Haloperidol in palliative care

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Haloperidol is one of 20 ‘essential’ medications in palliative care. Its use is widespread in palliative care patients. The pharmacology of haloperidol is complex and the extent and severity of some of its adverse effects, particularly extrapyramidal adverse effects (EPS), may be related to the route of administration. Indications for the use of haloperidol in palliative care are nausea and vomiting and delirium. Adverse effects include EPS and QT prolongation. Sedation is not a common adverse effect of haloperidol. It is important that palliative care practitioners have a comprehensive understanding of the indications, doses, adverse effects and pharmacology of haloperidol. This review is intended to address these issues. Palliative Medicine 2004; 00: 1–7

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Introduction

Haloperidol, a butyrophenone antipsychotic (neuroleptic, major tranquillizer) was first used in 1957.1 It was created by Dr Paul Janssen who was looking for compounds with morphine-like activity. He first discovered the analgesic dextromoramide, then a compound with morphine and phenothiazine-like properties which, after further modification yielded compounds with neuroleptic properties, including haloperidol (Figure 1). Dr Paul Janssen (Figure 2) revolutionized psychiatric care and is credited with the creation of five WHO ‘essential drugs’.

Haloperidol has been used predominately in the treatment of schizophrenia and related psychoses (mania, delirium). Indications for use in palliative care are nausea and vomiting, and delirium. It is considered internationally to be one of 20 essential medications in palliative care.2

Haloperidol can be administered orally, intramuscularly, subcutaneously or intravenously. Its use by the intravenous route is unlicensed in many countries. Haloperidol has complex pharmacology, which has not as yet been fully elucidated. The pharmacokinetics and pharmacodynamics of haloperidol following administration by different routes are important considerations when it is used in palliative care patients as the side-effect profile of haloperidol is significantly determined by its route of administration.

Because of the ‘age’ of this medication and its ‘out of patent’ status, relatively few good clinical trials have been performed, yet its clinical use is widespread. Its optimal usefulness in clinical practice has been diminished because of its poor evidence base. This pharmacological review summarizes the established literature on haloperidol and suggests the rationale for its safe and effective use in palliative care.

Pharmacology

In the 1950s haloperidol was believed to be quickly deactivated by hepatic enzymes, to have no active metabolites, and to induce its own metabolism.1 It is now known that haloperidol is extensively metabolized by hepatic enzymes (partially by members of the CYP450 family) and that there are active and toxic metabolites1,3 (Figure 3). Only 1% is excreted unchanged in the urine.3

Haloperidol’s metabolism is complex although some consider it to be the least complicated of the antipsychotics with fewer metabolites than most.4 Its metabolism consists of glucuronidation to an inactive metabolite (50–60%), reduction (and back oxidation) to reduced-haloperidol (an active metabolite) (23%) and N-dealkylation to a pyridium metabolite (a toxic metabolite) (20–30%).3 Other metabolites of haloperidol are probably not of clinical relevance.

Although in vitro studies suggest that the cytochrome P450 2D6 enzyme (CYP2D6) is only minimally involved in haloperidol’s metabolism, in vivo studies suggest otherwise. CYP2D6 is genetically polymorphic with 5–10% of Caucasians and 1–2% of Asians/Polynesians being slow metabolizers of CYP2D6 substrates.4 It is noninducible.4 Nonslow metabolizers of CYP2D6 substrates can be rendered slow metabolizers by the administration of CYP2D6 inhibitors e.g., paroxetine.4 Slow metabolizers of CYP2D6 substrates have 30% higher haloperidol, 80% higher reduced-haloperidol plasma concentrations and 70% higher ratios of reduced-haloperidol to haloperidol than non-slow metabolizers.3 The effect of CYP2D6 metabolizer status is more pronounced on reduced-haloperidol concentrations than on concent-
trations of other metabolites, suggesting that CYP2D6 is involved in the back oxidation of reduced-haloperidol to haloperidol.3

A correlation between steady state haloperidol concentrations and CYP2D6 substrate metabolizer status is, however, only seen at doses of less than 20 mg as are routinely used in palliative care.3 At higher doses no correlation is seen, perhaps due to cytochrome P450 3A4 (CYP3A4) involvement in reduction/back oxidation to reduced-haloperidol at doses greater than 20 mg.3

As a result of this variable metabolism, haloperidol has a variable half-life (12–35 hours).5 The pharmacokinetic parameters are outlined in Table 1. Orally administered haloperidol is subject to first pass metabolism5–7 and the oral to parenteral conversion most commonly used is a half to two thirds.6

Reduced-haloperidol is not detected in plasma until several hours after oral haloperidol administration.9 The ratio of reduced-haloperidol to haloperidol concentrations over the range 0–300 mcg/L follows a sigmoid but variable pattern.3 Haloperidol concentrations reach steady state after around one week while reduced-haloperidol concentrations take around four weeks.3 In some cases the concentrations of reduced-haloperidol may exceed that of the parent.4 Reduced haloperidol is not detected after intravenous haloperidol administration for even longer than after oral administration which suggests that first pass metabolism, at least initially, is responsible for increased reduced-haloperidol concentrations.9

Haloperidol's main mechanism of action is via dopamine receptor antagonism in the central nervous system. It exhibits partial selectivity for dopamine 2 receptors particularly in the corpus striatum where it is thought to exert its antipsychotic activity.10 It also acts on some alpha adrenoreceptors (α-1), opioid (sigma), muscarinic cholinergic, histamine and serotonin receptors. Its actions on 5-HT2 receptors occur at high doses. Long term treatment with haloperidol in animals results in upregulation of dopamine receptors. Actions at sigma-opioid receptors may add to dopamine blockade in producing dystonic reactions to haloperidol.10

There is a linear relationship between the dose of haloperidol administered and plasma concentrations, although as mentioned earlier there is large interindividual variation.3

Reduced-haloperidol has low affinity for dopamine 2 and dopamine 3 receptors but equal affinity for sigma opioid receptors to the parent drug.3,9 It has a clinical effect and exhibits 10–20% of the activity of haloperidol in animals.4 A correlation between reduced-haloperidol concentrations and clinical outcome has been demonstrated in humans. The interconversion between reduced-haloperidol and haloperidol is subject to large interindividual variation which may explain the curvilinear response between haloperidol and clinical effect seen in some patients.4 The exact clinical significance of reduced-haloperidol however remains unclear.

Clinical indications

The indications for haloperidol in a study of hospitalized patients were those of delirium (69%), psychosis (11%),
affective disorders/dementia (11%) and nausea/vomiting (9%). This suggests that its main indication in the general hospital population is in the management of delirium and other psychiatric disorders. However, in the palliative care setting the more common indication is nausea and vomiting. Delirium, despite its high prevalence in the dying and the fact that haloperidol is the drug of first choice, is a less common indication.

**Nausea and vomiting**

The emetogenic process involves two distinct areas of the brain – the chemoreceptor trigger zone (CTZ) and the vomiting centre (VC). Various neurotransmitters are found in these areas including dopamine, acetylcholine, gamma aminobutyric acid (GABA) and serotonin. The CTZ in particular, is dopamine-rich. It is stimulated by drugs, toxins and biochemical imbalances. Haloperidol acts at dopamine 2 and other receptors in various regions of the brain as an antagonist. Antagonism of dopamine 2 receptors in the CTZ results in alleviation of nausea and vomiting.

The evidence of efficacy of haloperidol as an antiemetic, although based on sound pharmacology, is not substantiated by any randomized controlled trials. The literature which does support the antiemetic properties of haloperidol consists of case series and reports. When used in combination with ondansetron, haloperidol has been reported to alleviate intractable nausea and vomiting of advanced cancer (n = 1 study). Clinical experience indicates that haloperidol is an effective antiemetic in the prophylaxis and treatment of opioid-induced nausea and vomiting.

Anecdotally antiemetic doses of haloperidol are generally 1.5–3 mg orally (or parenteral equivalent) over 24 hours. Higher doses appear to result in little if any therapeutic advantage. Haloperidol may be given in a single night time dose (because of its long half-life), which is often a compliance advantage in palliative care patients.

**Delirium**

The incidence of delirium is 25–85% in hospitalized cancer/AIDS patients and 65–85% in terminally ill patients. It is associated with high morbidity and mortality, and therapy is often suboptimal. It is proposed that causative factors induce a failure of high energy metabolism at an inter- and intraneuronal level resulting in a cholinergic/dopaminergic imbalance. Haloperidol, as a dopamine antagonist of dopamine 2 receptors in the basal ganglia and of the limbic parts of the forebrain, corrects the acetylcholine/dopamine systems imbalance.

In palliative care the aetiology of delirium is usually multifactorial. Organ failure and delirium-inducing medications such as opioids are frequently implicated. Reversal of the aetiology in the terminally ill may not always be possible, however palliation of the symptoms is a feasible clinical goal. Medication is often a component of delirium management and haloperidol remains the drug of first choice. This may be challenged by the newer atypical antipsychotics, but to date clinical studies have yet to establish their superiority except in terms of the adverse effects profile.

Haloperidol is considered by many to be the gold standard of delirium therapy in the medically ill. It is effective and has few anticholinergic, sedative, autonomic or hypotensive effects and can be given both parenterally and orally. Double blind, randomized controlled trials are, however, lacking. There have been no placebo controlled trials of drugs for the treatment of delirium that use modern Diagnostic and Statistical Manual (DSM) terminology or valid delirium assessment measures. There are ethical problems in treating a life-threatening condition such as delirium with placebo and in acquiring informed consent from delirious patients, thus it is unlikely that such trials will be conducted. It may, however be argued that it is unethical not to do such studies. There have been several uncontrolled trials and case reports. A single double-blind

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>12–35 hours (average 16 hours)</td>
</tr>
<tr>
<td>Oral availability</td>
<td>44–75% (average 60%)</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>1280–2130 L</td>
</tr>
<tr>
<td>Time to steady state</td>
<td>7–10 days</td>
</tr>
<tr>
<td>Protein binding</td>
<td>91.5% bound</td>
</tr>
<tr>
<td>Time to haloperidol measurable in plasma</td>
<td>1–1.5 hours (oral), immediate (iv), immediate (im)</td>
</tr>
<tr>
<td>Time to peak plasma concentration</td>
<td>4–6 hours +18 hours (oral), 5–15 mins (iv), 20–40 mins (im)</td>
</tr>
<tr>
<td>Decay post peak</td>
<td>Slow exponential (oral), steep over 1 hour then slow exponential (iv), like iv (im)</td>
</tr>
</tbody>
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comparator trial (in hospitalized AIDS patients) has confirmed the efficacy of haloperidol and chlorpromazine, but not lorazepam.\textsuperscript{23}

Delirium should not be treated with a benzodiazepine unless it is as an adjunct to primary therapy with haloperidol. If delirium is the correct diagnosis, haloperidol should be used and sole therapy with benzodiazepines should be avoided. By contrast, when used as sole therapy benzodiazepines may aggravate rather than alleviate delirium.\textsuperscript{1,18} In combination, benzodiazepines act synergistically with haloperidol and can result in greater clinical effect than haloperidol alone. The sedative and anxiolytic properties of benzodiazepines are sometimes useful in delirious patients.\textsuperscript{21,22} Benzodiazepines decrease the activity of the dopaminergic system by their enhancing action on pre- and postsynaptic GABA-inhibitory systems.\textsuperscript{22} The combination results in an additive correction of the acetylcholine/dopamine system imbalance seen in delirium as demonstrated in a controlled study comparing haloperidol alone with haloperidol in combination with a benzodiazepine in medically ill delirious patients.\textsuperscript{24}

Dosing of haloperidol in the treatment of delirium is titrated to effect. In palliative care patients a useful regimen may be 0.5–1.5 mg orally (mild), 1.5–5 mg orally (severe) and 10 mg subcutaneously or intravenously (very severe). These doses may be repeated every 30–40 minutes until symptoms are alleviated. Once control has been achieved the maintenance dose is 50% of the daily dose required to achieve control, and is usually between 1.5 and 20 mg orally per day.\textsuperscript{25}

**Adverse effects**

The side-effect profile of haloperidol includes extrapyramidal side-effects (EPS), tardive dyskinesia and QT interval prolongation. When haloperidol was first used in the treatment of schizophrenia in the late 1950s it was thought to be almost devoid of anti-adrenergic and autonomic effects,\textsuperscript{1,8} although tardive dyskinesia was a recognized problem on prolonged use.\textsuperscript{1} Later, in the 1970s when high or mega dose haloperidol was being used in the treatment of schizophrenia resistant to other antipsychotics, it was reported to have few adverse effects.\textsuperscript{1} When given intravenously haloperidol had virtually no adverse effects on neurological, cardiac, respiratory, renal, hepatic or bone marrow systems.\textsuperscript{9} High dose intravenous haloperidol is generally considered safe in most patients. Doses of up to 240 mg in 24 hours have been administered intravenously to acutely delirious patients with good effect and minimal adverse effects.\textsuperscript{22}

**Extrapyramidal side-effects**

The EPS of haloperidol are caused by dopamine blockade in the distal ganglia,\textsuperscript{1} and perhaps by blockade of sigma-opioid receptors.\textsuperscript{10} While haloperidol has been reported to cause a higher incidence of EPS, including acute dystonia, pseudo-parkinsonism, akathisia and tardive dyskinesia, than other antipsychotics, this has not been documented in well designed trials.\textsuperscript{1,3} This is compounded by what some researchers describe as the ‘primitive state’ of EPS-rating tools.\textsuperscript{12} Haloperidol is considered safe in the treatment of delirium but dystonic reactions and an initial worsening of symptoms have been reported rarely.\textsuperscript{26}

Early evidence in acutely schizophrenic patients treated with haloperidol found no relationship between reduced-haloperidol concentrations and haloperidol-induced EPS.\textsuperscript{9} This has been recently refuted in animal studies\textsuperscript{27} and in humans.\textsuperscript{3} In addition, reduced-haloperidol has equal affinity to sigma-opioid receptors to haloperidol but a much lower affinity for dopamine receptors.\textsuperscript{10} The incidence and severity of haloperidol-induced adverse effects are associated with both high reduced-haloperidol and high haloperidol concentrations and a high ratio between the two. Reduced-haloperidol concentrations, in particular correlate with the incidence and severity of EPS.\textsuperscript{3} In a study of acutely schizophrenic Chinese patients given 10 mg of haloperidol it was found that reduced-haloperidol concentrations were significantly higher in the 30 out of 48 patients who experienced EPS than in the 18 patients who did not.\textsuperscript{2} The incidence of haloperidol-induced EPS is higher in slow metabolizers of CYP2D6 substrates, suggesting a link between the CYP2D6 metabolizer status (either genetically determined or due to drug interaction) of the patient and the incidence and severity of haloperidol-induced EPS.\textsuperscript{3}

In some patients the emergence of haloperidol-induced EPS may be due to patient characteristics: in Saudi-Arabian schizophrenic patients haloperidol administration resulted in EPS in all 12 patients studied within 16–50 hours of administration.\textsuperscript{28} Haloperidol concentrations were 2.5–14 mg/L (mean 6.5 mg/L), which is within the reported normal range. In terminally ill delirious AIDS patients treatment with high dose intravenous haloperidol (in combination with lorazepam) resulted in haloperidol-induced EPS in 50% of cases, although clinical efficacy was good.\textsuperscript{29} The effect of the AIDS virus on subcortical structures of the brain increases sensitivity to the effects of haloperidol dopamine receptor blockade and hence EPS.\textsuperscript{23}

The atypical antipsychotics such as olanzapine, risperidone and quetiapine antagonize many CNS neurotransmitter receptors. They may cause less EPS than haloperidol although this is dose dependent.\textsuperscript{18,19,21} There have been no randomized controlled studies comparing the atypical antipsychotics with standard ones in delirium.\textsuperscript{18} Studies in schizophrenic patients have reported lower EPS with these newer agents.\textsuperscript{21} Clinical studies comparing haloperidol with olanzapine or quetiapine in
delirious patients resulted in EPS in five of eleven patients given haloperidol in one study and two of eleven in another. No EPS were seen in those treated with atypical antipsychotics.1

In the 1970s parenteral (intramuscular or intravenous) haloperidol was reported to cause fewer EPS than oral haloperidol even at high doses.30 In a retrospective chart review of 238 patients mentioned earlier in this paper, where 69% of patients were given haloperidol for delirium, 11% for psychosis, 9% for nausea and vomiting, 6% for affective disorder and 5% for dementia, the data were subanalysed by the route of administration.13 The incidence of haloperidol-induced EPS following intravenous haloperidol (0.5–90 mg over 24 hours) and oral haloperidol (0.5–20 mg over 24 hours) was 7.2% and 22.6% respectively. In addition, in a pilot study of ten patients given haloperidol either intravenously (4) or orally (6) the former had significantly less severe EPS than the latter.31 Lawson et al. in 1962 gave intravenous haloperidol to 50 obstetric patients and reported only two cases of mild EPS;24,31 Adams et al. studied 20 delirious patients treated with intravenous haloperidol at doses of 100–240 mg over 24 hours and reported no EPS at all.31 Extensive clinical experience of the use of haloperidol intravenously in seriously ill, delirious medical and surgical patients supports a lack of EPS by this route.1,12,24,31 High dose parenteral haloperidol was also reported to cause less EPS than low dose parenteral haloperidol possibly related to an increase in the anticholinergic activity of haloperidol at high parenteral doses (thereby antagonizing EPS) or the existence of an EPS ‘window’ – an upper limit and lower threshold of haloperidol concentrations for eliciting EPS.30 The EPS scales used in the above studies were based on a modified version of a scale developed by Simpson and Angus where 10 items (arm dropping, shoulder, elbow and wrist rigidity, head dropping, glabellar tap, tremor, salivation, akinesia and akathisia) were rated on a 0–5 scale. Daily scores were calculated by adding individual scores for each item.

In combination with benzodiazepines the incidence of haloperidol-induced EPS is so low it is almost non-existent. In delirious patients treated with intravenous haloperidol alone (4 patients) and in combination with diazepam (10 patients), only 1 of 14 developed more than minimal EPS.24 The average EPS ratings were 2.3 and 0.125, respectively, which was statistically significant (P < 0.001). Benzodiazepines decreased the incidence of intravenously administered haloperidol-induced EPS from low to almost zero. An explanation for this protective effect may be found in the mechanism of action of benzodiazepines as a clinically effective treatment of acute dystonic reactions.32

There are several theories as to why parenterally administered haloperidol causes less EPS than oral haloperidol:

- The parenteral route is used more commonly in delirium than the oral route. In delirium the dopamine/achetylcholine ratios are altered leading to a lower susceptibility to EPS11,31 (and lower acetylcholine concentrations seen in delirium protect against EPS).

- Delirium occurs in a normal cross-section distribution of the population, while schizophrenic patients may have pre-existent subtle damage to their basal ganglia, placing them at higher risk of EPS.

- Oral haloperidol undergoes first pass metabolism resulting in an increase in reduced-haloperidol peak concentrations which results in more EPS.11,31

- EPS do not emerge until 12 to 16 hours after an intravenous dose of haloperidol, reflecting either a gradual onset of metabolic changes in the CNS, a delay in distribution into the CNS5 or time for concentrations of reduced haloperidol to reach an EPS-inducing threshold.

- The duration of use of haloperidol in delirium is generally brief, usually less than a week, so perhaps the exposure is too limited for the neurological side effects to emerge.

**QT prolongation**

Haloperidol’s ability to prolong the QT interval has prompted some authors to suggest that ECG monitoring should occur when intravenous haloperidol is used.11 Multiforme ventricular arrhythmias (torsades de pointes) have been reported with the use of intravenous haloperidol, even with continuous infusion, and are considered a risk of high dose haloperidol by any route.11 This risk is relative, with each medication accorded an adjusted odds ratio (AOR) for QT lengthening.33 The AOR of haloperidol rates is 3.6 (0.96–13.6), thioridazine 5.3, risperidone 1.8 and droperidol 6.7. Other risk factors for QT prolongation include long QT syndrome (genetic), electrolyte abnormalities (especially hypokalaemia), cardiac disease, female gender and older age, thus the influence of medication may or may not be of relevance.33 It is difficult to determine the true risk for torsades de pointes and sudden cardiac death related to haloperidol. There would appear to be a risk, but how to estimate this in the
severely physically ill delirious or terminal patient is unclear.

Sedation
Although sedation has been reported with haloperidol, this is a rare adverse effect and many clinicians consider the drug to be nonsedating. It has, in the past, been termed a ‘stimulant’ tranquilizer. Doses as high as 350 mg over 24 hours have been given intravenously to delirious patients without any sedation occurring. Any haloperidol-induced sedation is at its maximum during the first hour after intravenous administration (distribution phase). After oral administration the onset of any sedation is gradual and lasts several hours. When used in delirium, which is by definition a disorder of consciousness, particularly in hypoactive/torpid deliria, containment of the symptoms with haloperidol (in the absence of a benzodiazepine) may actually enhance alertness and attention. To consider haloperidol as a sedative agent is incorrect.

Discussion/conclusions
Haloperidol is a useful drug in palliative care although, as with many medications in this field of medicine, there is a paucity of good published clinical trials. The efficacy of haloperidol in the alleviation of delirium in the terminally ill is based on mostly observational evidence collected from studies of delirious critically ill patients. Likewise the adverse effects profile of haloperidol in palliative care, particularly the EPS, has been based on either schizophrenic patients or those with delirium. Delirium, an imbalance of the dopaminergic/acetylcholinergic systems, may protect against the development of extrapyramidal adverse effects. Some patients may be more susceptible to the extrapyramidal adverse effects of haloperidol either through disease e.g., AIDS patients; or through their metabolizing enzymes which may (CYP2D6) or may not (CYP3A4) be polymorphically expressed. The enzymes involved in the different stages of haloperidol’s metabolism have not been fully elucidated. From studies of CYP2D6 genetically slow and nonslow substrate metabolizers it would appear that CYP2D6 does indeed have a role in the metabolism of haloperidol at least at low haloperidol concentrations. Likewise CYP3A4 also appears to play a part. It would be prudent then to consider the patient’s CYP2D6 substrate metabolizing status and likely interactions with other drugs when administering haloperidol. Testing for genetically fast and slow metabolizers of CYP2D6 substrates is available in some centres, using a blood sample, although this is rarely clinically indicated. Clinicians should be aware of drugs which are known to inhibit CYP2D6 such as paroxetine and may therefore lead to higher haloperidol plasma concentrations. Finally the decreased incidence and severity of haloperidol-induced EPS after parenteral compared with oral haloperidol is fairly well established in anecdotal reports and small studies. The mechanism for this has still to be elucidated. If EPS are a result of high reduced-haloperidol concentrations which are to some extent a result of CYP2D6 and CYP3A4 metabolism (including first-pass), large peaks of reduced haloperidol concentrations may occur with oral but not parenteral haloperidol administration even at steady state. Certainly if the pharmacokinetics and particularly the metabolism of haloperidol are closely examined, sound pharmacological reasons for this can be found. The clinical importance of this in palliative care is that parenteral administration of haloperidol may be the safest, and the preferred, route of administration and is certainly not to be avoided if subcutaneous administration of other medications in the terminal phase is occurring. Prescribers using higher doses may be concerned about the emergence of extrapyramidal adverse effects and may be reassured to know that the incidence is low when haloperidol is used by this route.

References


