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Are New Drugs Cost-effective for Patients Undergoing Ambulatory Surgery?

The ability of the anesthesiologist to meet the increased demands for ambulatory surgery has been facilitated by the availability of shorter-acting intravenous and inhaled anesthetics, analgesics, and neuromuscular relaxants. Clinical studies suggest that these compounds can improve the recovery profile after short surgical procedures.[1–6] Newer adjunctive drugs (*e.g.*, sympatholytic drugs, non-opioid analgesics, antiemetics) also may prove useful in decreasing side effects and recovery times after ambulatory surgery.[7–11]

In the current issue of ANESTHESIOLOGY, three articles describe the safety and efficacy of two newer drugs, ketorolac[9] and ondansetron,[10,11] in the outpatient setting. However, for a new drug to replace an existing drug in clinical practice, it may no longer be sufficient to simply demonstrate efficacy in randomized, double-blind, placebo-controlled trials.[9–11] Increasingly, hospital pharmacy and therapeutic committees are asking for evidence that a new drug is either superior in achieving the desired effect or that it is associated with a decreased incidence of side effects compared to the existing drug it will be replacing. Furthermore, limitations in health-care resources increasingly require that the practitioner examine the economic consequences of replacing current therapeutic regimens with newer drugs and techniques.

In the past, anesthesiologists have not been constrained by the effects of using scarce resources for an individual patient. However, there is no reason to believe that our specialty will be exempt from the pressures to reduce or at least control health-care costs in the future.

In assessing the financial impact of using a new drug or technique, four measures are commonly used: (1) cost-minimization, (2) cost-effectiveness, (3) cost-utility, and (4) cost-benefit analyses.[12,13] The cost-minimization analysis compares alternative treatment regimens in terms of direct resource costs for the supplies and personnel. This simplistic view assumes that the consequences of each treatment regimen are identical. This type of analysis would lead to a recommendation that diazepam and morphine be used in preference to midazolam and fentanyl for outpatient surgery. Thus, cost-minimization analysis does not consider indirect costs to the patient and family (*e.g.*, treatment of side effects, prolonged recovery room stay, additional costs for a caretaker).

The cost-effectiveness analysis, on the other hand, compares the total costs (direct and indirect) of a given clinical outcome measure for different therapeutic regimens. Even if a therapeutic regimen is associated with additional costs, it may be the preferred regimen if the improvement in outcome is adequate to decrease the unit cost.[12]

When outcome is measured in units that consider the utility of the subject by placing a value on "quality of human life," the analysis is termed a cost-utility ratio. Thus, the cost-utility ratio for a new drug regimen may be described in terms of the cost of a quality-adjusted year of life.[13] For anesthesiologists, the relative values in terms of outcome are often subjective and arbitrary, making it difficult to apply these principles rigorously in our clinical practice.

A cost-benefit analysis involves a monetary estimate of the ratio of total costs to benefits. Although the concept is appealing, there are major practical limitations in placing monetary values on theoretical benefits to patients undergoing general anesthesia. The two basic approaches used for estimating benefits include: (1) increased earnings in patients receiving a specific therapy and (2) willingness of the patient to pay extra for a new drug or service. The former approach discriminates against those patients who do not market their labor—whereas the latter approach involves asking patients how much they are willing to pay to avoid a given outcome (*e.g.*, postoperative pain or nausea/vomiting)—and assigns this benefit to the group as a whole in proportion to those who would be expected to achieve a favorable outcome. The difficulty with this approach relates to the lack of consistency in what patients are willing to pay for the same outcome. For example, a patient undergoing chemotherapy may be

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willing to pay more to avoid nausea than would a healthy outpatient undergoing a brief surgical procedure. Cost-benefit assessments are further complicated by the need to adjust monetary values downward for future benefits, while maintaining the value for current costs. Finally, most studies in the anesthesia literature involve relatively small group sizes. The incidence of side effects noted in these clinical studies may not apply to the population as a whole. Therefore a "sensitivity analysis" is required to test the stability of the analysis over a wide range of assumptions and values.

Regardless of the deficiencies of these economic models, the increased costs of all new drugs will be more closely scrutinized in the future. For drugs like ketorolac and ondansetron, their increased cost relative to other comparable drugs (*e.g.*, morphine, fentanyl, codeine, metoclopramide, droperidol) must be balanced against their potential for decreasing perioperative morbidity (namely, postoperative pain or emesis, respectively). These evaluations should not be limited to the cost of the study drug *per se,* but also should assess the need for adjunctive drugs (*e.g.*, "rescue" medications, reversal agents), the cost of a prolonged recovery room stay or unexpected hospitalization, and the indirect costs resulting from a delay in the resumption of normal activities.

Nausea and vomiting is a major factor contributing to delays in discharge and unanticipated admissions after ambulatory surgery.[14,15] The availability of anesthetic agents associated with a lower incidence of postoperative emesis[1,16,17] may contribute to a more rapid recovery and earlier discharge from the outpatient facility. Thus, the increased cost of a new drug like propofol must be balanced against its potential for decreasing postoperative morbidity (*e.g.*, postoperative nausea and vomiting, excessive drowsiness and lethargy), which may result in a more rapid and pleasant recovery from anesthesia.*[,16,17] Similarly, if use of the newly released muscle relaxant mivacurium (as an alternative to the intermediate-acting nondepolarizing muscle relaxants) results in a decrease in the requirement for reversal agents, it may contribute to a reduction in the incidence and severity of postoperative emesis, as well as complaints of excessive thirst after ambulatory surgery.[18]

Early clinical studies comparing ketorolac with morphine suggested that ketorolac offered advantages with respect to a lower incidence of side effects.[19,20] However, more recent comparative studies involving fentanyl and ketorolac have failed to find clinically significant differences.[21-23] The study by Wong *et al.*[9] compared intravenous and oral ketorolac with a standard regimen consisting of intravenous fentanyl followed by an oral acetaminophen-codeine combination. Although there were no differences in emetic sequelae between the two groups during the intravenous phase of the study, patients in the oral ketorolac group had a lower incidence of postoperative somnolence and nausea, as well as an earlier return of bowel function, compared to those receiving oral acetaminophen with codeine. However, the patients did not feel these benefits improved "the quality of life assessment," suggesting that these advantages were of limited clinical significance. These data raise concern regarding the patients' willingness to pay extra for the limited benefits in using an expensive nonsteroidal antiinflammatory drug as an alternative to an inexpensive opioid analgesic.[24] A better cost-benefit profile for ketorolac (*vs.* opioid analgesics) may be achieved in patients at greater risk for postoperative respiratory depression and/or emetic sequelae. Comparisons of oral ketorolac with other less expensive oral nonsteroidal antiinflammatory drugs (*e.g.*, ibuprofen, diclofenate) will be necessary to determine the ultimate role of ketorolac in clinical practice.

The study by McKenzie *et al.*[11] suggested that ondansetron is an effective prophylactic antiemetic in outpatients undergoing ambulatory surgery. While prevention of nausea and vomiting is important in the outpatient setting, the routine use of prophylactic therapy is controversial. In fact, prophylactic use of antiemetic drugs such as droperidol may contribute to an increased incidence of side effects after discharge from the outpatient facility.[25] The cost-effectiveness of ondansetron therapy is difficult to determine from data presented in this large, multicenter study[11] because a majority of the outpatients would not have developed postoperative emetic sequelae and, therefore, would not have derived any obvious benefit from receiving the drug.

Controlled clinical trials comparing ondansetron to other commonly used antiemetic drugs (*e.g.*, droperidol, metoclopramide) suggest that this new 5-hydroxytryptamine antagonist may possess some distinct advantages (*e.g.*, greater antiemetic efficacy, lack of sedative effects and dysphoric reactions)[26-29] over cur-

* Marais ML, Maher MW, Wetchler BV, Korttila K, Apfelbaum JL: Reduced demands on recovery room resources with propofol (Diprivan) compared to thiopental-isoflurane. Anesthesiology Review 16:29-39, 1989.

rently available antiemetic drugs. Future studies should focus on other patient populations at high risk for postoperative emesis (*e.g.*, previous history of postanesthetic emesis, motion sickness, women undergoing surgery during days 1–7 of their menstrual cycle, and outpatients undergoing laparoscopy, lithotripsy, or strabismus or ear, nose, throat surgery).[30] These studies may determine a subset of outpatients who would benefit from routine prophylactic antiemetic therapy with ondansetron.

The optimal dose *and* timing of ondansetron administration also need to be determined in these high-risk populations. The cost-efficient use of this expensive new drug requires the administration of the lowest effective dose. Earlier clinical studies[26,27] demonstrated the safety and efficacy of 8 mg ondansetron (*vs.* placebo). In the study by Scuderi *et al.*,[10] there were no significant differences in the antiemetic effectiveness of the 1-, 4-, or 8-mg doses of ondansetron. To be cost-effective in the prevention and/or treatment of postoperative emesis, ondansetron will need to be available in smaller unit doses (*e.g.*, 1-mg ampules) or in multidose vials. Excessive waste also discourages cost-conscious practitioners from using these otherwise effective new compounds.

With the increased emphasis on ambulatory surgery, the availability of anesthetic, analgesic, and neuromuscular relaxants with a more rapid recovery profile and fewer postoperative side effects has assumed increased importance.†,‡ Although these new drugs may allow more complex surgical procedures to be performed in the outpatient setting, reductions in reimbursement have emphasized the importance of cost-effectiveness analyses. Future clinical studies involving new anesthetic drugs also must provide information about important outcome variables such as the quality of life, psychologic well-being, and time to resumption of normal physical and mental activities. Thus, clinical acceptance of new drugs in the future may not only require evidence that they are safe and effective, but that they improve outcome and are cost-effective when compared to traditional agents. In the current healthcare environment, new drugs are required to meet these higher standards.

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‡ Smith I, White PF: Anaesthesia for day-case surgery. Current Anaesthesiology and Critical Care 3:77–83, 1992.

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