◆ EDITORIAL VIEWS

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The "Big Little Problem" of Postoperative Nausea and Vomiting

Do We Know the Answer Yet?

IN the past decade, ANESTHESIOLOGY and other journals have published numerous studies about the use of ondansetron to prevent or manage postoperative nausea and vomiting (PONV). Although these studies have differed in sample size, patient population, and dosing regimen, most have concluded that some dose of ondansetron either decreases the number of episodes of vomiting per patient or increases the percentage of patients who never vomit. In the present issue of ANESTHESIOLOGY, Tramèr *et al.*[1] compile the results of all these studies into a metaanalysis and conclude that, if the likelihood of PONV is "very high" (defined as an incidence of vomiting of 40-80% in the control group), 8 mg of ondansetron given prophylactically increases the percentage of patients who never vomit by 20%, *i.e.,* only one of every five patients treated benefits from this treatment, at least according to these criteria. In addition, 3 of every 100 patients treated prophylactically with ondansetron develop unexpected abnormalities in liver enzymes, and another 3 develop a headache. Tramèr *et al.* conclude that "ondansetron prophylaxis of PONV does not work very well."

Tramèr *et al.*'s results raises several questions that the reader should consider: 1. What is a metaanalysis, and what caveats should one consider when interpreting its results? 2. Is the therapeutic outcome evaluated by Tramèr *et al.* appropriate? 3. Is prophylactic use of ondansetron economically justified?

Metaanalyses are increasing in prevalence, although the technique is uncommon in the anesthesia literature. In a metaanalysis, the investigators survey databases such as MEDLINE to identify all articles published on a topic. These articles are then reviewed to ascertain the quality of the work, based on criteria such as whether the original investigators state a method of randomization explicitly. The metaanalyst then compiles these results, weights each study according to criteria such as sample size, and arrives at an overall score for the treatment being evaluated.

The benefit of a metaanalysis is its ability to uncover statistical significance that was not apparent in small, statistically underpowered studies. However, their validity is questioned by some.[2] First, metaanalyses might experience a "publication bias"—small studies with positive results are more likely to be published than similarly sized studies with negative results. Tramèr *et al.* address this issue, but argue that there is a "dearth of empirical evidence" to support the existence of publication bias. This conflicts with my experience as a reviewer that negative results prevail in unpublished studies of ondansetron and with my belief that publication bias exists. Nevertheless, Tramèr *et al.* suggest that publication bias, if it exists, might exaggerate the true benefit of ondansetron, and hence it is difficult to explain their results on this basis alone.

A second problem with metaanalyses is that they compile data that may not be collected uniformly. In the present instance, this does not appear to be a major difficulty, Tramèr *et al.* are fortunate that many studies of ondansetron prophylaxis of PONV are similar in design, a result that stems from (in part) their common sponsorship (the manufacturer).

A final problem with metaanalyses is that they depend on outcome measures reported in the published studies. If these outcome measures are optimal, then their use in a metaanalysis is appropriate. However, most studies of the effect of ondansetron on PONV focus on the same outcome measures, again the result of the common sponsorship of many studies. Several years ago, I[3] criticized these types of studies[4,5] because they

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reported surrogate measures of outcome rather than what I considered to be more meaningful measures such as patient satisfaction. In other words, they reported only the incidence of vomiting, rather than the incidence of unplanned hospital admission or decreased stay in the recovery room. Many investigators have touted, but rarely demonstrated, the latter two as the expected effect of successful treatment with antiemetics. However, I still contend that measures such as patient satisfaction are more important than the number of episodes of vomiting. Unfortunately, because most studies of PONV and ondansetron focus only on outcome measures such as the percentage of patients free of vomiting in the postoperative period, Tramèr *et al.* had no choice but to use these measures in their metaanalysis.

My stance[3] has led to many heated discussions, often with investigators who defend their use of surrogate outcomes in studies of PONV. These investigators claim that a patient who does not vomit is, by definition, more satisfied that one who does. Although there are reports that patients who do not vomit are more satisfied than those who do,[6] one cannot extrapolate that a greater incidence of patients free of vomiting with ondansetron treatment implies that ondansetron increases patient satisfaction. Although this argument appears superficially to be correct, I offer two counterpoints:

1. If I gave my patients pancuronium postoperatively for 24 h, none would vomit. Yet, I doubt that anyone would accept that my patients benefitted from this outrageous approach.
2. Any therapy, including antiemetics, may induce adverse events that mitigate against the positive effects of the therapy.

The latter argument is supported by Tramèr *et al.*'s metaanalysis. They demonstrate that for every 100 patients treated with ondansetron, three who would not otherwise report a headache do so, and three who would not demonstrate abnormalities in hepatic function do so. Perhaps the increased occurrence of headache in patients treated with ondansetron explains why investigators have rarely, if ever, been able to demonstrate that patient satisfaction is improved by ondansetron. Tramèr *et al.*'s observation offers the reader an important message — efficacy of new drugs should be judged not only by their purported successes but also by their reported adverse events.

I reiterate my concern of several years ago. If ondansetron is "so good," then it should be easy to demonstrate its efficacy by at least one of the three measures suggested previously (duration of PACU stay, unplanned hospital admissions, or patient satisfaction). The absence of convincing data for any of these three measures leaves me to question the utility of this drug, at least when used as a "routine" treatment of surgical patients. Finally, Tramèr *et al.* recommend a dose of 8 mg. In my institution, acquisition cost for this dose is $33. Using Tramèr *et al.*'s approach, five high-risk patients would need to be treated to yield one patient with a "successful" outcome, *i.e.,* it costs $165 to yield each additional vomiting-free patient. If the risk of postoperative vomiting is $< 40\%$, then Tramèr *et al.* suggest that the benefit will be even smaller and the cost will be even higher, possibly >$330 per vomiting-free patient. Further, some patients who are treated "successfully" develop abnormalities in liver enzymes or develop a headache, perhaps further escalating the cost per true success.

In the present era of cost-containment, anesthesia practitioners need to be informed about the economics of anesthesia care so that they converse with hospital administrators and pharmacists about cost-effective selection of anesthetic drugs. The May 1997 issue of ANESTHESIOLOGY contained a number of relevant research and review articles and editorials; Tramèr *et al.*'s metaanalysis provides further information for these discussions. In particular, some of the "success" with ondansetron is negated by the occurrence of headaches and liver enzyme abnormalities. However, until studies with more extensive outcome measures are performed, I contend that our leverage at the negotiating table is compromised.

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Intubation Difficulty Scale

Anticipated Best Use

REALISTICALLY characterizing the difficulty of tracheal intubation is an important responsibility of care-givers. The Intubation Difficulty Scale (IDS), introduced in this issue of ANESTHESIOLOGY by Adnet *et al.*[1], is a numerical score of total intubation difficulty and is based on seven parameters known to be associated with difficult intubation.[1] The scoring of each individual parameter represents a divergence from an "ideal" condition (*i.e.*, the parameter has no difficulty), and the total score represents the sum divergence from a zero difficult "ideal" intubation. The seven parameters are number of supplementary attempts, number of supplementary operators, number and type (in chronologic order) of alternative techniques used, laryngoscopic grade, subjective lifting force, the use of external laryngeal manipulation, and mobility or position of the vocal cords.

The IDS is a quantitative measure of the total intubation difficulty encountered during a chosen procedure or sequence of procedures and is calculated after the fact. Therefore, the IDS for a given patient depends on the appropriateness of the choice of procedure or sequence of procedures, and it is not a means of predicting difficulty for an individual intubation. It is anticipated that there will be two very good and broad uses of the IDS.

First, the IDS communicates the total intubation difficulty for a given patient to the next care-giver, and the score alone may greatly influence the choice of future care. However, the IDS alone does not shed any light on the cause of an increased IDS. For this reason, it will be very important to communicate the scores of the individual elements of the IDS in every case so that subsequent care-givers can identify the problem element(s) and the final solution to the problem element(s). For example, if three direct rigid laryngoscopy attempts by two operators were followed by a final successful flexible fiberoptic endoscopy-aided technique (see definition of "N3" in reference 1), then this information could and should direct future clinical care.

Second, for populations of patients who are the same in every respect, save one variable, the IDS may then reflect the importance of the variable. For example, in identical patients, the variable could be intubation technique A *versus* intubation technique B. In identical patients who are treated identically, the IDS could test and reflect the predictive power of a single preoperative test such as high or low oropharyngeal classification or long or short mandibular space. For a final example of using homogenous groups, a consistently different IDS for different practitioners (*i.e.*, anesthesia residents) may be a measure of skill or judgment. It is possible that the IDS could be revealing of important information in nonhomogeneous populations of patients if the number of patients was sufficiently large to permit multivariate analysis of factors.

In summary, the new IDS appears be the best indica-

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