Chlorpromazine for psychosis induced aggression or agitation (Protocol)

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Chlorpromazine for psychosis induced aggression or agitation

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To examine whether chlorpromazine oral or intramuscular is an effective treatment for psychosis-induced agitation/aggression.

BACKGROUND

Description of the condition

Agitated or violent behaviour constitutes 10% of all emergency psychiatric treatment (Tardiff 1982). Overall, the prevalence of violence in people who have schizophrenia, major depression or manic/bipolar disorder is about 11 to 13%. An even higher percentage of people with alcoholism (25%) or substance misuse (35%) have, at some stage, presented with violence or aggression. Even when additional factors such as alcohol and drug use are taken into account, psychotic symptoms such as delusions or hallucinations are significantly and strongly associated with aggressive and violent behaviour (Swanson 1990).

Description of the intervention

In 1950, the discovery of the antipsychotic properties of chlorpromazine was termed as a “psychopharmacological revolution” for the practice of modern psychiatry (Lopez-Munez 2005; Turner 2007). Although the newer generation antipsychotics have, to a certain extent, taken its place, chlorpromazine is still in wide use. We found one survey of clinicians’ preferences for drug management of the acutely aggressive situation and chlorpromazine was the favoured drug of clinicians in Oxford, UK in 1994 (Cunnane 1994). UK guidelines do not recommend the use of chlorpromazine for rapid tranquillisation because it is a local irritant if given intramuscularly and, based on cohort and case control studies, there is said to be a risk of cardiovascular complications, hypotension, especially in the doses required for rapid tranquillisation (NICE 2005). Despite this, chlorpromazine is still widely used because of its marked sedating effect and its ability to treat violent patients without causing stupor (BNF 2008). In many situations chlorpromazine may be the only choice available. Chlorpromazine remains one of three antipsychotic drugs on the World Health Organisation’s Essential Medicine list. This list comprises of medication for the basic health care system, all of which must be designated safe, effective and cost effective for priority conditions (WHO 2007).
How the intervention might work

The discovery of neuroleptic drugs in 1952 provided a new strategy for seeking a biological basis of schizophrenia (Seaman 2004). Chlorpromazine is in the phenothiazine family of compounds and may work by its ability to block dopaminergic receptor in limbic forebrain. Besides this action it also blocks to different degrees adrenergic, dopamine reuptake, histaminic, muscarinic and serotonergic receptors (Kalyana 2006). It may be the antihistaminic effects that cause the sedation associated with use of chlorpromazine.

Chlorpromazine is mainly indicated for schizophrenia or other psychosis, mania, short-term adjunctive management of severe anxiety, psychomotor agitation, excitement and violent or dangerously impulsive behaviour (BNF 2008). Time to peak plasma levels is approximately three hours (oral) (Bazier 2007), either 15 to 30 minutes (Keltner 2001) or one to four hours (I/M) (Bazier 2007) (texts differ), and either ten minutes (Keltner 2001) or two to four hours (I/V) (Bazier 2007) (texts differ). Chlorpromazine and its metabolites are mainly excreted from body in urine with elimination half-life is approximately 16 to 30 hours (Kalyana 2006).

Why it is important to do this review

Mental health problems impose a significant burden in developing countries (Shah 2000). As about 1% of any population suffers from schizophrenia (Sartorius 1972) and around 80% of the world live in developing countries (CIA 2008), most care of people with serious mental illnesses such as schizophrenia must take place in these low and middle income situations. There is no evidence that the prevalence of psychiatric emergencies differ across the globe and it seems reasonable to assume that most episodes of severe aggression and agitation in people with severe mental health problems will be taking place in the low and middle income countries. In many of these countries aggressive episodes are not taken place in these low and middle income countries. In many of these countries expensive antipsychotic drugs may be available, but they are generally not affordable (WPA 2003). Even in high income countries older and expensive medications, such as chlorpromazine, may be favoured (Cunnane 1994). Even in 2003, chlorpromazine was the most frequently prescribed of the first generation antipsychotic drug in the UK at a time when the older group of antipsychotics accounted for 44% of all antipsychotic prescriptions (NHS 2008). We, however, know of no systematic reviews of the use of this old drug in the emergency situation.}

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised control trials. We excluded quasi-randomised trials, such as those where allocation is undertaken on surname. If a trial was described as double blind, but it was implied it had been randomised, we included these trials in a sensitivity analysis.

Randomised cross-over studies will be eligible but only data up to the point of first cross-over because of the instability of the problem behaviours and the likely carryover effects of all treatments.

Types of participants

People currently within an aggressive episode thought to be due to psychotic illness. Should studies also have involved people with other diagnoses, such as drug or alcohol intoxication, organic problems including dementia, non-psychotic mental illnesses or learning disabilities, we included these as long as the proportion of the other groups do not exceed that for psychotic people.

Types of interventions

1. Chlorpromazine alone: given orally or intramuscular any dose compared with:
   a. Other antipsychotic given orally or intramuscularly: any dose
   b. Benzodiazepine alone given orally or intramuscularly: any dose
   c. Anticonvulsive alone given orally or intramuscularly: any dose
   d. Placebo or no intervention
2. Chlorpromazine: in combination with other drugs compared with:
   a. Other intervention, or placebo or no intervention

Types of outcome measures

Primary outcomes

Not tranquil or asleep by up to 30 minutes (IM) or 60 minutes (orally)
Secondary outcomes

1. Tranquillisation or asleep
   1.1 Not tranquil
   1.2 Not asleep
   1.3 Time to tranquillisation / sleep
   1.4 Time to tranquillisation
   1.5 Time to sleep
2. Death
3. Specific behaviours
   3.1 Self-harm, including suicide
   3.2 Injury to others
   3.3 Aggression
      3.3.1 Another episode of aggression by 24 hours
      3.3.2 No clinically important change in aggression
      3.3.3 No change in aggression
      3.3.4 Average endpoint aggression score
      3.3.5 Average change in aggression scores
4. Global outcomes
   4.1 No overall improvement
   4.2 Use of additional medication
   4.3 Use of restraints/seclusion
   4.4 Relapse - as defined by each study
   4.5 Recurrence of violent incidents
   4.6 Needing extra visits from the doctor
   4.7 Refusing oral medication
   4.8 Not accepting treatment
   4.9 Average endpoint acceptance score
   4.10 Average change in acceptance scores
5. Service outcomes
   5.1 Duration of hospital stay
   5.2 Re-admission
   5.3 No clinically important engagement with services
   5.4 No engagement with services
   5.5 Average endpoint engagement score
   5.6 Average change in engagement scores
6. Mental state
   6.1 No clinically important change in general mental state
   6.2 No change in general mental state
   6.3 Average endpoint general mental state score
   6.4 Average change in general mental state scores
7. Adverse effects
   7.1 Clinically important general adverse effects
   7.2 Any general adverse effects
   7.3 Any serious, specific adverse effects
   7.4 Average endpoint general adverse effect score
   7.5 Average change in general adverse effect scores
   7.6 No clinically important change in specific adverse effects
   7.7 No change in specific adverse effects
   7.8 Average endpoint specific adverse effects
   7.9 Average change in specific adverse effects
8. Leaving the study early
   8.1 For specific reasons
   8.2 For general reasons
9. Satisfaction with treatment
   9.1 Recipient of treatment not satisfied with treatment
   9.2 Recipient of treatment average satisfaction score
   9.3 Recipient of treatment average change in satisfaction scores
   9.4 Informal treatment provider not satisfied with treatment
   9.5 Informal treatment providers’ average satisfaction score
   9.6 Informal treatment providers’ average change in satisfaction scores
   9.7 Professional providers not satisfied with treatment
   9.8 Professional providers’ average satisfaction score
   9.9 Professional providers’ average change in satisfaction scores
10. Acceptance of treatment
    10.1 Not accepting treatment
    10.2 Average endpoint acceptance score
    10.3 Average change in acceptance scores
11. Quality of life
    11.1 No clinically important change in quality of life
    11.2 Not any change in quality of life
    11.3 Average endpoint quality of life score
    11.4 Average change in quality of life scores
    11.5 No clinically important change in specific aspects of quality of life
    11.6 No change in specific aspects of quality of life
    11.7 Average endpoint specific aspects of quality of life
    11.8 Average change in specific aspects of quality of life
12. Economic outcomes
    12.1 Direct costs
    12.2 Indirect costs

All outcomes are grouped by time: by 30 minutes, up to two hours, up to four hours, up to 24 hours and finally over 24 hours.

Electronic methods for identification of studies

Electronic searches

We searched the Cochrane Schizophrenia Group Trials Register (June 2008) using the phrase:

"("anadep" or "chlora" or "chlorprom" or "chlor p-z" or "chromeda" or "cpz" or "elmarine" or "esmind" or "fenactil" or "hibanil" or "hibernal" or "klorazin" or "klorpro" or "largactil" or..."
Searching other resources
We also searched reference lists of included and excluded studies for additional relevant trials.

Data collection and analysis

Selection of studies
Authors MG and UA independently inspected citations identified from the search. We identified potentially relevant reports and ordered full papers for reassessment. Where difficulties or disputes arose we asked author CEA for help and if it was impossible to decide, those full papers were ordered for assessment. This process was repeated for the full papers. If it was impossible to resolve disagreements these studies were added to those awaiting assessment and the authors of the papers contacted for clarification.

Data extraction and management
1. Extraction
Authors MG and UA independently extracted data from included studies. Again, any disagreement was discussed, decisions documented and, if necessary, authors of studies were contacted for clarification. With remaining problems CEA helped clarify issues and those final decisions were documented.
2. Management
Data were extracted onto standard, simple forms.
3. Scale-derived data
We included continuous data from rating scales only if the measuring instrument had been described in a peer-reviewed journal (Marshall 2000) and the instrument is either a self-report or completed by an independent rater or relative (not the therapist).

Assessment of risk of bias in included studies
Again working independently, MG and UA assessed risk of bias using the tool described in the Cochrane Collaboration Handbook (Higgins 2005). This tool encourages consideration of how the sequence was generated, how allocation was concealed, the integrity of blinding at outcome, the completeness of outcome data, selective reporting and other biases. We would not have included studies where sequence generation was at high risk of bias or where allocation was clearly not concealed.

If disputes arose as to which category a trial has to be allocated, again, resolution was made by discussion, after working with the third reviewer (CEA).

Measures of treatment effect
1. Binary data
For binary outcomes we calculated a standard estimation of the fixed-effect risk ratio (RR) and its 95% confidence interval (CI). For statistically significant results we calculated the number needed to treat/harm statistic (NNT/H), and its 95% confidence interval (CI) using Visual Rx (http://www.nntonline.net/) taking account of the event rate in the control group.
2. Continuous data
2.1 Summary statistic
For continuous outcomes we estimated a fixed-effect weighted mean difference (WMD) between groups. We did not calculate effect size measures.
2.2 Endpoint versus change data
We preferred to use scale endpoint data, which typically cannot have negative values and is easier to interpret from a clinical point of view. Change data are often not ordinal and are very problematic to interpret. If endpoint data were unavailable, we used change data.
2.3 Skewed data
Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we aim to apply the following standards to all data before inclusion: (a) standard deviations and means are reported in the paper or obtainable from the authors; (b) when a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution, (Altman 1996)); (c) if a scale starts from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above will be modified to take the scale starting point into account. In these cases skew is present if 2SD>(S−S min), where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied. When continuous data are presented on a scale which includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. Skewed data from studies of less than 200 participants were entered in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at means if the sample size is large and were entered into syntheses.

Unit of analysis issues
1. Cluster trials
Studies increasingly employ ‘cluster randomisation’ (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intraclass correlation in clustered studies, leading to a ‘unit of analysis’ error (Divine 1992) whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997, Gulliford 1999).

Where clustering is not accounted for in primary studies, we presented data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intraclass correlation co-efficient of their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering had been incorporated into the analysis of primary studies, we present these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a ‘design effect’. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation co-efficient (ICC) [Design effect = 1+(m-1)ICC] (Donner 2002). If the ICC was not reported it was assumed to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed taking into account intraclass correlation co-efficient and relevant data documented in the report, synthesis with other studies would have been possible using the generic inverse variance technique.

2. Cross-over trials
A major concern of cross-over trials is the carryover effect. It occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in schizophrenia, we will only use data of the first phase of cross-over studies.

3. Studies with multiple treatment groups
Where a study involved more than two treatment arms, if relevant, the additional treatment arms were presented in comparisons. Where the additional treatment arms were not relevant, these data were not reproduced.

**Dealing with missing data**

1. Overall loss of credibility
   At some degree of loss of follow up data must lose credibility. We are forced to make a judgment where this is for the very short-term trials likely to be included in this review. Should more than 40% of data be unaccounted for by 24 hours we did not reproduce these data or use them within analyses.

2. Binary
   In the case where attrition for a binary outcome is between 0 and 40% and outcomes of these people are described, we included these data as reported. Where these data were not clearly described, we assumed the worst primary outcome, and rates of adverse effects similar to those who did continue to have their data recorded.

3. Continuous
   In the case where attrition for a continuous outcome is between 0 and 40% and completer-only data were reported, we have reproduced these.

**Assessment of heterogeneity**

1. Clinical heterogeneity
   We considered all included studies without any comparison to judge clinical heterogeneity.

2. Statistical
   2.1 Visual inspection
   We visually inspected graphs to investigate the possibility of statistical heterogeneity.
   2.2 Employing the I-squared statistic
   This provided an estimate of the percentage of inconsistency thought to be due to chance. I-squared estimate greater than or equal to 50% was interpreted as evidence of high levels of heterogeneity (Higgins 2002).

**Assessment of reporting biases**

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in section 10.1 of the Cochrane Handbook (Higgins 2005). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were ten or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible, we sought statistical advice in their interpretation.

**Data synthesis**

Where possible we employed a fixed-effect model for analyses. We understand that there is no closed argument for preference for use of fixed or random-effect models. The random-effect method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This does seem true to us, however, random-effect does put added weight onto the smaller of the studies - those trials that are most vulnerable to bias. For this reason we favour using fixed-effect models employing random-effect only when investigating heterogeneity.

**Subgroup analysis and investigation of heterogeneity**

If data are clearly heterogeneous we checked that data are correctly extracted and entered and that we had made no unit-of-analysis...
errors. If the high levels of heterogeneity remained we did not undertake a meta-analysis at this point for if there is considerable variation in results, and particularly if there is inconsistency in the direction of effect, it may be misleading to quote an average value for the intervention effect. We would have wanted to explore heterogeneity. We pre-specify no characteristics of studies that may be associated with heterogeneity except quality of trial method. If no clear association could be shown by sorting studies by quality of methods a random-effect meta-analysis was performed. Should another characteristic of the studies be highlighted by the investigation of heterogeneity, perhaps some clinical heterogeneity not hitherto predicted but plausible causes of heterogeneity, these post-hoc reasons will be discussed and the data analysed and presented. However, should the heterogeneity be substantially unaffected by use of random-effect meta-analysis and no other reasons for the heterogeneity be clear, the final data were presented without a meta-analysis.

Sensitivity analysis

If necessary, we analysed the effect of including studies with high attrition rates in a sensitivity analysis. We aimed to include trials in a sensitivity analysis if they are described as 'double-blind' but only implied randomisation. If we found no substantive differences within primary outcome when these high attrition and 'implied randomisation' studies were added to the overall results, we included them in the final analysis. However, if there was a substantive difference we only used clearly randomised trials and those with attrition lower than 50%.

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BNF 2008

CIA 2008

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Divine 1992

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Egger 1997

Elbourne 2002

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WHO 2007

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* Indicates the major publication for the study

HISTORY

CONTRIBUTIONS OF AUTHORS
Muhammad Gul - took lead in review and helped write protocol.
Uzair Ahmed - took lead in review and helped write protocol.
Clive E Adams - helped write protocol.
DECLARATIONS OF INTEREST

None known.

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- No sources of support supplied