Conclusions

Olanzapine and haloperidol plus promethazine were effective in controlling aggressive or violent behaviour as a result of mental illness by producing rapid tranquillisation and sedation. Patients given the combined drug required less medical attention or additional drugs within four hours of intervention than those given olanzepine.

We thank the doctors and nurses who helped assess the clinical outcomes during the trial and the staff of the department of psychiatry at the Christian Medical College. Members of the Rapid Tranquillisation-India II Collaborative Group were Joncy Philip, Ravi Nesan, Jaishankar, Stalin Selvaraj, Rajesh Gopalakrishnan, Naveen Thomas, Titus Samson Premkumar, Susan Jeyabalan, Thangadurai P, Basanth Kumar, Anto Praveen Rajkumar, Satyaraj, Helen Charles, Sheeba Chandy, Devakumari K P, Karunakaran K P, P Raja RSK, Kasthuri Narasimhan, Parameswari R, Beulah Sam, Bhavani, Geetha R, Ida Priscilla.

Contributors: See bmj.com.
Funding: This trial was funded by an intramural grant from the fluid research fund (22F484) of the Christian Medical College, Vellore. The study drugs were purchased from commercial sources, were supplied by the hospital pharmacy services, and were provided free of cost to participants.
Competing interests: None declared.
Ethical approval: This study was approved by the institutional review board of the Christian Medical College, Vellore.

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Accepted: 1 August 2007

Rapid tranquillisation in psychiatric emergency settings in Brazil: pragmatic randomised controlled trial of intramuscular haloperidol versus intramuscular haloperidol plus promethazine

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BMJ 2007;335:869-72
doi:10.1136/bmj.39339.448819.AE

This article is an abridged version of a paper that was published on bmj.com on 22 October 2007. Cite this version as: *BMJ* 22 October 2007, doi: 10.1136/bmj.39339.448819.AE (abridged text, in print: *BMJ* 2007;335: 869-72).

ABSTRACT

Objective To determine whether haloperidol alone results in swifter and safer tranquillisation and sedation than haloperidol plus promethazine.
Design Pragmatic randomised open trial (January-July 2004).
Setting Psychiatric emergency room, Rio de Janeiro, Brazil.
Participants 316 patients who needed urgent intramuscular sedation because of agitation, dangerous behaviour, or both.
Interventions Open treatment with intramuscular haloperidol 5-10 mg or intramuscular haloperidol 5-10 mg plus intramuscular promethazine up to 50 mg; doses were at the discretion of the prescribing clinician.
Main outcome measures The primary outcome was proportion tranquil or asleep by 20 minutes. Secondary outcomes were asleep by 20 minutes; tranquil or asleep by 40, 60, and 120 minutes; physically restrained or given additional drugs within 2 hours; severe adverse events; another episode of agitation or aggression; additional visit from the doctor during the subsequent 24 hours; overall antipsychotic load in the first 24 hours; and still in hospital after 2 weeks.
Results Primary outcome data were available for 311 (98.4%) people, 77% of whom were thought to have a psychotic illness. Patients allocated haloperidol plus promethazine were more likely to be tranquil or asleep by 20 minutes than those who received intramuscular haloperidol alone (relative risk 1.30, 95% confidence interval 1.10 to 1.55; number needed to treat 6, 95% confidence interval 4 to 16; P=0.002). No differences were found after 20 minutes. However, 10 cases of acute dystonia occurred, all in the haloperidol alone group.
Conclusions Haloperidol plus promethazine is a better option than haloperidol alone in terms of speed of onset of action and safety. Enough data are now available to change guidelines that continue to recommend treatments that leave people exposed to longer periods of aggression than necessary and patients vulnerable to distressing and unsafe adverse effects.
Trial registration Current Controlled Trials ISRCTN83261243.

INTRODUCTION

For control of agitated and violent behaviour in clinical settings, guidelines in the United States and United Kingdom recommend the use of intramuscular haloperidol, lorazepam, both combined, or olanzapine.[1 2] However, little information on comparative effectiveness or safety is available. Haloperidol alone, or the combination of haloperidol with lorazepam, is widely used.[3-5] In Brazil and India, many people consider it standard practice to add promethazine to haloperidol.[6] Promethazine is a sedative antihistamine with anticholinergic properties.

To date, although four randomised trials have compared lorazepam with haloperidol, only two report relevant data (relative risk not sedated by four hours 1.00, 95% confidence interval 0.44 to 2.23).[7] One trial compared lorazepam with haloperidol plus promethazine (relative risk not tranquil/asleep by 30 minutes 0.26, 0.10 to 0.68).[8] The combination of lorazepam plus haloperidol has been compared with haloperidol alone in only one randomised trial (relative risk needing additional injection by four hours 0.95, 0.79 to 1.15).[7] Olanzapine has been compared with haloperidol twice (relative risk no response by two hours 1.00, 0.73 to 1.38) and with lorazepam twice (relative risk no response by two hours 0.92, 0.66 to 1.30).[9] Finally, midazolam has been compared with the haloperidol-promethazine mix once (relative risk not tranquil/asleep by 30 minutes 2.9, 1.75 to 4.8), but respiratory depression is a particular problem with this benzodiazepine.[10]

Our two TREC-I trials are the only randomised trials that used haloperidol plus promethazine as the control.[6 11] This combination treatment was both effective and safe in comparison with midazolam or lorazepam but has never been compared with intramuscular haloperidol alone. This study aimed to determine whether haloperidol alone has any advantage or disadvantage compared with haloperidol plus promethazine for managing agitated/aggressive patients presenting to a psychiatric emergency room.

Table 1 | Main results. Values are numbers (percentages) unless stated otherwise

	Haloperidol plus promethazine group (n=160)	Haloperidol group (n=156)	Relative risk (95% CI)	Difference in risk (95% CI)
By 20 minutes				
Tranquil/asleep (primary outcome)	115 (72)	86 (55)	1.30 (1.10 to 1.55)	16.7 (6.3 to 27.2)
Asleep	31 (19)	13 (8)	2.33 (1.26 to 4.27)	11.0 (3.5 to 18.5)
Unknown	3 (2)	2 (1)		
By 40 minutes				
Tranquil/asleep	129 (81)	118 (76)	1.07 (0.95 to 1.20)	5.0 (−4.1 to 14.1)
Asleep	57 (36)	54 (35)	1.03 (0.76 to 1.39)	1.0 (−9.5 to 11.5)
Unknown	3 (2)	2 (1)		
By 60 minutes				
Tranquil/asleep	139 (87)	127 (81)	1.07 (0.97 to 1.17)	5.5 (−2.6 to 13.5)
Asleep	77 (48)	77 (49)	0.98 (0.78 to 1.22)	−1.2 (−12.3 to 9.8)
Unknown	3 (2)	2 (1)		
By 120 minutes				
Tranquil/asleep	146 (91)	138 (89)	1.03 (0.96 to 1.11)	2.8 (−3.9 to 9.4)
Asleep	97 (61)	94 (60)	1.01 (0.84 to 1.20)	0.4 (−10.4 to 11.2)
No additional tranquillising drugs	152 (95)	143 (92)	1.04 (0.98 to 1.10)	3.3 (−2.2 to 8.8)
Restraints not needed	122 (76)	111 (71)	1.07 (0.94 to 1.22)	5.1 (−4.6 to 14.8)
Unknown	3 (2)	2 (1)		
Within 24 hours				
No other episode of aggression	129 (81)	124 (80)	1.01 (0.91 to 1.13)	1.1 (−7.7 to 10.0)
Unknown	6 (4)	12 (8)		
Doctor not called to see patient	123 (77)	102 (65)	1.18 (1.02 to 1.36)	11.5 (1.7 to 21.4)
Unknown	7 (4)	11 (7)		
Accept oral drugs*	132 (84)	129 (84)	0.97 (0.88 to 1.06)	−3.0 (−10.9 to 4.9)
Unknown	11 (7)	11 (7)		
Mean (SD) chlorpromazine equivalents (mg)	245 (194)	234 (182)	Mann-Whitney U=11885.500; P=0.46	
Serious adverse effect†	1 (1)	11 (7)	0.09 (0.01 to 0.68)	−6.4 (−10.6 to −2.2)
By 2 weeks				
Discharged	62 (39)	73 (47)	0.83 (0.64 to 1.07)	−8.0 (−18.9 to 2.8)
Unknown	3 (2)	3 (2)		

*Two patients in each group excluded as not prescribed oral drugs.
†Patients with unknown outcome excluded from analysis.

METHODS

Selection of participants—We did this TREC trial of Rio de Janeiro, Brazil (TREC Rio 2) in a single public psychiatric hospital with a catchment of approximately 1.5 million people. Patients were eligible for the trial if they needed acute intramuscular sedation because of agitation, dangerous behaviour, or both.

Interventions—We compared giving haloperidol alone with the standard treatment of haloperidol plus intramuscular promethazine. Doses of the drugs were at the doctor's discretion. Interventions were supplied as either two ampoules of haloperidol 5 mg or two ampoules of haloperidol 5 mg plus one of promethazine 50 mg.

Procedures—Allocation to treatment group was random. The attending doctor recorded the severity and cause of the episode before treatment allocation. An attending nurse assessed patients every 20 minutes for the first hour after administration of treatment. We checked the severity of episode at trial entry for a randomly selected sample of 42 (13%) patients and the accuracy of assessment of primary outcome in another randomly selected sample of 68 (22%) patients, using a rater who was blind to treatment allocation.

Outcomes— The primary outcome was "tranquillisation or asleep by 20 minutes." Patients were considered tranquillised when they were neither agitated nor restless and not displaying threatening verbal behaviour or physical aggression. Secondary outcomes were: asleep by 20 minutes; tranquil or asleep by 40, 60, and 120 minutes; physically restrained or given additional drugs within two hours; severe adverse events; another episode of agitation/aggression; needing additional visits from the doctor during the subsequent 24 hours; overall antipsychotic load in the first 24 hours; and still in hospital after two weeks.

Statistical analysis—We compared sociodemographic and clinical characteristics between groups at trial entry. For primary and secondary outcomes, we used intention to treat analysis to calculate relative risk, risk difference, and number needed to treat.

RESULTS

Recruitment was from 6 January 2004 to 1 July 2004. During this period, 6433 people attended the emergency room. Of these, 618 presented some degree of violent behaviour and, when collaborating doctors were in attendance 100% (316) were randomised (mean age 40.1 years)—160 to haloperidol plus promethazine and 156 to haloperidol alone. Primary outcome data were available for 311 (98.4%) participants.

Baseline characteristics were similar between the two treatment groups. However, the proportion of men was higher in the haloperidol plus promethazine group. Behavioural disturbance was rated as intense or extreme for 62% of participants. The underlying cause was thought to be psychosis for 77% of people. Agreement for severity of episode was good (weighted κ=0.85, 95% confidence interval 0.73 to 0.98).

Of people allocated haloperidol alone, 29% received 5 mg and the rest 10 mg. Of those allocated haloperidol plus promethazine, half received 5 mg of haloperidol and the rest 10 mg.

Primary outcome

In absolute terms, 17% (95% confidence interval 6% to 27%) more patients were tranquil or asleep after 20 minutes in the haloperidol plus promethazine group than in the intramuscular haloperidol alone group (relative risk 1.30, 95% confidence interval 1.10 to 1.55; number needed to treat 6, 4 to 16; P=0.002) (table 1). Inter-rater agreement on time from injection to tranquillisation or sleep was good (κ=0.83, 0.67 to 0.99). We did two post hoc analyses, controlling for sex and dose of haloperidol. The relative risk for the primary outcome remained stable in both analyses (relative risk controlling for sex 1.29, 1.08 to 1.53; relative risk for those receiving 5 mg haloperidol 1.31, 0.96 to 1.31; relative risk for those receiving 10 mg haloperidol 1.29, 1.05 to 1.59).

Secondary outcomes

The difference for the outcome of tranquil or asleep at 20 minutes was no longer apparent by 40, 60, and 120 minutes (table 1). We found no difference between the interventions for the use of additional tranquillising drugs or use of restraints within the first two hours. For outcomes occurring by 24 hours after injection, we found no differences for another episode of agitation or refusing to take oral medication. Doctors were called more frequently to see patients allocated haloperidol alone than those in the combination treatment group. When patients with acute dystonia were removed from the analysis the difference was no longer significant (n=304; relative risk 1.18, 0.96 to 1.26; P=0.16).

Important adverse effects were reported for 12 people (table 2). Two people had seizures (one haloperidol plus promethazine, one haloperidol alone). Nine people had acute dystonia; all of these had been allocated to haloperidol alone. One person had both of these adverse events (haloperidol alone). We reanalysed these data, controlling for haloperidol dose. The relative risk for any important adverse effect remained almost the same, changing from 0.09 to 0.07 (95% confidence interval 0.01 to 0.75).

DISCUSSION

This trial sought to investigate whether following international guidelines and changing routine care in Brazil from haloperidol plus promethazine to haloperidol alone for managing agitated/aggressive patients

Table 2 | Incidence of important adverse reactions in first 24 hours

Allocated intervention	Type of reaction	Time after administration (hours:minutes)	Treatment*
Haloperidol (10 mg)	Acute dystonia	0:15	Promethazine (50 mg)
Haloperidol (10 mg)	Acute dystonia	0:33	Promethazine (50 mg)
Haloperidol (10 mg)	Acute dystonia	1:20	Promethazine (50 mg)
Haloperidol (10 mg)	Acute dystonia	1:50	Promethazine (50 mg)
Haloperidol (10 mg)	Acute dystonia	15:00	Promethazine (50 mg)
Haloperidol (5 mg)	Acute dystonia	15:30	Promethazine (50 mg)
Haloperidol (10 mg)	Acute dystonia	18:20	Promethazine (50 mg)
Haloperidol (5 mg)	Acute dystonia	20:45	Promethazine (50 mg)
Haloperidol (5 mg)	Acute dystonia	22:50	Diazepam (10 mg) plus promethazine oral (25 mg)
Haloperidol (10 mg)	Acute dystonia plus seizure	0:30	Diazepam (10 mg) plus promethazine (50 mg)
Haloperidol (10 mg)	Seizure	16:55	Diazepam (10 mg)
Haloperidol (5 mg) plus promethazine (25 mg)	Seizure	1:30	Clonazepam oral (2 mg)

*Intramuscular unless stated otherwise.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Rapid tranquillisation of people with aggressive behaviour due to mental illness is sometimes necessary

Guidelines are often influenced by local practice, have limited evidence, and vary in which drugs they recommend

The combination of haloperidol plus promethazine has been shown to be effective and safe in pragmatic trials in Brazil and India

WHAT THIS STUDY ADDS

Around 60% of participants given either drug regimen were tranquillised or sedated within 20 minutes of administration, and 90% by two hours

Haloperidol caused 55% of participants to be tranquil or asleep within 20 minutes, compared with 72% with haloperidol-promethazine

Because of the high incidence (7%) of serious adverse effects, administering intramuscular haloperidol alone for emergency treatment of acutely aggressive mentally ill people is no longer justifiable

presenting to a psychiatric emergency room offered any benefit. We found no evidence of benefit. Haloperidol alone does swiftly tranquillise aggressive psychotic people; it is just not as fast nor as safe as when it is combined with promethazine.

Routine care in Rio de Janeiro is not so different from many situations worldwide as to render the results of this study impossible to generalise. The pragmatic design helped to ensure a complete dataset, and the high reliability of agreement in rating of the primary outcome between blinded and non-blinded raters suggests that observation bias as a result of raters being unblinded was small.

The rate of acute movement disorders of 6.4% (95% confidence interval 3.3% to 11.8%) in the haloperidol alone group in this study is in keeping with estimates from other sources.[7 9 12 13] Guidelines recommend access to anticholinergic drugs if haloperidol is to be used alone,[1 2] but evidence from this and other studies suggests that routine use of a more sedative drug with anticholinergic properties has advantages.[6 11]

Strengths and limitations

This study tested a treatment commonly used in routine care worldwide, recruited large numbers of participants, with nearly complete follow-up, and was not funded by industry. The open evaluation of the treatments could have resulted in the introduction of bias. Allocation was, however, fully concealed and randomisation was successful; intervention doses were monitored for differences that could have resulted from open giving, and no differences were found; and a sample of outcomes were blindly verified with excellent levels of agreement.

Conclusions

Sole use of intramuscular haloperidol leaves people exposed to the dangers of violence for longer than necessary and carries with it the risk of acute dystonia. Haloperidol routinely combined with promethazine is swiftly effective and safe and is the treatment for acute aggression due to psychosis for which most trial based evidence exists.

New atypical antipsychotics are now being used in the emergency situation, although trials are few.[9] Before guidelines recommend these drugs, they should be compared with well evaluated, accessible benchmark treatments that are more effective and safe than sole use of haloperidol.

We thank the medical, nursing, and pharmacy staff of Institute P Pinel, Rio de Janeiro, for their kindness, patience, interest, and enthusiasm. We also thank Gill Rizzello and Lelia Duley for comments on the manuscript. Gisele Gadret Mendes Diniz provided data for total emergency attendances at the hospital.

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Funding: Brazilian Research Council (CNPq).
Competing interests: None declared.
Ethical approval: Ethics committees from Escola Nacional de Saúde Pública Fundação Oswaldo Cruz, Instituto Phillipe Pinel; the members of the consumer advocate group of Rio de Janeiro (SOSINTRA—society of family and friends of the mentally ill in Rio de Janeiro); National Council of Ethics in Research, Brazil.
Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 4 September 2007