

North Staffordshire and Stoke-on-Trent Area Prescribing Committee

Medicine Review Summary

Droperidol 2.5mg/1ml injection

Verdict:	
Formulary inclusion:	Approved by the Area Prescribing Committee (APC) for inclusion in the North Staffordshire Joint Formulary
Formulary category:	Red
Restrictions:	To be prescribed by, or on the advice of, a specialist in paediatric anaesthetics
Reason for inclusion:	The APC were satisfied with the evidence for efficacy and safety, dosing convenience, cost implications and intended place in therapy
Link to formulary:	Primary care: http://www.northstaffordshirejointformulary.nhs.uk/ Secondary care: http://uhns/clinicians/clinical-guidance/clinical-guidelines/prescribing-formularies/
Link to medicine review summary:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet → Clinicians → Support services → Pharmacy → Joint Formulary Related Documentation → North Staffordshire & Stoke-on-Trent Area Prescribing Committee Medicine Review Summary Verdict Sheets
Link to full review:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet → Clinicians → Support Services → Pharmacy → Joint Formulary Related Documentation → New Medicine Committee (NMC) Medicines Reviews

Review summary:
<p>Formulary application</p> <p>Dr Catherine Stewart (consultant paediatric anaesthetist, UHNM) submitted an application to include droperidol in the North Staffordshire Joint Formulary. The submission is supported by Dr Charles Baker (clinical director, consultant anaesthetist, UHNM). Dr Stewart attended the New Medicines Committee meeting on 04/09/2019 to support the application.</p> <p>This is the first time the New Medicines Committee has reviewed an application to include droperidol in the North Staffordshire Joint Formulary.</p> <p>The UHNM paediatric anaesthetics team propose that droperidol is prescribed as rescue therapy (3rd line antiemetic) for post-operative nausea and vomiting in children and adolescents aged 2 – 18 years old who do not respond adequately to dexamethasone or ondansetron (as monotherapy or in combination). The New Medicines Committee recommended that prescribing is restricted to secondary care (red RAG rating), and to specialists in anaesthetics.</p> <p>Droperidol has been prescribed for several decades in adults and children as an antiemetic and antipsychotic.</p> <p>Droperidol was withdrawn from the UK market by Janssen Cilag in March 2001 due to concerns regarding use in</p>

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chronic conditions and droperidol's potential to increase QTc. Droperidol was re-introduced to the UK market in May 2009 after further scrutiny of evidence showed that droperidol's effect on QTc is modest, reversible and of short duration. Dr Stewart stated she has used droperidol successfully in paediatric patients at other NHS Trusts. In practice, most patients only require a single stat dosage.

Droperidol is recommended as a 3rd line option in current national guidelines for the prevention of post-operative nausea and vomiting in children (The Association of Paediatric Anaesthetists of Great Britain & Ireland (APA) Guidelines on the Prevention of Post-operative Vomiting in Children 2016). Droperidol is also recommended in regional paediatric and adolescent guidance for treatment of persistent post-operative nausea and vomiting where ondansetron and dexamethasone are contraindicated or not clinically effective (Partners in Paediatrics Bedside Clinical Guidelines 2018-2020).

Droperidol, though more expensive than ondansetron or dexamethasone, is still relatively inexpensive.

It is predicted that droperidol's inclusion in the North Staffordshire Joint Formulary will improve patients' and carers' experience plus minimise post-operative complications and reduce overall cost of treatment for paediatric patients at high risk of post-operative nausea and vomiting.

Licensed indications:

- Prevention and treatment of post-operative nausea and vomiting (PONV) in adults and, as second line, in children (2 to 11 years) and adolescents (12 to 18 years).
- Prevention of nausea and vomiting induced by morphine derivatives during post-operative patient controlled analgesia (PCA) in adults.

Dosing:

Adults: 0.625 mg to 1.25 mg (0.25 to 0.5 ml).

Elderly (over 65 years): 0.625 mg (0.25 ml)

Adult Renal/hepatic impairment: 0.625 mg (0.25 ml)

Children (2 to 11 years) and adolescents (12 to 18 years): 10 to 50 microgram/kg (up to a maximum of 1.25 mg).

Children (below the age of 2 years): not recommended.

Administration of droperidol is recommended 30 minutes before the anticipated end of surgery. Repeat doses may be given every 6 hours as required.

The APA guidelines advises a maximum paediatric and adolescent dose (age 2- 18 years old) of 25mcg/kg (maximum 1.25mg) is administered

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The dosage should be adapted to each individual case. The factors to be considered here include age body weight, use of other medicinal products, type of anaesthesia and surgical procedure.

Related guidance:

National Guidance:

The Association of Paediatric Anaesthetists of Great Britain & Ireland (APA) Guidelines on the Prevention of Post-operative Vomiting in Children 2016

The current APA guidelines state droperidol can be effective for both prophylaxis and treatment of post-operative vomiting, particularly in situations where dexamethasone is contraindicated. The APA Guidelines recommend droperidol should be considered as monotherapy or as combination therapy with ondansetron. Combination therapy is recommended if patient is at high risk of post-operative vomiting or where monotherapy as failed. Prophylactic antiemetic therapy for all patients is not recommended due to unnecessary exposure to possible side effects. The APA recommend that only patients identified as high risk of post-operative vomiting should be offered prophylaxis.

The APA guidelines advises a maximum paediatric and adolescent dose (age 2- 18 years old) of 25mcg/kg (maximum 1.25mg) is administered

Regional Guidance:

Droperidol is listed as a third line option for post-operative nausea and vomiting in children and adolescents aged 2-17 years old, in the Partners in Paediatrics Bedside Clinical Guidelines 2018-2020. Droperidol 25mcg/kg IV (maximum 1.25mg) is recommended if patient is experiencing persistence nausea and at least 1 episode of vomiting after receiving ondansetron within the last 8 hours, and if dexamethasone (2nd line treatment) is not clinically appropriate. The Partners in Paediatrics consists of the following NHS Trusts:

Birmingham Community Healthcare NHS Foundation Trust

Birmingham Women's and Children's NHS Foundation Trust

Black Country Partnership NHS Foundation Trust

Dudley Clinical Commissioning Group

East Cheshire NHS Trust

George Eliot Hospital NHS Trust

Midlands Partnership NHS Foundation Trust

Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Foundation Trust

South Warwickshire NHS Foundation Trust

The Dudley Group NHS Foundation Trust

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The Royal Orthopaedic Hospital NHS Foundation Trust

The Royal Wolverhampton NHS Trust

The Shrewsbury & Telford Hospital NHS Trust

University Hospitals Birmingham NHS Foundation Trust

University Hospitals Coventry & Warwickshire NHS Trust

University Hospitals of Derby and Burton Hospitals NHS Foundation Trust

University Hospitals of North Midlands NHS Trust

NICE: Not reviewed

SMC: Not reviewed

RDTC: Not reviewed

MTRAC: Not reviewed

Background information:

Post-operative vomiting is estimated to be twice as frequent amongst paediatric patients compared to adult patients. Incidence rates amongst paediatric patients are estimated at 13-42%.

Severe post-operative vomiting can result in complications which extend hospital admission or can lead to unanticipated hospital admission following day-case surgery. Dr Stewart estimated at least one paediatric patient per annum has an unexpected hospital admission post day-surgery due to severe PONV which persists despite dexamethasone and ondansetron. Complications of persistent PONV can include wound dehiscence, dehydration, pulmonary aspiration and electrolyte imbalance.

Risk factors for post-operative vomiting include

-Age

-History of post-operative vomiting and/or motion sickness

-Gender (female patients are at greater risk of post-operative vomiting from puberty onwards)

-Duration of surgery (> 30 minutes under general anaesthetic)

-Type of surgery e.g. strabismus surgery

Droperidol has been used as an antipsychotic and antiemetic for several decades in adults and children. Droperidol was withdrawn from the UK market by Janssen Cilag in March 2001 due to concerns regarding use in chronic conditions and droperidol's potential to increase QTc. Droperidol was re-introduced to the UK market in May 2009

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after further scrutiny of evidence showed that droperidol's effect on QTc is modest, reversible and of short duration.

Droperidol is recommended as rescue therapy for paediatric and adolescent patients aged 2 years or older who do not respond to or for whom ondansetron and/or dexamethasone are contraindicated, by national and regional paediatric anaesthetics guidance.

Efficacy:

Droperidol is a butyrophenone neuroleptic. Its pharmacologic profile is characterised mainly by dopamine-blocking and weak α 1-adrenolytic effects. Droperidol is devoid of anticholinergic and antihistaminic activity.

Droperidol's inhibitory action on dopaminergic receptors in the chemotrigger zone in the area postrema, gives it a potent antiemetic effect, especially useful for the prevention and treatment of postoperative nausea and vomiting and/or induced by opioid analgesics.

A 1999 meta-analysis of published double blinded, randomised controlled trials compared the efficacy and safety of ondansetron, metoclopramide and droperidol. 58 studies were included (4 were excluded for methodological reasons). Ondansetron was more effective than droperidol in preventing vomiting in children, but ondansetron and droperidol were equally effective in adults. Ondansetron and droperidol were more effective than metoclopramide in preventing vomiting.

A 2000 systematic review including 29 trials in paediatrics concluded that the NNT for droperidol in paediatric patients (number needed to treat) was 4.2 at a dose of 75mcg/kg, which is above the licensed maximum dose. At a dose of 10-20 mcg/kg, the NNT to prevent early vomiting was 7.8. For a dose of 40-50 mcg/kg, the NNT to prevent early vomiting in children decreased to 6.6. All outcomes showed an improvement in early onset PONV (0-6 hours post-operative) with droperidol compared with placebo. The same systematic review (Henzi et al) stated that all outcomes showed that droperidol showed a statistically significant improvement in PONV in children. There was evidence of dose-responsiveness for late anti-vomiting efficacy with IV doses. For the lowest dose-range, 5-20 mcg/kg, the NNT to prevent late vomiting was 7.3. With a dose of 50 mcg/kg, the NNT decreased to 4.4. For the most frequently used dose used in reviewed trials, 75 mcg/kg (which is above the current maximum licensed dose in children), the NNT further decreased to 3.8. Confidence intervals overlapped, however, NNT point estimates improved by 92%. The NNH (number needed to harm) for extrapyramidal symptoms was 91 for children (in any patient NNH was 408). The review also concluded that drowsiness and sedation are dose dependant

The combination of ondansetron and droperidol may be synergistic. Chan et al (2006) studied 400 adult patients

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scheduled for laparoscopic gynaecologic surgery who were randomly assigned to receive 1) saline IV; 2) ondansetron 4 mg IV; 3) droperidol 1.25 mg IV; or 4) a combination of droperidol 1.25 mg and ondansetron 4 mg IV five minutes before induction of anaesthesia. Patients were reviewed regularly for 48 hours. Changes in the heart rate adjusted QTc interval were measured from electrocardiograms recorded before and 5 minutes after study drug administration. In a subgroup of 160 patients, QTc intervals were measured again at 2–3 h after surgery. During the first 48 h after the surgery, the proportion of patients experiencing PONV was 68% (95% CI 58–77) in the control group. A single dose of ondansetron or droperidol decreased the incidence of PONV to 30% (95% CI 21–40) and 28% (95% CI 20–38), respectively. The predicted incidence of PONV after drug combination, 11.8% (7.1–11.9), was similar to that observed, 12.1% (6.4–20.2), $P = 0.94$. The corresponding predicted and observed treatment responses in the combination group were 88.2% and 87.9%, respectively. There was a modest and transient increase in QTc interval after administration of ondansetron, droperidol, or their combination. The changes were however similar among groups. The authors concluded that the interaction between ondansetron and droperidol was additive. Both drugs acted independently of each other through their specific mechanisms of action. The incidence of QTc prolongation did not increase with the drug combination.

Safety:

Droperidol was withdrawn from the UK market by Janssen Cilag in March 2001 due to concerns regarding use in chronic conditions and droperidol's potential to increase QTc. Droperidol was re-introduced to the UK market in May 2009 after further scrutiny of evidence showed that droperidol's effect on QTc is modest, reversible and of short duration. One comparison study involving a paediatric cohort (Mehta et al, 2010) found that both droperidol and ondansetron were associated with modest increases in QTc intervals when administered at therapeutic antiemetic doses. The study authors concluded that ondansetron and droperidol, in therapeutic anti-emetic doses, produce equivalent, clinically insignificant QT prolongation and negligible Tp-e prolongation, suggesting that neither is torsadogenic in healthy children at these doses. Furthermore many general anaesthetics are also associated with an increased QTc interval so it is difficult to differentiate the effects of that and therapy for PONV. The most frequently reported adverse effects are drowsiness and sedation (reported as common side effects, with an incident rate of $\geq 1/100$ to $< 1/10$). Hypotension is reported as a less frequent side effect, but with an incident rate of $\geq 1/100$ to $< 1/10$. Symptoms associated with extra-pyramidal side effects (akathisia, dystonia) have been reported as uncommon side effects ($\geq 1/1,000$ to $< 1/100$) but incidences of extra pyramidal side effects are reported as occurring very rarely ($< 1/10,000$). Tachycardia, anxiety and agitation are reported as uncommon side effects ($\geq 1/1,000$ to $< 1/100$).

Symptoms potentially associated with neuroleptic malignant syndrome (reported as a rare side effect with an incident rate of $\geq 1/10,000$ to $< 1/1,000$) have occasionally been reported i.e. changes in body temperature,

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stiffness and fever. An alteration in mental status with confusion or agitation and altered consciousness, have been seen. Autonomic instability may manifest as tachycardia, fluctuating blood pressure, excessive sweating/salivation and tremor. In extreme cases NMS may lead to coma, or renal and/or hepato-biliary problems.

Isolated cases of amenorrhoea, galactorrhoea, gynaecomastia, hyperprolactinaemia, and oligomenorrhoea have been associated with prolonged exposure in psychiatric indications. In practice, a single stat dose is usually sufficient to treat PONV, though doses can be repeated every 6 hours.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic medicinal products - frequency unknown

Droperidol may enhance CNS depression produced by other CNS-depressant drugs. Any patient subjected to anaesthesia and receiving potent CNS depressant medicinal products or showing symptoms of CNS depression should be monitored closely.

Concomitant use of metoclopramide and other neuroleptics may lead to an increase in extrapyramidal symptoms and should be avoided

It is advised to use droperidol with caution in patients with epilepsy (or a history of epilepsy) and conditions predisposing to epilepsy or convulsions.

Mild to moderate hypotension and occasionally (reflex) tachycardia have been observed following the administration of droperidol. This reaction usually subsides spontaneously. However, should hypotension persist, the possibility of hypovolaemia should be considered and appropriate fluid replacement administered.

Patients with, or suspected of having, the following risk factors for cardiac arrhythmia should be carefully evaluated prior to administration of droperidol:

- a history of significant cardiac disease including serious ventricular arrhythmia, second or third
- degree atrio-ventricular block, sinus node dysfunction, congestive heart failure, ischemic heart disease and left ventricular hypertrophy;
- family history of sudden death;
- renal failure (particularly when on chronic dialysis);
- significant chronic obstructive pulmonary disease and respiratory failure;
- risk factors for electrolyte disturbances, as seen in patients taking laxatives, glucocorticoids, potassium-wasting diuretics, in association with the administration of insulin in acute settings, or in patients with prolonged vomiting and/or diarrhoea.

Patients at risk for cardiac arrhythmia should have serum electrolytes and creatinine levels assessed and the presence of QT prolongation excluded prior to administration of droperidol.

Continuous pulse oximetry should be performed in patients with identified or suspected risk of ventricular arrhythmia and should continue for 30 minutes following single I.V. administration.

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General

To prevent QT prolongation, caution is necessary when patients are taking medicinal products likely to induce electrolyte imbalance (hypokalaemia and/or hypomagnesaemia) e.g. potassium-wasting diuretics, laxatives and glucocorticoids

Patients who have, or are suspected of having, a history of alcohol abuse or recent high intakes, should be thoroughly assessed before droperidol is administered.

In case of unexplained hyperthermia, it is essential to discontinue treatment, since this sign may be one of the elements of malignant syndrome reported with neuroleptics.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with droperidol and preventive measures undertaken.

The dose should be reduced in the elderly and those with impaired renal and hepatic function

This medicinal product contains less than 1 mmol sodium (23 mg) per 1 ml, i.e. essentially 'sodium-free'.
Droperidol is contraindicated in patients with:

- Hypersensitivity to droperidol or to any of the excipients;
- Hypersensitivity to butyrophenones;
- Known or suspected prolonged QT interval (QTc of > 450 msec in females and > 440 msec in males). This includes patients with congenitally long QT interval, patients who have a family history of congenital QT prolongation and patients treated concomitantly with medicinal products known to have a risk of torsades de pointes through QT prolongation (see section 4.5);
- Hypokalaemia or hypomagnesaemia;
- Bradycardia (< 55 heartbeats per minute);
- Known concomitant treatment leading to bradycardia;
- Pheochromocytoma;
- Comatose states;
- Parkinson's Disease;
- Severe depression

Drug Interactions

Substances inhibiting the activity of cytochrome P450 iso-enzymes (CYP) CYP1A2, CYP3A4 or both could decrease

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the rate at which droperidol is metabolised and prolong its pharmacological action. Hence, caution is advised if droperidol is given concomitantly with strong CYP 1A2 and CYP3A4 inhibitors.

Substances which can cause torsades des pointes through QT interval prolongation are contraindicated (e.g. amiodarone, sotalol, cisapride, macrolide antibiotics etc)

Substances which can cause extrapyramidal side effects should not be administered concurrently with droperidol. Examples include metoclopramide and other neuroleptics.

Alcohol (in beverages or in medicines) should be avoided

Place in therapy:

The UHNM paediatric anaesthetics team propose that droperidol is prescribed as rescue therapy (3rd line antiemetic) for children and adolescents who do not respond adequately to dexamethasone or ondansetron (as monotherapy or in combination).

Cost:

It is predicted that 20-40 patients per year may be prescribed droperidol.

Most patients will respond to a single dose peri-operatively (30 minutes before the anticipated end of surgery). Repeat doses may be given every 6 hours as required.

The maximum licensed single dose for children and adolescents aged 2-18 years old is 50mcg/kg or 1.25mg stat. In practice a maximum of 25mcg/kg (up to 1.25mg) is administered stat (as per APA guidelines) and a single dose is clinically effective.

Droperidol is more expensive compared to dexamethasone and ondansetron prescribed as monotherapy or in combination. However, annual expenditure for droperidol is expected to be off-set by savings made by preventing unplanned overnight admissions or extended hospital admissions.

Maximum cost per dose of antiemetics for post-operative nausea and vomiting in children and adolescents (aged 2-17 years old), inclusive of VAT	
Ondansetron (0.1mg/kg up to a maximum 4mg per dose)	4mg Orodispersible tablet - £ [redacted] per 4mg dose 4mg/2ml injection = £ [redacted] per 4mg dose (administered as IV injection over at least 30 seconds)
Dexamethasone (0.15mg/kg up to a maximum of 6.6mg)	3.3mg/ml injection = £ [redacted] per 6.6mg dose (administer as slow IV injection over 3-5 minutes)
Droperidol (maximum 1.25mg per dose)	2mg/ml injection = £ [redacted] per 1.25mg dose

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	(administered as slow IV injection over 3-5 minutes)- NB prices based on Panpharma product	
Predicted droperidol expenditure (based on Panpharma product prices)		
	Cost per patient (inclusive of VAT)	Predicted annual droperidol expenditure (inclusive of VAT) based on 40 patients per annum.
Droperidol 1.25mg stat dose (maximum licensed single dose)	██████	██████
Droperidol 1.25mg administered every 6 hours for up to 48 hours (8 doses)	██████	██████
SUMMARY OF PREDICTED ANNUAL EXPENDITURE FOR DROPERIDOL	Minimum annual droperidol expenditure is predicted to be £██████ if all patients receive a single dose only. Maximum annual droperidol expenditure will be £██████ if all patients received a maximum of 8 doses – in practice this is unlikely as most patients respond to a single dose.	

References:

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