

## ***Dexmedetomidine and Opioid Interactions: Defining the Role of Dexmedetomidine for Intensive Care Unit Sedation***

COMPANION articles in this issue of ANESTHESIOLOGY deal with the pharmacology of dexmedetomidine in humans and compare its sedative, ventilatory, and analgesic properties to those of the potent opioid narcotic remifentanyl.<sup>1,2</sup> The marketing authorization label for dexmedetomidine, a highly selective  $\alpha_2$ -adrenoceptor agonist, stipulates its use for sedation in mechanically ventilated patients, and it is within this clinical context that these articles should be considered. Because the use of remifentanyl has recently been validated in this clinical setting,<sup>3</sup> it is a more relevant comparator than it may seem at first blush.

The best method of sedating the mechanically ventilated patient in the intensive care unit has vexed clinicians who have virtually thrown the pharmacopoeia at this problem. However, we still encounter patients for whom the first-line combination of a  $\gamma$ -aminobutyric acid-mediated compound, such as propofol or a benzodiazepine, together with an opioid narcotic, does not accomplish the goal of safely providing sedation with cardiorespiratory stability that facilitates weaning from the ventilator.<sup>4</sup>

The findings of Hsu *et al.*,<sup>1</sup> using a sophisticated pharmacokinetic approach but possibly controversial analytical methodology, build on a collection of studies extending over more than 15 yr that established the benign effect of dexmedetomidine<sup>5</sup> or clonidine<sup>6</sup> on ventilation, especially when compared to an opiate narcotic. Hsu *et al.*<sup>1</sup> commented on the fact that the introduction of carbon dioxide (in the hypercarbic ventilatory response phase of the study) resulted in an arousal from dexmedetomidine-sedated and at times deeply asleep subjects; a similar "awakening" was noted when the subjects were

observed in their "pseudonatural" sleep phase of the study protocol. The fact that even deeply sedated patients receiving dexmedetomidine can be easily aroused has been noted before,<sup>7</sup> albeit by auditory and tactile stimuli, and draws attention to a recent rodent study that establishes the similarity of the neurologic substrates involved in the hypnotic state produced by dexmedetomidine and that which occurs during non-rapid eye movement sleep.<sup>8</sup> In a functional magnetic resonance imaging crossover study in human volunteers, dexmedetomidine induced no significant difference in the blood flow signal compared with that seen in the natural sleep state.<sup>9</sup> These findings contrast with those seen during treatment with  $\gamma$ -aminobutyric acid-mediated hypnotic/sedative agents such as benzodiazepines, in which a qualitatively different pattern of neuronal activity was found in humans.<sup>9</sup>

Is the similarity between dexmedetomidine-induced sleep and non-rapid eye movement sleep necessarily good for sedation in the intensive care unit setting? What's "good" about a good night's sleep? Although reparative and restorative functions are facilitated by the neuroendocrine milieu that accompanies natural sleep, the salubrious properties of sleep are usually considered only in the context of the morbidity and even mortality of the sleep-deprived state.<sup>10</sup> The intensive care unit setting is not conducive to a good night's sleep; in fact, the typical nonsurgical intensive care unit patient has less than 2 h of encephalographic sleep within a 24-h epoch.<sup>11,12</sup> It is hypothesized, although not yet proven, that sleep deprivation is pathogenically involved in the development of delirium and psychotic reactions that occur with a frequency of 60-80% in mechanically ventilated patients.<sup>13</sup> Although it seems intuitive that avoidance of sleep deprivation can be best provided by drugs that most closely resemble the neurobiology and physiology of natural sleep, this has not yet been confirmed.

In the accompanying article, Cortinez *et al.*<sup>2</sup> compared the analgesic effects of systemically administered dexmedetomidine and remifentanyl in humans using an experimental heat pain model.<sup>2</sup> Clinical trials reveal that  $\alpha_2$  agonists produce significant analgesia in humans when administered by the intrathecal or epidural routes<sup>14</sup>; however, the analgesic action of systemically administered  $\alpha_2$  agonists, assessed by a reduction in the requirement for postoperative opiate narcotics, is modest at best and may be confounded by the coexistent sedative effect.<sup>15</sup> Human experimental pain studies examining

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the analgesic profile of systemically administered  $\alpha_2$  agonists paint an inconsistent picture. Although pain intensity decreased modestly in experiments using the cold pressor test,<sup>16</sup> only moderate attenuation of the unpleasantness of pain was reported in a model of ischemic pain, no reduction in pain was observed in studies using noxious heat or electricity, and no antihyperalgesic or antiallodynic effects were detected in models of secondary mechanical hyperalgesia.<sup>17,18</sup> How can the attenuation of heat-evoked pain by dexmedetomidine, now reported by Cortinez *et al.*,<sup>2</sup> be reconciled with these earlier studies?<sup>16-18</sup>

The authors are to be commended for the use of advanced pharmacokinetic-pharmacodynamic modeling techniques, but differences in methodology and analysis must be considered further. Interpretation of analgesic drug studies may be confounded by the placebo effect, unblinding of subjects, and carryover phenomena. The study by Cortinez *et al.*<sup>2</sup> does not control for placebo effects and blinding (the two of eight subjects who received placebo were excluded from the final analysis). Significant carryover effects may have resulted because all subjects studied during the dexmedetomidine infusion had first received remifentanyl. Even though the investigators allowed time for washout to be effected as evidenced by the return of the visual analog score to baseline, enough opiate narcotic may still be present to produce the well-described synergistic analgesic interaction with  $\alpha_2$  agonist.<sup>19</sup>

The analgesic effect at each drug concentration was quantified by plotting individual noxious heat-*versus*-pain intensity functions, an approach that allows a more comprehensive characterization of an analgesic drug profile than algorithms examining a single pain intensity (e.g., pain threshold).<sup>20</sup> However, it is not possible to determine whether their sigmoid Emax model best fits their findings, because the raw data are not provided. Psychophysical experiments suggest that the relation between increments in noxious heat and visual analog pain scores is best described by an exponential function<sup>21</sup>; therefore, an alternative modeling approach has been advocated to take these issues into consideration.<sup>22</sup> Limitations inherent to the sigmoid Emax model may explain why the findings of Cortinez *et al.* differ from those of other studies.

How can the findings in these two articles be applied for the sedation of mechanically ventilated patients? It is likely that weaning from the ventilator can be accomplished with less agitation in patients continuously treated with dexmedetomidine than in patients whose sedative drugs may have to be discontinued to avoid ventilatory depression. The ease with which dexmedetomidine-sedated patients can be aroused may facilitate a "daily wake-up" routine that has been shown to improve outcome significantly in mechanically ventilated pa-

tients.<sup>23</sup> The similarity between dexmedetomidine-induced hypnosis and natural sleep may maintain cognitive and immunologic function that deteriorates in sleep-deprived states. Until otherwise demonstrated, it may be prudent to include an opiate narcotic to enhance modest analgesic effects of systemically administered dexmedetomidine when pain is likely to be a significant component of a patient in the intensive care unit. Without randomized clinical trials with an appropriate comparator, each of these conclusions should be considered speculative.

**Mervyn Maze, M.B., Ch.B., F.R.C.P., F.R.C.A., FmedSci,\*  
Martin S. Angst, M.D.†** \*Imperial College, London, and Chelsea and Westminster NHS Healthcare Trust, London, United Kingdom. m.maze@ic.ac.uk  
†Stanford University School of Medicine, Stanford, California.

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## What Makes a "Good" Anesthesiologist?

ALTHOUGH good clinical care in anesthesia has many components,<sup>1</sup> the ability to diagnose and treat acute, life-threatening perioperative abnormalities is near the top of most anesthesiologists' lists. In comparison to other industries performing hazardous work, health care lags behind in its capability to ensure that its personnel are uniformly and provably skilled practitioners.<sup>2,3</sup> How to measure clinician performance challenges all domains of medicine and is particularly difficult for hazardous and complex domains such as anesthesiology that involve invasive therapies with the proverbial "hours of boredom, moments of terror." In this issue of *ANESTHESIOLOGY*, Murray *et al.*<sup>4</sup> report on their team's continuing effort (see also the December 2003 issue of *ANESTHESIOLOGY*<sup>5</sup>) to develop a validated test of this performance ability of anesthesiologists using mannequin-based simulation scenarios.

Simulation offers advantages in assessing this skill because real acute events are relatively uncommon, are diverse in pathophysiology, and cannot be observed without intervention should mistakes be made. In developing their test, the authors used the same principles and experiences that have guided the careful development of tests of basic clinical skills using "standardized patients" (actors). These have been used in the Educational Commission for Foreign Medical Graduates Clinical Skills Assessment<sup>5,6</sup> and are now being used for step II of the United States Medical Licensing Examination. In the 2003 article, Murray *et al.* described a simulation-based test for medical students; in the current article,

they extend the test population to anesthesia residents. Their primary goal was to establish the psychometric property of the examination, defining how its results depend on differences among cases, subjects, raters, and four types of rating scales. They also wished to assess its "construct validity" by testing the construct that senior residents (clinical anesthesia [CA]-2 or CA-3) would perform better than junior residents (CA-1).

Key design decisions were that the test would cover only the "technical" response to the events, not any nontechnical skills (*e.g.*, communication or leadership), and that it would involve the anesthesiologist working alone, not in a team.<sup>7-11</sup> Although the ability to respond with the appropriate technical actions is a critical performance skill, it may not be enough. In aviation, it was found that 70% of US airliner crashes involved crews with adequate stick and rudder skills, flying aircraft that could be flown to safety.<sup>12</sup> Aviation then shifted considerable emphasis in training and assessment to nontechnical skills of individuals and crews. Several research groups, mine included, believe that measuring technical ability is similarly a necessary but not sufficient assessment of anesthesiologists' skills.<sup>7-11</sup>

The authors' chosen statistical technique, generalizability theory,<sup>13</sup> offers a means to tease out the different contribution of the examinees, the raters, and the cases to the total variance seen across the test sessions. Perhaps the most important finding of the generalizability theory analysis was that far more variance was attributable to the cases and the case-subject interaction than was attributable to the raters or the rating system. The corollary to this finding is that—at least for the skills they assessed—a fair test needs a large number of cases<sup>6-10</sup> but only a few raters. Because time and costs are limited, these findings drove the design decision to use extremely short case scenarios lasting only 5 min, allowing a large number of cases to be presented in a 1-h test session.

The emphasis of this article on psychometrics highlights a conundrum of measuring the performance of professionals.<sup>14</sup> Observing anesthesiologists doing full

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cases could be sensitive to the complexities of the job but would likely lack psychometric rigor. Conversely, to achieve a fair test with robust psychometric properties, it may be necessary to control the work situation carefully, perhaps missing some of its complexity. Consider this analogy. What is the best way to pick a “good runner”? One could use a sprint (*e.g.*, 100 m), which could be scored objectively with low interrater variance. It could surely distinguish between the fit and the unfit, but is it a good surrogate for races of 1,500 m or 10 km? Having a good test requires not only psychometric validity and content validity, but it also requires context validity and ultimately predictive validity for the tasks and skills of interest. In the anesthesia case, 300 s is a short time to step into a clinical situation, make a reasonable assessment, and implement key actions. Scenarios must be chosen that are unambiguous, require little diagnostic investigation, and have rapidly applicable therapies. In real patient care, such hyperacute situations with unambiguous findings and treatments may be the exception. With ultrashort simulations, is there a risk of missing the forest for the trees?

Perhaps so, but we have to start somewhere, and these two articles by Murray's group represent the most systematic and carefully controlled test development to date in anesthesiology regarding technical performance of acute event management. It is hard to argue that competent anesthesiologists should not be able to perform well on such a test, even if it is artificial. To corroborate this extrapolation, it would be wise not only to assess its psychometrics when applied to more experienced personnel, but also to look at the details of individual success or failure to be sure that they are not artifacts of the artificially limited test.

One should also be careful about the “constructs” that are tested for construct validity. In this study, CA-2 and CA-3 residents were grouped together to be compared to CA-1 residents. Why not test the construct of steady improvement year by year? In a study by Devitt *et al.*<sup>15</sup> of Canadian anesthesia students, residents, community anesthesiologists, and university faculty, they assumed a construct that performance of these populations would increase in that order. They argued that university anesthesiologists would perform best because they usually did their own cases, did more complex cases, and were immersed in an academic environment. However, this construct might not be equally applicable to many US centers, where faculty may supervise others rather than perform their own cases. Also, is “experience” itself a guarantee of success on all tasks? We<sup>9,16</sup> and others<sup>17</sup> have demonstrated this in simulation studies involving residents, faculty, and community anesthesiologists in which some highly experienced personnel failed catastrophically in managing certain acute events, whereas some juniors performed exceptionally well. A further step in test development should be to create benchmark

metrics of performance by true clinical experts. One means to select a cohort of known experts would be to use peer ratings<sup>18</sup> by experienced clinicians. Those rated as expert by a large fraction of their peers probably do have outstanding clinical skills. The considerable work in surgery on metrics for testing surgical psychomotor skills<sup>19,20</sup> is a useful guide, but establishing metrics for decision making in anesthesiology may be more difficult.

The context of performance assessment also must be considered. High-stakes summative assessment (*e.g.*, United States Medical Licensing Examination or specialty board certification) is only one application. Performance testing is relevant for less exacting purposes such as “formative assessment” of students and trainees, pedagogical research, and research on human factors in medical systems. For these applications, some degree of psychometric rigor may be traded off against better applicability and scope of test content. Even a perfect test of intraoperative medical management should be only one element of a multifaceted assessment of the anesthesiologist's skills.

Ultimately, the public's desire for safer care with greater accountability will be the main driver for the health professions to conduct credible, regular, and never-ending assessments of the performance of their members.<sup>21</sup> The science of performance assessment in anesthesia has been advanced substantially by Murray *et al.*, but even they have only scratched the surface of a complex set of questions that will challenge our profession and the rest of health care for the foreseeable future.

**David M. Gaba, M.D.** Stanford University School of Medicine, Stanford, California, and VA Palo Alto Health Care System, Palo Alto, California. gaba@stanford.edu

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## Severing the Link between Acute and Chronic Pain

### The Anesthesiologist's Role in Preventive Medicine

FROM the new "prehabilitation" movement for preventing injuries in athletes to workplace injury-reduction strategies and the precautionary security efforts against terrorist attacks that have become a national priority, the age-old adage of "prevention over cure" is clearly paramount in most facets of our lives today. In medicine, disease prevention is currently recognized as beneficial from both health and economic perspectives. As the safety of the immediate perioperative period continues to improve,<sup>1</sup> anesthesiologists have begun to incorporate this prevention-focused perspective into decisions that they make on the operative day. There is a growing recognition that these decisions can have consequences extending well beyond the safe conduct of patients through the perioperative period.<sup>2</sup> One long-term consequence of the pain and tissue trauma that accompanies surgical procedures may be pain that persists after tissue healing appears to be complete.<sup>3</sup> The article by Reuben in this issue of *ANESTHESIOLOGY* reviews the development of Complex Regional Pain Syndrome (CRPS) after orthopedic surgery and perioperative interventions that may prevent the CRPS associated with such procedures.<sup>4</sup>

Approximately 20% of the patients who present to chronic pain clinics with the diagnosis of CRPS have a history of prior surgical procedures, primarily orthopedic, in the affected region.<sup>5,6</sup> Despite the limited data and associated methodologic limitations identified by Reuben, the prevalence of CRPS after some common orthopedic procedures has been estimated. Data on the number of procedures performed annually in the United States (table 1) provide an appreciation for the number

of cases of CRPS that may follow specific types of surgery. The figures in table 1 are only examples of the 7.4 million surgical procedures performed in 1996 on the musculoskeletal system and the 643,000 performed on the cranial and peripheral nerves.<sup>7</sup> Given that the incidence of CRPS<sup>8</sup> is conservatively<sup>9</sup> estimated to be 6.28/100,000 for a combination of CRPS I and CRPS II, the number of new cases among a U.S. population of 289 million should be 18,149 per year, of which it could be estimated that 20% (3,630) are associated with prior orthopedic surgery.<sup>5,6</sup> This figure is considerably less than the estimates provided at the bottom of table 1. When these estimates are coupled with data on the economic and psychosocial costs of chronic pain states to individuals and society,<sup>10,11</sup> the burden of CRPS that accompanies acute surgical procedures appears substantial.

Preventive strategies include interventions to prevent a disease from occurring—*primary prevention*—and measures aimed at early detection or prevention of recurrence and treatment of presymptomatic and symptomatic individuals with an established disease to reduce morbidity—*secondary prevention*. Successful preventive medicine strategies are often based on an understanding of the epidemiology, pathophysiology, and the population at risk. Unfortunately, our knowledge of these aspects of CRPS is deficient. Apart from the type of surgery after which CRPS may develop, it would be desirable to know if other subgroups, in addition to those with a prior history of CRPS, are at risk of developing the disease as a consequence of surgical procedures. For example, CRPS is diagnosed at a much greater frequency in women, with a female to male preponderance greater than 2:1,<sup>6,12</sup> and evidence suggests that women report greater levels of pain after acute surgical procedures.<sup>13</sup> Furthermore, a comparison of patients who had a single episode of CRPS *versus* those who had recurrence indicated that the primary difference was that the latter group was younger.<sup>14</sup>

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**Table 1. Numbers of Procedures for Specific International Disease Classification (ICD-9) Procedure Codes, Rate of Complex Regional Pain Syndrome (CRPS) for Specific Procedures, and Corresponding Numbers of Cases of CRPS Associated with Common Orthopedic Surgical Procedures**

Procedure (ICD-9 Code)	N† (in thousands/yr)	Rate‡ (%)	CRPS (in thousands/yr)
Arthroscopic knee surgery (80.26)	657	2.3–4.0	15.1–26.3
Carpal tunnel surgery (04.43)	366	2.1–5.0	7.7–18.3
Ankle fractures (79.*6 and 79.*7)	257	13.6	35.0
Total knee arthroplasty (81.54)	247	0.8–13.0	2.0–32.1
Wrist fractures (79.*2 and 79.*3)	194	7.0–37.0	13.6–71.8
Fasciectomy for Dupuytren's Contracture (82.35)	20	4.5–40	0.9–8.0
Total	1741	4.3–11.0	74.3–191.5

\* Refers to any number 0–9. † See reference 7. ‡ See reference 4.

Many of the commonly performed surgical procedures on extremities may be necessary in patients with preexisting CRPS, who are presumably at greater risk for recurrence or exacerbation of their disease. In patients without a prior history of CRPS, data presented by Reuben suggests that a multimodal approach may limit the development of CRPS, at least for anterior cruciate ligament reconstruction. Although it is reasonable to speculate whether the benefits of such an intervention are worth the costs and the risks, it must be recognized that the proposed multimodal approach makes good sense with respect to perioperative pain management. The question of how long to wait, if at all, before performing surgery on patients with a prior history of CRPS remains an open one.

The interventions reviewed by Reuben are built around some combination of regional anesthesia, sympathectomy, and manipulation of inflammatory mediators. The importance of the sympathectomy that accompanies brachial plexus or epidural blockade was emphasized by successful interventions with stellate ganglion blocks or intravenous sympathectomy with clonidine. Spinal blockade was not mentioned. Although it blocks noxious stimuli sufficiently for surgery to be performed and it produces a sympathectomy, the effects of a single intrathecal dose of local anesthetic may be too short-lived to be useful for preventing CRPS. The success of multimodal therapy, which combines acetaminophen, nonsteroidal antiinflammatory drugs, femoral nerve block, and intraarticular administration of local anesthetic, clonidine, and morphine sulfate for arthroscopic knee surgery, emphasizes the potential of more than a single analgesic modality for preventing CRPS. Less familiar pharmacologic tools include the free radical scavengers, particularly vitamin C, which decreased the incidence of CRPS when administered for a period of almost 2 months. The serotonin type 2 receptor antagonist ketanserin may also be an effective component of a multimodal therapy designed to prevent CRPS if administered for several days starting before surgery. One nonpharmacologic intervention that may be beneficial is physical therapy, which is most effective when acute pain is managed optimally.<sup>15</sup> Clearly, maximal multimodal therapy requires

a concerted team approach. Importantly, most of the interventions described as beneficial for reducing CRPS also make sense for reducing acute pain.

The CRPS that can accompany orthopedic procedures is not an isolated phenomenon and is another manifestation of the long-term pain that is not an uncommon sequela of certain surgical procedures. The best known of these is the phantom and stump pain that is present in 70% of patients 1 yr after amputation of an extremity.<sup>16</sup> Approximately 50% of patients report some type of pain 1 yr after thoracotomy<sup>17</sup> or breast surgery.<sup>18,19</sup> Some level of residual pain is reported for up to several months after the procedure in about half of patients undergoing lower abdominal surgery.<sup>20–22</sup> Approximately 25% of patients report pain 1 yr after sternotomy<sup>19,23</sup> or herniorrhaphy.<sup>19,24</sup> What may be even more significant is the fact that even relatively low levels of residual pain appear to significantly affect social and physical function and overall perception of health.<sup>20,21,24</sup> The ability to prevent the long-term residual pain that accompanies these procedures and the means of prevention continue to be controversial.<sup>25</sup> However, several studies suggest that it is possible,<sup>20,22,26</sup> even if modest interventions are generally unsuccessful at limiting short-term pain and analgesic use.<sup>27</sup> By marshaling the evidence for prevention of CRPS after orthopedic procedures, Reuben continues to demonstrate that the choice of perioperative analgesic regimen may have important long-term consequences, the economic and psychosocial impacts of which have yet to be measured.

Overall, Reuben has challenged us as physicians and scientists to do better. The data he summarizes are provocative because they raise the possibility that interventions routinely used to reduce the acute pain that accompanies orthopedic surgery may also be effective at reducing CRPS, which is an all-too-frequent consequence of such surgery. As specialists whose role continues to be questioned and for whom reimbursement is often limited for procedures used to treat acute pain, anesthesiologists cannot afford to ignore the opportunities and challenges that such observations present to play a role in preventive medicine.

Allan Gottschalk, M.D., Ph.D.,\* and Srinivasa N. Raja, M.D.†  
 \* Department of Anesthesiology and Critical Care Medicine, Division of Neuroanesthesia; † Department of Anesthesiology and Critical Care Medicine, Division of Pain Medicine, The Johns Hopkins University, Baltimore, Maryland. sraja@jhmi.edu

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