

AN OPEN TRIAL OF ZUCLOPENTHIXOL IN MANAGEMENT OF ACUTE PSYCHOSES : A MULTICENTERED STUDY

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ABSTRACT

In an open trial, patients with ICD-10 diagnosis of acute functional psychoses were administered injection Zucloperthixol acetate (Acuphase) in the initial phase. Patients were rated with CGI, BPRS -24 item and UKU side effect rating scale at baseline, 24 hours and 72 hours. Of the 120 patients recruited, 119 finished this part of the trial. The most common side effect was sedation, which was preferable as most of the patients were in the acute state. The issues concerning less dosing efficacy and the rapid onset of antipsychotic activity are discussed.

Patients who had been administered zucloperthixol acetate in the acute phase were maintained with injection zucloperthixol decanoate (depot) starting at 72 hours over the baseline. Patients were assessed at 72 hours, one week, 2 weeks, 3 weeks, 4 weeks and 8 weeks using the same instruments. The issues concerning the dosage and therapeutic efficacy are discussed.

Key words : Zucloperthixol acetate, acute psychoses, zucloperthixol decanoate, depot.

Violence and aggression constitute a major problem in psychiatry. For a psychiatrist the main concern when working with such severely ill patients is to limit or prevent physical violence and disruptive behaviour. Earlier severely aggressive patients were confined to the custodial care system of mental hospitals. Today with the availability of different modes of treatment including pharmacotherapy and psychotherapy treatment of acutely violent and psychotic patients is made much effective and easier. Parenteral neuroleptics achieve a quicker onset of action and prevent non-compliance. Zucloperthixol is one such neuroleptic drug belonging to the thioxanthene group. Zucloperthixol acetate in thin vegetable oil ('viscoleo') when given intramuscularly has a rapid onset of action with sustained effect of 2-3 days duration (Hebenstreit, 1990). Short acting parenteral

neuroleptics such as haloperidol have a disadvantages as their duration of action is short.

The long-acting depot preparation of zucloperthixol is in the form of decanoate in vegetable oil. It is for intramuscular administration and has its therapeutic effects for 2 to 4 weeks. Zucloperthixol decanoate has been found useful in the maintenance treatment of chronic psychoses namely schizophrenia (Wistedt et al., 1991). Depot injections overcome the problems of first pass metabolism by the liver and give a predictable and constant serum level. In addition the total number of injections over an extended period of weeks and months remains quite small and that enhances treatment compliance. The authors investigated Zucloperthixol in an open prospective, multicentered study of acutely psychotic patients - to evaluate the safety and efficacy.

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MATERIAL AND METHOD

STUDY POPULATION AND SCHEDULE :

One hundred and twenty patients were recruited satisfying the study criteria for inclusion in trial, after obtaining written informed consent. Before starting the study the protocol was duly cleared by the ethical committees of the three participating centres, namely Institute of Psychiatry and Human Behaviour (IPHB), Goa; KEM Hospital (KEM), Mumbai and National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. All patients were admitted in the hospital and were screened for other physical illnesses. Routine biochemical investigations including liver functions were done. A wash out period of 15 days was required to be given if they received a prior depot neuroleptic or it was 6 hours if other oral or parenteral neuroleptics were administered. All patients were started on zuclopenthixol acetate (Acuphase) supplied in 1 ml vials and 2 ml vials containing 50 mg/ml of zuclopenthixol acetate in thin vegetable oil (Viscoleo). The dose was repeated if required after 24 hours and if not a second dose was given after 72 hours. Concomitant medication with only benzodiazepines, antihistaminics and hypnotics was permitted. Antiparkinsonian agents (trihexyphenidyl hydrochloride or promethazine) were added as and when required. No other psychotropic agents were administered. Ongoing medical therapy for chronic diseases (such as diabetes mellitus, hypertension and tuberculosis) whenever indicated was continued.

At 72 hours, the 2nd dose of acuphase and the 1st dose of Zuclopenthixol decanoate (Depot) were given together; the dose of depot being the double of that of acuphase in mg. For most cases these values were 200 and 100 mg respectively. Subsequently depot injections were administered at an interval of 2 weeks for the next 8 weeks in most cases as required by the study protocol. The dosage was kept constant as far as possible. The patients were seen in the outpatient during this phase of the trial.

INCLUSION CRITERIA

1. Age : 18-65 years.
2. Either Sex
3. Acutely ill psychotic patients (rated moderately ill or above on CGI) requiring psychopharmacological management diagnosed according to ICD-10 (CDDG-1992) : new cases or exacerbation of chronic psychoses.

EXCLUSION CRITERIA

1. Patients with epilepsy, clinically relevant physical or neurological illness.
2. Patients with alcohol or drug abuse in the last one year or on other non-marketed text preparation.
3. Pregnant and lactating women.

INSTRUMENTS

All patients were assessed for clinical status and side effects using the following instruments at baseline and after 24 hours, 72 hours, 1week, 2 weeks, 3 weeks, 4 weeks and 8 weeks :

1. Clinical Global Impression Scale (CGI-S):
This brief instrument has been developed by NIMH, USA as a ready reckoner of psychiatric status (Guy,1976). Another version of this scale is called Clinical Global Impression of Improvement CGI-I. These scales have been used widely in western countries as well as in India. Both were used in this study.
2. Brief Psychiatric Rating Scale (BPRS):
This is a 24 item interviewer-rated questionnaire widely use for monitoring clinical improvement. Originally developed by Overall and Gorham (1962), this instrument has been used extensively in various studies in India and abroad.
3. UKU Side Effect Rating Scale (UKU):
This interviewer-rated instrument is divided into 4 categories of side effects viz. psychiatric, neurologic, autonomic and others (miscellaneous). This was developed by Scandinavian Psychopharmacology Society (Lingjaerde et al.,1987) and has been used in various Indian and international studies.

GENERAL FEATURES**Results :**

The mean age of the patients was 32.1 ±11.1 years. Sixty-two (51.7%) were males. The average duration of the index psychotic episode was 14.9 weeks.

Table 1 shows the diagnostic break-up. The most major diagnostic groups were acute polymorphic psychosis with features of schizophrenia and paranoid schizophrenia (26% each). Other major groups were bipolar affective disorder (BPAD)-mania with psychotic features (13%), undifferentiated schizophrenia (11%) and manic episode with psychotic features (8%).

Table 2 describes the dropouts. A total of 33 dropouts occurred till the end of depot medication (8 weeks). The common causes were inadequate response in 14 (11.7%) and comorbid problems including emergent depression in (10%).

TABLE 1
DIAGNOSTIC BREAK-UP (N=120)

Diagnosis	Frequency	%
Acute polymorphic psychosis without features of schizophrenia	7	5.8
Acute polymorphic psychosis with features of schizophrenia	31	25.8
Acute schizophrenia like psychosis	7	5.8
Acute psychosis with predominant delusions	1	0.8
Manic episode with psychotic feature	9	7.5
BPAD-mania with psychotic feature	16	13.3
Paranoid Schizophrenia	31	25.8
Undifferentiated Schizophrenia	13	10.8
Delusional disorder	1	0.8
Psychosis NOS	4	3.3
Total	120	100

TABLE 2
DETAILS OF DROPOUTS (N=33)

Observed reason	Number
1) Inadequate response to treatment	14
2) Comorbid problems including emergent depression	12
3) Side effect other than depression	3
4) Discontinued without appropriate reasons	4

DOSING PATTERN

The majority (114, 95%) received 100 mg acuphase in their first injection. Only 5 (4.2%)

received 50 mg acuphase as the first dose. At 72 hours the majority (97, 80.8%) received 100 mg as their second dose of acuphase, 20 (16.7%) needed only 50 mg of acuphase as the second dose and only 2 (1.7%) needed 150 mg of acuphase at 72 hours. Sixteen (13.3%) required an additional injection of 100mg acuphase within first 72 hours.

At 72 hours all 119 patients received 200 mg of Zuclopenthixol depot along with their second dose of acuphase. The patients were given depot injections at two weekly intervals subsequently till the end of the trial (8 weeks). Twenty (16.7%) of patients received 400 mg of zuclopenthixol decanoate in their subsequent depot injections. Eight (6.7%) received 600 mg as their depot injections in third and fourth dosage. Rest (91, 75.8%) received 200 mg depot in all subsequent injections.

RESULTS PERTAINING TO ZUCLOPENTHIXOL ACETATE (ACUPHASE)

There was only one dropout till this stage of the trial and 119 patients' data are available. Table 3 describes the CGI-S findings. Only one patient was rated as mildly ill at the baseline and this happened by mistake. The number of patients in the category of 'severely ill' dropped from 66 (55%) at baseline to 25 (20.8%) at 72 hours. Alongside there was an increase in the category of 'mildly ill' (0.8% to 15%) over the same period. These changes were found to be statistically significant.

TABLE 3
C.G.I.-S FINDINGS WITH ACUPHASE (N=119)

Severity of illness	Baseline(intake)	24 hrs.	72 hrs.
Normal	0(0)	0(0)	2(1.7)
?Mentally ill	0(0)	0(0)	0(0)
Mildly ill	1(0.8)	10(8.3)	18(15)
Moderately ill	14(11.7)	29(24.2)	25(20.8)
Markedly ill	35(29.2)	42(35)	48(40)
Severely ill	66(55)	39(32.5)	25(20.8)
Extremely ill	4(3.3)	0(0)	1(0.8)
Missing Values	0(0)	0(0)	1(0.8)

Significance of Difference (chi-square)

- 1) Between baseline & 24 hrs. 70.42 df=12 p<0.01
- 2) Between baseline & 72 hrs. 55.17 df=20 p<0.01

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CGI-I showed a similar trend of increase in the categories of 'very much improved' and 'much improved'. Put together about 27% were found to be in these two categories at 24 hours and this figure increased to 34% at 72 hours. BPRS also showed a corresponding significant drop in overall scores. The mean value decreased from 77 at baseline to 63 at 24 hours and 58 at 72 hours. All these changes also were statistically significant.

RESULTS PERTAINING TO ZUCLOPENTHIXOL DECANOATE (DEPOT)

The end of the trial for acuphase was the beginning of the trial for depot. Therefore the baseline for assessment started at 72 hours for depot. Eighty-seven (72.5%) patients completed the trial (8 weeks). Patients continued to improve with depot zuclopenthixol. Table 4 shows the CGI-S findings. At the baseline about 61% were included in the categories of 'markedly ill' and 'severely ill'. At 4 weeks only 13% and at 8 weeks only 11% were rated in those categories.

TABLE 4
CGI-S FINDINGS WITH DEPOT (N=87)

Severity of illness	Baseline 72 hours	4 weeks	8 weeks
Normal	2(1.7)	12(10.0)	16(13.3)
? Mentally ill	0(0.0)	16(13.3)	30(25.0)
Mildly ill	18(15.0)	32(26.7)	18(15.0)
Moderately ill	25(20.8)	21(17.5)	10(8.3)
Markedly ill	48(40.0)	9(7.5)	9(7.5)
Severely ill	25(20.8)	6(5.0)	4(3.3)
Extremely ill	1(0.8)	0(0.0)	0(0.0)
Missing Values	1(0.8)	24(20.0)	33(27.5)

Significance of difference (chi-square) between

1) baseline & 4 weeks: 58.39; df=20; p<0.001

2) baseline & 8 weeks: 35.47; df=20; p<0.017

Alongside the categories of 'normal' and 'questionably mentally ill' recorded a steady increase in the ratings (from 2% to 23% and 48% respectively). All these changes were found statistically significant.

On CGI-I also a steady improvement was noted. The category of "very much improved" was rated in 10% of the cases at the baseline, in 24% at 4 weeks and in 35% at 8 weeks. These changes were found significant only between the baseline and 4 weeks but not between the baseline and 8 weeks.

The findings on BPRS showed a similar pattern. The mean total score of 58 at the baseline dropped to 39 at 4 weeks and to 36 at 8 weeks. These changes were also found statistically significant.

SIDE EFFECTS

Apart from the sub group of neurologic side effects the other three sub groups of UKU side effects rating scale did not show much findings. There were few exceptions.

In the 'psychic' sub group at 24 hours 87 patients (72.5%) showed increased sedation whereas 61 (50.8%) complained about the same at 72 hrs. As the trial progressed this complaint came down very considerably (e.g. at the end of 8 weeks only 3 (2.5%) patients complained of increased sedation).

Depression and asthenia were the other side effects that showed an increase as the trial progressed. While at 72 hours only 3 patients (2.5%) complained of depression and one (0.8%) of asthenia, these number progressed to 18 (15%) in each category at the end of 8 weeks.

TABLE 5
NEUROLOGIC SIDE EFFECTS WITH ACUPHASE & DEPOT
(% of patients having side effects)

Visits (Time of Visit)	1 (intake)	2 (24 hours)	3 (72 hours)	4 weeks	8 weeks
Tremor	0	7.5	15.7	13.5	8
Rigidity	1.7	9.2	21.8	26	26.4
Akinesia/Hypokinesia	1.7	9.2	24.4	21.9	23
Dystonia	0	7.5	11.8	3.1	0
Hyperkinesia	0	0	0	1	1.1
Akathisia	0	0	0	5.2	4.6

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There were very few autonomic side effects. Increased salivation was the commonest affecting 5 (4.2%) to 8 (6.7%) patients between 72 hours and 3 weeks. Orthostatic dizziness was found only in 2.5% of patients. Micturition difficulties were seen only in one patient.

In the other section only headache was worth mentioning affecting 3 patients (2.5%) between the first and second weeks.

Neurologic side effects are depicted in table 5. About 8% had tremors at 24 hours, 16% at 72 hours, 14% at 4 weeks and 8% at 8 weeks. Rigidity was more common affecting 10% at 24 hours, 22% at 72 hours and 20% at 4 and 8 weekly assessments. Hypokinesia had a similar pattern. Dystonia was more common in the beginning (8% at 24 hours and 11% at 72 hours) but it affected only 3% at 4 weeks and none at 8 weeks. Akathisia was absent in the beginning but was found later to affect 5% of patients at 4 weeks and also at 8 weeks. Hyperkinesia was rare, affecting only 1% at the end of 4 weeks and at 8 weeks.

DISCUSSION

In this multicentered open trial of zuclopenthixol the efficacy of two preparations were evaluated. It was found that injection zuclopenthixol acetate in thin vegetable oil (viscoleo) was effective in bringing down the severity of psychosis in acute psychotic conditions within 72 hours. This efficacy was evident using CGI-S, CGI-I and BPRS-all three instruments. This was achieved with just one injection of acuphase. Only 16 (13.3%) patients needed another injection of acuphase within 72 hours. This finding is consistent with earlier reports of acuphase's efficacy in acute psychosis (Amdisen *et al.*, 1986 & 1987; Selasberg & Barr, 1991).

Acutely Psychotic patients are often given aqueous parenteral neuroleptics (such as Haloperidol) during the initial days of treatment. As the effect of such preparations is short lasting several injections are often given during one 24-hour period. Apart from causing additional pain and attendant risk of developing injection-

related complications, this system of giving multiple injections disrupts the patients-staff relationship. Therefore a parenteral neuroleptic with rapid onset of action and longer duration of effect is likely to be a better alternative. Zuclopenthixol acetate as acuphase does just that (Hebenstreit, 1990; Babon & DeBleeker, 1990).

No local side effects or reactions were noted with acuphase (Baastrup *et al.*, 1992). Dystonias were observed in few patients and were often mild unlike the severe dystonias seen with other potent antipsychotic drugs (Matar *et al.*, 1990). Rigidity and hypokinesia were noted in less than a quarter of the patients as reported earlier (Korner *et al.*, 1993). Sedation was a significant side effect with acuphase, which was desirable in the acute phase of the illness. Babon and DeBleeker (1990) have reported similar findings. Autonomic side effects were low as also reported by Ivanov *et al.* (1992).

Once the acutely ill patients were stabilized with acuphase they were shifted to injection zuclopenthixol decanoate in vegetable oil (depot). At 72 hours after intake, one injection of acuphase and a double dose depot injection were given together in the same syringe. This made the treatment easier, acceptable and facilitated compliance with a monotherapeutic regime (Hebenstreit, 1990). Over the period of next 8 weeks depot zuclopenthixol was found to be effective in controlling the psychotic condition as indicated by periodic assessments. Previous studies have reported similar findings (Denker *et al.*, 1980; Ahlfors *et al.*, 1980; Wistedt *et al.*, 1991).

During the entire schedule for depot medication most of the patients showed an improvement in their side effects profile. Sedation in particular came down significantly and so did tremor and dystonia. However rigidity and hypokinesia continued to effect about a quarter of the patients. Overall the side effects were mild as reported earlier (Hebenstreit, 1990).

Depression and asthenia were emergent side effects during the period of depot medication and this side effect has not been discussed adequately in previous literature. Few patients needed to be discontinued from the trial because

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they became quite depressed during the trial. This area merits future research.

Future studies would do well to include double blind cross over placebo-controlled designs across various psychotic conditions and age groups.

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REFERENCES

- Ahlfors, U.G., Denker, S.J., Gravem, A. & Remvig, J. (1980) Clopenthixol decanoate and perphenazine enanthate in schizophrenic patients. A double-blind Nordic multicenter trial. *Acta Psychiatrica Scandinavica*, 61(Suppl.), 279, 77-91.
- Amdisen, A., Aaes-Jorgensen, T., Thomsen, N.J., Madsen, V.T. & Nielsen, M.S. (1986) Serum concentrations and clinical effect of zuclopenthixol in acutely disturbed psychotic patients treated with zuclopenthixol acetate in viscoleo. *Psychopharmacology*, 90, 412-416.
- Amdisen, A., Nielsen, M.S., Denker, S.J., Fensbo, C., Ahlfors, U.G., Gravem, A., Baastrup, P.C., Bjerkenstedt, L., Gunby, B. & Wiesel, F.A. (1987) Zuclopenthixol acetate in Viscoleo - a new drug formulation. An open Nordic multicenter study of zuclopenthixol acetate in Viscoleo in patients with acute psychoses including mania and exacerbation of chronic psychoses. *Acta Psychiatrica Scandinavica*, 75, 99-107.
- Baastrup, P.C., Ahlfors, U.G., Berkenstedt, L., Denker, S.J., Fensbo, C., Gravem, A., Pedersen, V., Elgen, K., Brekke, B., Fredsluns-Andersen, K., Lindhohn, H., Lybeck, I., Morawski, R., Nummi, K., Silfverhjelm, H., Vartiainen, H., Wiesel, F.A. & Aarvold, A. (1992) A controlled Nordic multicenter study of zuclopenthixol acetate in oil solution, haloperidol and zuclopenthixol in the treatment of acute psychosis. *Acta Psychiatrica Scandinavica*, 87, 48-58.
- Babon, D. & DeBleeker, E. (1990) Zuclopenthixol acetate and haloperidol in acute psychotic patients - A randomized multicenter study. Proceedings from the symposium "New Strategies in the Treatment of Psychotic Patients", 8th World Congress of Psychiatry, Athens, (13-19 October 1989), *Excerpta Medica*, 1990, 47-59.
- Denker, S.J., Lepp, M. & Malm, U. (1980) Clopenthixol and flupenthixol depot preparations in outpatient schizophrenics. A one year double-blind study of clopenthixol decanoate and flupenthixol palmetate. *Acta Psychiatrica Scandinavica*, 61(Suppl.), 279, 10-28.
- Guy, W. (1976) ECDEU Assessment manual for psychopharmacology: Publication ADM 76-338. Rockville, Md: US Department of Health, Education and Welfare, 217-222.
- Hebenstreit, G.F. (1990) Clinical experience with zuclopenthixol acetate and co-injection of zuclopenthixol acetate and zuclopenthixol decanoate: Proceedings from the symposium "New Strategies in the Treatment of Psychotic Patients", 8th World Congress of Psychiatry, Athens, (13-19 October 1989). *Excerpta Medica*, 1990, 37-48.
- Ivanov, B., Millanover, V., Minov, V., Mevorah, E., Krastev, S., Issiover, K. & Tzafarov, P. (1992) A long term drug trial with zuclopenthixol presented at the XXIII CTNP Congress.
- Korner, A., Pedersen, V. & Bech, P. (1993) A meta analysis of the antipsychotic and anti manic effects of zuclopenthixol acetate. Presented at the 4th World Congress of

JOHN FERNANDES et al.

Psychiatry, Rio de Janeiro, June, 6-12.

Zuclopenthixol acetate in viscoleo in acutely disturbed psychotic patients. *Isr. J. Psychiatry Relat. Sci.*, Vol. 28, No. 2, 60-63.

Lingjaerde, O., Ahlfors, U.G., Bech, P. et al. (1987) The UKU side effect rating scale. *Acta Psychiatrica Scandinavica*, Vol.76, (suppl.), 334.

Wistedt, B., Koskinen, T., Thelander, S., Nerdrum, T., Pedersen, V. & Molbjerg, C. (1991) Zuclopenthixol decanoate and haloperidol decanoate in chronic schizophrenia, A double blind multicenter study. *Acta Psychiatrica Scandinavica*, 84, 14-21.

Matar, A.M., Abdel-Mawgoud, M. & Skov, S. (1990) Zuclopenthixol : a new generation of antipsychotic drugs, an open clinical trial, *Journal of Clinical Psychopharmacology*, 10, 282-286.

Overall, J.E. & Gorham, D.R. (1962) The Brief Psychiatric Rating Scale. *Psychol. Rep.*, 10, 799-812.

World Health Organization (1992) International Classification of Diseases, mental and behavioural disorders, Edn.10, Clinical Descriptions and Diagnostic Guideline (ICD-10, CDDG), Geneva : WHO.

Sclasberg, A. & Barr, F. (1991)

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