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Zuclopenthixol acetate in psychiatric emergencies: looking for evidence from clinical trials

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Abstract

Background: Case series and reviews have suggested the effectiveness of zuclopenthixol acetate in the acute management of disturbed behaviour caused by serious mental illnesses. This review investigates the trial-based evidence for these suggestions. *Methods*: All randomized clinical trials comparing zuclopenthixol acetate to other 'standard' treatments for the acute management of those with serious mental illnesses were identified and, if possible, their results summated. *Results*: Six trials were identified. All had methodological problems and one did not meet the minimal methodological inclusion criteria. The summary data do not demonstrate that zuclopenthixol acetate is better than 'standard care' for altering behaviour, decreasing the need for supplementary medication, avoiding side-effects, or postponing early discharge against medical advice. One trial, however, presented data that suggested an earlier, more intense level of sedation. *Conclusions*: Recommendations of reviews and open studies for the use of zuclopenthixol acetate in preference to 'standard' treatments in the psychiatric emergency are not supported by evidence from randomized controlled trials.

Keywords: Acuphase; Epidemiology; Meta-analysis; Schizophrenia; Systematic review; Thioxanthene; Zuclopenthixol acetate

1. Introduction

In psychiatric emergencies, with acutely disturbed behaviour due to psychotic phenomenology, where patients are in danger of being violent, medication may be required to avoid or to reduce the risk of serious injury (Atakan and Davis, 1997). Baastrup et al. (1993) have suggested that drugs used in these situations should have a rapid onset of action, low frequency of administration, low levels of side effects, no pain at the injection site, and be safe to use.

Originally, clopenthixol was a mixture of two chemical isomers: *cis*(*Z*)- and *trans*(*E*)-clopenthixol. The *cis*(*Z*)-isomer, named zuclopenthixol, is the active form with affinity for both dopamine D_1 and D_2 receptors. This compound is produced in three preparations: zuclopenthixol dihydrochloride (a relatively short-acting preparation), zuclopenthixol decanoate (an intramuscular depot injection that has an effect lasting weeks) and zuclopenthixol acetate (an intramuscular depot injection that acts for 2–3 days). The acetate preparation was synthesized in the mid-1980s and the new formulation for intramuscular use was obtained by dissolving zuclopenthixol acetate in vegetable oil (Baastrup et al., 1993).

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During the last decade, several open clinical studies reported the effectiveness of zuclopenthixol acetate for management of disturbed, psychotically induced, behaviour (Amdisen et al., 1986, 1987; Balant et al., 1989; Chakravarti et al., 1990; Lowert et al., 1989; Predescu et al., 1991; Romain et al., 1996; Schlosberg and Barr, 1991; Tan et al., 1993). The short-acting depot preparation is now used in Australia, Canada, New Zealand, South Africa and the UK, and has a specific product licence for the management of acute exacerbation of serious mental illnesses (British National Formulary, 1997). The use of zuclopenthixol acetate is recommended in both reviews (Atakan and Davis, 1997) and guidelines (Maudsley, 1995). It has also been suggested, although only within a conference poster presentation, that by using reduced doses of zuclopenthixol acetate, patients in the community with acute exacerbation of symptoms will be less likely to be hospitalized (Abdullahi and Gadd, 1993).

A systematic review of relevant randomized controlled trials was carried out in order to investigate the randomized evidence relevant to these claims (Fenton et al., 1999).

2. Methods

2.1. Types of studies

Any randomized trials that compared zuclopenthixol acetate with other neuroleptic drugs for those with psychotic illnesses were sought. A level of 'acute management' was not pre-specified, as it was expected that the use of the intervention, zuclopenthixol acetate, would occur only within the context of a crisis (see Table 1). Participants with dementing illnesses or problems associated with substance misuse were not the focus of this review.

2.2. The search

Electronic searches were undertaken in the Cochrane Schizophrenia Group's Register of Trials (June 1997), The Cochrane Library (Issue 2, 1997) and MEDLINE (SilverPlatter, 01/1966–06/1997). Full details of all searches are published in the maintained version of this review within the Cochrane Library (Fenton et al., 1999). Reference lists of the included papers were also screened. Appeals for unpublished data were made to the research community (Coutinho et al., 1997) and the Medical Information Department of Lundbeck Limited.

2.3. Study selection

Two reviewers (M.F., E.C.) independently inspected citations and acquired full reports that were relevant. Additional quality rating of full reports was undertaken using a validated tool that rates the reporting of randomization (0–2), blinding (0–2) and description of withdrawals (0–1) (Jadad and McQuay, 1993). As a minimum standard, only studies that clearly reported as randomized (score 1 or 2) were included.

2.4. Data collection

Again working independently, the reviewers (M.F., E.C.) extracted data from all selected trials. Attempts were made to contact authors for additional or missing information.

2.5. Data synthesis

Data were entered in RevMan 3.0 and synthesis was undertaken using the MetaView part of this program (Update Software, 1996). Where possible, odds ratios (ORs) and 95% confidence intervals (CI) were estimated for binary data. Where appropriate, ORs were pooled using the Peto method (Peto et al., 1977). Heterogeneity between ORs was investigated by χ^2 test, and a P-value of 0.10 was used for rejecting the null hypothesis of homogeneity. Mean difference was used for continuous variables. In order to avoid applying parametric tests to non-parametric data, the normal distribution of continuous data was evaluated as proposed by Altman and Bland (1996) and skewed data were not summated.

Table 1
Characteristics of the included studies

Study	Method	Participants	Interventions	Outcomes
Chouinard et al., 1991, 1994	Randomized: stratified by sex. No further information. Double-blind: placebos used. Parallel design. Duration: 9 days. Consent mentioned.	Diagnosis: schizophrenia (DSM-III). History: acutely ill. $N=40$. Age: 18–65. Sex: both. Setting: hospital.	(1) Zuclopenthixol acetate i.m.: dose 50–150 mg every 3 days + placebo oral. (2) Haloperidol orally: dose 10–30 mg/day + placebo. Anti-parkinsonian drugs and additional zuclopenthixol acetate (50 mg) and haloperidol (10 mg) as required.	Mental status: BPRS, CGI and clinical interview. Behaviour: NOSIE and NCGI. Sedation (sedation scale). Side effects: ESRS, blood pressure, pulse, ECG, blood tests, physical examination.
France, 1988[a] Ropert et al., 1991	Randomized: no further information. Not double-blind. Parallel design. Duration: 6 days.	Diagnoses: psychosis or mania (ICD9). History: acutely ill or exacerbation of chronic illness. $N=118$. Age: no information. Sex: both. Setting: hospital.	(1) Zuclopenthixol acetate i.m.: dose 100 mg every 2–3 days. (2) Chlorpromazine i.m.: dose 100–300 mg 1–3 times a day, switched to oral when patients were co-operative. No further information.	Mental state: BPRS, BRMS, CGI, and staff. Sedation: no further information. Side effects: UKU, SERS, blood tests.
Nordic, 1993[a] Baastrup, 1993	Randomized: no further information. Not double-blind. Multi-centre. Parallel design. Duration: 6 days.	Diagnoses: psychosis or mania (ICD9). History: acutely ill or exacerbation of chronic illness. $N=169$. Age: 18–65. Sex: both. Setting: hospital.	(1) Zuclopenthixol acetate i.m.: dose 50–200 mg (not less than 24 h interval between injections). 2. Haloperidol i.m.: dose 5–10 mg (maximum of 4 times a day). (3) Zuclopenthixol i.m.: dose 10–20 mg maximum of 4 times a day). Anti-parkinsonian drugs and benzodiazepines allowed. Patients taking i.m. haloperidol or zuclopenthixol were switched to oral treatment when they had become co-operative.	Mental state: BPRS, CGI, BRMS.Sedation according to Lingjaerde et al (1987).Side effects: UKU, SERS, blood tests.
South Africa, 1996[a] Uys and Berk, 1996	Randomized: no further information. Double-blind: stated, but unlikely as no oral placebo in intervention group 1. Evaluation of outcome blind. Parallel design. Duration 28 days. Consent mentioned.	Diagnoses: psychosis or mania (ICD9). History: acutely ill or exacerbation of chronic illness. $N=42$. Age: 18–65. Sex: male. Setting: hospital.	(1) Zuclopenthixol acetate i.m.: dose 150 mg every 3 days. (2) Clothiapine i.m. or oral: dose 80–160 mg a day. Anti-parkinsonian drugs, lithium and benzodiazepines allowed.	Mental state: BPRS, CGI, BRMS. Sedation: Likehart Scale. Side effects: UKU, SERS.
South Africa, 1997 Brooks et al., 1998	Randomized: no further information. Double-blind: stated, but unlikely as no oral placebo in intervention group 1; evaluation of outcome blind. Duration: 28 days (data from trial only used from first 6 days results). Consent mentioned.	Diagnoses: schizophrenia, schizophreniform disorder, substance-induced psychotic disorder (not included in this review). History: acutely ill or exacerbation of chronic illness. $N=44$. Age: 18–65. Sex: both. Setting: hospital.	(1) Zuclopenthixol acetate i.m.: initial dose of 150 mg and then oral zuclopenthixol 25 mg a day. (2) Haloperidol i.m.: dose 10 mg and then oral haloperidol 10 mg a day. Anti-parkinsonian drugs and benzodiazepines allowed.	Mental status: BPRS, CGI, SAS. Sedation: Likehart scale. Side effects: no further information.

[a] Studies with methodological problems.

3. Results

3.1. The search

Searching MEDLINE for trials of zuclopenthixol for those with serious mental illnesses identified 357 citations. Most of these were not trials, and only two were studies that could be included in the final review (Chouinard et al., 1991; Baastrup et al., 1993). Searching the Cochrane Library and the Cochrane Schizophrenia Groups Register identified 44 citations to randomized or controlled clinical trials. The same two studies and a conference proceeding describing another relevant study (Uys and Berk, 1996) were identified in these 44 citations. Contacting the author of the conference proceeding (Dr. M. Berk, University of Witwatersrand, Republic of South Africa) resulted in identification of an additional trial (Brook et al., 1997), and Lundbeck Limited provided one more study (Ropert et al., 1988).

One final trial (Bourdouxhe et al., 1987; Bobon and De Bleeker, 1989a,b) was identified, but excluded as the process of randomization was clearly reported in the study as having been violated.

3.2. The studies

Table 1 presents a summary of included studies. All trials were randomized, but none made clear the process by which allocation to groups was undertaken. Only Chouinard et al. (1991) used double-blind evaluation of outcomes. Three studies actively excluded people from analysis because of "protocol non-compliance" (Ropert et al., 1988, 2%; Baastrup et al., 1993, 12% and Uys and Berk, 1996, 10%). Further inquiry revealed that "protocol non-compliance" was that these people had received additional medication but no information is available regarding to which group to these individuals had been originally allocated. Additional post-randomization withdrawals were described more clearly.

Studies tended to present results by graphical display, making data extraction impossible. It was also common to use *P*-values as measure of association between intervention and outcomes, instead of showing the strength of the association. Moreover, it was not possible to extract data from imprecise *P*-values such as $P<0.05$ or $P>0.05$.

All studies were undertaken in an inpatient setting. Three were of 6 days duration, one, 9 days and Brook et al. (1997), 28 days. They included people from 18 to 65 years old, with acute psychoses, mostly schizophrenia. All participants in the included studies were not only acutely ill, but also exhibited considerable behavioural disturbance. Brook et al. (1997) largely focused on those with drug-induced psychoses, but it was possible to extract some data relating to those with schizophrenia.

3.3. Behaviour and mental state symptoms

Data relating to behaviour changes (Nurses Observation Scale for Inpatient Evaluation scores, Honingfeld and Klett, 1965) were presented in only one study (Chouinard et al., 1991) and there was no difference between zuclopenthixol acetate (mean 177, S.D. 9, $N=20$) and oral haloperidol (mean 182, S.D. 9, $N=20$, $P=0.1$). The number of people absconding or refusing to continue in the study was reported in two studies, and did not differ between groups (pooled OR 0.71, CI 0.23–2.18) (Fig. 1). All studies reported some improvement in mental state scores [Brief Psychiatric Rating Scale — BPRS Overall and Gorham, 1962); Global Clinical Impression — CGI (Guy, 1976); Bech–Rafaelsen Mania Scale — BRMS (Bech et al., 1979)], but none found statistically significant differences between zuclopenthixol acetate and 'standard treatment'. All studies, with the exception of Chouinard et al. (1991), presented these data in graphs, so no pooled measure could be calculated.

Binary data for 'no improvement' were provided in two studies. Pooled data shows no difference in the zuclopenthixol acetate and 'standard care' group (OR 0.84, CI 0.34–2.05) (Fig. 1).

3.4. Sedation

Most studies used different instruments to evaluate sedation, and findings were not consistent. Chouinard et al. (1991) found that more people

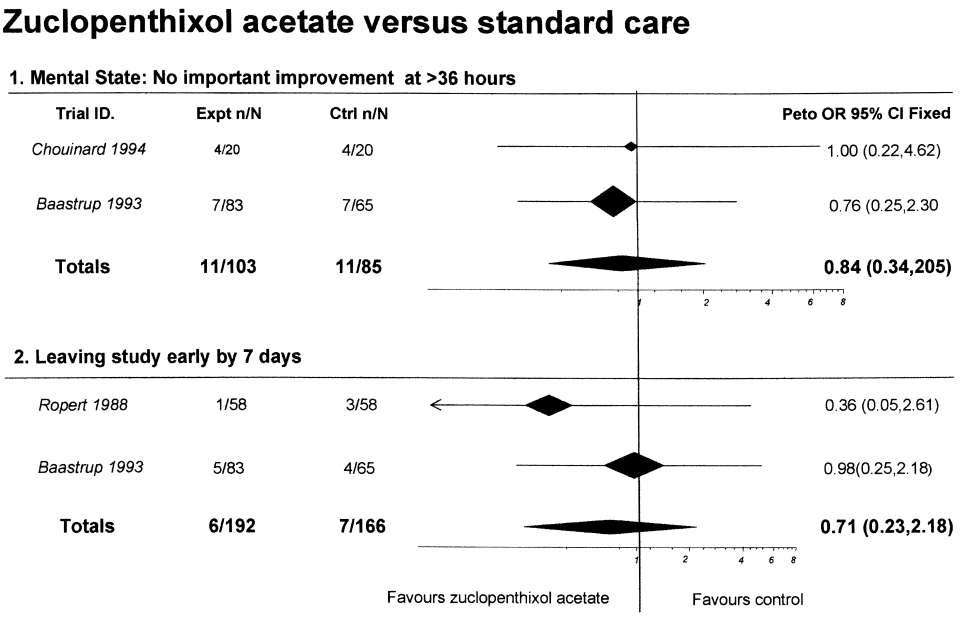

Fig. 1. Zuclopenthixik acetate versus standard care.

receiving zuclopenthixol acetate were sedated at 4 h (OR 0.18, CI 0.04–0.93) and at 8 h (OR 0.25, CI 0.06–1.07) when compared with those allocated to haloperidol. Ropert et al. (1988) also reported more sedation for those on zuclopenthixol acetate, but no numerical data were presented. Baastrup et al. (1993) and Uys and Berk (1996) stated that they found no difference between zuclopenthixol acetate and other 'standard' neuroleptic drugs, but, again, no numerical data were presented. It was impossible to extract data from Brook et al. (1997) for only those with schizophrenia.

3.5. Side effects

For the outcome of 'Use of anti-parkinsonian drugs', it was possible to obtain pooled measures. The analysis, however, suggested that the patterns of use of those drugs were not homogeneous ($\chi^2=7.61$, 1d.f., $P=0.006$). Uys and Berk (1996) showed how people receiving zuclopenthixol acetate were more likely to receive anti-parkinsonian drugs than those receiving clothiapine (OR 6.40, CI 1.5–26.8). When only homogeneous studies were pooled (Baastrup et al., 1993, Chouinard et al., 1991) there was no difference between zuclopenthixol acetate and either haloperidol or zuclopenthixol dihydrochloride for this particular outcome (OR 0.70, CI 0.36–1.34). Specific side effects, such as dystonia, dyskinesia, dry mouth, blurred vision and dizziness were inconsistently reported, limited data showed no evidence of differences between zuclopenthixol acetate, and other 'standard' care.

4. Discussion

The enthusiasm of open clinical studies regarding the 'effectiveness' of zuclopenthixol acetate for those with acute psychotic disturbance is in contrast with the paucity of evidence from a few randomized trials. Moreover, the randomized-controlled trials have important methodological flaws and their findings are poorly reported.

This review did not find any suggestion that zuclopenthixol acetate is more effective than 'standard' care in controlling aggressive/disorganized behaviour or acute psychotic symptoms. Recommendations on the use of zuclopenthixol acetate in preference to 'standard' and 'non-standard' treatments for the management of psychiatric

emergencies have, at present, to be viewed with caution.

Of course, lack of evidence of effectiveness is not the same as evidence of lack of effectiveness. Zuclopenthixol acetate may well be a useful preparation for use in the psychiatric emergency; it is just that these studies have not been able to show this or have presented results in a way that rendered the data useless. For example, there are no data relating directly to tranquillization, but three studies suggest that patients allocated to zuclopenthixol acetate had more intense and earlier sedation than those given other drugs. Only one out of these studies, however, reported numerical data relating to this (Chouinard et al., 1991), and so much valuable information was lost.

No conclusion can be drawn as regards the differences for side effects between zuclopenthixol acetate versus 'standard' neuroleptics. The fact that Uys and Berk (1996) used more anti-Parkinsonian drugs for those taking zuclopenthixol acetate was to be expected, as clothiapine is a low potency neuroleptic with less anti-cholinergic properties than zuclopenthixol.

This review made clear the need for good-quality controlled clinical trials to address the effectiveness and risk of side effects of zuclopenthixol acetate for those with acute and dangerous psychotic behavioural disturbances.

5. Recommendations for future studies

The reviewers recognize that the psychiatric emergency is a uniquely difficult research environment. Nevertheless, adherence to a good-quality pragmatic, trial protocol could avoid many of the problems seen in the studies included and excluded from this paper.

In the included studies, there were no descriptions of how the trialists undertook power calculations and on what assumptions these calculations were based. Using data from the outcome of 'no important improvement at 36 h' (Fig. 1), with only a 3% difference between the groups, over 4000 would be needed in an appropriately powered two-arm study (α 0.05, β 0.85). For other outcomes such as 'renewed aggression', the numbers needed may be considerably smaller. The reviews also recognize that it is rare for schizophrenia trials to be able to record outcomes such as 'harm to self or others'. In a trial of zuclopenthixol acetate for those with gross behavioural disinhibition, however, where such an outcome would be relatively common, it would seem possible to expect to see differences between groups, if one really existed, with much smaller group sizes. However, despite the randomization of 446 people (includes the excluded study) the information in this meta-analysis cannot even provide data on which to base a power calculation for this important outcome.

The choice of comparison intervention could also be a debatable point and, although, ideally, it may be desirable to see zuclopenthixol acetate pitted against placebo it is probably impossible, unethical and dangerous to do this. The use of the 'standard' care, as long as this was not zuclopenthixol acetate, would seem the pragmatic solution. This would allow minimal disruption of normal practice and the use of interventions that staff were familiar with. The use of a 'standard care' comparison group would, of course, lead to zuclopenthixol acetate being compared to several other drugs, perhaps within the same trial. If, however, this preparation is the choice for management of the acutely disturbed person in the psychiatric emergency (Atakan and Davis, 1997), then zuclopenthixol acetate should be able to prove itself better than the many other drugs currently in use.

For many of the outcomes of interest in this important question, blinding may not be so important. A non-blind, pragmatic, protocol for a well-randomized trial, with 'harder' outcomes such as 'renewed aggression' or 'harm to self', would decrease the difficulty of a study such as this, and increase the utility and generalizability of the findings.

The quality of reporting in the trials in this review underline the need for the CONSORT statement (Begg et al., 1996). As well as clear description of the means of randomization, an intention-to-treat analysis and description of the group origin of those withdrawing is also important. Simple measures in the presentation of data would make studies much more informative.

Binary outcomes should be reported, as often they are easier to interpret clinically. Authors should present measures of association between intervention and outcome (relative risks, odds-ratios) and the precision of these data in the form of confidence intervals. If *P*-values are used, then the exact value should be reported.

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