

## Rapid tranquillisation: time for a reappraisal of options for parenteral therapy

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**Background** When parenteral treatments are indicated for acutely disturbed behaviour, previous guidelines have recommended droperidol or haloperidol in combination with benzodiazepines. However, there has been recent concern over cardiotoxicity and sudden death associated with some antipsychotic medication and droperidol has now been withdrawn.

**Aims** To ascertain what alternatives can be recommended to replace intramuscular droperidol.

**Method** Selective review of current guidelines and the literature pertaining to rapid parenteral tranquillisation.

**Results** Current guidelines recommend haloperidol as an alternative to droperidol. There is evidence of cardiotoxicity with haloperidol and it has a propensity to cause extrapyramidal side-effects that may exacerbate disturbed behaviour and reduce longer-term compliance. The rapid-acting intramuscular formulations of atypical antipsychotic agents show promise.

**Conclusions** It is recommended that the mainstay of pharmacological rapid tranquillisation should be parenteral benzodiazepines used with due care.

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Acute behavioural disturbance in psychiatric patients may require urgent treatment. This may result from psychotic symptoms, such as persecutory delusions or command hallucinations, or alternatively from non-psychotic symptoms such as high levels of anxiety (Atakan & Davies, 1997). The clinical management of such problems involves many elements including risk assessment to try to prevent the escalation of disturbed behaviour, 'talking down' patients, containment and the minimisation of risk to others. If non-pharmacological methods have failed to resolve the situation and oral medication is not an option, then rapid tranquillisation with intramuscular or intravenous antipsychotics, benzodiazepines or other sedative drugs may be indicated. Tranquillisation literally means calming without sedation. Clearly in situations of acute behavioural disturbance, sedation may also be an appropriate goal. This review concentrates solely on parenteral pharmacological methods of both calming and sedating patients, jointly referred to as 'rapid tranquillisation'. The review covers only methods of rapid tranquillisation for acutely disturbed patients and not the treatment of more specific conditions.

### PAST PRACTICE

A survey of prescribing practices in a general psychiatric in-patient setting found the most commonly prescribed medications for rapid tranquillisation to be diazepam and haloperidol, followed by droperidol and chlorpromazine (Pilowsky et al, 1992). Similar findings were made in a survey of 67 consultants and senior registrars in psychiatry in the Manchester area of the UK. This study found 90% of clinicians would use an antipsychotic drug: 49% would use haloperidol, 34% chlorpromazine and 15% droperidol. This would be used by 24% of the total sample in combination

with a benzodiazepine – diazepam or lorazepam (Simpson & Anderson, 1996). If the drug needed to be administered parenterally, 80% of the clinicians surveyed indicated that they would give it intramuscularly. The short-acting depot zuclopenthixol acetate was the initial drug of choice for 10%, while 34% indicated they would use this if their first-line antipsychotic agent was ineffective (Simpson & Anderson, 1996).

These treatments are not without side-effects. A survey of around 100 incidents of rapid tranquillisation conducted by Pilowski et al (1992) found few adverse events, but those reported were potentially serious, including cardiorespiratory problems, with cardiac arrests in 2% and cardiovascular complications in 3%. Although not reported in this study, dystonic reactions are not uncommon in patients administered an intramuscular antipsychotic. These reactions can be severe, and extremely unpleasant; they may exacerbate disturbed behaviour (Royal College of Psychiatrists Psychopharmacology Subgroup, 1997) and in newly diagnosed cases of schizophrenia may have long-term consequences due to lack of compliance with treatment (van Harten et al, 1999).

There has been little research into the effectiveness of rapid tranquillisation treatments. However, what work has been conducted confirms the effectiveness of antipsychotics (usually haloperidol or droperidol) and benzodiazepines (usually lorazepam or diazepam) alone and especially in combination (Garza-Trevino et al, 1989). This led to the development of a number of guidelines (Atakan & Davies, 1997; Kerr & Taylor, 1997; Royal College of Psychiatrists Psychopharmacology Subgroup, 1977). These recommend non-pharmacological and oral therapy (when liquid and rapidly dissolving formulations may be particularly useful) before embarking on parenteral treatment. However, if the latter proves necessary, two options – intramuscular droperidol and lorazepam, or intravenous haloperidol and diazepam – are recommended in the first instance, with a repeat treatment 10 minutes after intravenous treatment and 30 minutes after intramuscular treatment in the event of non-response. Intravenous administration to acutely behaviourally disturbed patients is no mean undertaking, though it can be highly effective when administered in appropriate circumstances by well-trained staff. The more rapid absorption

of droperidol compared with haloperidol when given intramuscularly (Atakan & Davies, 1997) has led to droperidol becoming the antipsychotic of choice of many psychiatrists. This practice is supported by a randomised, controlled trial comparing haloperidol with droperidol showing a benefit of the latter drug in acutely agitated patients (Resnick & Burton, 1984).

## RECENT PROBLEMS

Concern has been growing about the cardiac effects of antipsychotics (Thomas, 1994). In 1999, the newly introduced atypical antipsychotic sertindole was withdrawn by the manufacturer following concerns about its electrocardiographic (ECG) effects and a number of sudden deaths of patients on this medication. A change in the rate-corrected QT interval (QT<sub>c</sub>) in the ECG with medication may be an index of cardiotoxicity. Several psychotropic drugs are associated with prolongation of the QT<sub>c</sub> (Thomas, 1994; Royal College of Psychiatrists Psychopharmacology Sub-group, 1997; Haverkamp et al, 2000), which can precede the serious ventricular arrhythmia torsade de pointes (Faber et al, 1994). A recent naturalistic study examining the QT<sub>c</sub> of patients on a range of antipsychotic medication found that a prolonged QT<sub>c</sub> was significantly associated with thioridazine and droperidol (Reilly et al, 2000). The Committee on Safety of Medicines (CSM) views QT<sub>c</sub> prolongation as an important marker of arrhythmia risk and, in December 2000, issued a directive restricting the use of thioridazine (Anon., 2001; <http://www.doh.gov.uk/cmoc/cemcmo200018.pdf>). In January 2001, Janssen-Cilag withdrew droperidol from the market (Anon., 2001; <http://www.open.gov.uk/mca/ourwork/monitorsafeequalmed/safetymessages/droleptan.htm>). The data concerning the risk of QT<sub>c</sub> prolongation with droperidol were obtained from patients treated for a minimum of 2 weeks with the oral formulation (Reilly et al, 2000). However, the company decided to withdraw the parenteral formulation for commercial reasons. As a result, the mainstay of the pharmacological armamentarium for rapid tranquillisation is no longer available.

## CURRENT OPTIONS

The choice of medication in a parenteral formulation in the UK is limited. Promazine

and prochlorperazine are available for injection but the former has a weak anti-psychotic effect and the latter is primarily used as an anti-emetic. Beyond these two drugs, the only other antipsychotic options available are chlorpromazine, haloperidol and zuclopenthixol acetate. In addition, parenteral formulations of the benzodiazepines lorazepam and diazepam are available.

### Chlorpromazine

Chlorpromazine has many disadvantages because its intramuscular injection is painful and it has a propensity for causing hypotension, particularly in the elderly (Swett et al, 1977; Musey et al, 1986). In addition, an association between high-dose chlorpromazine and sudden death has been mooted (Jusic & Lader, 1994). Consequently, chlorpromazine is not recommended for intramuscular use (Royal College of Psychiatrists Psychopharmacology Sub-group, 1997). It also carries a risk of prolonged unconsciousness with intravenous administration (Quenstedt et al, 1992).

### Haloperidol

Haloperidol given intramuscularly appears to be effective for rapid tranquillisation (Neborsky et al, 1981). While it is generally thought to be safe and is recommended in previous guidelines (Atakan & Davies, 1997; Kerr & Taylor, 1997), serious adverse events have been described including sudden death (Jusic & Lader, 1994), cardiac arrests (Goldney et al, 1986) and neuroleptic malignant syndrome (Konikoff et al, 1984). The study that demonstrated increases in QT<sub>c</sub> associated with thioridazine and droperidol found an association with haloperidol just short of significance ( $P=0.06$ ; Reilly et al, 2000), and there are case reports of torsade de pointes occurring with this drug (Zee-Cheng et al, 1985; Haverkamp et al, 2000). Behavioural disturbance itself may cause QT<sub>c</sub> prolongation. Psychiatric emergency patients have been found to have a QT<sub>c</sub> around 50 ms longer than psychiatric out-patients (Hatta et al, 2000) and a recent controlled study in disturbed patients found significant increases in QT<sub>c</sub> in a small number of patients given placebo (David et al, 2002). Acutely behaviourally disturbed patients may be at particular risk if QT<sub>c</sub> prolongation occurs since adrenalin may sensitise the heart making arrhythmias

more likely (Royal College of Psychiatrists Psychopharmacology Sub-group, 1997; Haverkamp et al, 2000). Thus the administration of haloperidol to acutely disturbed patients, particularly intravenously as recommended in some guidelines (Kerr & Taylor, 1997), is controversial. In addition, studies investigating the effects of intramuscular atypical antipsychotic agents (Brook et al, 2000; Wright et al, 2001a; Jones et al, 2001) have demonstrated the propensity of haloperidol to cause dystonia and other extrapyramidal side-effects. These side-effects can have long-term implications for compliance with treatment (van Harten et al, 1999) and may even exacerbate disturbed behaviour in the short-term (Royal College of Psychiatrists Psychopharmacology Sub-group, 1997). A meta-analysis comparing typical and atypical antipsychotic drugs (Geddes et al, 2000) generated a flurry of correspondence (<http://www.bmj.com/cgi/content/full/321/7273/1371>) from patient organisations and psychiatrists because it recommended the use of typical agents in the acute phase of schizophrenia. Much of the criticism centred on the unfavourable side-effect profile of typical drugs, especially extrapyramidal symptoms. Such symptoms seen in schizophrenia are not solely related to antipsychotic use. Dyskinesia has been reported in patients who have never received antipsychotic medication, with a prevalence that increases with age (Fenton, 2000). A study from India of people with schizophrenia found that never-medicated patients aged over 50 years suffered from rates of parkinsonism, akathisia and dyskinesia over twice those seen in age-matched control subjects (McCreadie et al, 1996). This suggests that disturbance of basal ganglia function might be an inherent factor in the pathology of schizophrenia, or at least one that develops over time. The use of drugs that compound these problems, particularly haloperidol (which is contraindicated in patients with 'basal ganglia disease' according to the British National Formulary; British Medical Association & Royal Pharmaceutical Society of Great Britain, (2000)), therefore requires caution, particularly in the elderly.

### Zuclopenthixol

Some psychiatrists use the short-acting depot antipsychotic zuclopenthixol acetate for rapid tranquillisation (Simpson & Anderson, 1996). Because of the potential

dangers of injecting a previously untreated patient with a drug that has a long half-life, this practice is contrary to a Royal College of Psychiatrists' consensus statement that recommends its use only when 'circumstances are exceptional' in antipsychotic-naïve patients (Thompson, 1994). Previous guidelines recommended the use of zuclopenthixol acetate only when initial control of disturbed behaviour had at least partially been established with a short-acting antipsychotic and/or a benzodiazepine (Atakan & Davies, 1997; Kerr & Taylor, 1997). Its use is also limited by the delayed onset (around 8 hours) of its antipsychotic effects (Chakravarti et al, 1990), maximum serum concentrations that are only reached after around 36 hours (Clopixol Acuphase data sheet, Lundbeck), and the number of times the drug can be administered (four injections or 400 mg; British Medical Association & Royal Pharmaceutical Society of Great Britain, 2000). Further, sudden deaths and fatal cardiac events have been reported to the Medicines Control Agency (MCA) of the UK with this antipsychotic (Royal College of Psychiatrists Psychopharmacology Sub-group, 1997).

### Benzodiazepines

Benzodiazepines can be used for rapid tranquillisation owing to their sedative and anxiolytic properties. In addition, these drugs enhance gamma-aminobutyric acid activity which can inhibit dopamine-mediated transmission, possibly providing a direct antipsychotic effect (Stimmel, 1996). The most serious adverse effect of benzodiazepines is respiratory depression when high doses are given, although this can be readily reversed using the benzodiazepine partial agonist flumazenil. Of concern when treating acute behavioural disturbance are numerous case reports of behavioural disinhibition with benzodiazepines (Bond, 1998). This has been argued to be a particular risk in patients with pre-existing poor impulse control (Van der Bijl & Roelofse, 1991; Bond, 1998) or hostility, and when using high doses of benzodiazepines (Rothschild, 1992). Conversely, it has been suggested that the incidence of aggressive dyscontrol following treatment with benzodiazepines is less than 1% with no predictive indicators (Dietch & Jennings, 1988) and a controlled study has not shown disinhibition to be a side-effect of benzodiazepine use (Rothschild et al, 2000). Some of these discrepancies may

relate to the difficult task of differentiating behavioural dyscontrol from the behaviour for which the benzodiazepine is being administered in the first place. Nevertheless, it is prudent to exercise care and doses should be kept as low as practically possible (Van der Bijl & Roelofse, 1991). Another practical issue relates to concern that around 20% of psychiatric patients who are first given benzodiazepines while in hospital are still prescribed them at discharge (Summers & Brown, 1998). Good clinical practice always involves repeated assessment of prescribed medication so that drugs used for rapid tranquillisation are not continued indefinitely on an 'as required' basis orally when no longer indicated. This is especially important with drugs such as benzodiazepines that carry a high risk of dependency. However, these concerns notwithstanding, the wide therapeutic index of these drugs makes them useful alternatives to antipsychotics for rapid tranquillisation. Diazepam emulsion is effective when given intravenously (Lerner et al, 1979), but is not appropriate for intramuscular use because of its erratic absorption (Gamble et al, 1975). Consequently, intramuscular lorazepam, which is better absorbed (Greenblatt et al, 1979), is the benzodiazepine of choice (Atakan & Davies, 1997; Kerr & Taylor, 1997).

### FUTURE POSSIBILITIES

The advent of atypical antipsychotic drugs has led to significant changes in the treatment of schizophrenia, not least because of the greater patient tolerability of these drugs compared with the typical antipsychotics (Barnes & McPhillips, 1999). At present, only oral preparations are available for use. The advent of injectable extended-release forms of the atypical antipsychotic agents may be a useful development in view of the unpleasant side-effects that can occur with current drugs in such formulations (Davis et al, 1994; Weiden et al, 1996; Fleischhacker & Hummer, 1997). Rapid-acting injectable forms of atypical antipsychotic drugs may also provide valuable new treatment options.

### Olanzapine

Two double-blind, randomised, controlled trials have now been conducted examining the effect of intramuscular olanzapine in patients with acute behavioural disturbance.

The first trial examined, in 270 patients, doses of 2.5–10 mg compared with haloperidol 7.5 mg and placebo (Wright et al, 2001b). All the active treatments were more effective at reducing the behavioural disturbance than placebo, with a dose-effect relationship for olanzapine. Dosages of 7.5 mg and 10 mg of olanzapine were found to be as good as or better than haloperidol 7.5 mg. No significant serious adverse event was seen with any of the treatments, but haloperidol caused significantly more episodes of acute dystonia and tremor than olanzapine. There was no significant increase in QT<sub>c</sub> intervals in patients with any treatment, in line with previous data regarding oral treatment in large numbers of patients (Czekalla et al, 2001). The findings in acutely disturbed patients were broadly confirmed in a second study comparing olanzapine 10 mg with haloperidol 7.5 mg and placebo in 311 patients (Wright et al, 2001a). This study demonstrated a more rapid onset of action of olanzapine compared with haloperidol, with the former producing significantly greater reductions in disturbed behaviour 30 minutes after injection than haloperidol. In addition, olanzapine was associated with significantly fewer extrapyramidal side-effects, including dystonia.

### Ziprasidone

Ziprasidone is an atypical antipsychotic agent that is yet to be launched in the United Kingdom in any formulation. However, an intramuscular formulation of the drug exists. An open-label flexible dose comparison with haloperidol in 132 patients found ziprasidone 5–20 mg to be as good as or better than haloperidol 2.5–10 mg in reducing agitation (Brook et al, 2000). This study reported that ziprasidone produced significantly fewer extrapyramidal side-effects compared with haloperidol. The registration of ziprasidone in the USA was delayed because of concerns that the drug led to prolongation of the QT<sub>c</sub> interval. However, studies requested by the Food and Drug Administration have shown the drug to cause only a modest average increase in QT<sub>c</sub>, with durations that predispose to torsade de pointes being rare (see FDA Approval Letter and Labelling: <http://www.fda.gov/cder/foi/label/2001/20825lbl.pdf>). As a result, the drug was registered in the USA in February 2001, though it carries explicit warnings

regarding its use in patients at risk of QT<sub>c</sub> prolongation.

## CONCLUSION

Options for the pharmacological management of acutely disturbed behaviour have recently become restricted owing to the withdrawal of droperidol. Haloperidol is an alternative antipsychotic option recommended in a number of current guidelines. However, caution is advised regarding the use of parenteral haloperidol (especially intravenously) in the light of an increasing awareness of the cardiotoxic effects of some antipsychotic drugs and the propensity of haloperidol to cause extrapyramidal side-effects. Given these concerns, clinical experience of the use of intramuscular formulations of atypical antipsychotic drugs is awaited with interest so that their place in therapy can be fully evaluated. In the meantime, the current gap in our armamentarium is probably best filled by an increased use of benzodiazepines, particularly intramuscular lorazepam or intravenous diazepam. Caution needs to be exercised when using these drugs, although the risk of induced behavioural disinhibition appears to be low. At higher doses, respiratory depression can occur but this can be readily reversed with appropriate treatment. Resuscitation equipment and flumazenil should be readily available, especially if using the intravenous route. In addition, regular reviews of treatment are essential to prevent medication used for rapid tranquillisation being continued inappropriately.

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## CLINICAL IMPLICATIONS

- Droperidol has been withdrawn because of concerns over cardiotoxicity and sudden death.
- An alternative choice of parenteral antipsychotic is not immediately evident. Haloperidol, chlorpromazine and zuclopenthixol acetate are all associated with potentially serious side-effects. Parenteral atypical antipsychotic formulations are awaited.
- Benzodiazepines, particularly intramuscular lorazepam, used with due care may be the safest replacement for intramuscular droperidol.

## LIMITATIONS

- The review is not systematic.
- There is little randomised, controlled evidence regarding the effects of drugs used for rapid tranquillisation.
- Some of the concerns regarding antipsychotic drugs are based on case reports and anecdote.

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