PROPOSED ALTERNATIVE MEDICATIONS

FOR

DRUG SHORTAGE EMERGENCIES

SOUTHERN NEVADA HEALTH DISTRICT

BENZODIAZEPINES (ADULT USAGE)

PREFERENCE	GENERIC NAME	TRADE NAME	DOSE	ROUTE	BENEFITS	PROBLEMS
Current Choice	Midazolam	Versed	5-10 mg	IV/IO/IM/IN	• Rapid-acting • Water-soluble.	
Alternative 1	Diazepam	Valium	5-15 mg	IV/IO/IM	• Similar dosing to midazolam. • Inexpensive. • Effective anxioloytic and anticonvulsant	• Cannot be diluted with water. • Long half-life
Alternative 2	Lorazepam	Ativan	1-2 mg	IV/IO/IM/PR	• Rapid-acting. • Effective anxiolytic. • Effective anticonvulsant.	• Requires refrigeration for long-term storage. • Different dosing than midazolam.
Alternative 3	Lorazepam	Ativan	1-4 mg	PO/SL	• Anxiolysis	• Slow-acting. • Cannot be used for seizures.
Alternative 4	Diazepam	Diastat	10-20 mg	PR	• Alternative to parenteral access for seizures. • Dose easy to dial in.	• More costly. • Rectal only. • Rectal administration
Alternative 5	Droperidol	Inapsine	0.625-1.25 mg	IV/IO/IM	• Effective • Anti-emetic	• Not benzodiazepine • QT prolongation

BENZODIAZEPINES (PEDIATRIC USAGE)

PREFERENCE	GENERIC NAME	TRADE NAME	DOSE	ROUTE	BENEFITS	PROBLEMS
Current Choice	Midazolam	Versed	0.1 mg/kg	IV/IO/IM/IN	• Rapid acting • Water-soluble.	
Alternative 1	Lorazepam	Ativan	0.05 mg/kg	IV/IO/IM/PR	• Rapid acting • Effective anxiolytic and anticonvulsant.	• Requires refrigeration for long-term storage. • Different dosing than midazolam.
Alternative 2	Diazepam	Valium	0.1-.03 mg/kg	IV/IO/IM	• Similar dosing to midazolam. • Effective anxiolytic and anticonvulsant.	• Cannot be diluted with water. • Long half-life.
Alternative 3	Diazepam	Diastat	2-5 years 0.5 mg/kg 6-11 years 0.3 mg/kg >12 years 0.2 mg/kg	PR	• Alternative to parenteral access for seizures. • Dose easy to dial in.	• More costly • Rectal only. • Rectal administration.

INDUCTION AGENTS

PREFERENCE	GENERIC NAME	TRADE NAME	DOSE	ROUTE	BENEFITS	PROBLEMS
Current Choice	Etomidate	Amidate	0.15-0.3 mg/kg	IV/IO/IM	• Rapid-acting. • Hemodynamic stability.	• Adrenal suppression. • No pediatric usage. • No analgesia.
Alternative 1	Ketamine	Ketalar	1-2 mg/kg	IV/IO/IM	• Effective. • Bronchodilator • Preserves respiratory drive.	• Emergence phenomenon. • Hypertension. • Increased secretions.
Alternative 2	Propofol	Diprivan	1-2 mg/kg	IV/IO	• Effective • Short-acting. • Anticonvulsant.	• IV access required. • Hypotension common. • No anxiolysis or analgesia. • No pediatric usage.
Alternative 3	Midazolam	Versed	0.1 mg/kg	IV/IO/IM/IN	• Rapid acting • Water-soluble.	• Higher doses required than for anxiolysis. • Respiratory depression.

ANTI-EMETICS (ADULT USAGE)

PREFERENCE	GENERIC NAME	TRADE NAME	DOSE	ROUTE	BENEFITS	PROBLEMS
Current Choice	Ondansetron	Zofran	4-8 mg	IV/IO/IM	• Inexpensive • Effective • Safe	• None
Alternative 1	Ondansetron	Zofran	4-8 mg	PO	• Inexpensive • Effective • Safe	• Slower-onset • Oral administration
Alternative 2	Droperidol	Inapsine	0.625-1.25 mg	IV/IO/IM	• Effective • Profound sedative	• QT prolongation
Alternative 3	Promethazine	Phenergan	12.5-25.0 mg	IV/IO/IM	• Effective	• Phenothiazine • Tissue necrosis with extravasation • EPS reactions • Sedating
Alternative 4	Prochlorperazine	Compazine	5-10 mg	IV/IO/IM	• Effective.	• Phenothiazine • EPS reactions • Sedating

ANALGESICS

PREFERENCE	GENERIC NAME	TRADE NAME	DOSE	ROUTE	BENEFITS	PROBLEMS
Current Choice	Morphine	Duramorph	0.1 mg/kg	IV/IO/IM	• Inexpensive • Effective • Long-acting.	• Respiratory depression. • Long-acting.
Alternative 1	Fentanyl	Sublimaze	1.5 mcg/kg	IV/IO/IM	• Effective • Short-acting. • Few cardiovascular effects.	• Stiff chest with rapid administration.
Alternative 2	Hydromorphone	Dilaudid	0.0125 mg/kg	IV/IO/IM	• Effective • Intermediate-acting.	• Respiratory depression.
Alternative 3	Ketamine	Ketalar	1-2 mg/kg	IV/IO/IM	• Effective • Anxiolytic. • Dissociation.	• Trauma only. • Emergence phenomenon. • Increases secretions.
Iternative 4	Nalbuphine	Nubain	0.3 mg/kg	IV/IO/IM	• Schedule V • Inexpensive.	• Mixed agonist/antagonist. • Unpredictable effect. • Can precipitate narcotic withdrawal in patients on chronic opiates.

775-827-9354

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Inapsine® (Droperidol) Safety Review
University Medical Center of Southern Nevada
Medication Safety Evaluation Committee
March 6, 2012

Prepared by: Jayme Hara, PharmD, BCPS

Executive Summary: Inapsine® (droperidol)

Therapeutic Class: Butyrophenone

Similar Drugs: Haloperidol

Indication: Prophylaxis of nausea and vomiting associated with surgical and diagnostic procedures; treatment of nausea and vomiting; treatment of acute agitation

Mechanism of action[1]: True mechanism unknown. Antiemetic effect thought to due to binding at postsynaptic gamma-aminobutyric acid (GABA) receptors in the chemoreceptor trigger zone. Droperidol may also block dopaminergic receptors. Selectively blocks postsynaptic α-adrenergic receptors which may cause vasodilation and hypotension.

Pharmacokinetics[1]:
- Onset of action: 3-10 minutes (IM/IV)
- Peak Response: 30 minutes (IM/IV)
- Absorption: Rapid
- Duration: 2-4 hours, may persist up to 12 hours (IM/IV)
- Metabolism: Liver
- Excretion: Renal 75%; Feces 22%
- Half-life: 2 hours

Adverse Events[1,2]:
- **Common:** Hypotension (mild to moderate, generally subsides without treatment), tachycardia (generally subsides without treatment), dysphoria, post-op drowsiness, restlessness, hyperactivity, anxiety, extrapyramidal signs and symptoms (dystonias, akathisias, hyperactivity)
- **Serious:** QT interval prolongation, torsade de pointes (TdP), ventricular tachycardia, cardiac arrest, neuroleptic malignant syndrome

FDA Approved Doses[1,2]:
- Maximum initial dose 2.5mg IM or slow IV, additional doses of 1.25mg may be given to achieve desired clinical effect

History:
- 1970 – FDA approval
- 2001 – Black Box Warning (BBW)
- 2008 – FDA Clarification of BBW

Black Box Warning[3]:
Cases of QT prolongation and/or torsade de pointes have been reported in patients receiving droperidol at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation and some cases have been fatal.

Due to its potential for serious proarrhythmic effects and death, droperidol should be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs.

Cases of QT prolongation and serious arrhythmias (e.g. torsade de pointes) have been reported in patients treated with droperidol. Based on these reports, all patients should undergo a 12-lead ECG prior to administration of droperidol to determine if a prolonged QT interval (i.e. QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, droperidol should NOT be administered. For patients in whom the potential benefit of droperidol treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for 2-3 hours after completing treatment to monitor for arrhythmias.

Droperidol is contraindicated in patients with known or suspected QT prolongation, including patients with congenital long QT syndrome.

Droperidol should be administered with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g. congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia, hypomagnesemia, or administration of other drugs known to increase the QT interval). Other risk factors may include age over 65 years, alcohol abuse, and use of agents such as benzodiazepines, volatile anesthetics, and IV opiates. Droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect.

FDA Clarification of Black Box Warning[4,5]:
The droperidol boxed warning applies to the approved doses of this product as delineated in the product label. The FDA has received no data to support or dispute any speculation that lower, unapproved doses (< 2.5 mg) of droperidol might or might not be sufficiently caridotoxic so as to merit an equal level of concern as the approved doses.

Evidence:
In 1999, Domino et al. published a meta-analysis comparing droperidol, ondansetron and metoclopramide for postoperative nausea and vomiting. A total of 7, 324 patients were included in the analysis, and they found that droperidol and ondansetron were equally effective with no difference in the risk of adverse drug events.[6]

In 2002, Chase et al. published a retrospective review of the safety of droperidol use in a large, inner-city emergency department. They found six possible serious adverse events (AE) in the 2,468 patients that received droperidol. All six AEs occurred in patients with serious other comorbidities. They documented 2 cases of respiratory depression, 3 post-droperidol seizures, and 1 cardiac arrest. The cardiac arrest occurred in a cocaine-intoxicated patient, with a normal QT interval, 11 hours after droperidol administration.[7]

In 2003, Shale et al. published a retrospective review of the safety and efficacy of droperidol for treatment of severely agitated and violent patients. A review of medication records from October 1998 to May 2001 showed that 4,145 doses of droperidol 5mg were given in their emergency department. Based off of that sample, over the previous decade, they estimate that more than 12,000 patients received droperidol 5 mg in the emergency department with no clinically significant dysrhythmia.[8]

In 2003, Kao et al. published a literature search to evaluate the evidence regarding the association between droperidol and QT prolongation or TdP. Based off of systemic reviews, randomized controlled trials, abstracts and case reports, they found a dose dependent association between droperidol and QT prolongation, but there was no strong evidence to link droperidol to the development of TdP or sudden death.[9]

In 2004, Mullins et al. published a review of the 270 MedWatch reports submitted to the FDA between November 1, 1997 to January 10, 2002. After excluding duplicate reports, they found 99 death reports, of which 83% were foreign where they use significantly higher doses than in the United States (25-600 mg). The authors concluded that "cardiovascular deaths after therapeutic doses ($\leq$ 2.5 mg) of droperidol are rare. Mandatory electrocardiographic screening appears unnecessary."[10]

In 2005, White et al. published a randomized, double-blind, placebo-controlled study to evaluate the effects of low-dose droperidol on the QT interval when used for antiemetic prophylaxis during general anesthesia. Patients were randomized to receive saline, 0.625 mg droperidol, or 1.25 mg droperidol. They found that QT changes in the droperidol groups did not differ significantly from the saline group (Table 1), and they concluded that small doses of droperidol were not associated with clinically significant prolongation of the QT interval.[11]

Table 1. Effects of droperidol on QT interval

	Control (n=20)	0.625 mg Droperidol (n=20)	1.25 mg Droperidol (n=20)
Mean maximum ΔQTc (msec)	12 ± 35	15 ± 40	22 ± 41

In 2007, Nuttall et al. published a large retrospective study analyzing the incidence of TdP with low-dose droperidol administration in the general surgical population (maximum initial dose droperidol 2.5 mg). They evaluated data from three years before and three years after the FDA black box warning (n = 291,188 patients). They report an incidence of QT prolongation, ventricular tachycardia or death at 48 hours post-op of 1.66% before the BBW, and 1.46% after the BBW. Despite a decline in droperidol use from 12% before the BBW to 0% after the BBW, the incidence of ECG abnormalies were similar (Table 2). They found one possible TdP case in the 16,791 patients exposed to droperidol, although the event occurred 10 hours after droperidol administration.[12]

Table 2. QTc Prolongation, Ventricular Tachycardia (VT) or Death at 48 hrs post-op

	Before BBW (7/1998 – 6/2001)	**After BBW (7/2002 – 6/2005)**
Surgical Patients	139,932	151,256
Estimated Droperidol exposure	16,791 (12%)	0

QTc prolongation, VT or death at 48 hrs post-op	2,231 (1.66%)	2,207 (1.46%)

In 2010, Halloran et al. published an evaluation of the FDA black box warning. They reviewed the adverse events reported to the FDA between 1997- 2002. Over the four year period, between 11 million and 25 million doses of droperidol were sold annually, and they found only one fatality possibly related to droperidol causing TdP.[13]

Conclusion:
The QT interval is only a surrogate measure for TdP, and although studies have shown a dose dependent association between droperidol and QT prolongation, the evidence suggests low-dose droperidol is both safe and effective. The FDA has also clarified that the black box warning does not apply to doses < 2.5mg, as the risk of prolonged QT and TdP is not clear at these lower doses.

UMC currently has a policy referring to the IV administration of haloperidol, another butyrophenone associated with QTc prolongation, which specifically states that cardiac monitoring is unnecessary since direct cardiac effects have been found to be minimal.[14] The evidence suggest the same is true about droperidol.

Recommendation:
Low dose IV droperidol (doses $\leq$ 2.5mg) should be permitted without ECG monitoring.

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