11 and the fluphenazine decanoate treatment group a mean of 2.07, ranging from 0 to 12, these mean scores were not significantly different.

Twenty two of the pipothiazine palmitate treatment group and 19 of the fluphenazine decanoate treatment group were regarded as being normal on admission. Two of the pipothiazine palmitate treatment group and six of the fluphenazine decanoate treatment group reported side-effects that questionably or moderately interfered with their functions. Two of the pipothiazine palmitate treatment group and three of the fluphenazine decanoate treatment group showed signs of mild or moderate extrapyramidal side-effects.

Treatment Period Evaluation

Medication

Nine patients had their dose of pipothiazine palmitate increased after four weeks' treatment and a further two after eight weeks to the average level recommended by the manufacturer. At the 24-week visit, the mean dose of pipothiazine palmitate prescribed was 39.8 mg (standard error 2.4 mg; range 25-50 mg). One patient on pipothiazine palmitate was withdrawn from the study when she became pregnant.

Two patients on fluphenazine decanoate had their dose increased after four weeks' treatment. One patient complained of feeling restless and had the dose of fluphenazine decanoate reduced after four weeks' treatment, another complained of discomfort, possibly because of the injection, and had the dose reduced after sixteen weeks' treatment. At the 24-week visit, the mean dose of fluphenazine decanoate prescribed was 19.4 mg (standard error 1.8 mg; range 12.5 — 50 mg).

Two patients treated with pipothiazine palmitate were prescribed benzhexol hydrochloride concomitantly at eight weeks, one because of tremors, the other because of up-rolling of the eyes.

Efficacy

It may be seen from Table I that the BPRS score after 28 weeks' treatment increased for six patients in each treatment group; two patients receiving fluphenazine decanoate showed a marked increase in BPRS score. Further, thirteen patients receiving pipothiazine palmitate showed a decrease in BPRS score after 28 weeks' treatment as compared with only five patients receiving fluphenazine decanoate. Although favouring pipothiazine

Table I
Assessments of efficacy following 28 weeks treatment

Brief Psychiatric Rating Scale	Pipothiazine treatment group	Fluphenzine treatment group
Better	13	5
No change	10	17
Worse	6	6
n.s.	0	2
w.d.	1	0
Total	30	30

$x^2 = 5.35$; $p > 0.05$

Clinical Global Impression

Therapeutic Effects compared with beginning of trial:

Marked	0	0
Moderate	1	0
Minimal	1	0
Unchanged or worse	27	29
n.s.	0	1
w.d.	1	0
Total	30	30

$x^2 = 2.07$; $p > 0.05$

Severity of illness:

Better	4	6
No change	23	21
Worse	2	3
n.s.	0	0
w.d.	1	0
Total	30	30

$x^2 = 0.67$; $p > 0.05$

n.s. = not stated
w.d. = withdrawal (due to pregnancy)

palmitate, these differences in efficacy were not statistically significantly different (chi-squared is 5.35 with 2 degrees of freedom: $0.10 > p > 0.05$).

The mean BPRS score at each visit, together with the 95 percent confidence limits for the mean values both on admission and after 28 weeks treatment, are plotted on Fig. 1. Although there were small fluctuations in BPRS score over the study period, what differences there were, both within treatment group over time and between treatment group at any time, were small and remained within the confidence limits. This impression was confirmed by the analyses of variance; the main effect of time having an F ratio of 6.06 (with 7 and 371 degrees of freedom, $p = 0.11$) and the interaction between treatment and time having an F ratio of 3.54 (with the same numbers of degrees of freedom, $p = 0.44$).

In respect of the question in the CGI that compared therapeutic effects with the beginning of the trial, 27 of the patients in the pipothiazine palmitate treatment group and 29 in the fluphenazine decanoate treatment group were recorded as being unchanged or worse; two patients in the pipothiazine palmitate treatment group were recorded as having improved slightly or decidely compared with no patients in the fluphenazine decanoate treatment group (Table i).

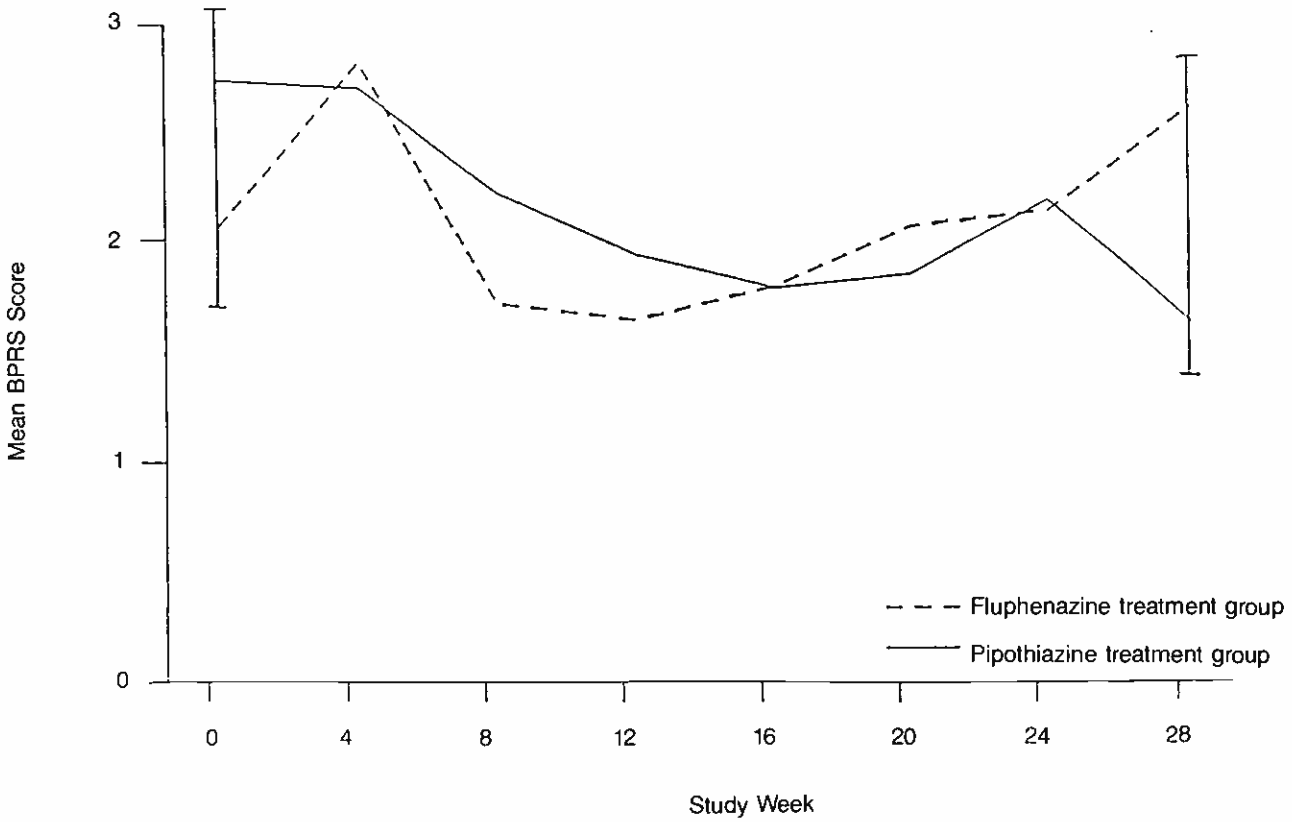

Fig. 1 Mean Brief Psychiatric Rating Scale (BPRS) Scores at Each Visit

Tolerance

The Side-effects Checklist, EPS questions and the side-effects question in the CGI revealed little difference in tolerance between the two treatments; it is interesting to note that four patients receiving fluphenazine decanoate, but none receiving pipothiazine palmitate, complained of dystonia (Table II).

The mean Side-effects Checklist scores at each visit, together with the 95 percent confidence limits for the mean values both on admission and after 28 weeks treatment are plotted on Fig. 2. As with the components of the EPS scale and the Side-effects question in the CGI scale recorded in Table II, there were small fluctuations over the study period but what differences there were both within treatments over time and between treatments at any time, were small and remained well within the confidence limits. Analyses of variance confirmed this impression, the main effect of time having an F ratio of 1.79 (with 7 and 392 degrees of freedom, $p = 0.08$) and the interaction between treatment and time having an F ratio of 0.53 (with the same numbers of degrees of freedom, $p = 0.81$).

In addition to the Side-effects Checklist, specific side-effects reported at each visit and which were not present on admission were recorded (Table III). A higher proportion of patients receiving pipothiazine palmitate reported at least one new side-effect (40%) than did those receiving fluphenazine decanoate (27%): a large part of this difference being accounted for by the seven patients receiving pipothiazine palmitate who reported mild to moderate dry mouth compared with only two receiving fluphenazine decanoate.

Table II
Assessment of tolerance following 28 weeks treatment

	Pipothiazine treatment group	Fluphenazine treatment group
Side-effects Checklist:		
	n = 30	n = 30
Better	13	12
No change	8	9
Worse	8	8
Not stated	0	1
Withdrawn	1	0
$x^2 = 9.88$; $p > 0.05$		
Extrapyramidal Side-effects Scale:		
Akinesia:		
Better	0	1
No change	29	28
Worse	0	0
Not stated	0	1
Withdrawn	1	0
$x^2 = 1.70$; $p > 0.05$		
Akathisia:		
Better	0	1
No change	28	26
Worse	1	0
Not stated	0	3
Withdrawn	1	0
$x^2 = 2.01$; $p > 0.05$		
Parkinsonism:		
Better	1	1
No change	24	24
Worse	4	2
Not stated	0	3
Withdrawn	1	0
$x^2 = 0.60$; $p > 0.05$		
Dystonia:		
Better	0	0
No change	29	23
Worse	0	4
Not stated	0	3
Withdrawn	1	0
$x^2 = 1.70$; $p > 0.05$		
Clinical Global Impression Scale:		
Side-effects:		
Better	1	5
No change	25	22
Worse	2	0
Not stated	1	3
Withdrawn	1	0
$x^2 = 4.84$; $p > 0.05$		

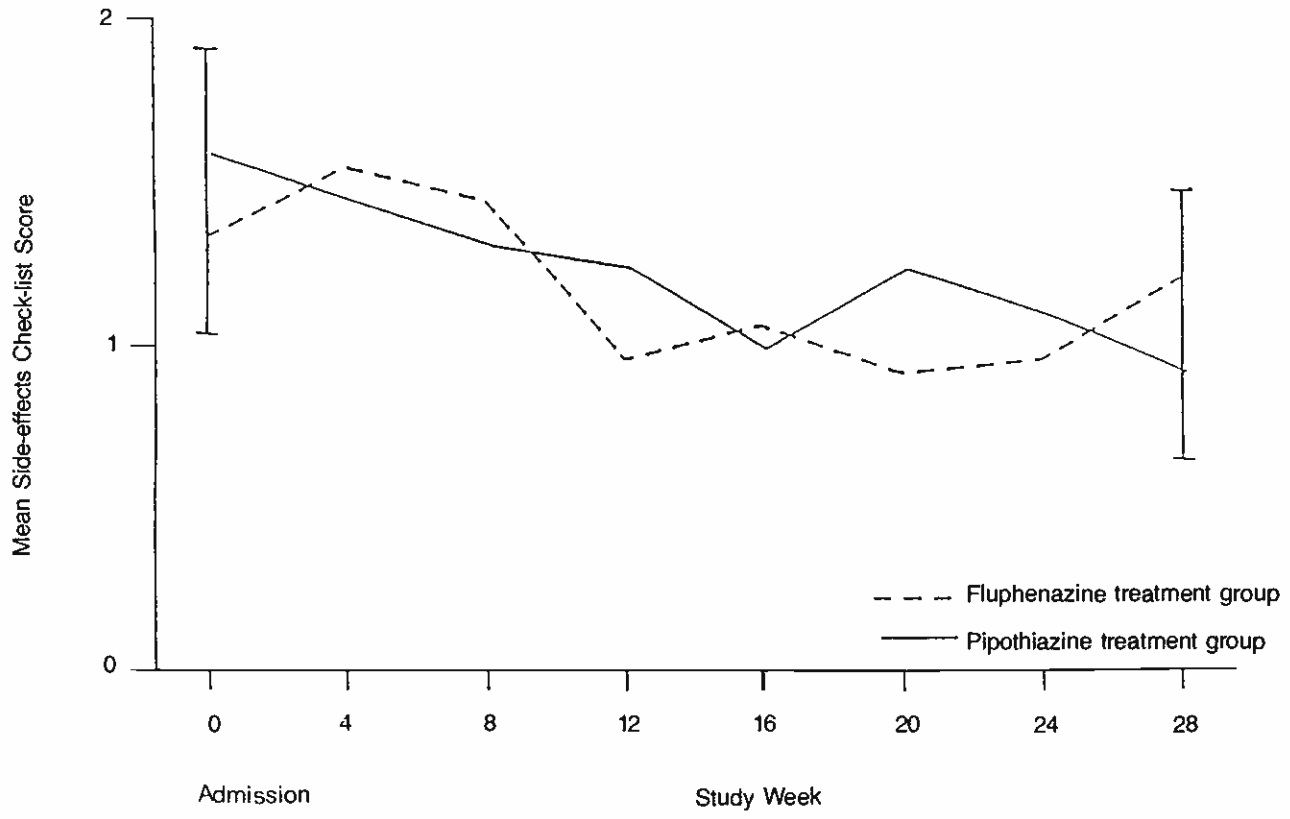

Fig. 2: Mean Side-effect Check-list Score at Each Visit

Table III
New* side-effects reported

	Pipothiazine treatment group	Fluphenazine treatment group
Number of patients reporting each		
Dry mouth	7	2
Tremor	3	2
Nausea	3	0
Headache	1	0
Stiffness	2	1
Slowness	1	0
Tired, drowsy	2	1
OG crisis	0	3
Salivation	0	1
Number of patients reporting at least one 'new' side-effect	12 (40%)	8 (27%)

*That is, excluding side-effects that were present at week O.

DISCUSSION

In this study in maintained schizophrenia, 55 of the 60 patients admitted had previously been maintained on one of the study treatments, fluphenazine decanoate. The evidence from the study that there is no observable difference in efficacy between either of the treatments suggests first, that pipothiazine palmitate is as efficacious as fluphenazine decanoate and secondly, that it may be used as an alternative therapy for patients previously prescribed fluphenazine decanoate.

This is confirmed by the observed tolerance of both study treatments. As it is suspected (9) that fluphenazine decanoate has a half-life of up to about six weeks after repeated dosing, cross-tolerance in the pipothiazine treatment group to both molecules has been shown by the results of this study. While there was a higher incidence of patients reporting new side-effects in the pipothiazine treatment group, 12 patients (40%) compared with 8 (27%) in the fluphenazine treatment group, this was accounted for by the greater incidence of dry mouth. Equally, no fall-off in the efficacy of pipothiazine palmitate was noted during the early period of the study.

Both treatment groups demonstrated a slight increase in extrapyramidal side-effects: parkinsonian for the pipothiazine treatment group, dystonic for the fluphenazine treatment group. Two patients in the pipothiazine treatment group required additional anti-parkinsonian therapy.

It is concluded that pipothiazine palmitate is at least as efficacious and well-tolerated as fluphenazine decanoate and may be safely and effectively used as a change in therapy.

ACKNOWLEDGEMENT

The authors are grateful to Assoc Prof Teo Seng Hock, Medical Director of Woodbridge Hospital for his encouragement in the project and to May & Baker Ltd for their help in processing the statistical data. Special thanks also go to Mdm Zohora for typing the manuscript.

REFERENCES

1. Albert JM , Elie R, Cooper SF: Long-term double-blind evaluation of pipothiazine palmitate and fluphenazine enanthate. Curr Ther Res 1980; 27: 897-907.
2. Johnston RE , Niesink F: A versatile new sustained-action neuroleptic: Pipothiazine palmitate in psychiatric practice. J Int Med Res 1979; 7: 187-93.
3. St. Laurent J , Carle R , Dumais B et al. Monthly intermittent chemotherapy of chronic schizophrenic outpatients with pipothiazine palmitate. Can Psychiatr Assoc J 1974; 19: 583-91.
4. Singh AN, Saxena B: A comparative study of prolonged action (depot) neuroleptics: pipothiazine palmitate versus fluphenazine enanthate in chronic schizophrenia patients. Curr Ther Res 1979; 25: 121-32.
5. Scholosberg A, Shadmi M: A comparative study of two long-acting phenothiazines: pipothiazine palmitate and fluphenazine decanoate. Curr Ther Res 1979; 25: 642-54.
6. Lapierre MD , Berliss H , Monpremier P et al:Methodology and results of a long-term study of long-acting neuroleptics: pipothiazine palmitate and fluphenazine decanoate. In: Obiols J , Ballus C , Moncnus E G et al (Eds.): Biological Psychiatry Today, Amsterdam. Elsevier/North Holland Biomedical Press, 1979.
7. Woggon B , Dick P, Fleishhaur HJ et al. The efficacy of pipothiazine palmitate and fluphenazine decanoate compared in a multi-centre double-blind trial. Int Pharmacopsychiatr 1977; 12: 193-209.
8. Dixon WJ (Chief Editor) BMDP Statistical Software Berkeley, Los Angeles, London: University of California Press, 1985.
9. Jann MW , Ereshefsky L , Saklad S R:Clinical pharmacokinetics of the depot antipsychotics. Clin. Pharmacokinet 1985; 10: 315-33.