TDM monograph Haloperidol

Synonyms: Haldol

Summary

Indication:	**Approved indications:** • Schizophrenia or schizoaffective disorder • Acute treatment of delirium • Psychosis or mania in bipolar disorder type 1 • Chorea in Huntington's disease • Dementia with psychosis • Severe, persistent aggression in children with a developmental disorder • Tic disorders • Postoperative nausea **Off-label indications:** • Nausea and vomiting in the palliative phase • Obstructive ileus in the palliative phase • In combination with an SSRI for obsessive-compulsive disorder **Indications for TDM:** • Insufficient effect • Suspected adverse effects • Doubt about adherence • Drug interactions
Sample material:	Serum or plasma
Time of sampling:	For evaluation it is recommended that samples are taken at roughly the same interval after administration. For depot injections, a trough sample should be taken (i.e. sampling directly before administration of new injection)
Storage conditions:	Whole blood: store for 24 hours at 2–8 °C; Serum or plasma: store for 7 days at 2–8 °C. Keep protected from light.
Interpretation:	Therapeutic: 1-10 ug/L Toxic: > 20 ug/L
Evidence level:	3

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Introduction

Haloperidol is a widely used first-generation antipsychotic with a broad spectrum of indications in both acute and long-term management of psychotic disorders and agitation. Its primary mechanism of action is antagonism of dopamine D2 receptors, particularly within the mesolimbic pathway, which underlies its antipsychotic efficacy. Haloperidol also exhibits secondary activity at other receptors, including sigma and potentially 5-HT2 receptors, which may contribute to both therapeutic effects and adverse reactions.
Due to its narrow therapeutic window, considerable interindividual pharmacokinetic variability, and susceptibility to drug-drug interactions, plasma concentrations can vary markedly even at comparable doses. Therapeutic drug monitoring (TDM) therefore serves as a valuable tool to clarify the relationship between dose, plasma level, and clinical effect, enabling individualized therapy. This guideline outlines the pharmacology, clinical indications, and practical application of TDM for haloperidol.

Dosing guidelines (1-4)

Schizophrenia / schizoaffective disorder

- **Oral**: 2–10 mg/day in 1–2 doses; first episode 2–4 mg/day; up to 20 mg/day in very severe cases; adjust every 1–7 days. **Intramuscular (IM) decanoate (depot)** : 10–15× oral daily dose every 4 weeks (≈25–150 mg); maintenance 50–200 mg/4 weeks; up to 300 mg/4 weeks in severe cases.

Delirium in adults

- **Oral, adults**: 1–10 mg/day in 1–3 doses, start low and titrate every 2–4 hours up to 10 mg/day if agitation persists. **Oral, elderly**: 0.5–1.5 mg twice daily (max. 1 week); in crisis up to 10 mg/day short term, terminal phase up to 20 mg/day, then taper.
- **IM, adults:** 1–10 mg/day, titrate every 2–4 hours up to 10 mg/day if needed. **IM, elderly** (crisis, if oral not possible): single 2.5 mg dose for severe motor agitation.

Children and adolescents

- Schizophrenia / schizoaffective disorder: **≥12 years**: 0.01–0.025 mg/kg/day in 1–2 doses; increase weekly by 0.25–0.5 mg to usually 1–5 mg/day. **6–12 years**: same starting dose; increase weekly by 0.25–0.5 mg to 0.05–0.075 mg/kg/day (max. 0.15 mg/kg/day).
- Autism / PDD with severe aggression**: ≥12 years**: 0.01–0.025 mg/kg/day in 1–2 doses; titrate weekly to usually 1–5 mg/day. **6–12 years**: same starting dose; titrate weekly to 0.05–0.075 mg/kg/day

Dosing guidelines in patients with altered pharmacokinetics

In adults with liver cirrhosis:

- **Mild to moderate cirrhosis (Child-Pugh A and B):** start at 50% of the normal dose (see also section K);
- **Severe cirrhosis (Child-Pugh C):** start at 25% of the normal dose (see also section K).

In renal impairment:

- No dose adjustment is necessary. However; a low starting dose should be considered in serious renal impairment.

In adults with obesity:

- For obesity with a BMI of 40 kg/m² or higher, dose adjustment is not necessary.

After bariatric surgery in adults:

- After bariatric surgery, the effectiveness of oral administration is insufficiently known; as a precaution, monitoring of clinical effect and side effects is recommended during the first year after surgery, with dose adjustment if necessary. No effect of bariatric surgery is expected for parenteral administration.

Indications/Criteria for TDM

Reasons to apply TDM include: insufficient clinical response despite an adequate dose, the unexpected occurrence of significant adverse effects such as extrapyramidal symptoms or QT prolongation, suspected noncompliance, and the use of concomitant medications that affect haloperidol pharmacokinetics (e.g., CYP2D6 or CYP3A4 inhibitors/inducers). It may also be valuable for patients with a poor metaboliser of ultrarapid metabolisor CYP2D6 polymorphism. TDM is additionally useful in special populations, such as elderly patients, pediatric patients, those with liver or kidney dysfunction, or critically ill patients, where pharmacokinetics are more difficult to predict.

Reference values (2, 5-8)

A value between 1 and 10 µg/L is therapeutic.
A value above 20 µg/L is considered toxic.

Efficacy

There is compelling evidence for a relationship between haloperidol plasma levels, dopamine D_2 receptor occupancy, and clinical effect (5, 6). A meta-analysis of 18 studies demonstrated that the optimal therapeutic range in many patients with schizophrenia lies between 4–26 µg/L, with higher concentrations appearing to provide no additional clinical benefit (7). Pharmacodynamic studies indicate that optimal receptor occupancy is often achieved at plasma concentrations up to 10 µg/L. Consequently, this value is commonly used as the upper limit of the therapeutic range (2, 8).

Relationship with occurrence of side effects & toxicity

Serum levels above 20 µg/L are often associated with an increased risk of toxic effects, such as pronounced extrapyramidal symptoms, sedation, hypotension, and potential arrhythmias. Laboratory and clinical literature describe a biphasic relationship between concentration and effect: up to approximately 10 µg/L, increasing concentration correlates with enhanced therapeutic effect, whereas above this level, clinical benefit does not further increase and the risk of toxicity rises (8).

Patients with a chronic psychiatric disorder who are receiving long-term haloperidol treatment may tolerate higher plasma levels due to receptor adaptation (4).

In severe overdoses, life-threatening side effects may occur, such as coma, respiratory depression, and neuroleptic malignant syndrome (9).

In addition, the combination of high haloperidol levels with certain risk factors (such as cardiac arrhythmias) can contribute to heart toxicity, including QT prolongation and torsades de pointes (10).

Sampling & storage conditions

Whole blood: store for 24 hours at 2–8 °C;
Serum: store for 7 days at 2–8 °C.
Keep protected from light.

Background information

Pharmacodynamics

Haloperidol's pharmacodynamic profile is defined by strong antagonism of central dopamine D_2 receptors, with antipsychotic effects emerging when receptor occupancy reaches roughly 60–80%. Plasma concentrations predict this occupancy fairly well, and the relationship is steep: modest increases in exposure can rapidly push D_2 binding into ranges associated with extrapyramidal symptoms. Higher

occupancy is also linked to less favorable subjective experiences, reflecting a narrow balance between therapeutic benefit and tolerability (5, 6).

Pharmacokinetics

Absorption:

After oral administration, haloperidol is well absorbed. Because of first-pass metabolism, its oral bioavailability is 60–70%. The Cmax is reached 2–6 hours after oral dosing and 20–40 minutes after intramuscular administration. After intramuscular injection of the decanoate formulation, Cmax occurs after 3–9 days, followed by a decline with a half-life of approximately 3 weeks. Steady-state plasma concentrations are reached within 2–4 months.

Distribution:

Plasma protein binding is 88–92%. The volume of distribution ranges from 8–21 L/kg body weight.

Metabolism:

Haloperidol is metabolized mainly through glucuronidation, which accounts for approximately 50–60% of its metabolism. To a lesser extent, it is metabolized by CYP3A4, CYP2D6, and through carbonyl reduction. At higher doses, the relative contribution of glucuronidation in the metabolization pathway is reduced. The active metabolite, hydroxyhaloperidol, can be re-oxidized back to haloperidol via CYP3A4 and CYP2D6 (11).

Elimination:

It is excreted as metabolites in the urine (33%) and in the feces (21%). Less than 3% is excreted unchanged in the urine. The elimination half-life is 12–36 hours after oral administration and 13–36 hours after intramuscular dosing.

Other:

In acute psychosis or delirium, clinical effects begin 10–20 minutes after oral or intramuscular administration. In Child-Pugh A, B, and C cirrhosis, AUC increases to approximately 1.35×, 2.34×, and 3.56× normal, respectively (3).

Pharmacogenetics

For CYP2D6 genetic variants (3, 12, 13):

- Poor metabolizers: plasma concentrations may be increased; reduce the dose to about 60% of the standard dose.
- Intermediate metabolizers: plasma concentrations may be increased, but this is not clinically relevant.
- Ultrarapid metabolizers: plasma concentrations may be decreased; increase the dose to about 150% of the standard dose.

CYP3A4 is also important in the metabolism of haloperidol; however, guidelines do not recommend upfront dose adjustments based on a variant genetic profile (14).

Interactions

Haloperidol inhibits CYP2D6. It is metabolized by CYP3A4 and CYP2D6, and its plasma concentration decreases when strong CYP3A4 inducers or CYP2D6 inducers are used. Concentrations may increase when combined with CYP3A4 inhibitors such as cobicistat and ritonavir (3).
Haloperidol can prolong the QTc interval, and the risk of serious cardiac arrhythmias is increased when combined with other agents associated with severe arrhythmias such as torsade de pointes. Haloperidol doses above 5 mg per day are classified as having a moderate QT-prolonging potential, whereas doses of 5 mg per day or lower are classified as having a low QT-prolonging potential. The interaction is not considered clinically relevant when low-dose haloperidol (5 mg per day or less) is combined with another drug that also has a low QT-prolonging potential (10).

PK parameters

Haloperidol	**F** (%)	**Cl** (L/h^{-1})	**Vd** (L/kg)	$\mathbf{t_{1/2}}$ (h^{-1})	Protein binding	Tmax	Ref.
Adults, oral formulation	60-70% (first pass)	10-68	8-21	15-37 hrs	88-92%	2-6 hrs	(3)
Intramuscular	NA	10-68	8-21	13-36 hrs	88-92%	20 mins	(3)
Parenteral (haloperidol decanoate, depot)	NA	10-68	8-21	21 days	88-92%	3-9 days	(15)

Population models

Population	**Model**	**Kabs** (h^{-1}) **/ F**	**Vd** (L/kg) **/ F**	**Kelm** (h^{-1}) **/ F**	**CL** (L/h^{-1}) **/ F**	Ref.
Critically ill adult ICU-patients	1-comp	NA (intravenous dosing)	18.6		51.7	(16)
Japanese patients > 16 years old with various chronic psychiatric conditions	1-comp	Not reported	Age below 65: 34.4 Age above 65: 11.56		42.4	(17)
Terminally ill adults in a hospice	1-comp	0.236 (oral) 20 (subcutanous)	18.8		29.3	(18)

Colophon

This guideline has been updated by dr. Robert J. van de Peppel, internist and clinical pharmacologist in training, under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)
An earlier version of this document was written in 2014 by M. van Soest and I. van Berlo-van de Laar.
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