

# Editor's Notes

## The QT Interval and Droperidol— Do We Have to Use It on the Q.T.?

By Stephen Jackson, M.D.



Anesthesiologists have become more attuned and sensitive to the importance that our patients place on post-procedure nausea and vomiting. After all, without prophylaxis, PONV occurs in 20 percent to 30 percent of the general surgical population and in as much as 70 percent to 80 percent of patients at high risk for PONV. When I began practice, four decades ago, the most frequently administered anesthetic was diethyl ether. Its high blood/gas partition coefficient and strong emetogenic properties produced a characteristic pattern of slow emergence and frequent and prolonged PONV.<sup>1,2</sup> As a consequence of ether's potent residual analgesia lasting beyond emergence and well into the early postoperative period, what patients remembered most vividly about their anesthetic experiences often was not pain, but rather bouts of distressing PONV. Indeed, during the Age of Ether, patients came to expect PONV as “an unpleasant given” and dreaded it. However, in light of the significantly higher rates of morbidity and mortality then associated with anesthesia and surgery, the major focus of patients, families and their physicians was on survival, not PONV.

In those days, when one entered a hospital, one was greeted with the pervasive aroma of ether in the ambient atmosphere, a memorable fragrance that clung to everyone's garments and hair, even long after departure from the facility. For anyone who had suffered through a previous unpleasant ether experience, be it the psycho-physiological trauma of a mask induction or just “plain old garden variety” PONV, even a mere waft of ether could arouse—via almost an anamnestic response—memories powerful enough to induce nausea. I, myself, recall recovering from an ether anesthetic, pain free and fortunately without any nausea, but to my amazement, saw two of my family visitors leave abruptly after approaching me because of nausea induced by my exhaled ether breath!

No matter where encountered, nausea and vomiting is intensely unpleasant, and is universally feared and shunned in our allegedly genteel and civilized society. Now that survival itself has become almost a non-issue for almost all surgical patients, PONV has “peristalsed” itself to the top of the list of undesired consequences. Indeed, positive patient satisfaction-survey responses tend to hinge largely on freedom from PONV. Not unexpectedly, many of our pre-anesthetic patients with a previous surgical history, whether they are to undergo minor outpatient or major inpatient surgery, indicate that their *major* fear is

that of post-*anesthetic* nausea and vomiting (PANV). Some even recount PONV of several days duration and relate *that* to their anesthesia, a conclusion often willingly abetted by their surgeon. Non-anesthesia risk factors—surgical, post-operative medication and patient-specific—now have been integrated into evidence-based, guideline-supported prophylactic treatment algorithms that have reduced the incidence of PANV/PONV.

So, where forth goes this meandering? In this issue of our *Bulletin*, several respected academicians (James Moore, M.D., of UCLA, Steven Shafer, M.D., and Danielle Ludwin, M.D., of Columbia University, and Christian Apfel, M.B., Ch.B., of UCSF) share their opinions and recommendations on the disappearance of droperidol from our prophylaxis-treatment-rescue anti-emetic armamentarium. Overzealous and misinformed “accreditors” and “inspectors” misguidedly have enforced a controversial FDA black box pronouncement<sup>3</sup> that simply passes neither scientific muster nor my editor's eye for logic and transparency. Inspid regulators and intimidated sycophant pharmacists and administrators have bludgeoned anesthesiologists to forsake a drug that otherwise was rated by an expert panel as the “*overwhelming first choice for PONV prophylaxis.*”<sup>4</sup> Are we as a specialty really willing to “cave” to this scientifically unjustified bureaucratic tyranny? It seems to me that we have failed to grab the gauntlet. Many of our local leaders have permitted this travesty to be foisted on our patients because of local political considerations, balancing the inconvenience of standing up for what is right against the simpler path of “getting along by going along.” Dr. Moore, on the other hand, provides us with a sample template policy for the use of droperidol, one which includes restricted formulary use criteria deployed at UCLA (pages 28 - 34).

Droperidol, a butyrophenone derivative and similar to haloperidol and the phenothiazine antipsychotics, antagonizes D<sub>2</sub> receptor binding within both the chemoreceptor trigger zone and the area postrema. Anesthesiologists have safely and effectively administered hundreds of millions of doses of this inexpensive drug for the prevention and treatment of PONV for over three decades. Despite this record of safety, the FDA in 2001 unleashed its “black box” warning (replete with mandates for monitoring its use) for doses of 2.5 mg or greater.<sup>3</sup> A black box warning is the most serious warning that the FDA can require on a drug's labeling, and droperidol's came as a total surprise. The scientific evidence supporting this FDA action has since been contested by a hoard of experts.<sup>5</sup>

But, all of this controversy revolves about the effects of droperidol on lengthening the QT interval and its *supposed* predisposition to the development of a rapid polymorphic ventricular tachycardia (torsades de pointes).<sup>6</sup> The QT interval includes the total duration of ventricular activation and recovery,

basically corresponding to the duration of the ventricular action potential. The normal QT interval decreases as heart rate increases, and as such, the normal range is rate dependent. The commonly used scientifically unexact formula for relating the QT interval duration to heart rate was developed by Bazett in 1920 and called the corrected QT interval (QT<sub>c</sub>). The normal value is less than or equal to 440 msec, but some authorities believe it to be 460 msec in females. Another property of the QT interval is that its duration is lead dependent, varying by as much as 50 msec, and it is longest in the mid-precordial leads. Torsades de pointes is a syndrome characterized by prolonged ventricular repolarization with QT intervals generally exceeding 500 msec. There are congenital potassium and/or sodium channelopathies that result in inborn long QT interval syndromes, with at least ten LQTS genes and hundreds of mutations having been identified. Variable penetrance of this genetic heterogeneity results in a broad range of possible phenotypes, including subclinical forms. Multiple drugs are associated with an acquired form of prolonged QT interval and include: quinidine, procainamide, disopyramide, sotalol, amiodarone, propafenone, epinephrine, haloperidol, pimozide, risperidone, cisapride, diphenhydramine (!), terfenadine, erythromycin, clarithromycin, trimethoprim-sulfamethoxazole, and, lest we forget, our “cutie” drug droperidol. But where are the black boxes for all the other drugs?

White has written that low dose droperidol deployed for antiemetic prophylaxis had no significant effect on the prolongation of the QT interval,<sup>7</sup> and stated elsewhere that “preoperative ECG is not necessary before droperidol use.”<sup>8</sup> Apfel, however, has commented that some patients in White’s study did have prolongations of their QT intervals (as much as 120-133 milliseconds) that *could* be of clinical significance, especially if those effects were “due to clinically unapparent mutations on the cardiac potassium channel (HERG) receptor.”<sup>9</sup> This notwithstanding, Apfel further comments that “the FDA warning applies to the use of the FDA-approved dosage which is 2.5 mg and higher. Doses used in anesthesia [less than 2.5 mg] are therefore off label so that the black box warning doesn’t apply.” Indeed, Ludwin and Shafer’s recent editorial in *Anesthesia and Analgesia* (reprinted on pages 35 - 41) agrees that the FDA black box warning label “should not be removed, but should be clarified” and “brought into line with the evidence, the regulatory guidelines, and the longstanding safety history of low dose droperidol” by adding a statement that doses less than 2.5 mg are to be considered as being off-label, doses for which “the FDA has no position on [their] safety or efficacy.”<sup>10</sup> Apfel further declared that it is not legally appropriate for the California Department of Health Care Services to issue financial penalties to hospitals for what inspectors might deem to be failure to heed the black box warnings and mandates, such as the requirement for a pre-treatment ECG followed by continuous ECG monitoring for several hours

## Editor's Notes (cont'd)

---

after administration! He endorses the editorial by Ludwin and Shafer because “this ‘pro-droperidol’ article helps to bring the risk/benefit ratio back into balance.”

This *Bulletin's* articles provide you with the informational wherewithal necessary for wrestling with the “powers that be” to make hassle-free availability of low dose droperidol a reality so that you won't have to do such “on the Q.T.” As I stated in a 2004 editorial,<sup>11</sup> “The question arises as to whether anesthesiologists have an *ethical* obligation to use droperidol when, based on an extensive scientific literature and clinical experience of safety, we believe it to be medically indicated. The first imperative of the ASA's ethical guidelines is that of “placing our patient's interests foremost, faithfully caring for the patient.”<sup>12</sup> Do we as a specialty have an ethical duty to continue to advocate for droperidol's appropriate use?

1. Dodd R and Bunker J. *Diethyl Ether: Its Effects in the Human Body*. Charles Thomas, Springfield, Illinois. 1968.
2. Dent S, Ramachandra V, Stephen C. Postoperative vomiting: incidents, analysis, and therapeutic measures in 3,000 patients. *Anesthesiology* 1955; 16:564-572.
3. “Black Box” Warning on Droperidol: Report of the FDA Convened Expert Panel. <http://www.fda.gov/medwatch/SAFETY/2001.htm>.
4. Gan T, Meyer T, Apfel C, et al. Society for Ambulatory Anesthesia Guidelines for the Management of Postoperative Nausea and Vomiting. *Anesth Analg* 2007; 105:1615-1628.
5. Habib A, Gan T. PRO: The Food and Drug Administration Black Box Warning on droperidol is not justified. *Anesth Analg* 2008; 106:1414-1417.
6. *Hurst's The Heart*. Twelfth Edition. Fuster, Walsh, O'Rourke, Poole-Wilson (Eds) McGraw Hill Medical, New York. 2008.
7. White P, Song D, Abrao J, et al. Effect of low-dose droperidol on the QT interval during and after general anesthesia: a placebo-controlled study. *Anesthesiology* 2005; 102:1101-1105.
8. White P, de Leon-Casasola O. Controlling preoperative nausea and vomiting: New directions for an ongoing problem. Supplement to *Anesthesiology News*, November 2008.
9. Apfel C. Personal communication.
10. Ludwin D, Shafer S. CON: The black box warning on droperidol should not be removed (but should be clarified!). *Anesth Analg* 2008; 106:1418-1420. See reprint on pages 35 - 41 of this *Bulletin*.
11. Jackson S. Hypergraphia and droperidol—a case study. *CSA Bulletin* 2004; 53(#4):2-4.
12. American Society of Anesthesiologists Guidelines for the Ethical Practice of Anesthesiology. <http://www.asahq.org/publicationsAndServices/standards/10.pdf>-2008-11-21.