Introduction
A retrospective review and study (n=4,252) to determine the most commonly prescribed medications in a population of hospice patients.

**Top ten of the 100 most frequently prescribed medications in hospice patients:**

1. Acetaminophen
2. Lorazepam
3. Morphines
4. Atropine
5. **Haloperidol**
6. Prochlorperazine
7. Albuterol
8. Docusate
9. Bisacodyl
10. Scopolamine

• European Study/Survey (n=90), whose aim was to identify a consensus of appropriate treatment for common symptoms in the end of life care for patients with cancer (based on consensus opinion).

• Four essential drugs were identified:
  o Morphine
  o Midazolam
  o Haloperidol
  o Antimuscarinic

History

- Haloperidol has its origin in the research process of central analgesic molecules derived from pethidine (meperidine) and methadone, carried out by the Belgian company Janssen Pharmaceutica in an attempt to discover a new analgesic.

- Early animal studies revealed a potent tranquilizer which exhibited antipsychotic activity as well as analgesic qualities. In addition, it was found this molecule produced Parkinsonism.
Landmarks in the history of Haloperidol:

• 1939 Otto Eisleb synthesized pethidine, a fundamental molecule in the history of the discovery of Haloperidol

• 1953 Paul Janssen begins to carry out research

• 1958 Synthesis of R-1625 (Haloperidol) by Bert Hermans

• 1961 Johnson & Johnson acquires Janssen Pharmaceutica

• 1963 Arvid Carlsson demonstrates Haloperidol-induced changes to dopamine levels in the brain; the “dopaminergic hypothesis of schizophrenia” is born

• 1967 Synthesis of long-acting injectable Haloperidol (Haloperidol deconate)

• 1969 Haloperidol patent granted in the United States

• 1976 Solomon Snyder confirms that Haloperidol is a dopamine receptor antagonist

• 1982 Market launch of Haloperidol decanoate (Haldol®)

Haloperidol (Haldol®)

- A butyrophenone chain which appears to be essential for D2 receptor binding
- Contains a piperidine ring and a ketone group
- The presence of the hydroxyl group enhances the binding of Haloperidol to the D2 receptor
Haloperidol Pharmacology:

Pharmacodynamics
Pharmacokinetics

Pharmacodynamics may be simply defined as what the drug does to the body, as opposed to pharmacokinetics, which may be defined as what the body does to the drug.
Haloperidol Pharmacodynamics

• Potent dopamine antagonist with a strong affinity for the D$_2$ dopamine receptor

• Weaker affinity to serotonin

• NMDA receptors, opioid (kappa, sigma, delta), muscarinic, histamine, alpha-1 adrenergic, substance P, and sodium channels
Haloperidol Pharmacodynamics

References


## Haloperidol Pharmacokinetics

<table>
<thead>
<tr>
<th>ABORPTION</th>
<th>DISTRIBUTION</th>
<th>METABOLISM</th>
<th>ELIMINATION</th>
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<tbody>
<tr>
<td>Onset of action:</td>
<td>Extensive protein binding with a free fraction in the plasma of 10%</td>
<td>Metabolized extensively in the liver by CYP3A4</td>
<td>-42% excreted renally</td>
</tr>
<tr>
<td>Oral: Tmax 2-6h</td>
<td></td>
<td>-Oral – first pass metabolism</td>
<td>-Glucuronide metabolites excreted in the bile</td>
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<tr>
<td>IM: Tmax 20 min</td>
<td></td>
<td>Metabolites:</td>
<td></td>
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<tr>
<td>IV: Tmax 5-15 min</td>
<td></td>
<td>-Reduced Haloperidol</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>-Haloperidol glucuronide - inactive</td>
<td></td>
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<td></td>
<td></td>
<td>-Pyridium: toxicity</td>
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</tbody>
</table>
Haloperidol Pharmacokinetics Cont’d

- SQ, Topical, PR – no pharmacokinetic data available

- **Duration of Action**: (1-6 h) relative to route of administration, dose [peak concentration (T-max)], severity of clinical situation, and is a function of distribution, metabolism, and elimination.

- Half life ($t_{1/2}$): Oral $t_{1/2}$ - 26h, IM $t_{1/2}$ - 21h, IV $t_{1/2}$ - 20h
Haloperidol Pharmacokinetics - References


Hepatic Disease

• Haloperidol is subject to hepatic blood flow, protein binding, and intrinsic enzyme activity.

• It is thus potentially affected by liver disease and dose modification may be necessary.


Renal Disease

• No need for alteration of drug dosing in renal insufficiency.


• ↓ dose

Drug Interactions

• Decreased levels of Haloperidol
  o Carbamazepine
  o Phenobarbital
  o Phenytoin

• Increased levels of Haloperidol
  o Fluoxetine (Prozac®)
  o Venlafaxine (Effexor®)
  o Nefazodone (Serzone®)
  o Fluvoxamine (Luvox®)
  o Alprazolam (Xanax®)

Adverse Effects

• Extrapyramidal Side Effects
• QT Interval Prolongation and Torsades de Pointes
• Neuroleptic Malignant Syndrome
• Seizures
Extrapyramidal Side Effects (E.S.E.)

• Symptom complex resulting from a dopaminergic-cholinergic imbalance at the level of the basal ganglia.

• The high affinity of Haloperidol for the D2 receptor results in a relative increase in interneuronal acetylcholine.

• Results in:
  - Acute dystonia – spasm of muscles – tongue, face, neck or back
  - Parkinsonism
  - Neuroleptic malignant syndrome
  - Akathisia
  - Tardive dyskinesia
E.S.E. (Cont’d.)

• Double-blind randomized trial (n=244)

• Haloperidol, chlorpromazine and lorazepam

• Low-dose Haloperidol is effective in treatment of delirium with an extremely low prevalence of extrapyramidal side effects.

• Not clinically significant

Prospective blinded study (n=10)

IV vs. PO

Patient receiving IV Haloperidol experienced significantly less intense extrapyramidal symptoms

Delirious patients have relatively lower levels of acetylcholine, which may lessen the severity of E.S.E.

E.S.E. (Cont’d.)

- Extrapyramidal Syndrome Presenting as Dysphagia: a case report
- Usually responds to diphenhydramine

QT Interval Prolongation and Torsades de Pointes (TdP)

- 1997-2008
- 70 cases of QT prolongation and/or TdP
- 54 cases TdP with 80% preceded by QT prolongation
- 3 patients experienced sudden cardiac arrest
- Increased Risk:
  - IV
  - ↑ Doses
  - High risk medically complex situations
  - Pre-existing heart disease
  - Electrolyte imbalance
  - Antiarrhythmic agents

QT Interval Prolongation and TdP

References


Neuroleptic Malignant Syndrome

- A neurologic emergency associated with neuroleptics
- D₂ blockade
- FEVER – Fever, Encephalopathy, Vitals unstable, Elevated enzymes (Increased CPK), Rigidity of muscle
- Hyperkalemia, Hypercapnia, Acidosis, DIC, Leukocytosis, tremor
- Incidence .07-2.2%
- Risks: IV, ↑ dose (rapid), Agitation, Cachexia, Dehydration


Seizures

• Lowers seizure threshold

• Among the first generation antipsychotics, it is the phenothiazine class (chlorpromazine) that carries the greatest risk (1.2%)


Adverse Effects by System

- Cardiovascular: hypotension, hypertension, tachycardia, dysrhythmia(s), QTc prolongation-torsades de pointes, sudden death
- CNS: restlessness, anxiety, extrapyramidal reactions, dystonic reactions, pseudoparkinsonian signs and symptoms, tardive dyskinesia, neuroleptic malignant syndrome, altered central temperature regulation, akathisia, insomnia, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, seizures
- Dermatologic: hyperpigmentation, pruritus, rash, contact dermatitis, alopecia, photosensitivity (rare)
- Gastrointestinal: nausea, vomiting, anorexia, constipation, diarrhea, hypersalivation, dyspepsia, cholestatic jaundice, obstructive jaundice
- Genitourinary: urinary retention
- Hematologic: leukopenia
- Ocular: blurred vision
- Respiratory: laryngospasm, bronchospasm

Spectrum Health Drug Quick Reference - Haloperidol (Haldol®)
Clinical Indications

- Delirium
- Nausea and vomiting
- Bowel Obstruction
- Hiccups
- Palliative Sedation
- Anxiety
Delirium

- There is a legitimate evidence base for the treatment of delirium with Haloperidol and it is advocated for this use by most experts

- Hyperactive, hypoactive, mixed
Delirium (Cont’d)

- Prospective randomized trial (n=73)
- Tertiary care university hospital in Montreal, affiliated ICU
- Olanzapine vs. Haloperidol
- Clinical efficacy was similar in both treatment arms
- ↑ E.P.S. with Haloperidol (n=6) (↓ severity)
- Similar ↓ need for benzodiazepines

Delirium (Cont’d)

- Randomized double-blind trial (n=28)
- Korea University Medical Center
- Delirium significantly reduced in both groups
- E.P.S. (n=1), mild in Haloperidol group

Delirium (Cont’d)

- Randomized, double-blind, placebo-controlled trial (n=430)
- Large university hospital, Netherlands
- Low dose Haloperidol (1.5mg/d) administered prophylactically for elderly hip surgery patients
- No efficacy demonstrated in reducing post-op delirium
- Reduced severity and duration of delirium
- Reduced hospital stay (↓ cost)


Treatment of Delirium

- Mild agitation – 2mg PO, IV, IM
- Moderate agitation – 5mg
- Severe agitation – 7.5-10mg
- Decrease dose by 1/3 for elderly patients
- May repeat q 30 min – patient calm yet arousable to voice
- If serious agitation persists, double dose in 30 min – may repeat
- When symptom control is achieved, 24hr dose QD, BID

Goldstein, Morrison. Evidence-Based Practice of Palliative Medicine. 2013.
Nausea and Vomiting

A review of the literature which identified 3 studies which provided enough information on baseline symptoms, interventions, outcome measures, and evaluation tools.

- Haloperidol may be effective in patients experiencing nausea and vomiting.
- No randomized controlled trials evaluating Haloperidol for nausea and vomiting.
- The clinical use of Haloperidol for nausea and vomiting must be guided by clinical experience, judgment, case reports, and expert opinion.

Nausea and Vomiting (Cont’d)

• 0.5mg – 1.5mg q 6-12h, up to 5mg q 12h IV/SQ

• SQ/IV = ½ PO

Nausea and Vomiting (Cont’d)

- Retrospective study

- Trial 1 (n=23), 74% reported the use of LDH ↓ their CINV

- Trial 2 (n=10), 70% reported relief

ABHR Gel in the Treatment of Nausea and Vomiting in the Hospice Patient

Moon, R. Inter J of Pharma Compounding. 2006.
Nausea and Vomiting (Cont’d)

Haloperidol “has been extremely effective in doses from 5-20mg/d and remains our antiemetic of choice in most situations.”

Bowel Obstruction

• May be useful as an antiemetic in the treatment of malignant bowel obstruction

• However, has not been compared with other antiemetics in a randomized controlled trial.


Intractable Hiccups (IH)

- Retrospective chart review (n=240)
- 3 subjects with IH were identified
- Haloperidol (n=1), Chlorpromazine, Baclofen, and Carbamazepine proved effective

IH (Cont’d)

• 2 case studies in which IM Haloperidol (2mg) followed by a PO regimen (2d) was effective in treatment of IH without recurrence

• Mention of 7 additional cases

Anxiety

• Useful in treatment of anxiety when benzodiazepines are not sufficient for symptom control

• Psychotic symptoms accompany the anxiety

• Avoids excessive sedation

Palliative Sedation

- Palliative sedation is often used at end of life for refractory symptoms such as delirium, nausea, dyspnea, and pain
  - 0.5mg – 5mg PO/SQ a 2-4h
    - OR
  - 1-5mg IV/SQ then infusion 5-15mg/d SQ/IV

Palliative Sedation (Cont’d)

• National Taiwan University Hospital (n=251)
• 70 patients received palliative sedation
• 35 patients received Haloperidol
• Did not influence survival time
• Surveys of staff and families indicated Haloperidol was an effective agent for palliative sedation

Innovative Uses of Haloperidol:

- Analgesic Adjunct
- Pruritus
Analgesic Adjunct

- Anesthesia and psychiatric literature provide well-designed studies and case reports that demonstrate the efficacy of Haloperidol as well as other neuroleptics as an analgesic adjunct
- Mixed results
- Most studies appear to be in the favorable camp
- $\mu$, NMDA, $\alpha_1$ adrenergic, substance P receptors
- $\text{Na}^+$ channels
- Isometric similarity to meperidine
Analgesic Adjunct References


Analgesic Adjunct (Cont’d)

- Well designed retrospective study
- N=240
- Patients receiving short-acting opioids
- Low-dose methadone in conjunction with adjuvent **Haloperidol** resulted in excellent pain control without dose escalation or opioid-induced hyperalgesia

Pruritus

Organic Causes of Pruritus:
- Hepatic disease
- Renal disease
- Infection
  - Bacterial
  - Parasitic
  - HIV
- Diabetes
- Carcinoid
- Malignancy
- Collagen vascular disease

“Psychologic” causes of pruritus and self-excoriation:
- Anxiety disorder (primary or secondary)
- Obsessive-compulsive disorder
- Depressive disorder (primary or secondary)
- Personality disorder (especially borderline)
- Psychosis
- Habit
Pruritus

When there is a psychological component, or delusional ideation, or agitation is prominent, the author recommends considering Haloperidol

Conclusion

• Effective and essential medication for symptom management in Hospice and Palliative patients due to its unique pharmacodynamic profile.

• Dose: start low and go slowly

• Adverse effects: increased in medically complex patients with high risk clinical situations
Questions?