# CME Haloperidol for Postoperative Nausea and Vomiting: Are We Reinventing the Wheel?

Ashraf S. Habib, MBBCh, MSc, FRCA

Tong J. Gan, MB, FRCA, FFARCS(I)

Small-dose droperidol (0.625–1.25 mg) has a long established record of efficacy and safety when used for the management of postoperative nausea and vomiting (PONV).[1] However, the use of this cost-effective antiemetic has significantly declined after the Food and Drug Administration (FDA) "black box" warning.[2] Many hospitals have actually removed droperidol from their formulary, even though most experts and practicing anesthesiologists believe that this warning is not justified.[3,4] In many parts of Europe, droperidol is no longer available after the manufacturer stopped its production because of financial reasons.

Much of the initial arguments against the black box warning focused on the fact that droperidol was inexpensive, and hence cost-effective, and that the use of the more expensive serotonin receptor antagonists as an alternative would have a major economic impact. However, more recently, ondansetron, the most commonly studied serotonin receptor antagonist, became generic (acquisition costs for 4 mg IV <$US1), and therefore the issue of cost is no longer applicable. Does this mean that we can forget about droperidol and move on? No!

First, droperidol is highly effective against nausea. In a large multicenter study, droperidol 1.25 mg was found to possess greater antinausea efficacy than ondansetron, and without any increase in the incidence of sedation or other side effects.[5] A subsequent meta-analysis confirmed the superior antinausea efficacy of droperidol.[6]

Second, the combination of ondansetron and droperidol provides enhanced antiemetic prophylaxis for patients at high risk for PONV.[7]

Finally, droperidol is also a useful drug for the treatment of established PONV.[8] Given that postoperative nausea occurs much more commonly than postoperative vomiting, a drug with a strong effect against nausea and lacking the side effect of sedation is highly desirable.

The search for an alternative to replace droperidol led to the logical choice of an older member of the butyrophenone family: haloperidol. This drug received FDA approval as an antipsychotic in 1967 (droperidol was approved by the FDA in 1970). Haloperidol has been used for the control of agitation in medical and surgical patients, and for the management of delirium.[9] Haloperidol has a long half-life of 18 h.[10] It has a number of potential side effects including akathesia, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, anticholinergic side effects, and cardiac arrhythmias.[11] Torsade de pointes has also been reported with oral, IM, and IV haloperidol. The dose of IV haloperidol associated with the induction of torsades de pointes varied greatly in the literature, and has been reported to occur with as little as 9 mg over 7 h[9] to as large a dose as 825 mg over 24 h.[12] It was suggested that patients receiving doses of 35 mg/d or higher were at greatest risk for developing torsades de pointes.[9]

Small doses of haloperidol are used for the management of PONV. A systematic review using published and unpublished data from 1962 to 1988 suggested that haloperidol, at 1–2 mg, doses considerably lower than those used for the treatment of psychosis and agitation, might be effective

Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina.

Accepted for publication January 14, 2008.

Address correspondence and reprint requests to Ashraf S. Habib, MBBCh, MSc, FRCA, Duke University Medical System, Box 3094, Durham, NC. Address e-mail to habib001@mc.duke.edu.



DOI: 10.1213/ane.0b013e31816a6aff

for the prophylaxis and treatment of PONV.[13] However, many of the more dated studies included in this review had unsatisfactory designs and data reporting. Several recent studies have investigated the efficacy and safety of haloperidol when used for the management of PONV. Wang et al. reported that both haloperidol 1 mg and droperidol 0.625 mg were better than placebo for PONV prophylaxis with no significant differences between the two drugs. There were also no differences in QTc interval among the three groups in this study.[14] Two other studies evaluating haloperidol 1 and 2 mg reported similar efficacy to ondansetron 4 mg with no differences in the effect on the QT interval.[15,16]

In this journal issue, two studies by Rosow et al. report on the use of haloperidol 1 mg alone and the combination of haloperidol 1 mg with ondansetron 4 mg for the prophylaxis of PONV.[17,18] The results confirmed the antiemetic efficacy of haloperidol and showed improved efficacy of the combination of haloperidol with ondansetron compared with ondansetron alone. Although these studies were adequately powered, they had a number of limitations including the lack of strict control over a number of potential confounders, such as the anesthetic technique, absence of blinding of anesthesia care providers in one study, and a short duration of follow-up being limited to the postanesthesia care unit in one study, and 8 h postoperatively in the second study. These studies also did not directly address whether haloperidol, similar to droperidol, has better antinausea efficacy than ondansetron, as the monotherapy study was not adequately powered to investigate the nausea end-point, and did not include patients at high risk for PONV. This study also does not tell us whether the long half-life of haloperidol, when compared with ondansetron, resulted in improved efficacy against late PONV, due to the short period of follow-up. In the second study, the incidence of nausea was significantly reduced with the combination of haloperidol and ondansetron compared with ondansetron alone.[17] This might suggest a good antinausea efficacy of haloperidol, but needs to be confirmed in future studies. The authors did, however, look carefully for the potential side effects of haloperidol, namely prolongation of the QT interval, sedation, and extrapyramidal side effects. The QTc interval was mildly prolonged with both ondansetron and haloperidol, with no significant differences between the two drugs. There were no arrhythmias, excessive sedation, or extrapyramidal side effects in the two studies.

In the third study published in this issue, Chu et al. reported that the combination of haloperidol 2 mg with dexamethasone 5 mg was, as expected, associated with a significantly lower incidence of PONV compared with either drug alone.[19] They also included a group which received droperidol 1.25 mg. It is interesting to note that the long half-life of haloperidol (18 h) compared with droperidol (3 h) did not result in improved efficacy against late PONV. This might have been due to the strong binding affinity of droperidol to the emetic receptors, resulting in a long duration of action despite its short plasma half-life.[20] Although the authors performed a large study involving 400 patients, it is unfortunate that they did not specifically assess the severity of nausea, since superior antinausea efficacy might be an advantage of haloperidol. The authors confirmed Rosow et al.'s findings regarding the lack of sedation, extrapyramidal symptoms, and clinically significant QT interval prolongation with small-dose haloperidol.

In September 2007, the FDA issued an alert highlighting revisions to the labeling for haloperidol.[21] The updated labeling included a warning stating that torsades de pointes and QT prolongation have been observed in patients receiving haloperidol, especially when the drug is administered IV or in higher doses than recommended. The updated warnings noted that particular caution is advised in treating patients who have other QT-prolonging conditions, including electrolyte imbalance (particularly hypokalemia and hypomagnesemia), underlying cardiac abnormalities, hypothyroidism, familial long QT syndrome, or who are taking drugs known to prolong the QT interval. The warning also emphasized that haloperidol is not approved for IV administration, and that electrocardiogram monitoring is recommended if haloperidol is given IV.

There are still many unanswered questions regarding the use of small-dose haloperidol for PONV prophylaxis. For instance, proper dose–response studies need to be conducted. The optimum timing of administration of haloperidol, as well as the safety and side effect profile of repeated doses of this long-acting drug, need to be established. So are we going to see large high quality studies confirming the antiemetic effects of haloperidol and addressing these unanswered questions? Unfortunately, it is probably unlikely that a commercial entity would be interested in conducting such large trials on this generic drug.

In summary, the available evidence suggests that small-dose haloperidol appears to be safe and effective when given as a single dose of 1–2 mg for PONV prophylaxis. However, well designed, adequately controlled studies are needed to confirm those findings, and to provide additional safety and efficacy information before widespread use of this drug can be recommended. In the absence of these data, we believe that droperidol would be a better choice. The only advantage of haloperidol is that it does not have a black box warning. Since the mechanism of action of haloperidol and its effect on QTc are probably very similar to those of droperidol, it appears that the FDA's black box warning on droperidol, a drug that has been well studied and widely used, has caused the anesthesia community to reinvent the wheel!

## REFERENCES


1. White PF. Droperidol: a cost-effective antiemetic for over thirty years. Anesth Analg 2002;95:789–90
2. Habib AS, Gan TJ. Food and drug administration black box warning on the perioperative use of droperidol: a review of the cases. Anesth Analg 2003;96:1377–9
3. Gan TJ, White PF, Scuderi PE, Watcha MF, Kovac A. FDA "black box" warning regarding use of droperidol for postoperative nausea and vomiting: is it justified? Anesthesiology 2002;97:287
4. Habib AS, Gan TJ. The use of droperidol before and after the FDA black box warning: a survey of the members of the Society of Ambulatory Anesthesia (SAMBA). J Clin Anesth 2008;20:35–9
5. Fortney JT, Gan TJ, Graczyk S, Wetchler B, Melson T, Khalil S, McKenzie R, Parrillo S, Glass PS, Moote C, Wermeling D, Parasuraman TV, Duncan B, Creed MR. A comparison of the efficacy, safety, and patient satisfaction of ondansetron versus droperidol as antiemetics for elective outpatient surgical procedures. S3A-409 and S3A-410 Study Groups. Anesth Analg 1998;86:731–8
6. Henzi I, Sonderegger J, Tramer MR. Efficacy, dose-response, and adverse effects of droperidol for prevention of postoperative nausea and vomiting. Can J Anaesth 2000;47:537–51
7. Habib AS, El-Moalem HE, Gan TJ. The efficacy of the 5-HT(3) receptor antagonists combined with droperidol for PONV prophylaxis is similar to their combination with dexamethasone. A meta-analysis of randomized controlled trials. Can J Anaesth 2004;51:311–9
8. Gan TJ, Meyer TA, Apfel CC, Chung F, Davis PJ, Habib AS, Hooper VD, Kovac AL, Kranke P, Myles P, Philip BK, Samsa G, Sessler DI, Temo J, Tramer MR, Vander Kolk C, Watcha M. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2007;105:1615–28
9. Sharma ND, Rosman HS, Padhi ID, Tisdale JE. Torsades de Pointes associated with intravenous haloperidol in critically ill patients. Am J Cardiol 1998;81:238–40
10. Cheng YF, Paalzow LK, Bondesson U, Ekblom B, Eriksson K, Eriksson SO, Lindberg A, Lindstrom L. Pharmacokinetics of haloperidol in psychotic patients. Psychopharmacology (Berl) 1987;91:410–4
11. Hassaballa HA, Balk RA. Torsade de pointes associated with the administration of intravenous haloperidol: a review of the literature and practical guidelines for use. Expert Opin Drug Saf 2003;2:543–7
12. Metzger E, Friedman R. Prolongation of the corrected QT and torsades de pointes cardiac arrhythmia associated with intravenous haloperidol in the medically ill. J Clin Psychopharmacol 1993;13:128–32
13. Buttner M, Walder B, von Elm E, Tramer MR. Is low-dose haloperidol a useful antiemetic?: a meta-analysis of published and unpublished randomized trials. Anesthesiology 2004; 101:1454–63
14. Wang TF, Liu YH, Chu CC, Shieh JP, Tzeng JI, Wang JJ. Low-dose haloperidol prevents post-operative nausea and vomiting after ambulatory laparoscopic surgery. Acta Anaesthesiol Scand 2007;Epub ahead of print
15. Lee Y, Wang PK, Lai HY, Yang YL, Chu CC, Wang JJ. Haloperidol is as effective as ondansetron for preventing postoperative nausea and vomiting. Can J Anaesth 2007;54:349–54
16. Aouad MT, Siddik-Sayyid SM, Taha SK, Azar MS, Nasr VG, Hakki MA, Zoorob DG, Baraka AS. Haloperidol vs. ondansetron for the prevention of postoperative nausea and vomiting following gynaecological surgery. Eur J Anaesthesiol 2007; 24:171–8
17. Grecu L, Bittner EA, Kher J, Smith SE, Rosow CE. Haloperidol plus ondansetron versus ondansetron alone for prophylaxis of postoperative nausea and vomiting. Anesth Analg 2008;106:1410–3
18. Rosow CE, Haspel KL, Smith SE, Grecu L, Bittner EA. Haloperidol versus ondansetron for prophylaxis of postoperative nausea and vomiting. Anesth Analg 2008;106:1407–9
19. Chu CC, Shieh JP, Tzeng JI, Chen JY, Lee Y, Ho ST, Wang JJ. The prophylactic effect of haloperidol plus dexamethasone on postoperative nausea and vomiting in patients undergoing laparoscopically assisted vaginal hysterectomy. Anesth Analg 2008; 106:1402–6
20. Fischler M, Bonnet F, Trang H, Jacob L, Levron JC, Flaisler B, Vourc'h G. The pharmacokinetics of droperidol in anesthetized patients. Anesthesiology 1986;64:486–9
21. Available at: http://www.fda.gov/CDER/Drug/InfoSheets/HCP/haloperidol.htm. Accessed December 14, 2007