**Haloperidol: An alternative butyrophenone for nausea and vomiting prophylaxis in anesthesia**

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**Droperidol and Food and Drug Administration actions**

Postoperative nausea and vomiting (PONV) continues to be the most common surgical complication.

In 1970, the US Food and Drug Administration (FDA) approved droperidol for use as an antiemetic. This effect is produced through blockade of dopamine D₂ receptors of the chemoreceptor trigger zone in the area postrema of the brain. Since its approval, several million patients have received droperidol, establishing a long history of relatively safe and effective use. However, in December 2001, the FDA issued a “black box” warning for droperidol. The FDA based its actions on 100 reports of adverse cardiovascular events reported between November 1997 and December 2001. Twenty episodes of torsades de pointes (TdP) and 5 deaths are believed to have occurred with droperidol at or below the labeled dose range. This warning greatly limits the use of droperidol because of stringent patient prescreening, selection, and monitoring criteria that now must be met.

The FDA recommends that every patient have a preoperative electrocardiogram with corrected QT interval (QTc) determination before droperidol use and electrocardiographic monitoring for 2 to 3 hours postoperatively. It is obvious that these recommendations are expensive and difficult to implement, making the use of droperidol problematic. As a result, the use of droperidol is limited in anesthesia.

**Haloperidol**

Haloperidol is another butyrophenone with strong antiemetic properties. Its method and site of action are very similar to those of droperidol. Early research by the anesthesia community illustrates the efficacy of haloperidol. The dose that prevents nausea and vomiting in 80% of patients (ED₈₀) was established to be 0.015 mg/kg intravenously (IV) or 0.007 mg/kg intramuscularly (IM). It is interesting that these doses have a greater efficacy when given IM than IV. Most PONV antiemetic doses range from 0.5 to 1 mg.

**Droperidol vs haloperidol**

Why did droperidol, and not haloperidol, become the drug of choice for the prevention and treatment of PONV in anesthesia? The popularity of droperidol can be credited partially to research in the late 1970s comparing droperidol, haloperidol, and prochlorperazine (an aliphatic phenothiazine that is pharmacologically similar to butyrophenones). The results of this study demonstrated the potent action of haloperidol within the first 30 minutes after administration, which lasted about 4 hours. Droperidol had a slower onset of action, from 30 to 60 minutes after administration, and an extended duration of action, from 4 to 24 hours postoperatively. Prochlorperazine had an onset of action between that of haloperidol and droperidol and a duration of action of up to 4 hours (Tables 1 and 2). Prochlorperazine also exhibited a sedating effect not displayed by the other medications. Apparently, the longer duration of droperidol accounted for its popularity over haloperidol as an antiemetic. Consequently, haloperidol has been virtually ignored by the anesthesia community.

Studies demonstrate that the highest incidence of PONV occurs during the first 6 hours after emergence from anesthesia. Therefore, haloperidol seems quite suitable for PONV treatment and prevention. Other medical specialties recognize the efficacy of haloperidol as an antiemetic, and, indeed, many oncology programs use haloperidol as their primary dopaminergic blocking antiemetic.

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**Key words:** Butyrophenone, droperidol, haloperidol, postoperative nausea and vomiting, sudden cardiac death.
Ultimately, the use of multiple agents is the most effective method for controlling nausea and vomiting. For example, droperidol or haloperidol used in conjunction with a serotonin antagonist and/or a corticosteroid offers superior effectiveness in treating nausea and vomiting. Recently, European investigators substituted haloperidol for droperidol. The combination of 10 µg/kg of haloperidol (administered 30 minutes before emergence from anesthesia), a serotonin inhibitor, and a corticosteroid effectively reduced the incidence of PONV.

### Adverse reactions of butyrophenones

Adverse reactions common to butyrophenones include, extrapyramidal side effects, neuroleptic malignant syndrome, orthostatic hypotension, and serious electrocardiographic changes.

Hypotension is less likely with haloperidol than with droperidol because it has a decreased α blocking effect. As with droperidol, however, QTc prolongation and the development of TdP can occur with haloperidol. These effects occur mostly in psychiatric patients receiving a total of 35 mg (IV, orally, or IM) or more during a 24-hour period. There has been 1 report of TdP after a single dose of 7.5 mg. Research by cardiologists in patients with acute coronary syndrome demonstrated 1 case in which the QTc interval increased from 0.39 seconds to 0.55 seconds after 2 mg of haloperidol IV, although there was no progression to TdP. Doses of 5 mg or less are associated with minimal risk. As with droperidol, there are few studies investigating side effects of low-dose haloperidol.

Haloperidol should be avoided in patients at risk for developing QTc prolongation or TdP. This group includes patients with electrolyte disturbances (eg, hypokalemia, hypomagnesemia), congestive heart failure, cardiac hypertrophy, or acute or chronic dysrhythmias and patients taking tricyclic antidepressants or monoamine oxidase inhibitors. Individuals with acute cardiac syndromes (eg, angina or myocardial infarction) are also at risk.

### Summary

Butyrophenones have proven to be very effective...
antiemetics. Droperidol, with its long duration, was the primary antiemetic favored by anesthesia providers for prophylaxis and treatment of PONV. However, the FDA actions now limits the use of this dopaminergic antagonist. Haloperidol is a safe substitute if its use is avoided in patients in whom dopamine antagonism is contraindicated.

When given immediately before emergence from anesthesia, haloperidol provides antiemetic protection during the peak incidence of PONV. Antiemetic dose ranges are as low as 0.5 to 1 mg IV or IM.\(^2\)\(^3\)\(^9\) Episodes of breakthrough nausea and vomiting should be handled by redosing with 0.5 mg at a time and restricting the total dose to 2.0 mg per 24 hours. This course of therapy is our suggestion based on a report of QTc prolongation with a dose as low as 2 mg IV.\(^3\)\(^0\)

While haloperidol is an effective antiemetic when used alone, in high-risk patients, a multimodal approach is most effective for prophylaxis and treatment of PONV.\(^2\)\(^5\)\(^3\)\(^9\) By using haloperidol in conjunction with antagonists of other emetogenic pathways, successful control of PONV should be achieved.

## REFERENCES


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