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Pharmacokinetic–Pharmacodynamic Modeling and ICU Sedation

Unexplored Territories

IN this issue of ANESTHESIOLOGY, Barr *et al.*[1] make a useful contribution to our understanding of the clinical pharmacology of intensive care unit (ICU) sedation. It is estimated that approximately $1 billion is spent each year in the United States alone on drugs used for sedation in the ICU. Misuse of these drugs contributes to morbidity, mortality, and expense. Optimization of ICU sedation will require characterization of the clinical pharmacology of sedative drugs. Unfortunately, there are a paucity of studies that use blinded designs and intention-to-treat analysis, which report pertinent baseline data and which use specific dosing schedules and standardized cointerventions.[2] The report by Barr *et al.* is an example of the type of study needed to redress this deficiency.

Barr *et al.* characterize and compare the pharmacokinetics and pharmacodynamics of lorazepam and midazolam when used for postoperative sedation of surgical ICU patients. Lorazepam and midazolam are commonly used ICU sedatives, but it has been unclear which is the optimal agent. A previous and influential comparison of midazolam and lorazepam by Pohlman *et al.*[3] showed no difference in efficacy and, more notably, no difference in the duration of effect of the two drugs after discontinuation, despite known differences in their pharmacokinetics. In fact, the mean duration of effect was less for lorazepam than for midazolam, although the difference was not statistically significant. This report, along with economic considerations, led many institutions to adopt lorazepam for routine ICU sedation.

Simplistically, one might assume that the most reliable method of comparing the duration of effect of two drugs is by direct measurement, but the difficulty with this approach is that the conclusion cannot be extrapolated beyond the depth or duration of sedation (because drug half-time varies with the duration of administration) used in that particular study. Pharmacokinetic–pharmacodynamic modeling, as used by Barr *et al.*, takes us past this restriction.

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Any difference in the duration of effect of two drugs must arise from either pharmacokinetics or pharmacodynamics. Drug A may have a shorter duration of effect than drug B either because it is cleared from the effect site more rapidly (a pharmacokinetic difference) or because the difference in the concentrations defining appropriate sedation and "recovery" is smaller for drug A than for drug B (a pharmacodynamic difference). In their study, Barr *et al.* carefully characterized the pharmacokinetics of midazolam and lorazepam in ICU patients. Although their findings were significantly different from those previously reported for healthy volunteers, they confirm that the context-sensitive decrement times (the time required for a given percentage decrease in plasma concentration) were much smaller for midazolam than for lorazepam.

If the plasma concentrations of midazolam decrease more rapidly than those of lorazepam after discontinuation of drug administration, the only way that the effect of lorazepam could be shorter-lived than that of midazolam would be if the concentration "decrement" (the difference between the concentration associated with adequate sedation and the concentration associated with return of an appropriate level of consciousness) is less for lorazepam than for midazolam. This question can be approached with pharmacodynamic modeling. Barr *et al.* use the Ramsay scale, subjectively evaluated ordinal scores of 1–6 (with 6 being unresponsive), to assess the level of sedation. The pharmacodynamic model assumed that the probability of a level of sedation greater than or equal to some value ss (where ss ranges from 2–6) is given by

$$P\ (\text{Sedation} \geq \text{ss}) = C^{\gamma}/(C^{\gamma} + C_{50,\text{ss}}^{\gamma})$$

where $C_{50,ss}$ is the plasma benzodiazepine concentration, P (Sedation $\geq$ ss) is 50%, and γ determines the slope of the concentration–effect curve. Using this model, the authors predict midazolam $C_{50,ss}$ values of 68, 101, 208, 304, and 375 ng/ml for sedation scores of 2–6, respectively, and the comparable values for lorazepam were 34, 51, 104, 152, and 188 ng/ml. These estimates indicate that the relative concentration decrements for recovery from midazolam and lorazepam sedation are not different. However, there is a potential flaw in the pharmacodynamic model used by Barr *et al.* The reader may have noted that the ratio of $C_{50,ss}$ for lorazepam and midazolam is exactly 2 for each score. This occurs because the authors assume that the ratio of $C_{50,ss}$ values

for lorazepam and midazolam potency is the same for all levels of sedation. This is a major assumption that could introduce bias. However, this concern is mitigated by the authors' allowing γ, the parameter determining the shape of the concentration–effect relation, to be different for midazolam and lorazepam. This adjustment in the model should allow differences in the relative concentration decrements to be detected. Using this approach, the authors find only trivial differences in the relative concentration decrements for recovery after midazolam and lorazepam. This result derived by modeling is consistent with the observed midazolam:lorazepam concentration ratio during sedation of 1.8 and the observed midazolam:lorazepam concentration ratio at the time of extubation of 2.2. Furthermore, the observed concentrations have similar ratios at each level of sedation. Therefore, both formal modeling and empirical observations indicate that the relative concentration decrements for midazolam and lorazepam are not markedly different.

Given the well-characterized pharmacokinetic differences between midazolam and lorazepam and the minimal pharmacodynamic differences, one must conclude that the duration of effect of midazolam is less than that of lorazepam. How then do we explain the observations of Pohlman *et al.*[3]? The most likely explanation is that Pohlman *et al.* did not blind the clinicians involved in the study and did not carefully control cointerventions, such as the use of analgesics. The primary endpoint of their study, time to return to baseline mental status, may be uninterpretable because we cannot be certain of standardization of sedation or use of analgesics. However, we must also note that there were differences in the demographics of the patients studied by Barr *et al.* and Pohlman *et al.* Two are of particular interest. First, the duration of sedation was considerably longer in the study by Pohlman *et al.* Could tolerance be developing? Second, the patients in the study by Pohlman *et al.* had higher Acute Physiology and Chronic Health Evaluation scores than those enrolled in the Stanford study (18.5 *vs.* 9.0). This raises the question of whether underlying illness alters sedation requirements, a possible explanation for why the patients studied by Pohlman *et al.* required relatively high doses of both agents. It is well-known that the movement response to surgical stimulus is mediated by components of the central nervous system more primitive than the cerebral cortex. Is it possible that lung injury also elicits a response at levels below the cerebral cortex? This is certainly plausible from an evolutionary point of view. If this supposition were true, it would suggest that sedating patients with drugs that work primarily on the cerebral cortex might not be an efficient strategy. The supposition that underlying illness alters sedation requirements can also explain the clinical conundrum of patients who are difficult to sedate and require high doses of sedatives during the early phases of mechanical ventilation, when lung injury is at its peak, but who then prove to be oversedated when this injury resolves and weaning from the ventilator is begun. Hopefully, further studies of this important clinical problem will be conducted using the sophisticated modeling techniques described in the study in this issue of ANESTHESIOLOGY but that are longitudinal, focusing on how pharmacodynamics (and pharmacokinetics) change during the period of mechanical ventilation.

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The Upper Respiratory Tract Infection (URI) Dilemma

Fear of a Complication or Litigation?

EVERY day, each of us faces the dilemma of the child with an upper respiratory tract infection (URI), and we must decide whether to proceed or postpone the procedure and how long to postpone it. The decision often rests on our individual comfort level in managing predictable complications as well as our comfort level with the potential for litigation should an adverse outcome occur. In this issue of ANESTHESIOLOGY, Tait *et al.*[1] provide further insight into this dilemma. They conclude that "children with active and recent URIs (within 4 weeks) are at increased risk for adverse respiratory events" but that "with careful management, most of these children can undergo elective procedures safely without increased morbidity."

How does the practitioner sort out the science and doing what is right for the patient *versus* fear of lawyers? Reported adverse respiratory events include bronchospasm, laryngospasm, airway obstruction, postintubation croup, desaturation,[2–9] and anecdotal reports of atelectasis, pneumonia, and even death.[10–12] One of these URI-associated deaths was in reality related to unrecognized myocarditis, and the other was likely caused by inadequate monitoring and premature extubation.[11,12] Several, as the study by Tait *et al.*, found an increased risk in children passively exposed to smoke.[1,5,13] No studies are completely free of bias in terms of preselecting the population studied, *i.e.*, sending patients deemed to be at increased risk home to recuperate. No controlled study has demonstrated increased mortality.

Every anesthesiologist knows that airway-related events are increased. The greatest problem with the literature is that there is no single definition for a URI. Additionally, there is no uniformity regarding the types and duration of surgical procedures, types of airway instrumentation, or preferred choice of anesthetic agents for the child with a URI. Risk for a specific patient is unknown. The study by Tait *et al.* provides guidance for children with mild URI symptoms as well as those who have had a URI within the previous 4 weeks. The strength of the study is that specific anesthetic management was left to the discretion of the anesthesia team.

Children with a URI present with a broad spectrum of signs and symptoms. We have those with fever, purulent rhinitis, productive cough, and rhonchi. This cohort is easy—"canceled." Another cohort is those in whom symptoms develop a day or two before the elective procedure. The parents call the surgeon the night before, surgery is canceled, and then they return 2 weeks later with minimal or no symptoms. Alternatively, a conversation with the family clarifies the severity of the symptoms, and a decision is made to reevaluate the child the morning of surgery. Most children fall in the middle, *i.e.*, they have had a URI for days or even weeks, and they are stable or improving.

The study by Tait *et al.* excluded patients deemed to be ill and some who became ill just before elective surgery. It included primarily patients who had a recent URI and those with a URI. The diagnosis of a URI required only two symptoms and confirmation by a parent. I agree that the easiest way to make the diagnosis is to ask. Parents can tell us if the child is better, worse, or improving. Most of the patients studied by Tait *et al.* had what I consider a very mild URI; most anesthesiologists would have proceeded because in the winter, nearly half our population has these symptoms.[14] The decision to cancel a procedure should not be made lightly because the mother, the father, or both, took the day off from work and the economic consequences for the family are great. It is of most interest that the children with a recent URI fared as well as those with an acute URI. Delaying a procedure will not significantly change the incidence of adverse respiratory events. Little is gained except to create inconvenience for the family, the surgeon, and the surgical schedule.

It is not surprising that Tait *et al.* found airway instrumentation to be associated with adverse respiratory events because an irritated airway is further irritated by a foreign body, hence, a reduced incidence with face mask or laryngeal mask airway.[1,15,16] Association with airway procedures is also not a surprise because airway manipulation occurs.[3] The association with copious secretions and nasal congestion makes the obvious connection that the more symptomatic children are those most likely to have more events. History of prematurity

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as a risk factor was a new observation but also is not a surprise because many of these children have some degree of bronchopulmonary dysplasia and thus have long-term pulmonary dysfunction and a tendency to airway reactivity.[17,18] It is of interest that Tait *et al.* did not find an increased incidence of bronchospasm[2,9]; if strict criteria, such as altered carbon dioxide wave form, had been used, I suspect there would have been a difference. We also do not know how many received prophylactic bronchodilator therapy before anesthesia, nor do we know whether the use of atropine to block vagally mediated bronchoconstriction or the airway irritant effects of secretions would have made any difference.[19,20] The association with passive smoke exposure confirms the observations of other studies.[5,21] This is important because it places some responsibility on the parents.

What is the take-home message? Most children with mild URIs can be safely managed without the need to postpone surgery. Postponing does not reduce the incidence of adverse respiratory events if anesthesia is administered within 4 weeks of the URI. Airway hyperreactivity may require 6 or more weeks to heal, implying that a longer wait may be required.[22] One study reported no increased risk in patients who had had a URI within the previous 6 weeks.[5] Another study demonstrated that nearly 2,000 procedures would have to be canceled to prevent 15 cases of laryngospasm.[8] Does it make economic and practical sense to families to cancel this many cases to prevent an easily treatable problem occurring in a minority of patients?

If one examines the causes of pediatric cardiac arrest and death during anesthesia, the majority relate to anesthetic overdose, drug reactions, and underlying congenital heart disease or malformations. Inadequate ventilation, in particular laryngospasm, accounted for 9 of 150 cardiac arrests, 8 of which occurred at the time of induction; none were reported to have been associated with a URI, and all these patients were successfully resuscitated.[23] Likewise, in the closed claims studies of adults and children, no cases were reported to have been associated with URIs.[24–26] My conclusion is that anesthesia is safe and without significant morbidity and virtually no mortality in the majority of children with mild to moderate active URIs and those who have had a recent URI. Over the years, I have reviewed a number of malpractice cases in which the first thing the lawyer looks at is whether the child had symptoms of a URI. To associate bad outcome with any trivial symptom of a URI is ludicrous. Adverse events occur with anesthesia; generally, a bad outcome is caused by lack of experience with a particular age group or lack of timely recognition of the event or appropriate decisions to intervene and rescue the patient. The anesthesia community around the world anesthetizes thousands of children with varying degrees of URIs safely and without significant morbidity every day. We have the technology to deal with reasonably foreseeable complications. We have muscle relaxants to relieve laryngospasm, we have bronchodilators and inhalation agents to treat bronchospasm, we have laryngeal mask airways to avoid intubation in appropriate cases, and we have oxygen to treat hypoxemia. Children who are obviously ill and scheduled to undergo elective surgery should have their surgeries postponed until they are better if only for humane reasons, *i.e.*, so they do not have the double effects of a systemic illness, coughing, and the pain of a surgical incision. Of greater concern are reports of deaths during anesthesia in children with unknown myocarditis.[27–31] I am much more frightened that someday I will be one of the unlucky ones to anesthetize the child with a URI who also has unknown viral myocarditis. There is nothing any of us can do to avoid such situations because even postponing these patients' surgeries a few weeks is unlikely to alter the risk for fatal arrhythmias.

Anecdotally, the worst cases of laryngospasm that I have seen were induced with desflurane,[32] and the worst case of bronchospasm occurred in a child with anaphylaxis; neither had a URI. I believe that despite all the studies, all we can say regarding children with URIs is yes, there is an increased risk for laryngospasm, bronchospasm, desaturation, and postintubation croup. Yes, these are more likely if someone in the child's home smokes. No, waiting may not significantly reduce these risks unless we wait 4–6 weeks or longer. Yes, the child will likely have another URI by then if it is wintertime. Yes, I will provide the safest anesthesia possible for your child. Yes, I can reduce the risk for these complications because I will tailor my anesthetic prescription (*e.g.*, propofol instead of thiopental, laryngeal mask airway or face mask instead of an endotracheal tube if appropriate, albuterol in the operating room, and so forth) around the child's needs and the needs for the surgical procedure, but I cannot reduce that risk to zero. Yes, these same complications can occur even when the child does not have a URI. Yes, administration of anesthesia is risky and occasionally associated with unpredictable responses to anesthetic drugs.

We are left with our best clinical judgment about an individual patient undergoing a specific procedure for a specific duration of time by a specific surgeon that requires endotracheal intubation that may or may not involve admission to the hospital who also has or has had a recent URI and, by the way, whose grandparents have flown across the country and both parents (smokers) have taken a day off work. Good judgment, common sense, clinical experience, and informed consent always take precedence in making the decision to proceed with a specific case. As for the lawyers, I always make a note in the record that these issues have been discussed with both the surgeon and the family and that everyone has been informed of the risks and has agreed to proceed.

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