ORIGINAL ARTICLE

A Double Blind Comparison of Zuclopenthixol Acetate with Haloperidol in the Management of Acutely Disturbed Schizophrenics

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Summary

The aim of this study was to evaluate the efficacy and side effects of zuclopenthixol acetate compared with haloperidol in the management of the acutely disturbed schizophrenic patient. Suitable subjects diagnosed as having schizophreniform disorder or acute exacerbation of schizophrenia admitted to the psychiatric wards Hospital Kuala Lumpur were randomised to receive either zuclopenthixol acetate or haloperidol. They were rated blind for three consecutive days using the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) and UKU Side Effects Scale. Apart from repeat injections of the same medication, no other anti-psychotic was given for the duration of the study. 50 subjects entered the study of which 44 completed. 23 were given zuclopenthixol acetate and 21 haloperidol. Both groups significantly reduced BPRS and CGI scores on all 3 days compared to the initial rating ($p < 0.001$). There was however no difference between the zuclopenthixol acetate and haloperidol group scores on all days ($p > 0.05$). More subjects on haloperidol [7] than zuclopenthixol [1] required more than 1 injection during the study. Both groups had minimal side effects. Zuclopenthixol acetate was effective in the management of the acutely disturbed schizophrenic.

Key Words: Schizophrenia, Zuclopenthixol acetate, Haloperidol

Introduction

The management of the acutely disturbed schizophrenic patient is a challenging one requiring tactful communication as well as the use of parenteral anti-psychotics for sedation. The current drugs of choice are haloperidol and chlorpromazine. Chlorpromazine has been in use since the 1950s. It is very sedative but has the disadvantage of producing postural hypotension and the large volume of chlorpromazine (4 ml per 100 mgm) is often painful and if repeated may produce sterile abscesses.

Haloperidol is the most frequently used parenteral anti-psychotic used in the Casualty and Emergency Psychiatric Clinic at Hospital Kuala Lumpur (HKL). It is effective but the effect lasts 6-8 hours and may have to be repeated 3-4 times in the first day or even the next few days. This is unpleasant both for the patient as well as for the nursing staff.

Psychotic patients at Hospital Kuala Lumpur are more likely to be disturbed (verbal and physical violence, motor overactivity and restlessness) for a number of reasons: (a) due to the psychotic illness reacting to

hallucinations and delusions, (b) as a reaction to certification and admission to the psychiatric ward, (c) as a reaction to the overcrowded ward (1 in 5 male psychiatric patients have no bed to sleep on in a 6 month study period on Quality Assurance at HKL) [1], and (d) more than 80% of all psychiatric admissions to HKL are psychotic with the majority being schizophrenics [1].

Therefore there is a need to have an effective and rapid sedative anti-psychotic like haloperidol and it should preferably be effective for a longer period. Recently zuclopenthixol acetate has been introduced in Malaysia. Zuclopenthixol acetate has been shown to have a rapid onset of action and its effect lasts up to 3 days [2]. Several trials using zuclopenthixol acetate have been reported in the West. A randomised multicentre study on the use of zuclopenthixol acetate and haloperidol in acute psychotic patients carried out in Belgium on 105 patients concluded that zuclopenthixol acetate induced more sedation, caused fewer extrapyramidal side effects and required fewer administrations meaning less discomfort to patients [3]. Another large multicentre study was reported from Austria, this one being an open study on 176 psychotic patients. The main findings were that zuclopenthixol acetate had a rapid onset of action, had 2-3 days duration of action and had few extrapyramidal side effects [4]. In England, an open study of a single injection of zuclopenthixol acetate in 25 patients and assessed for 3 days post injection using the BPRS, CGI and UKU Side Effects Rating Scale supported the above findings about the rapid onset of action and a duration of action of 3 days for zuclopenthixol acetate [5].

Thus the literature from the West reporting clinical trials on zuclopenthixol acetate are favourable and suggest that it has an advantage over existing therapy in the form of fewer administrations and few side effects. No formal study on zuclopenthixol acetate has been carried out in Malaysia yet. This is a study on the efficacy and side effects of zuclopenthixol acetate compared with haloperidol on disturbed schizophrenic Malaysians. The objectives of this study are:

1. To compare the efficacy of zuclopenthixol acetate with haloperidol in the treatment of the acutely disturbed schizophrenic patient.
2. To compare the side effects of zuclopenthixol acetate and haloperidol in the treatment of the acutely disturbed schizophrenic patient.

Methods

Suitable subjects were assessed as they presented at the Casualty or Emergency Psychiatric Clinic and inclusion criteria include (a) age between 18 to 65 years, (b) diagnosed schizophreniform disorder or an exacerbation of chronic schizophrenia according to the DSM IIIR criteria [6], (c) have a score of 20 or more on the BPRS, (d) be acutely disturbed (verbally or physically aggressive, agitated or restless), (e) certified for compulsory admission to the psychiatric ward and (f) have informed consent from an accompanying relative to participate in the study.

Exclusion criteria for the study included (a) patients who have received short term oral and parenteral anti-psychotics within the last 6 hours, (b) patients who have received depot anti-psychotics within the last 2 weeks, (c) patients with clinically relevant somatic or neurologic diseases, (d) patients with known organic brain disorder and (e) pregnant patients.

Once patients fulfilling the above inclusion and exclusion criteria entered the study, basic demographic data were recorded: age, sex, duration of illness, marital status together with a brief summary of the psychiatric history.

The subjects were rated on 3 scales:

(a) Brief Psychiatric Rating Scale (BPRS). This is a very frequent and popularly used rating scale to assess the severity of a psychotic illness and is a reliable instrument [7].

(b) Clinical Global Impression (CGI). Also used to assess the severity and change in mental state.

(c) UKU Side Effects Rating Scale[8]. This is used to assess side effects of anti-psychotics. This was devised in Scandinavia and has been found to be reliable and also quantifies the severity of side effects.

Subjects were allocated to either zuclopenthixol acetate or haloperidol by randomisation. A total of 50 subjects were taken into the study and randomisation was done by the first author (CNC). The code was kept by the first author and not revealed to others who assessed the subjects to maintain blindness with the exception in case of adverse reactions, in which case the assessor will contact the first author.

The medication was put in identical individual boxes and labelled 1, 2, 3 etc and zuclopenthixol acetate or haloperidol vials were placed in the box according to the schedule code. Instructions as to dosage and contact person (phone and pager number) in case of queries were enclosed. For zuclopenthixol acetate, 100 mgm i/m was given to female subjects while 200 mgm i/m was given to male subjects for the first 10 allocated to the group. Subsequently all subjects allocated to this group were given 100 mgm i/m. For the haloperidol group 10 mgm i/m was given.

No concomitant anti-psychotic medication was allowed except for the use of procyclidine 10 mgm. i/m or benzhexol 2 mgm. in event of extrapyramidal side effects and lorazepam 2 mgm. on night as a hypnotic if required.

The raters were blind as to the medication used as the box was opened by the nursing staff and the injection given without the presence of the rater. The raters had been familiarised with the use of the various rating scales and the same rater rated the same subject on day 0, 1, 2 and 3. After the initial injection, the box was kept in the DDA Cupboard in the respective male or female ward.

Assessments were done on entry (Day 0) and subsequent mornings for 3 days preferably at about the same time. This was called Day 1 (12-24 hours after initial injection), Day 2 (36-48 hours after initial injection and Day 3 (60-72 hours after initial injection). On Day 0, BPRS and CGI were used while BPRS, CGI and UKU Side Effect Scales were rated on Days 1, 2 and 3.

Should any subject remain disturbed or deteriorate, the rater was called by the nursing staff to rerate the subject and if the BPRS score remained high or was higher, the medication was repeated 6 hourly till there was improvement for the duration of the 3 day study. The nurse was instructed to retrieve the box allocated to the subject and to give a repeat injection of the same medication without revealing the identity of the medication to the rater to maintain blindness.

Subjects were withdrawn in cases of unsatisfactory effect of the test preparation where it was considered necessary to transfer to another treatment or when side effects or complications that cannot be controlled by treatment with allowed concomitant medication occurred during the study period.

At the end of the study (Day 3), the subjects were transferred to oral/ depot anti-psychotic medication as seen fit by the clinician in charge of the subject.

The 2 groups were compared with regards to age, duration of illness and sex. The chi square test was used for comparison of frequency data. However where one of the expected frequencies falls below 5, the Fisher's Exact test was used. The mean differences between the zuclopenthixol scores and haloperidol scores using BPRS and CGI on days 0, 1, 2 and 3 were subjected to the t test using 2 independent means comparison. In addition the mean baseline scores on day 0 for both groups compared to days 1,2 and 3 were subjected to the t test using the 2 independent means comparison.

The study was initially estimated to be completed in a year but due to the difficulties in recruiting suitable subjects, it was extended to 3 years when 50 subjects were recruited. This was felt to be sufficient as the t test is a robust test and when a sample size is greater than 30, the assumption that the samples come from normally distributed populations is likely to be valid.

Results

Subjects

At the end of 3 years, a total of 50 subjects entered the study, 25 on zuclopenthixol acetate and 25 on haloperidol. 44 subjects completed the 3 day study, 23 from zuclopenthixol acetate and 21 from haloperidol group. 6 subjects were withdrawn from the study. 2 subjects were found later to have taken cannabis shortly before

Table I
Baseline comparison of various characteristics between the two treatment groups

Characteristics	Treatment Group Zuclopenthixol acetate N=23	Haloperidol N=21	Total
Age (x±sd)	31.0 (±8.7)	33.3(±10.0)	
Sex			
Male	15	13	28
Female	8	8	16
Ethnicity			
Malay	9	12	21
Chinese	9	7	16
Indians	5	2	7

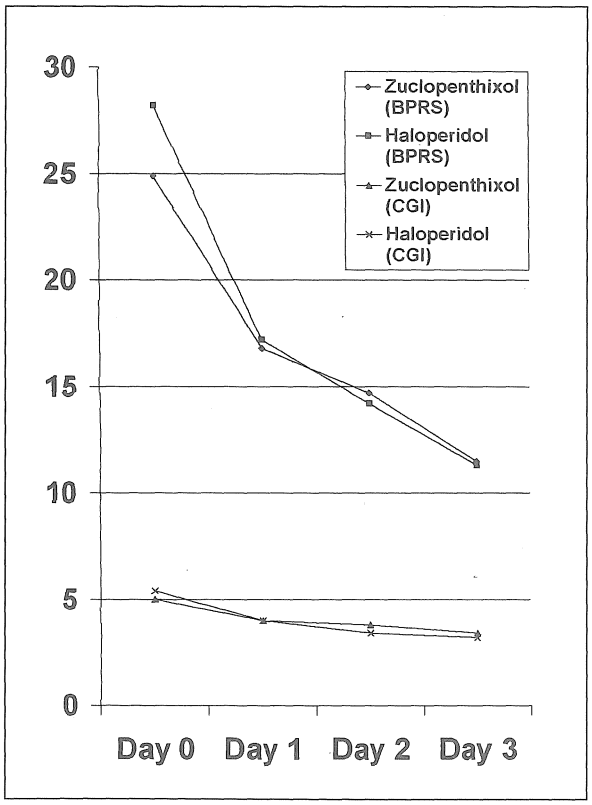

Fig. 1: BPRS & CGI Scores

admission and were rediagnosed as having a drug induced psychosis. Their urine tested positive for cannabis. The remaining 4 subjects had their consent withdrawn by other relatives after signing the consent initially.

The demographic characteristics of the 2 groups are as in Table I. The 2 groups had similar sex distribution. The haloperidol group had a higher mean age due to the females who happened to be much older than the rest. Other than that the 2 groups were comparable. There were 9 Malays, 9 Chinese and 5 Indians in the zuclopenthixol group while there were 12 Malays, 7 Chinese and 2 Indians in the haloperidol group.

Brief Psychiatric Rating Scale (Fig. 1)

The mean BPRS scores for the zuclopenthixol group for days 0, 1, 2 and 3 were 24.9, 16.8, 14.7 and 11.5 respectively. There was a significant reduction of BPRS scores for day 1, 2, and 3 compared to the baseline score (t test, $p < 0.001$).

The mean BPRS scores for the haloperidol group for days 0, 1, 2 and 3 were 28.2, 17.2, 14.2 and 11.3 respectively. Again there was a significant reduction of BPRS scores for day 1, 2 and 3 compared to the baseline score (t test, $p < 0.001$).

Although the haloperidol group had a higher mean BPRS score on day 0 than the zuclopenthixol acetate group, there was no significant difference (t test $p>0.05$). There was also no significant difference between the 2 groups on the subsequent days 1, 2 and 3 (t test $p>0.05$)

Clinical Global Impression (Fig. 1)

The mean CGI scores for the zuclopenthixol acetate group for days 0, 1, 2 and 3 were 5.0, 4.0, 3.8 and 3.4 respectively. There was a significant reduction in CGI scores for days 1, 2 and 3 compared to baseline (t test, $p < 0.001$).

The mean CGI scores for the haloperidol group for days 0, 1, 2 and 3 were 5.4, 4.0, 3.4 and 3.2. Again there was a significant reduction in CGI scores for days 1, 2 and 3 compared to baseline (t test, $p < 0.001$).

There was no difference in mean scores for both zuclopenthixol and haloperidol groups when compared for days 0, 1, 2 and 3 (t test $p>0.05$).

Side Effects

In the zuclopenthixol acetate group, 12 out of the 23 did not have any recorded side effects during the study period when rated on the UKU side effects scale. 6 subjects recorded side effects on day 1, 4 being rated mild (1 rigidity, 1 tremor, 1 decreased salivation and 1 orthostatic dizziness) and 2 moderate (1 dystonia and 1 orthostatic dizziness). There were 9 recorded side effects on day 2 of which 7 were rated mild (1 each dystonia, rigidity, tremor, decreased salivation, orthostatic dizziness and 2 hypokinesia) while 2 were rated moderate (1 hypokinesia and 1 decreased salivation). There were 10 recorded side effects on the third day of study, all of which were rated as mild (1 each dystonia, tremor, accommodation, decreased salivation and orthostatic dizziness, 2 with hypokinesia and 3 with rigidity).

In the haloperidol group, on day 1, there were 7 recorded side effects, all of which were rated mild (1 each rigidity, hypokinesia, increased salivation and orthostatic dizziness and 3 with tremor). On day 2, there were 6 recorded side effects, 5 of which were rated mild (1 with accommodation difficulties and 2 each with tremor and increased salivation). 1 subject had orthostatic dizziness which was rated as severe. On day 3, there were 5 reported side effects of which 4 were rated as mild (1 each dystonia, rigidity, tremor and decreased salivation) while there was 1 with severe orthostatic dizziness.

Dosage of zuclopenthixol acetate

In the first 20 subjects, 10 were randomised to the zuclopenthixol acetate group. If the subject was male 200 mgm. Zuclopenthixol acetate was given while 100 mgm. was given if the subject was female. 7 male subjects were given 200 mgm. 3 of them experienced marked sedation for the next 3 days. Although they could be assessed on the CGI and UKU, the BPRS could not be completed and the 3 were excluded from the mean BPRS scores. Subsequently, all those allocated to the zuclopenthixol acetate group were given 100 mgm. irrespective of sex. There were no further marked sedation in this group.

Repeat Injections

In the zuclopenthixol group, only 1 subject required an additional injection during the study period because of a worsening in mental state. In contrast 7 subjects from the haloperidol group required additional injections during the study period. This was significant ($p < 0.05$, Fisher's Exact Test). 2 of them required 2 further injections.

Discussion

The subjects in both the zuclopenthixol acetate and haloperidol group were of similar age as well as in sex distribution. Both groups showed significant improvement in their scores both on the BPRS and CGI on the 3 consecutive days. This indicates that both of them were effective in the treatment of acutely disturbed schizophrenics. There was no difference in efficacy between zuclopenthixol acetate and haloperidol.

The BPRS is a well established and reliable instrument of measuring severity in disturbed psychotics. The change in scores over time reflects the improvement made. This was even made better if the same assessor rated the subject over the 3 days as in our study. That the BPRS scores decreased significantly by the first day

showed that both antipsychotics had a rapid onset of action. This was maintained over the 3 day study period in the zuclopenthixol acetate group as evidenced by the finding that only 1 out of the 23 required a repeat injection.

Another strength of this study is that it allowed for repetition of injections during the 3 day period. To maintain blindness, both the zuclopenthixol acetate and haloperidol groups had identical standing instructions that allow for repeat injections 6 hourly. Zuclopenthixol had the advantage over haloperidol in that fewer repeat injections were required (1:7). This was statistically significant (Fisher's Exact Test $p < 0.05$).

One of the strengths of this study was that the raters were blind to the anti-psychotic used. This is methodologically better than open studies in which the raters knew the medication given and this can be criticised as a possible source of bias on the part of the assessors. To achieve this required considerable work and effort on the part of the coordinators who held the code and liaised between the assessors and the nursing staff whenever there was a difficult subject who required additional injections. This meant having to be on call at all times during the 3 year duration of the study. Disturbed schizophrenics who were suitable for the study appeared to be brought to the Casualty Department Hospital Kuala Lumpur at odd hours of the night and they needed sedation fast.

This meant that the assessors needed to carry with them the sealed packs of medication without knowing what was in them. To overcome this, the medications were stored in identical boxes and labelled according to the code in random order. About 3-4 packs were kept in a bag for the assessors to carry when they were on call. When they forgot to take it, some potentially suitable subjects were lost. In addition, a large number of suitable subjects were brought to the Casualty Department Hospital Kuala Lumpur by the Police without any relatives. This meant that they cannot be included in the study for lack of informed consent. 4 subjects who initially entered the study were withdrawn after other relatives of the subject objected.

The CGI scores reinforced the findings in the BPRS analysis in that both zuclopenthixol acetate and haloperidol were effective and there was no difference between the two.

The side effects in both groups were mostly mild and affected less than half of the zuclopenthixol acetate group and one third of the haloperidol group. This was similar to the findings of previous studies reported in Europe[3,4,5].

Conclusion

Zuclopenthixol acetate was effective in the management of the acutely disturbed schizophrenic and was comparable to haloperidol. The side effects were mild. Significantly less injections were given to the zuclopenthixol group compared to the haloperidol group. Zuclopenthixol acetate is useful in the acute management of the acutely disturbed schizophrenic patient especially in our crowded wards with limited nursing staff.

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