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Surrogate Outcomes: Meaningful Not!

DURING recent decades, better anesthetic agents and monitoring, coupled with improved surgical techniques, have minimized the morbidity and mortality associated with surgery. In turn, anesthesiologists have turned their focus to other issues of importance to patients and the healthcare system. These include decreasing the incidence of postoperative nausea and vomiting (PONV) and decreasing the time that a patient stays in the hospital after surgery.

As new antiemetic ("tron") drugs became available, patients found that these drugs enabled them to better tolerate emetogenic chemotherapy and radiotherapy. Not surprisingly, anesthesiologists adopted those drugs into clinical practice for both the prophylaxis and treatment of emesis. During the past decade, numerous clinical trials, some sponsored by the pharmaceutical industry and others by individual investigators, examined the influence of ondansetron, granisetron, and more recently dolasetron on PONV. Many studies noted that PONV might increase stay in the recovery room and the incidence of unplanned hospital admission and decrease patient satisfaction (all of which I term "true" outcomes). An obvious corollary was that decreasing the incidence of PONV would improve these important outcomes. However, rather than measure true outcomes, most studies evaluate efficacy by counting either the number of episodes of vomiting or the number of patients with no episodes of vomiting. In 1994, an editorial in *ANESTHESIOLOGY*¹ questioned whether these were valid endpoints, claiming that they were surrogates for the

true outcomes. Many clinicians and investigators accused this editorial of being unfair—after all, if fewer patients vomited, is it not a reasonable assumption that patient satisfaction will increase?

Two recent articles in *ANESTHESIOLOGY*, one by Tramèr *et al.*² in the December 1997 issue, the other by Scuderi *et al.*³ in the present issue, support the contention that surrogate measures are flawed. Tramèr *et al.*² performed a meta-analysis of the published studies with ondansetron. They concluded that in a group with a frequent incidence of PONV, prophylaxis with 8 mg ondansetron decreases the incidence of PONV by 20%. However, prophylaxis results in a 3% increase in the incidence of headache and a 3% increase in the incidence of abnormal liver enzymes. Thus, instead of 20% of patients benefiting from prophylaxis, only 14% actually benefit. Tramèr *et al.*⁴ also conclude in a separate meta-analysis that 1 mg of ondansetron is effective to *treat* PONV. It would therefore appear that treatment of PONV with a 1 mg dose is more cost-effective than giving 4–8 mg prophylactically to many patients who would not have vomited anyway.

Scuderi *et al.*³ examined the effect of prophylactic ondansetron on both surrogate and true outcomes. They studied 575 patients, a number sufficient to rebuff criticisms about inadequate sample size. Anesthetic management was consistent with that in many institutions in the United States. Half of the patients received 4 mg ondansetron preoperatively, the remainder received placebo. The investigators collected data on both surrogate outcomes (the incidence of PONV) and true outcomes (including time to PACU discharge, incidence of unplanned hospital admission, time to return to normal activities of daily living, patient satisfaction).

As in previous studies from those investigators and others, the incidence of PONV was less with ondansetron prophylaxis. However, when data from all patients were pooled, there was only a 4% improvement in patient's overall satisfaction with control of PONV, less than the 10% improvement that Scuderi *et al.*³ defined *a priori* as being clinically significant. There were no significant differences in other true outcomes.

In that surrogate measures suggested a benefit to antiemetics but true measures did not, which should

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the reader accept as meaningful? I contend that surrogate measures should be accepted only if they yield the same conclusions as their nonsurrogate endpoints. Scuderi *et al.*'s³ study provides good evidence that the surrogate measures are flawed and that, using true outcomes, *prophylaxis* with ondansetron is of little benefit. Coupled with Tramer *et al.*'s conclusion that *treatment* with 1 mg ondansetron is beneficial, there appears to be little evidence to support routine prophylactic administration of antiemetics. As evidence-based medicine becomes popular (*i.e.*, therapeutic decisions should be based on evidence rather than personal impression), we will be hard pressed to give antiemetics prophylactically. From the research standpoint, whenever surrogate outcomes are used, their relationship to more meaningful outcome measures should be considered carefully.

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The Role of Spirometry in Predicting Pulmonary Complications after Abdominal Surgery

Progressing toward an Answer

POSTOPERATIVE pulmonary complications in patients with obstructive pulmonary disease undergoing nonthoracic surgery vary over a wide range, depending on the complication, from the probably clinically insignificant microatelectasis to pneumonia or prolonged intubation. Patients classified as having chronic obstructive pulmonary disease (COPD) are three times more likely to have postoperative pulmonary complications. Spirometry can

define the extent of airway obstruction, is highly reproducible, is easily performed, and correlates with all-cause mortality. Yet Lawrence *et al.*¹ reviewed studies until mid-1989 but noted that numerous limitations prevented them from concluding that spirometry helped to predict which patients were at risk for postoperative pulmonary complications. In this issue of *ANESTHESIOLOGY* Warner *et al.*² present a case control retrospective analysis to address these limitations when questioning whether spirometry predicts postoperative pulmonary complications after abdominal surgery.

This study raises the standard for postoperative pulmonary complication studies by its combination of extensive multivariate matching between study groups, its study groups' severe and well-defined obstructive defect, its number of subjects over a 5-yr period, and its outcome definitions. However, this study should not be interpreted as proving that spirometry has no role in patient management, or that patients with COPD have no increase of postoperative pulmonary complications

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