SELECTIVE (5-HT₃) serotonin receptor antagonists first became available for the treatment and prevention of postoperative nausea and vomiting (PONV) in the early 1990s. Despite the undeniable efficacy of this class of drugs, this author¹ and others have questioned their use for routine PONV prophylaxis. In this issue of *Anesthesiology*, Tang *et al.*² have shown that the addition of a 5-HT₃ receptor antagonist (either ondansetron or dolasetron) to a prophylactic regimen of 0.625 mg droperidol and 4 mg dexamethasone did not result in any improvement in any of the efficacy or outcome variables studied. As interesting as this finding is, it is perhaps overshadowed by a concern as to the safety of droperidol, even in low doses. As the authors note, on December 5, 2001, the Food and Drug Administration (FDA) issued a so-called “black box” warning regarding the use of droperidol for antiemetic prophylaxis (FDA Strengthens Warnings for Droperidol. Available on the web at: http://www.fda.gov/bbs/topics/answers/2001/ANS0112.html. Accessed on: October 16, 2002).

This warning, the most serious for an FDA-approved drug was “intended to increase physician’s focus on the potential for cardiac arrhythmias during drug administration.”

The position that the FDA has taken may have a significant impact on clinical practice. It has been shown previously that 4 mg ondansetron is no more effective than either 0.625 or 1.25 mg droperidol in preventing either postoperative nausea or vomiting.³ The data presented by Tang *et al.* reaffirm this. As they note, “5-HT₃ antagonists are not beneficial for routine antiemetic prophylaxis in the ambulatory setting when a droperidol-dexamethasone combination is used.” However, reluctance on the part of clinicians to continue to use droperidol in the face of the FDA warning may render these results moot. The question facing clinicians is, are the clinical implications of these data now inconsequential as a result of the FDA decision? The answer is complex. The complexity is compounded by the lack of objective, quantifiable data. An independent analysis of the FDA data,⁴ obtained through the Freedom of Information act, determined that, of the 273 case reports collected from November 1, 1997 to February 2, 2002, 127 described serious adverse outcomes, including 89 deaths and 74 cardiac events. Of the 74 reported cardiac events, there were 5 cases of ventricular tachycardia or torsades de pointes, only one of which resulted in death. The challenge for clinicians then becomes how to interpret these “data.”

There is no question that droperidol has the potential for causing serious and even life-threatening arrhythmias, and appropriate warnings have always been contained in the labeling information supplied with the product. Recent advances in electrophysiology and molecular biology have provided insights into the various mechanisms that play a role in the prolongation of the electrocardiographic QT interval as well as QRs widening. A variety of drug classes have been identified that are associated with QT prolongation and/or arrhythmia induction, including antihistamines, butyrophenones, phenothiazines, and selective (5-HT₃) serotonin receptor antagonists. Mechanisms include blockade of the rapid component of the delayed potassium channel (Ikr) and blockade of the cardiac Na⁺ channels. While helpful in providing insight into why arrhythmias may occur, knowledge of the electrophysiology does little to help predict the potential incidence of these adverse events in clinical practice. Over its 30-yr history, there have been no case reports of arrhythmias associated with the use of low-dose droperidol for preventing or treating PONV. A quantitative systematic review⁵ identified 76 trials, which included 5,351 patients receiving 24 different droperidol regimens. There were no serious adverse events reported. By comparison, there has been one case report⁶ describing two separate instances of dysrhythmias associated with the use of ondansetron since its introduction into clinical practice. However, meta-analysis of ondansetron prevention trials, which included 7,177 patients, failed to identify any reports of serious adverse events.⁷ What level of assurance as to the safety of these drugs do these data provide? Objectively, we can estimate that the risk of serious adverse events is no greater than 0.06% for droperidol and 0.04% for ondansetron with a confidence interval of 95%.⁸ Are we as clinicians to be reassured by these numbers? How are we to reconcile these risk estimates with the findings presented by the FDA?

The answers to these questions are not straightforward. Reporting of suspected adverse events to the FDA is a voluntary process that does not adhere to the standards applied to prospective randomized controlled trials. There is little reason to suspect that all adverse events are either recognized or reported. There is also no valid estimate of the number of times a drug has been administered that would provide the necessary denomi-
nator for a true risk estimate. Worse still, an “association” of adverse events with drug administration cannot be used to prove cause and effect. At the same time, it must be noted that over the past 25 yr, 20% of new drugs have either acquired a black box warning or been withdrawn after being approved initially by the FDA, presumably at least in part from voluntary reporting of serious adverse events not recognized during preapproval clinical trials. Nevertheless, a valid estimate of risk is a prerequisite for evidence-based practice. The notion of primum non nocere is a cornerstone of medical practice. Furthermore, risk cannot be evaluated in isolation. It is, after all, the risk-benefit ratio that is the determining factor when considering whether a given risk is acceptable. A high risk of serious adverse events that might be acceptable for therapies directed at life-threatening conditions would be totally unacceptable when considering elective therapies, such as prevention of postoperative nausea and vomiting.

What then constitutes an acceptable risk for therapies directed at preventing or treating postoperative nausea and vomiting? Obviously, adverse events can span the spectrum from annoying to life-threatening. Our tolerance for the acceptability of the risk would then likely be a function of the perceived severity of the event. Does the problem become simplified if we consider only the most extreme case of serious adverse events that are life-threatening? It is perhaps tempting to assume that any risk of death associated with the administration of an antiemetic is unacceptable. Yet, if we hold rigidly to this position, we would effectively eliminate all currently available antiemetics from clinical use. It also assumes that there is no risk associated with not administering an antiemetic. While the risk of serious adverse events associated with postoperative vomiting is undoubtedly extremely low, the potential for serious consequences does exist. Is the risk of treatment greater than the risk of no treatment? Again, we have no data and thus cannot make a rational decision.

There are two well-recognized principles that may help explain why clinicians may have such difficulty in dealing effectively with this problem. The first, known as loss aversion, describes a tendency for individuals to be more sensitive to risk of loss than possibility of gain. The second, described as mental accounting, refers to the method employed by individuals to code and evaluate outcomes. As anesthesiologists, we are by nature myopically loss averse, realizing that there is always the very real possibility of seriously harming patients. The benefit to the patient from administering an anesthetic is rarely therapeutic. The anesthetic is in fact provided to make therapy (i.e., surgery) possible. As a result, our mental accounting will always place great emphasis on avoiding risky interventions, particularly in circumstances where the perceived benefit is judged to be small. The perceived risk associated with droperidol administration is an excellent example of this phenomenon. The only way to resolve this issue is to collect meaningful data. Only then can we rationally evaluate the true risk-benefit ratio for not only droperidol but other antiemetics as well. Neither the problem nor the solution is trivial. The need to effectively manage PONV, particularly given the volume of outpatient surgery currently being done in the U.S., has huge economic implications. The FDA has “committed to conducting a definitive pharmacokinetic and pharmacodynamic study to evaluate the effect of dose on QTc interval.” Unfortunately this represents a surrogate endpoint. The solution requires that we first establish an acceptable risk for antiemetic administration based on an estimate of the potential for adverse events associated with untreated postoperative vomiting. Second, prospective data collection must be undertaken to establish the risk associated not only with the administration of droperidol but also with other commonly used antiemetics. Failure to do so makes questioning the safety of droperidol or other antiemetics about as productive as arguing about how many angels can dance on the head of a pin.

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Do We Need Another Animal Pain Model?

The article by Vera-Portocarrero et al. in this issue of Anesthesiology titled “Nociception in persistent pancreatitis in rats: the effects of morphine and neuropeptide alterations” is of clinical interest due to the high prevalence of pancreatic pain. However, the presentation of yet another model of pain begs the question, do we need another animal model? I believe the resounding answer to this question should be “Yes!”

There are still numerous clinical scenarios for which we need improved treatments and the pain due to chronic pancreatitis is an excellent example of such a clinical entity. As a course of constant pain with intermittent flares, it has the additional complicating factor that approximately 50% of the subjects who develop it do so because of substance abuse. The pain of chronic pancreatitis can often be managed with narcotics, but often the patients can’t. The clinician is frequently faced with scenario of a patient who has substituted one addiction (alcohol) for another (narcotics). This does not mean that narcotics are not appropriate and that the pain cannot be managed in this fashion, but this management is often difficult at best and most clinicians would like to have some other options to employ, hence the need for new models.

Models exist that are useful for investigating pain from multiple viscera, for example pain due to kidney stones or cystitis, but clinically, chronic pancreatitis does not act like a bladder infection or a kidney stone. As a consequence the extrapolation of pain from one site to another may be of limited value. It should not be expected that the mechanisms of pain generation arising from a structure such as the colon, which is filled with sewer contents, should be identical to structures such as the bladder or pancreas, which have sterile contents.

This does not mean that all pain models are worth the lives of the mice, rats, cats, dogs, monkeys, guinea pigs, and other nonhumans sacrificed to the development of these pain models. If one looks to the literature using the PubMed search engine of the National Library of Medicine and uses the search terms “pain” and “model,” one finds over 5,000 references describing pain models and the use thereof. Buried in these references are roughly 30 animal models that have ever been usefully employed in more than one laboratory. One can predict which models would prove to be of value as they typically have two features in common: one feature is technical simplicity, and the other feature is direct applicability to a clinical situation. The model put forth by Vera-Portocarrero et al. has both of these qualities. In their model, a simple intravenous injection of dibutyltin dichloride induces acute or subacute pancreatitis with increased lipase and amylase concentrations and histologic evidence of pancreatic inflammation. This pancreatitis produces “clinical” sensitivity to abdominal palpation and thermal stimuli, which are improved with traditional analgesics. One can argue over use of the term “persistent” in the title when the model is only studied in a 1- to 3-week timeframe. However, the authors have presented an excellent argument that the pain does arise from the pancreas, that the methods are technically simple, and that the findings are clinically relevant. There is hope that this group from Galveston and others will use this new model to test nontraditional methods of treatment, so that clinicians faced with the difficult task of treating pancreatic pain may have some novel tools to employ.

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