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NEWSLETTER

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Opioid Prescribing: Methadone Risk Mitigation

by Joan M. Christie, MD

Methadone is a synthetic opioid with an exceptionally prolonged elimination half-life. It is modestly priced and has a unique ability among opiates to block NMDA receptors, leading to a resurgence in its use for chronic pain.[1] In 2007, for example, over 4 million prescriptions were issued for methadone, most for chronic, non-malignant pain. Even though it has an association with torsades de pointes ventricular tachycardia, methadone has been dubbed the "darling of the pain management community."

The number of unintentional overdose deaths from prescribed opioids now vastly exceeds unintentional deaths from all illegal drugs combined, and methadone plays a disproportionate role in such deaths. Sadly the intention to better manage chronic pain with methadone and other agents has led to what has been described in a recent editorial as "a rising tide of deaths."[2]

Increasing perioperative and prescription opioid deaths have prompted leaders in patient safety to address the safe use of opioids. The Anesthesia Patient Safety Foundation, FDA, and others have sponsored summits and initiatives on patient monitoring and opioid safety. Pain medicine and operating room anesthesia providers should be well versed with current evidence-based guidelines for methadone use and standards for methadone monitoring.

Methadone: Pharmacokinetics

Methadone is a phenylpropalamine synthetic opioid formulated as a racematic mixture of R and S enantiomeric forms. The S form may be responsible for QTc prolongation. Methadone is potent, has excellent oral absorption kinetics, and an inactive metabolite, EDDP. As a weak NMDA receptor antagonist,

See "Methadone," Page 13

Inside:

A Sad Parting: Patient Safety Pioneer Ellison C. Pierce, Jr., MD

Ellison C. Pierce, Jr., MD

The passing of Ellison C. Pierce, Jr., MD, affectionately known to so many as "Jeep," on April 3, 2011, at age 82 was a tremendous loss to everyone involved with anesthesia, in particular, and health care in general. Patients as well as providers will perpetually owe Jeep a debt of gratitude, for Jeep Pierce was the patient safety pioneer. He made a huge difference in the safety of health care for all of us. He saw what needed to be seen and said what needed to be said. He was on a perpetual mission to prevent patients from being injured or killed by anesthesia. When he started out on that mission, he didn't know that the impact would extend far beyond the specialty to which he devoted his life. While he'd had close calls in the OR, he never described a terrible event in his own career that motivated him to take on this cause. He took it on because he knew it was the most important thing that he could do for the specialty. And take it on he did, with all his energy, wisdom, and significant political savvy. When the specialty was faced with a "malpractice crisis" at the start of the 1980s, Jeep thought about protecting patients first, doctors second. That was a risky political move, but he didn't hesitate. He just did the right thing. As President of the ASA in 1982, he created the Patient Safety and Risk Management Committee, what appears to have been the first use of the now common term "patient safety." It was at the 1984 International Symposium on Anesthesia Mortality and Morbidity, which he co-organized, that he conceived of the idea of the Anesthesia Patient Safety Foundation. Through his charisma, political know-how, patience and persistence, he created the organization that has been the beacon for patient safety in anesthesia and far beyond.

Through APSF and his many connections in the world of medicine, Jeep's vision was moved forward to become what is now a worldwide movement to prevent needless injuries and deaths from

See "Sad Parting," Next Page

Farewell to a Legend and Friend

"Sad Parting," From Preceding Page

errors both human and system-induced. He was an attractor, someone we all wanted to help to accomplish his goals. When he assembled the team that would build the APSF, he was inclusive and strategic. He knew just how far he could go, just what kinds of people together were needed to do the job. He wasn't the one with all the detailed ideas. Yet, he instantly could spot a good one. And, he made the person who had it feel like a genius. He was generous and sincere with his praise; yet he wasn't looking for it himself (but he received a lot of it, including many awards for his pioneering work). He was happy and satisfied in himself to see the good work being done—the *APSF Newsletter*, the research grants program, the catalysis of new technologies, the development of simulation and teamwork training, and the innumerable special projects that came from APSF during these past 25 years, were all the result of an organization that was built from his astute sense of people, diplomacy, and timing.

But Jeep wasn't uni-dimensional. He had other loves as well. For his wife, Elizabeth, and his children, surely the most. And, in a social moment, he'd reveal his passion for organs and their magical music. He traveled the world to see the special ones. Functionally a "renaissance man," he loved opera and architecture too, but especially history. Winston Churchill was his hero; he read all he could about him (and displayed a Churchill bust in his vestibule). Jeep always had a delightful sense of humor and contagious laughter, and he was quick to help others, even when he himself might have been in need.

Passionate, persistent, patient, jovial, charming, and dedicated completely to a cause he believed in, he was transcendent. Jeep has left anesthesia practice an order of magnitude safer and the world a better place. We'll miss him.

The Ellison (Jeep) C. Pierce, Jr., MD, Research Award is a coveted award given every year by the APSF.

Vision

The vision of the Anesthesia Patient Safety Foundation is to ensure that no patient shall be harmed by anesthesia.

&

Mission

The APSF's Mission is to improve continually the safety of patients during anesthesia care by encouraging and conducting:

- safety research and education;
- patient safety programs and campaigns;
- national and international exchange of information and ideas.

APSF Executive Committee Invites Collaboration

From time to time the Anesthesia Patient Safety Foundation reconfirms its commitment of working with all who devote their energies to making anesthesia as safe as humanly possible. Thus, the Foundation invites collaboration from all who administer anesthesia, and all who provide the settings in which anesthesia is practiced, all individuals and all organizations who, through their work, affect the safety of patients receiving anesthesia. All will find us eager to listen to their suggestions and to work with them toward the common goal of safe anesthesia for all patients.

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NEWSLETTER

The Official Journal of the Anesthesia Patient Safety Foundation

The **Anesthesia Patient Safety Foundation Newsletter** is the official publication of the nonprofit Anesthesia Patient Safety Foundation and is published quarterly in Wilmington, Delaware. Annual contributor cost: Individual–$100, Corporate–$500. This and any additional contributions to the Foundation are tax deductible.

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Improving Patient Safety in the Office: The Institute for Safety in Office-Based Surgery

by Richard D. Urman, MD, MBA, and Fred E. Shapiro, DO

Economic realities of health care reimbursement and growing consumer demand have shifted health care delivery: from in-hospital to outpatient settings, and recently to physicians' offices. The number of offices, patients, variety, and complexity of procedures continues to increase with 12 million office-based procedures performed in 2009. This is due to decreased cost and improved provider patient access and convenience, without regulations similar to those at hospitals or ASCs (Ambulatory Surgical Centers) Office personnel often are not prepared for complications. An increased incidence of adverse events in office-based surgery has caught the public's attention due to highly publicized fatalities, such as the death of Kanye West's mother and of young, healthy patients undergoing routine procedures.

Currently, only 23 U.S. states have some regulation for office-based surgery. In addition, a vast majority of offices lack accreditation by one of the major accrediting agencies (AAAHC, AAAASF, JCAHO). Whether such procedures are performed with or without an anesthesia care team provider, current issues include patient and procedure selection, perioperative management, complications, and recovery. Non-patient related issues include proceduralists performing outside their scope of practice, substandard facilities, and lack of qualified office personnel. As of 2001, the ASA Closed Claims analysis has only 37 office-based cases, due to a 3-5 year lag between occurrence and entry into the database. One study showed that office-based claims were 3-times higher in severity (67% vs. 21% deaths), and in a higher proportion and amount of payment compared to ASCs. Further, 46% of office claims (vs. 13% for ASCs) were deemed preventable by better monitoring—e.g., by pulse oximetry in the postoperative setting.[1]

A controversial study by Vila et al. found a 10-fold increase in adverse incident and death in the office compared to the ASC setting in Florida.[2] A retrospective review by Keyes et al. examined 1.1 million accredited office cases and recorded 23 deaths.[3] Thirteen deaths were due to pulmonary embolism. The number of offices involved in this study represents a small fraction of office-based surgery practice, because the majority of offices are unaccredited. A Society for Ambulatory Anesthesia newsletter highlighted the need for better office education of surgeons, proceduralists, nurses, legislators and the public.[4] In addition, OBS practices face increased pressure by "medical necessity" policies instituted by commercial insurers.

What's the best way to improve patient safety in this "Wild West of Healthcare?" A recent editorial in the *New England Journal of Medicine* pointed out that, according to the Agency for Healthcare Research and Quality, only 10% of patient safety studies have been performed in outpatient settings. The authors called for "creating a culture of safety," acknowledging that safety oversight of office-based surgery is often "fragmented and disorganized and lacking in clear leadership."[5]

ISOBS honors pioneers in patient safety at 2010 inaugural reception: Left to right, front row: honorees Jeffrey Cooper, PhD, Ellison "Jeep" Pierce, Jr, MD.; back row: Fred E. Shapiro, DO, president and founder, Richard D. Urman, MD, MBA, chief executive officer.

Over the past decade, several professional organizations such as the ASA and ASPS (American Society of Plastic Surgeons) have generated recommendations and guidelines to improve office safety. In addition, anesthesiologists are leading in their attempts to collect ambulatory outcomes data through the Society for Ambulatory Anesthesia SCOR database and the Anesthesia Quality Institute to develop the National Anesthesia Clinical Outcomes Registry (NACOR).

As a result of concerns for patient safety, a few dedicated physicians representing different specialties came together to form **The Institute for Safety in Office-Based Surgery (ISOBS)**, a Boston-based, independent, 501(c)(3) non-profit organization. The Institute's mission is "to promote patient safety in office-based surgery and to encourage collaboration, scholarship, and physician and patient education." The ISOBS is an organization of individuals from diverse professional backgrounds. The idea is to have an entity endorsed by, and affiliated with, a range of anesthesia and non-anesthesia professional organizations. With leadership drawn from several specialties, the ISOBS would seek to engage these groups with the common goal of building consensus for best practices and defining uniform regulation, rather than having individual, uncoordinated efforts, or externally imposed regulations. In addition, the ISOBS wants to help patients learn about safe OBS practices and to obtain the tools needed to understand their health care provider's and facility's credentials. Thus, patient education is a large part of its mission.

The ISOBS was recently interviewed by the *Wall Street Journal* and a few other national newspapers, discussing the current issues facing office practices.[6,7] Less than 2 years after inception, the ISOBS recruited an excellent team of experts representing various medical, surgical, and dental specialties, in addition to board members from the business, law, and public policy sectors. The ISOBS plans to provide opportunities for safety training through a variety of tailored online educational modules: to enable office personnel to assess mastery of core safety competencies and to develop a "Certificate Program" for office practices that have successfully completed this educational process.

The ISOBS hopes to serve as a knowledge resource for patients and health care providers, detect educational gaps of the medical personnel involved in patient care, and encourage outcomes research and adverse event reporting. This is particularly timely given recently updated CMS guidelines that reflect future changes in cost and reimbursement of healthcare. In 2010, the Institute sponsored a CME course at Harvard Medical School, "Anesthesia in the Office-Based Setting: Safe, Simple, and Pain Free," followed by an inaugural reception to honor pioneers in patient safety, Drs. Ellison "Jeep" Pierce and Jeffrey B. Cooper (see photo).

See "ISOBS," Next Page

Safety Checklist for Office-Based Surgery

"ISOBS," From Preceding Page

The ISOBS has developed an OBS surgical safety checklist (see Figure).[8] Recent studies have shown that checklists can reduce costs, complications, and mortality, and improve patient safety and quality of care.[9,10] We hope to find the same results for the office.

The ISOBS will organize patient safety symposia at subspecialty meetings, to generate discussion regarding providers administering deep sedation and utilizing ASA outcome data collection systems.

The ISOBS has caught the attention of the Institute for Healthcare Improvement, the Massachusetts Medical Society, the Massachusetts Coalition for Prevention of Medical Error, Massachusetts Board of Registration, as well as national malpractice and health care organizations.

For additional information, visit **www.ISOBS.org.**

Richard D. Urman, MD, MBA, is an Assistant Professor of Anesthesia at Harvard Medical School, Director of Procedural Sedation Management at Brigham and Women's Hospital, and Chief Executive Officer for the Institute for Safety in Office-Based Surgery, Boston, MA.

Fred E. Shapiro, DO, is an Assistant Professor of Anesthesia at Harvard Medical School, President of the Massachusetts Society of Anesthesiologists, and President and Founder of the Institute for Safety in Office-Based Surgery, Boston, MA.

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See "ISOBS," Page 9

Safety Checklist for Office-Based Surgery

from the Institute for Safety in Office-Based Surgery (ISOBS)

Introduction
Preoperative encounter; with practitioner and patient

Patient

Patient medically optimized for the procedure?
☐ Yes
☐ No, and plan for optimization made

Does patient have DVT risk factors?
☐ Yes, and prophylaxis plans arranged
☐ No

Procedure

Procedure complexity and sedation/analgesia reviewed?
☐ Yes

NPO instructions given?
☐ Yes

Escort and post-procedure plans reviewed?
☐ Yes

Setting
Before patient in procedure room; with practitioner and personnel

Emergency equipment check complete (e.g. airway, AED, code cart, MH kit)?
☐ Yes

EMS availability confirmed?
☐ Yes

Oxygen source and suction checked?
☐ Yes

Anticipated duration ≤ 6 hours?
☐ Yes
☐ No, but personnel, monitoring, and equipment available

Operation
Before sedation/analgesia; with practitioner and personnel*

Patient identity, procedure, and consent confirmed? ☐ Yes

Is the site marked and side identified?
☐ Yes ☐ N/A

DVT prophylaxis provided?
☐ Yes ☐ N/A

Antibiotic prophylaxis administered within 60 minutes prior to procedure? ☐ Yes ☐ N/A

Essential imaging displayed?
☐ Yes ☐ N/A

Practitioner confirms verbally:

☐ **Local anesthetic toxicity precautions**

☐ **Patient monitoring (per institutional protocol)**

☐ **Anticipated critical events addressed with team**

☐ **Each member of the team has been addressed by name and is ready to proceed**

Before discharge
On arrival to recovery area; with practitioner and personnel

Assessment for pain?
☐ Yes

Assessment for nausea/vomiting?
☐ Yes

Recovery personnel available?
☐ Yes

Prior to discharge: (with personnel and patient)

Discharge criteria achieved?
☐ Yes

Patient education and instructions provided?
☐ Yes

Plan for post-discharge follow-up?
☐ Yes

Escort confirmed?
☐ Yes

Satisfaction
Completed post-procedure; with practitioner and patient

Unanticipated events documented?
☐ Yes

Patient satisfaction assessed?
☐ Yes

Provider satisfaction assessed?
☐ Yes

This checklist is not intended to be comprehensive. Additions and modifications to fit local practice are encouraged. *Adapted from the WHO Surgical Safety Checklist.

Developed by Alex Arriaga, MD, Richard Urman, MD, MBA and Fred Shapiro, DO.

Risks of Anesthesia Care in Remote Locations

by Julia Metzner, MD, and Karen B. Domino, MD, MPH

A 75-year-old, 100-kg, ASA 2 man was scheduled for endoscopic retrograde cholangiopancreatography (ERCP) under monitored anesthesia care (MAC). Monitors, including pulse oximetry, blood pressure, and ECG, were placed and the patient was turned prone for the procedure. He was given midazolam 2 mg and fentanyl 50 mcg IV, and he remained anxious. Additional midazolam 2 mg and fentanyl 150 mcg IV were given, but the patient could not tolerate insertion of the endoscope. Propofol 20 mg IV, followed by an infusion of 50-70 mcg/kg/min, was administered, and the procedure was begun with O_2 saturations 88-92% on 4 L/min O_2 by nasal prongs. After 20 minutes, the O_2 saturation decreased to 70%, and the patient became severely bradycardic, and was treated with atropine 1 mg. Attempts at bag-mask ventilation and placement of a laryngeal mask airway failed. Blood pressure was not obtainable and the procedure was aborted. It took 2-3 minutes to push aside the heavy endoscopy equipment, move in a gurney, and turn the patient supine to begin CPR. Although the patient was resuscitated after 10 minutes of CPR, he sustained severe anoxic brain damage, and life support was eventually discontinued.

The demand for anesthesia care for procedures performed outside the operating room (out-of-OR) has dramatically increased in recent years. Advances in diagnostic and interventional procedures, constraints on operating room time and costs, and the desire of patients for sedation and lack of recall, all contribute to the increase in popularity of anesthesia in remote locations. The delivery of safe anesthesia care may be difficult in out-of-OR settings due to a variety of challenges, including cramped, dark rooms, inadequate anesthesia support, unfamiliar environment, and variability of monitoring modalities. Although the majority of procedures in remote locations are relatively non-invasive, serious adverse outcomes, such as illustrated in the above case, can occur.

ASA Closed Claims Project Review

Because of these safety hazards, we analyzed claims for injuries from 1990 and later in the American Society of Anesthesiologists (ASA) Closed Claims database to compare injuries associated with claims for anesthesia care in remote locations (n=87) with anesthesia injuries in the operating room setting (n=3286).[1] The ASA Closed Claims Project is a structured evaluation of adverse anesthesia events obtained from closed malpractice claim files from professional liability insurance companies throughout the United States.[2] Claims for dental damage are excluded.

Patients in remote locations were older (20% greater than 70 years of age), sicker (69% ASA 3-5), and more often underwent an emergent procedure (36%) than patients in operating room claims.[1] The predominant anesthetic technique in remote location claims was monitored anesthesia care (MAC), which was

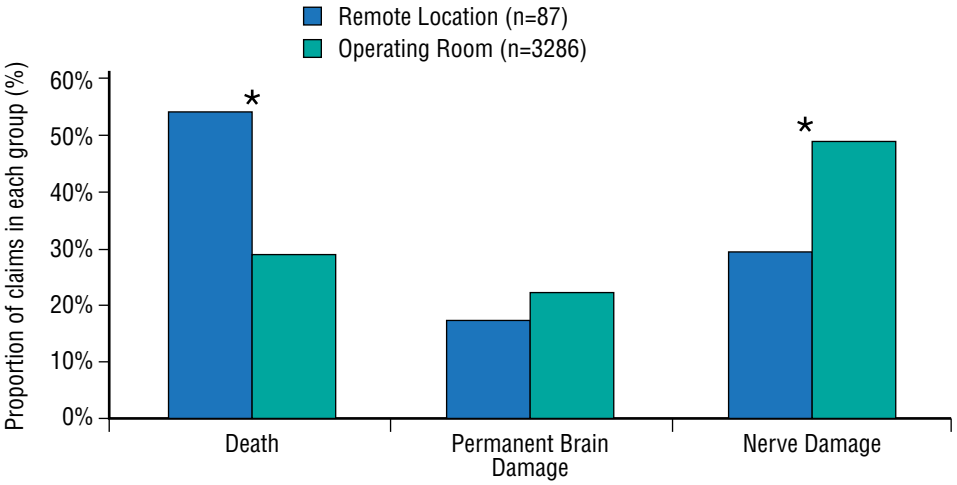

Figure 1. Severity of Injury in Remote Location vs. Operating Room Claims *p<0.001

8-times more frequent than in operating room claims (50% vs. 6 %).[1] The facilities most commonly involved were the gastrointestinal (GI) suite (32% of the remote location claims) and cardiology catheterization/electrophysiology laboratories (25% of remote location claims). Other locations included the emergency room, lithotripsy suites, and radiology, especially the magnetic resonance imaging (MRI) scanner.

The severity of patient injury was greater in remote location claims than in operating room claims, with the proportion of death almost double in the remote location claims (Fig. 1). In contrast, operating room claims were more often associated with temporary injuries, such as transient nerve injuries.[1] Although the most common mechanism of injury in both remote location and operating room claims was an adverse respiratory event, the proportion of respiratory events in remote locations was double that in the operating rooms (Fig. 2A). Inadequate oxygenation/ventilation was the most common respiratory-related adverse event in remote location claims, occurring 7 times more frequently than in operating room claims (Fig. 2B). The injuries in remote locations were more often judged as being preventable by better monitoring (Fig. 3).

Respiratory depression due to an absolute or relative overdose of sedative-hypnotic-analgesic drugs was responsible for 26 remote location claims, accounting for more than half of the claims in the GI suite. Other oversedation claims also occurred in radiology (MRI scanner), the lithotripsy unit, and cardiology laboratories. Patient factors for oversedation were obesity, sleep apnea, ASA status 3-5, and age greater than 70 years.

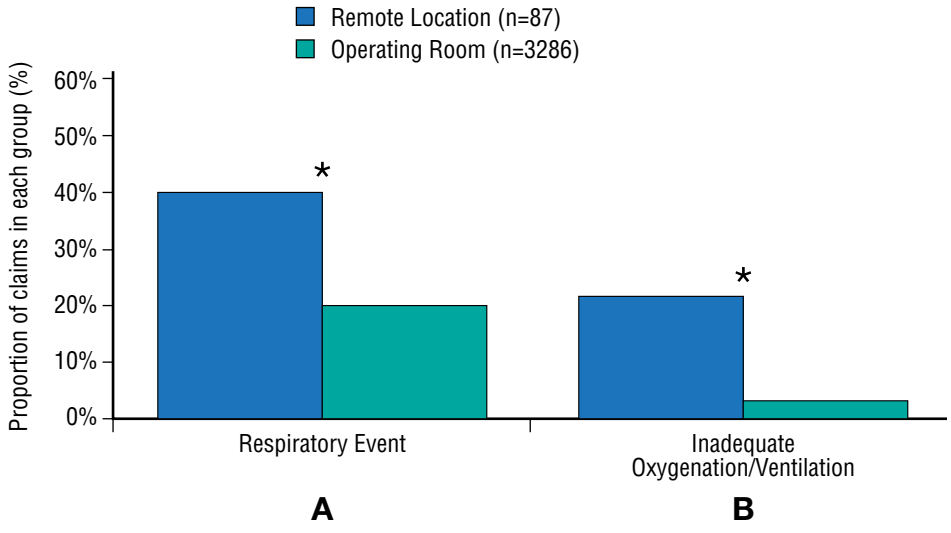

Figure 2A-B. Mechanisms of Injury in Remote Location vs. Operating Room Claims *p<0.001

See "Remote Locations," Next Page

Increased Monitoring Needed in Remote Locations

"Remote Locations," From Preceding Page

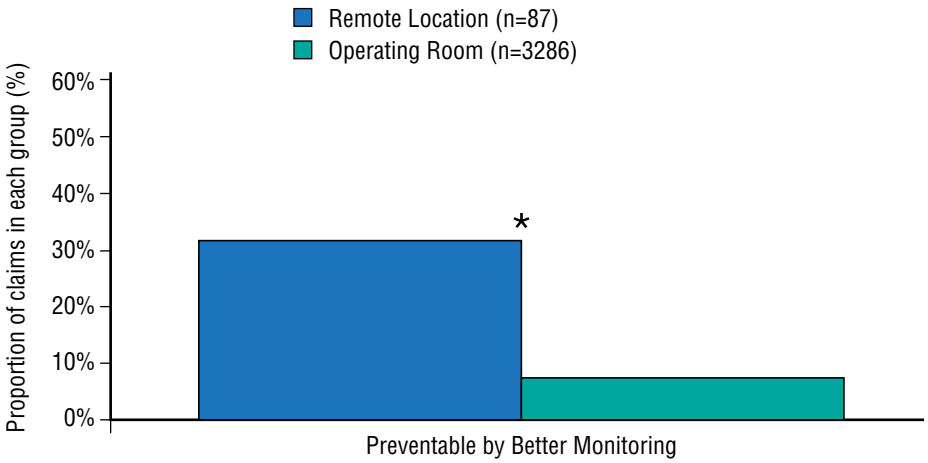

Figure 3. Proportion of Claims Preventable by Better Monitoring *p<0.001

Propofol was the most common drug used, either as a single agent or in combination with other drugs. Notably, a capnograph was employed in only a minority of claims associated with oversedation (15%) and no respiratory monitoring was used in 15% of these claims. Substandard care, preventable by better monitoring, was implicated in the majority of claims associated with death.

Monitoring for Respiratory Events

The above case illustrates the common clinical scenario for oversedation. The patient was sedated in a dark, cramped room, with intermittent intense procedural stimulation. Changing levels of noxious stimulation, pharmacokinetic features of the drugs, synergistic effects of polypharmacy, and variability of patient responses made sedation extremely challenging. The patient was breathing spontaneously, monitored by a pulse oximeter until apnea, desaturation, and bradycardia occurred, resulting in cardiopulmonary arrest and anoxic brain damage, with eventual withdrawal of life support. Delays in recognition and treatment of respiratory depression, as well as poor access to the patient, were at the heart of the problem!

In a report of 153 deaths occurring in the GI suite without the presence of anesthesia personnel, only half were monitored by pulse oximeter, and none by capnography.[3] A pulse oximeter monitors oxygen saturation, not ventilation, which is accomplished by a precordial or esophageal stethoscope, capnography, or electrical impedance monitoring. Detection of apnea or hypoventilation by pulse oximetry alone may be delayed in patients receiving supplemental oxygen.[4] Apnea lasting 20s or more is common in patients undergoing MAC and is not easily detected by clinical signs or pulse oximetry without the use of capnography or electrical impedance monitoring.[5,6] Capnography alerts practitioners to respiratory depression and apnea before hypoxemia develops, especially if supplemental oxygen is used. The ASA recently revised its standards of anesthesia monitoring to include use of capnography during monitored anesthesia care, particularly during upper endoscopy procedures.[7]

While capnography is useful in all patients undergoing sedation and MAC, it is especially important for sedation of patients with probable or known obstructive sleep apnea. In such a case, strong consideration should be given to securing the airway with general endotracheal anesthesia (instead of deep sedation) for procedures with poor access to the airway, such as those in the prone position, MRI scanner, or lithotripsy unit, due to the difficulty of immediate airway control and cardiopulmonary resuscitation.

In summary, data from the ASA Closed Claims Project demonstrates that MAC in remote locations poses a significant risk for oversedation and inadequate oxygenation/ventilation due to delays in recognition of respiratory depression. Knowledge of the pharmacokinetic properties of sedative/analgesic drugs, careful monitoring of respiration including capnography, and vigilance can minimize the risk of patient injury in these challenging settings. In addition, general anesthesia with endotracheal intubation may be safer than deep sedation in some patients (e.g., obstructive sleep apnea) and procedures (e.g., prone position, MRI scanner, poor access to patient's airway).

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Check out the Virtual Anesthesia Machine Website and the APSF Anesthesia Machine Workbook at www.anest.ufl.edu/vam

Dear SIRS

Wires Block APL Valve Interfering with Ventilation

S AFETY
I NFORMATION
R ESPONSE
S YSTEM

Dear SIRS refers to the Safety Information Response System. The purpose of this column is to allow expeditious communication of technology-related safety concerns raised by our readers, with input and responses from manufacturers and industry representatives. This process was developed by Dr. Michael Olympio, former chair of the Committee on Technology, and Dr. Robert Morell, co-editor of this newsletter. **Dear SIRS** made its debut in the Spring 2004 issue. Dr. A William Paulsen, current chair of the Committee on Technology, is overseeing the column and coordinating the readers' inquiries and the responses from industry.

The information provided is for safety-related educational purposes only, and does not constitute medical or legal advice. Individual or group responses are only commentary, provided for purposes of education or discussion, and are neither statements of advice nor the opinions of APSF. It is not the intention of APSF to provide specific medical or legal advice or to endorse any specific views or recommendations in response to the inquiries posted. In no event shall APSF be responsible or liable, directly or indirectly, for any damage or loss caused or alleged to be caused by or in connection with the reliance on any such information.

Dear SIRS:

I would like to report the sudden inability to provide manual positive pressure ventilation while using a Dräger Fabius GS anesthesia machine (Dräger, Lubeck, Germany). After completion of the anesthesia check-out procedure a patient was brought into the room for induction of general anesthesia. Monitors were applied and the patient was given an induction dose of anesthesia. Ventilation was confirmed, the patient was paralyzed, and his trachea intubated. After intubation the patient could not be ventilated. The anesthesia circuit connection was checked for a disconnect, but none was found. An ambu bag was obtained and the patient ventilated while the anesthesia machine was checked out. The temperature monitoring wire that was moved after induction in anticipation of the placement of an esophageal temperature probe was seen lodged under the APL valve (see Figures 1 and 2). The wire was easily removed from under the valve and the system was then able to generate positive pressure ventilation in the manual mode. This is a potentially dangerous problem that can be easily remedied, but many anesthesiologists may not think that a closed working APL valve functioning a minute ago could be the cause of the inability to generate positive pressure ventilation.

A literature search found several case reports of this same event happening with the gas sampling line of other Dräger anesthesia machines.[1-4] Dräger representatives have commented twice in letter form that the APL valve should be clear of wires and tubing.[5,6] Although ideal, in clinical situations that is often difficult to obtain. Does Dräger have an upgrade available for the Fabius GS that would solve this problem?

Sincerely,
Scott Groudine, MD
Professor of Anesthesiology
Albany Medical Center
Albany, NY 12110

Reply:

Thank you, Dr. Groudine, for your question. All new Apollo anesthesia machines (purchased since March 2009) and Fabius Family anesthesia machines (purchased since September 2009) have incorporated a design enhancement to the APL valve that reduces the potential of the problem discussed above. For those customers with Apollo or Fabius machines utilizing the older APL valve design, an upgrade is available. Please contact Dräger's Triage Center at 1-800-4-DRAGER for more information.

Thank you,
David Karchner
Director of Marketing, Perioperative Care
Dräger Medical Inc.
3135 Quarry Road, Telford, PA 18969

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Figures 1 and 2: Temperature wires for esophageal temperature probe lodged under APL valve prevent full closure and ability to generate positive pressure for manual ventilation.

Avoiding Catastrophic Complications from Epidural Steroid Injections

by Stephen E. Abram, MD, and Quinn H. Hogan, MD

Epidural steroid injections are frequently performed for patients with lumbar and cervical radiculopathy, the accepted indications. A review of Medicare insurance claims carried out in 2001 indicated a procedure rate of 26.5 per 1000 nationwide among Medicare recipients 65 and older.[1] The rate of serious complications resulting from these procedures is impossible to estimate in the U.S. because of the lack of mandatory reporting and the reluctance to report cases that are being or may become litigated. The ASA Closed Claims Project indicated that epidural steroid injections accounted for 40% of all claims involving pain management cases that occurred between 1970 and 1999.[2] Fourteen cases of spinal cord injury were reported, of which 6 resulted in paraplegia and 1 in quadriplegia. With the rapid increase in procedure rates for epidural steroid injections since that time, the incidence of these devastating complications has undoubtedly increased. Given the potential for serious complications following epidural steroid injections, it is important that the procedure be avoided for patients who are unlikely to respond, such as those with purely axial back pain, neural claudication, and non-radicular sources of back and leg pain.

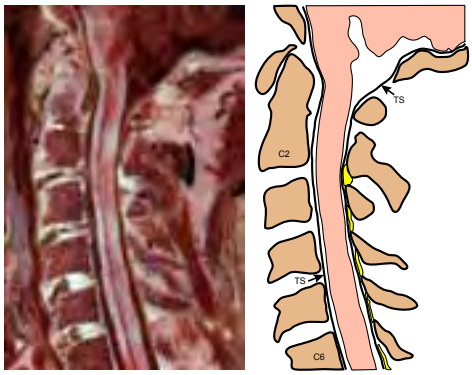
Unfortunately, physicians who participate as expert witnesses in malpractice claims report much of the information regarding spinal cord injury associated with epidural steroid injections verbally and informally. However, information from those sources as well as from the few published reports of complications can provide some insight into the mechanisms and causes of some very preventable complications.

The most likely causes of spinal cord injury following epidural steroid injection are epidural bleeding, epidural abscess, direct spinal cord trauma, and embolization of particulate matter into the arterial supply of the cord. The first 2 causes should be extremely rare with the use of meticulous aseptic technique and adherence to guidelines regarding the use of antithrombotic and thrombolytic agents (see Practice Advisory at ASRA.com). This discussion will concentrate on the 2 latter issues.

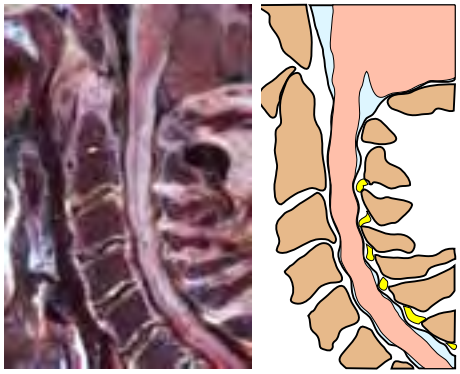
Direct Spinal Cord Injury

Some of the opinions and information presented here are based on medical records observed by physicians serving as expert witnesses in malpractice cases that are now closed. There are only a few published reports of such complications.

It is important to realize that although needle penetration of the spinal cord can produce injuries, with a wide range of severity, injection of any material into the cord is invariably devastating. It is critical, therefore, to insure proper needle placement prior to injecting anything, including contrast dye. The vast majority of serious injuries related to cord trauma are associated with cervical epidurals. Following are some suggestions that should help minimize the risk of serious injury:



Midline sagittal cryomicrotome section and index drawing of cervical vertebral column from C1 to C6 of a 65-year-old male. The C3 and C5 vertebral bodies are indicated by "3" and "5." The cord occupies a large share of the vertebral canal. Minimal epidural fat and veins are found in the anterior epidural space. There is no posterior epidural compartment because the dura is uniformly in contact with the ligamanta flava and lamina. From Hogan QH: Epidural anatomy examined by cryomicrotome section. Regional Anesthesia *1996;21:395-406. Reprinted with permission.*



Midline sagittal cryomicrotome section and drawing of cervical vertebral column of a 75-year-old male, revealing severe degenerative disc disease at all disc levels. Disc material has extruded into the spinal canal at levels C5-6 and C6-7. Thickening of the dura, buckling of the ligamanta flava, osteophyte formation at the vertebral body margins, and extruded disc material have resulted in cord compression and deformity with minimal cerebrospinal fluid surrounding the cord. The only posterior epidural space is at C7-T1 (just visible at the right picture margin). From Hogan QH: Epidural anatomy examined by cryomicrotome section. Regional Anesthesia *1996;21:395-406. Reprinted with permission.*

1. Obtain and view MRI scans prior to performing the procedure. Disc herniation may shift the cord posteriorly and obliterate the posterior subarachnoid space. In patients with previous cervical spine surgery there may be scar formation and adherence of dura to more superficial tissues at the proposed level of injection, increasing the risk of direct needle trauma to the cord. If there is pre-existing canal stenosis and spinal cord compression, the additional pressure created by the volume of drug injected, or by the pharmacological effect of those drugs, may result in neurological injury, particularly if there is already some loss of function.
2. Avoid epidural needle placement above C6-7. There is typically a small amount of epidural fat in the midline posteriorly at C7-T1, creating a space between the ligamentum flavum and the dura. Midline epidural fat is minimal at C6-7, and there is none at C5-6 and above. Low volume cervical injections often spread upward several segments. If it is felt that steroid placement at higher levels is indicated, it may be safer to introduce an epidural catheter in the upper thoracic spine and advance it under fluoroscopy to the desired level.
3. When possible, obtain a lateral view of the spine following needle placement prior to injecting. This is difficult at the lower cervical levels because of the superimposed shoulder joints, particularly in thick-necked patients. A "swimmer's view," with one arm at the side, the other raised above the head, has been used successfully to obtain a view of the needle within the spinal canal.[3]
4. Avoid deep sedation. The deeply sedated patient may become agitated and may move unexpectedly. Also, paresthesias may alert us to the fact that we have contacted the cord. There are many anecdotal accounts of patients who have had intense paresthesias and/or motor responses to contact of a needle with the spinal cord, as well as a number of cases in which general anesthesia or moderate to deep sedation appeared to block such responses.[4] Unfortunately, even in the non-sedated patient, needle entry into the cord may not result in a noticeable response.[5,6] Nevertheless, the vigilance of an awake patient offers at least some added safety.
5. Do not use the hanging drop technique to determine epidural needle placement, since this is not a reliable means of identifying the epidural space. I am aware of 2 malpractice claims in which spinal cord injury was associated with failure of the hanging drop technique to indicate epidural needle entry.

Ischemic Spinal Cord and Brain Injury

Reports of spinal cord, brainstem, and cerebellar infarction following cervical transforaminal epidural steroid injections began to appear in the scientific literature in the early 2000s.[7] It was postulated that such Injuries might result from accidental injection of particulate material into radicular arteries lying adjacent to the targeted nerve root. Demonstration of contrast dye spread into a radicular artery during transforaminal injection confirmed the likelihood of intra-arterial drug injection as a cause of ischemic injury,[8] and it has been shown that essentially all commercially-available steroid suspensions contain particles large enough to occlude arterioles and capillaries.[9] Spinal

See "ESI Complications," Next Page

Preventing Arterial Embolization of Particulate Steroids

"ESI Complications," From Preceding Page

cord injury has also been documented following transforaminal steroid injections at lumbar, sacral,[10] and thoracolumbar levels.[11] During intra-arterial injection, contrast is likely to spread epidurally as well as intravascularly, and the thin pattern of intra-arterial spread is easy to miss.[12] Digital subtraction fluoroscopy can enhance the visualization of the intravascular dye.[8] Undoubtedly, the use of small gauge needles increases the likelihood of intra-arterial spread. The use of a pencil point side port needle does not appear to offer protection against this complication.[13] Another possible mechanism of cord injury following foraminal injection is needle placement into the dorsal root ganglion. This structure is large and is positioned at the outer margin of the intervertebral foramen. The very short length of dorsal roots at this level (e.g., 1 cm) increases the likelihood of delivery of injectate into the substance of the cord.

Following are some suggestions to reduce the risk of intraneural injection or intra-arterial embolization of particulate steroids:

1. Following aspiration, inject contrast under live fluoroscopy. Obtain a still image a few seconds later to insure that the dye pattern has not changed. If available, use digital subtraction. Inject dye through small extension tubing to minimize needle tip movement between dye and steroid injection.
2. Consider a local anesthetic test dose with minimal sedation. Look for signs of systemic symptoms and numbness and paresthesias locally.
3. Consider the use of non-particulate steroids. This is controversial, as there is little evidence that soluble steroids have equivalent efficacy, and early studies indicated that soluble steroid preparations remain in the spinal canal only for brief periods.[14]
4. Consider using the interlaminar approach, particularly for cervical injections. The arteries supplying the spinal cord do not traverse the dorsal epidural space, so the risk of injecting a radicular artery or dorsal root ganglion by this approach is minimal. The evidence for the superiority of transforaminal epidurals is largely theoretical and is based mainly upon non-controlled case series.[15,16] Avoid transforaminal injections when contrast dye is contraindicated. Make sure patients are aware of the risks associated with both types of injections.

Conclusions

Epidural steroid injections can be helpful for hastening recovery from radiculopathy following disc herniation and can provide temporary relief for patients with chronic radicular pain. There is little evidence that they are of benefit for patients with axial back pain or neural claudication associated with spinal stenosis. There is little evidence that they reduce the need for spine surgery or that they improve long-term outcomes. It is important that patients understand the risks and benefits of these procedures and that we do everything possible to prevent rare but catastrophic neurological complications.

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Q&A

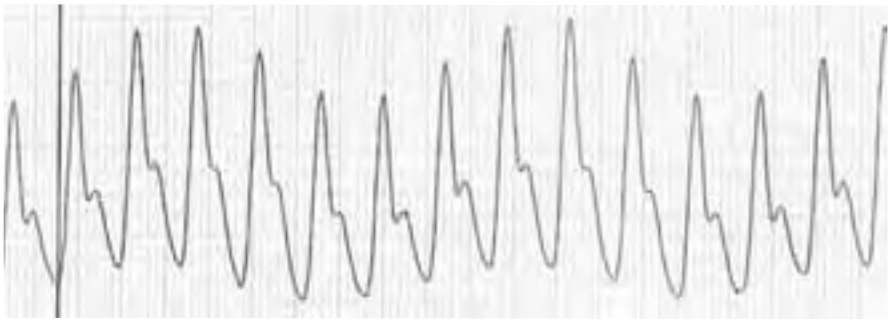
Validity of Using Pulse Oximeter to Detect Adequate Blood Flow to Lower Extremity Questioned

Q **Dear Q&A,**

In our institution we provide anesthesia for major spinal surgery including ALIF. We have always placed a pulse oximeter on the foot for detection of blood flow to the lower extremity. SSEP monitoring is also utilized. Our vascular surgeon questions the validity of the pulse oximeter when there is a loss of signal. Surveying 2 surrounding institutions that also provide anesthesia for ALIF procedures indicated that one requires pulse oximetry, the other relies on SSEP monitoring alone.

As we have provided anesthesia for our patients for ALIF procedures for many years, I can no longer find the original protocol on which we based our monitoring requirements. I sincerely appreciate any information you may provide in this area.

Name Withheld By Request



Pulse oximeter plethysmogram

A **Dear Reader,**

The issue here is to define what information we are expecting to receive from each monitoring modality, and how each modality may improve patient safety and outcomes. Pulse oximetry (SpO_2) and somatosensory evoked potentials (SSEPs) monitor very different aspects of anterior lumbar interbody fusion (ALIF).

Pulse Oximetry

The waveform displayed on the patient monitor that is associated with the pulse oximeter is called the plethysmogram, and is an indicator of changes in blood volume within the skin that is between apposing parts of the probe. Physiologically and mathematically the plethysmogram is related to the change in blood flow to the skin. Each stroke volume produces a measurable change in the plethysmogram waveform according to the flow delivered to that specific segment of skin. A loss of plethysmographic waveform is indicative of diminished blood flow to the tissues within the probe. There are many factors that play a role in blood flow to the skin of the extremities, including surgical occlusion of vessels, sympathetic nervous activity that increases vascular resistance, patient's temperature, and the patient's blood volume.

Surgical issues related to arterial vasculature complications during ALIF are well recognized. According to Fantini et al,[1] there is a 2.9% incidence of major vascular complications during anterior lumbar spinal surgery. Vascular injuries occurred during initial spinal exposure or during maintenance of exposure during discectomy, corpectomy, osteotomy, or spinal reconstruction. They described 9 injuries of the common iliac vein and a single aortic injury. If the aorta or common iliac arteries were displaced and mechanically occluded during surgical exposure, the plethysmogram would depict diminished amplitude or no amplitude if the occlusion was complete. Unfortunately, if the surgical injury occurred slightly more distal in the common iliac arteries, the pulse oximeter probes would have to be placed on both right and left toes in order to identify injury to either vessel. In this report the aortic injury resulted in a tear in the terminal aorta at the level of L3-L4. If the tear was significant, the blood flow would exit the aorta as the path of least resistance and no flow would be available to the common iliac arteries, an injury that could have been identified with careful attention to the plethysmogram. A small hole in the aorta might go undetected by the amplitude of the plethysmogram, and tears or other complications of the veins could not be detected by the plethysmogram from pulse oximetry. Faciszewski et al.[2] reported earlier studies indicated that injury to the iliac vein or vena cava occurred in 15.6% of cases. Their current study included

See "Q&A," Page 18

Numerous questions to the Committee on Technology are individually and quickly answered each quarter by knowledgeable committee members. Many of those responses would be of value to the general readership, but are not suitable for the Dear SIRS column. Therefore, we have created this simple column to address the needs of our readership.

Methadone Titration High Risk for Respiratory Depression

"Methadone," From Page 1

methadone is an attractive choice for chronic neuropathic pain syndromes. In humans the cytochrome P450 enzyme system, specifically CYP2B6 N-demethylation, is responsible for the majority of methadone metabolism, and CYP inducers or inhibitors dramatically change methadone elimination kinetics.

Methadone has an analgesic onset of .5 to 1 hour after oral administration, peaking in 1 to 7.5 hours. Steady-state peak effect may not be seen with continuous dosing for 3 to 5 days. Analgesic duration increases to 22-48 hours with repeat dosing. The V_{dds} is 1-8 L/kg, and methadone is highly protein bound (85-90%) with good bioavailability. The half-life elimination of 8-59 hours for methadone may exceed the duration of analgesia. Renal excretion of unchanged methadone is <10%.

Serum monitoring has been performed for prevention of opioid withdrawal and for forensic analysis. Toxic levels are considered to be >2 mcg/ml (SI: >6.46 µmol/L). CNS depressants act synergistically with methadone, and many methadone deaths also involve other drugs, most commonly alcohol and benzodiazepines.

Methadone

Onset of Action	0.5-1 hr
Peak Effect	1-7.5 hrs
Steady State Peak Effect With Continuous Dosing	3-5 days
Duration of Action With Repeat Dosing	22-48 hrs
Vdds	1-8 L/kg
$T^1/_2$ elimination	8-59 hrs
Renal Excretion of Unchanged Methadone	<10%
Toxic Levels	>2mcg/ml (SI: >6.46µmol/L)

Respiratory Depressant Effects

After an exponential rise in methadone deaths in non-malignant pain patients, the FDA issued a public safety advisory entitled "Methadone Use For Pain Control May Result in Death and Life Threatening Changes in Breathing and Heart Beat"(Nov 2006). The FDA alert was quickly followed by the following black box warning by the manufacturer.

Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids (see DOSAGE AND ADMINISTRATION). Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration. Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

A combined advisory committee (Drug Safety and Anesthetic and Life Support Drugs) has proposed that methadone deserves special attention in the FDA's proposed "Risk Evaluation and Mitigation Strategy" plan for extended and long acting opioids.

The manufacturers' black box warning for methadone clearly identifies severe respiratory depression as the most important untoward effect of methadone administration. Methadone is a difficult drug to initiate, to titrate, and to convert to, or from, other opioids. In addition standards for serum or urine monitoring have not been well defined for chronic pain. Cases of iatrogenic overdose are thought to occur because peak respiratory depressant effects occur later and persist longer than analgesia.

Some clinicians endorse the concept of "no ceiling effect for opioid prescription," a notion first promulgated to encourage adequate narcotic dosing for terminally ill cancer patients. The concept that there is no upper safe limit for opioid prescription is clearly inappropriate for methadone given the realities of the unique pharmacokinetics and patient responses to this drug.

Drug Monitoring and Respiratory Depression

Methadone serum monitoring has been employed for patients on maintenance for opioid addiction. Toxic levels used by medical examiners in forensic cases are those exceeding 2 mcg/ml (SI: >6.46 µmol/L). Respiratory depression and death have both occurred at levels well below those defined as toxic, while some patients appear to experience no toxicity at levels in the toxic range. Despite these observations, when treating chronic pain there seems no reason to ignore the accepted range for toxicity established for those who died secondary to methadone.

Serum methadone levels in chronic pain are useful to establish baselines, and thereafter, to identify levels known to be associated with toxicity.

Methadone tablets

Therapeutic monitoring may also be useful when enzyme inhibitors are added or to correlate pharmacodynamic observations with a pharmacokinetic data point. At steady-state kinetics, dose increases will result in increased serum levels which may provide prescribers with a reasonable endpoint for opioid titration if levels approach or exceed those considered to be toxic for humans. Pain patients are frequently taking concomitant CNS depressants which impose independent risk for respiratory depression and perhaps for QT prolongation. Alcohol, benzodiazepines, and illicit drugs are frequently associated with methadone deaths, and patients should be monitored for their use through urine drug screening.

The FDA recognizes the importance of prescribing and monitoring with the current REMS initiative. The concept of therapeutic drug monitoring evolved primarily for drugs with narrow therapeutic ranges, nonlinear and unpredictable kinetics, or serious dose-related side effects. Methadone is an ideal drug for therapeutic monitoring, and quantified serum or urine drug and metabolite levels are commercially available.

Clearly, much work remains to be done to refine therapeutic monitoring; however, new standards of care are beginning to emerge.

Cardiac Effects

In November 2006, the FDA issued a safety alert regarding deaths and cardiac arrhythmias with methadone. The black box warning also includes the following relevant language

In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

See "Methadone," Next Page

Risk of QT Prolongation with Methadone Cardiotoxicity

"Methadone," From Preceding Page

The QTc interval is slightly longer for women than for men and is frequently corrected for heart rate. The FDA industry standard for QTc monitoring in drug development and post-market ADEs is 450 ms independent of gender. A QTc interval of 500 ms or greater, for any gender, is considered significant for the risk of arrhythmia. Torsades does not occur in the absence of QT prolongation.

Experimental work has demonstrated that the common mechanism of drug-induced QT prolongation is blockade of hERG (human cardiac ether-a-go-go-related gene) which encodes I_{kr}. The I_{kr}, or delayed rectifier inward potassium channel, is responsible for resetting transmembrane cardiac muscle potential which then allows depolarization to occur. When repolarization is delayed *torsade de pointes*, a variant of ventricular tachycardia, may occur. The blockade of I_{kr} channels, and hence repolarization, is reflected as QTc interval prolongation on a surface EKG tracing. Methadone has been shown *in vitro* and *in vivo* to be a strong inhibitor of hERG. Absolute dose usually plays a significant role in QT effects with methadone. Doses >100 mg/day have been well studied and are associated with QTc interval effects which may reverse when dose is decreased. However, since sudden cardiac death has also been described with doses as low as 20 mg/day, therapeutic range is exceedingly narrow. Other factors influencing QTc include family or personal history of long-QT syndrome or sudden cardiac death, electrolyte abnormalities, structural cardiac disease, rhythm disturbances, CPY inhibitors, use of other QT prolonging drugs (especially cocaine), and total methadone dose.

Cardiotoxicity Monitoring

In 2009 an independent expert advisory panel to the FDA published guidelines for therapeutic QTc monitoring in methadone treatment. The adjacent table describes 5 recommendations for methadone monitoring including informed consent, history, baseline EKG screening, Qt risk stratification, and drug interactions. Please see also the further elaboration of recommendations on page 15.

Dosing should be conservative, and respect delayed respiratory depression during titration. Incomplete cross tolerance and NMDA effects may result in acceptable analgesia at very low doses. A total daily dose not exceeding 120 mg/day if possible is preferable. Risk factors specific to the patient should be acknowledged such as sleep apnea, structural heart disease, benzodiazepines, and CYP inhibitors.

Serum methadone blood levels should be obtained during dose titrations and at steady-state to ensure that known forensic levels are not reached or exceeded. Urine drug screening is recommended to assess compliance and to detect illicit substances.

The expert panel approach to QTc monitoring and other recommendations provide a significant positive step toward risk reduction in patients taking methadone. Methadone should be used for patients in need, with careful attention to risk mitigation strategies.

Dr. Christie is an attending anesthesiologist in St. Petersburg, FL, and a clinical associate professor of surgery at the University of South Florida. She is a long-serving member of the APSF editorial board.

Expert Panel Guidelines for Cardiac Monitoring

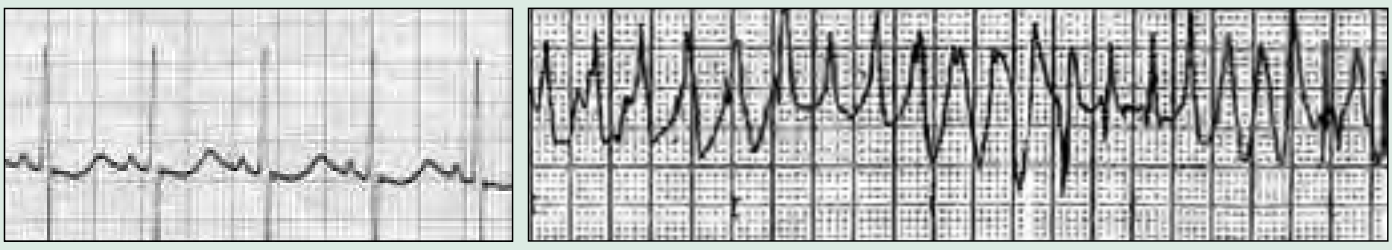
Recommendation 1. Disclosure.
Clinicians should inform patients of arrhythmia risk when they prescribe methadone.

Recommendation 2. Clinical History.
Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.

Recommendation 3. Screening.
Obtain a pretreatment electrocardiogram for all patients to measure the QTc interval and a follow-up electrocardiogram within 30 days and annually. Additional electrocardiography is recommended if the methadone dosage exceeds 100 mg/day or if patients have unexplained syncope or seizures.

Recommendation 4. Risk Stratification.
If the QTc interval is >450 ms but <500 ms discuss the potential risks and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500 ms consider discontinuing or reducing the methadone dose, eliminating contributing factors, such as drugs that promote hypokalemia, or using an alternative therapy.

Recommendation 5. Drug Interactions.
Clinicians should be aware of interactions between methadone and other drugs that possess QT interval prolonging properties or slow the elimination of methadone.



QT prolongation (left) and torsades de pointes arrhythmia (right) have been observed with methadone use in large daily doses.

Methadone Titration High Risk for Respiratory Depression

"Methadone," From Preceding Page

6 Recommendations: Methadone Prescribing and Risk Mitigation

1 Patient Selection

- Determine if patient has risk factors for long Qt syndrome.
- Determine if patient is taking concomitant respiratory depressants, particularly benzodiazepines or alcohol.
- Determine if patient has pulmonary risk factors such as sleep apnea, obesity, COPD.

2 Informed Consent

- Discuss opiate side effects including death.
- Discuss FDA black box warnings including arrhythmia.
- Discuss risk factors specific to the individual patient.
- Discuss methods used to monitor side effects and compliance including EKGs, office visits, appropriate consultations, and drug testing.

3 Cardiac Screening

- Obtain pretreatment EKG to assess baseline Qt interval.
- Repeat at one month, every year, and more frequently if methadone dose exceeds 100mg per day or if the patient has any cardiac or neurologic symptoms

4 Risk Stratification

- Qt 450 to 500msec: discuss risks and benefits, monitor more frequently, reduce dose.
- Qt >500msec: Reduce dose, discontinue, or choose alternate therapy. Treat underlying conditions contributing to long Qt and providing close monitoring, probably with cardiology involvement.

5 Drug Interactions

- Beware of CYP inhibitors and Qt prolongers.
- Obtain accurate list of all medications at each visit.
- Adjust dose if untoward effects on EKG, therapeutic drug screening, or by history and physical examination.
- Obtain serum methadone blood levels during dose titrations and at steady state
- Ensure that known forensic levels are not reached or exceeded.
- Urine screening to assess compliance.

6 Dosing

- Go low and slow.
- Do not use loading doses.
- Respect delayed respiratory depression during titration.
- Stop upward titration when no pharmacodynamic response.
- Do not exceed 100mg total dose per day if possible.

Opioid Prescribing: REMS Sleep, Need Reawakening

by Gregory W. Terman, MD

On September 27, 2007, the Food and Drug Administration Amendments Act (FDAAA) was signed into law. This law signaled a very significant addition to FDA authority including additional requirements, authorities, and resources with regard to drug safety both pre- and post-marketing—including the authority to require Risk Evaluation and Mitigation Strategies (REMS). These REMS may be demanded from the sponsor (usually a drug company), either before or long after the drug has been approved, to ensure that the benefits of a drug outweigh its risks. On February 6, 2009, the FDA sent letters to 16 manufacturers of 24 opioid analgesics informing them that they would be required to submit REMS on their products (www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163654.ht). These products primarily included extended release opioids as well as methadone. Statistics from 2007 showed that these 24 products were prescribed 21 million times for 3.7 million unique patients. This was a big deal. In this copy of the *APSF Newsletter*, Dr. Joan Christie gives a nice summary of a risk mitigation strategy for prescribing one of these products—methadone—including patient evaluation, informed (patient and doctor) prescribing, and appropriate monitoring. I will take a slightly different tack in this article—describing what progress has been made in implementing prescription opioid REMS during the last 2 years. For those short on time, the grim answer is still, "not much."

The risks of prescription opioids are real. The roughly 600% increase in opioid prescribing from 1997-2007, based in large part on pain doctors such as myself, entreating physicians to not be afraid of treating pain patients with opioids, was accompanied by a 300% increase in accidental deaths related to prescription opioids according to the Centers for Disease Control (CDC). Although it is not an exact science, to be certain that people dying with opioids in their bloodstream died of those opioids, there is no denying that mortality thought to be caused by prescription drugs is one of the few causes of death still on the upswing in the CDC Health US 2010 report. Neither can we deny the data that someone dies from causes labeled "unintentional drug overdose" every 19 minutes in this country—making it the leading cause of accidental death in 17 states (even "besting" the number of motor vehicle accident deaths in those states). Further, although other sedatives (including alcohol, benzodiazepines, and illicit drugs) are also often associated with these deaths, the numbers of prescription opioid-associated deaths have, for most of the last decade, been greater than the number of heroin- and cocaine-associated deaths combined. It is little wonder then that in May of 2009, at an FDA public forum discussing opioid REMS, I found myself, on behalf of the American Pain Society Board of Directors, "pledging to help the FDA at every opportunity to develop, deploy, and determine efficacy of (opioid) REMS." Of course, we also stipulated that these REMS should not endanger patient access to opioids necessary to treat their pain. I reminded the forum that opioid treatment and pain treatment have never been synonyms and that, indeed, many American Pain Society members have never written an opioid prescription for pain (in their jobs as nurses, psychologists, and basic scientists). We, and hundreds of other groups and individuals, submitted comments concerning REMS to an online "docket," which was open at least intermittently from May 2009 till October 2010. Throughout this process the FDA has been nothing if not responsive to its "stakeholders."

A proposal for opioid REMS was published by the FDA in June 2010. Shortly afterwards, on July 22-23, 2010, a joint meeting of the Anesthetic and Life Support Drugs and the Drug Safety and Risk Management advisory committees discussed the proposed REMS but voted them down, 25 to 10 (www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm). Nevertheless, the role of advisory committees is advisory only, and the FDA is expected to come out with their final opioid REMS requirements in the next few months (if not sooner). The manufacturers of the covered products will then have 120 days to respond. Thus, one can say that the REMS sleep at the moment, and when they will wake is not yet known.

While the FDA is deciding on their course of action, it is important to note that other government agencies (both federal and state) have also noticed the prescription opioid overdose problem. Most of these actions will likely restrict, or at least "guide," prescribers and dispensers in treating their patients in pain, and I admit that I am always nervous when legislators dabble in medicine. Despite this bias, however, it was even clear to me last July (when I voted FOR the REMS as a reasonable first step) that many of the concerns advisory committee members had with the proposed REMS were outside the FDA's jurisdiction to correct (even under FDAAA). In the last part of this article I will discuss some of these concerns—largely replicating my May 2009 comments to the FDA, but with updates of some of the non-FDA activities taking place in the country that are relevant to the topic.

1. REMS should cover the entire class of opioid medications—not just long-acting opioids. This has certainly been a concern about the way the FDA views opioid REMS from the start. People can die from any opioid. Past experience has shown us that any attempt to regulate only a few opioids will drive prescribers, users, and particularly misusers of these medications to other, less stringently regulated, opioids that may be less effective therapeutically and actually may pose greater addictive or toxicologic risks. Indeed, it may be said that it is only for the opioid abuser that any opioid will do! Whether such class-wide REMS would drive prescribers or smaller manufacturers to completely abandon opioids is not known, but would likely depend on other details of the REMS. For example:

2. There should be NO REMS registry requirements for patients using opioids. Registries have historically been an important mechanism by which the FDA attempted to improve safety (an "element to assure safe use" or "ETASU" in REMS). By the word "registry" I refer to a database filled with names of patients, prescribers, dispensers, or distributors who are allowed to be involved in the medical use of a particular drug and which is populated solely on the basis of a willingness to sign up to be in the database. In the REMS accompanying the approval of buccal fentanyl (Onsolis) in July 2009 for example, registries were huge components. In order for a patient to receive the drug, the prescriber, the patient, the pharmacy, and the distributor will all be in separate databases (registries) maintained by the manufacturer. Obviously, if this was done for every opioid on the market, access to opioids for patients in pain would be compromised. In fact, no evidence exists to suggest that a federal or state patient registry diminishes abuse or misuse of medications. In contrast, evidence DOES exist suggesting that such an approach can stigmatize patients and impose significant burdens on all parties, resulting in stilted prescribing and, perhaps, inadequate pain management. Enhancements in the current state Prescription Monitoring Programs (PMPs), including integrating these into a national program, would be a better system for helping to monitor where drugs are going—providing real-time information for prescribers concerning other prescriptions their patients have filled recently. Improved PMPs would allow identification of patients receiving opioids from several prescribers (a risk factor for opioid associated overdoses, along with a history of drug abuse and psychiatric comorbidities). The Office of National Drug Control Policy (ONDCP) has also consistently encouraged expansion of PMPs (e.g., www.whitehousedrugpolicy.gov/news/press10/071510.html) but at least 8 states still have no PMP, and of those that do, most are only rudimentary and slow, and even the best programs have no way as yet to share information across state lines. Indeed, after my talk at the FDA, encouraging expansion of PMPs, in May 2009, I returned home to my own state (Washington) to hear that our PMP had been shut down due to lack of funds (a decision that has now, thankfully, been reversed).

3. Demonstrated prescriber and dispenser knowledge concerning opioid pharmacology should be expected of all who seek DEA licensure. It seems appropriate that clinicians be required to demonstrate competence in safe and effective prescribing or dispensing of opioids for

See "REMS Sleep," Next Page

REMS Recommendations Revisited

"REMS Sleep," From Preceding Page

therapeutic purposes. Broad participation and compliance would be most likely if demonstrated competence were a prerequisite for DEA registration. The content of competency testing should be developed with appropriate expert input—independent of drug company influences. Indeed, over the last year a number of pain treatment curricula/guidelines (including appropriate opioid prescribing) have become available through state mandates and public and private funding mechanisms. The use of such education as a pre-requisite for DEA licensure would likely require new congressional legislation, but this may still be the fastest route to consistent and effective change compared with waiting for changes in all prescriber Boards in all 50 states. In my state of Washington again, for example, opioid guidelines for chronic pain treatment were crafted by a panel of "pain experts" in the state supported by all of the state health care payers. These were published in 2007 (and updated in 2010) as an "educational initiative" (www.agencymeddirectors.wa.gov/opioiddosing.asp). However, in July 2010 a bill (WA HSB 2876) was passed into law requiring all health care boards in the state whose licensees prescribe opioids to develop "rules" for chronic pain treatment. These rules are due to go into effect in July of this year and at present show considerable similarity to the previous educational guidelines. How these rules will affect the efficacy and safety of opioid prescribing for pain in Washington State, not to mention how this approach might compare to 49 other approaches to this problem in other states is, of course, unknown. This leads to the next issue:

4. All implemented REMS should be measurable and, when necessary, easily reversible. Frequent intentional evaluations of all REMS components for their positive and negative impacts must be tied to their implementation. Indeed, in the FDA's initial REMS proposal, frequent evaluations of REMS effects were mandated. However, many advisory committee members were concerned that there was no scientifically valid method detailed for collecting appropriate statistics and no current baseline data from which to compare changes. Again, the FDA is not a funding mechanism for appropriate studies in this area, and unfortunately, the NIH has thus far demonstrated minimal interest in supporting research on either the mechanism or prevention of prescription opioid-associated deaths.

5. REMS education programs should also be aimed at the public. Most surprising to me in my initial introduction to this field was learning that much of the problem with opioid overdosing is due, not to prescribing per se, but to drug diversion. My initial presumption was that poor dosing practices were causing the problem, but in some studies of prescription opioid-related deaths more than half of decedents had NO prescription for the opioids that probably killed them. Worse, more than half of those patients (labeled "non-medical" users) received the drug from someone that they knew who HAD gotten the drug by prescription. No amount of education of prescribers or dispensers about opioid pharmacokinetics will save these people. However, that does NOT mean that there is nothing we can do! Product-specific patient education materials were stipulated in the proposed REMS and are available already in many instances. This information can and should be discussed with patients by providers. In particular, focusing drug education on appropriate use (it is only for them), storage (keep under lock and key), and and disposal (per FDA guidelines) of the drugs are key safety interventions we can perform for our patients and their families. In addition, public education programs must be intensified concerning the dangers of sharing opioid prescription drugs and the urgent need for treatment of opioid-induced sedation. Such public education programs should be combined with new and creative "give back" and/or "buy back" programs enabling collection and appropriate disposal of unused prescription opioids to further reduce availability and diversion. Again the ONDCP is supporting these efforts and last September's National Take Back Day drew 121 tons of drugs in 4 hours. Unfortunately, all of the sites in my area were police stations, where some patients might be reluctant to take their excess drugs. The next Take Back Day is scheduled for April 30. In short, we must be aware of these and other steps to avoid diversion. If every realtor knows that the most common visitor to an open house is one who wants to check the medicine cabinet, doctors probably should, too.

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UPDATE:

While this article was in press the Office of National Drug Policy released a comprehensive plan for combating Prescription Drug Abuse (http://www.whitehousedrugpolicy.gov/prescriptiondrugs/index.html). As a part of their 4-prong plan (including increased provider and patient edutcation, Prescription Drug Monitoring Programs, prescription drug takeback programs, and DEA efforts to shut down so-called "pill mills"), the FDA sent letters to manufacturers of long-acting optiates updating their general, primarily educational, requirements for REMS for these drugs (e.g., http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM251595.pdf)). Readers are referred to these ONDCP and FDA plans to compare them to the suggestions mentioned in this article.

Q&A

Utility of Lower Extremity Pulse Oximetry in ALIFS

"Q&A," From Page 12

a single aortic laceration with no common iliac vein lacerations. The literature suggests that venous injury is much more likely than an arterial injury, making the use of the pulse oximeter placed on the toes of questionable value in routine monitoring of ALIF.

Summary of the use of pulse oximeter plethysmogram measured on the toe in ALIF:

- Abrupt changes in the plethysmogram can signal arterial vascular compromise either from bleeding from a tear or from occlusion of an arterial vessel.
- A slow progressive decrease in plethysmogram amplitude may signal growing hypovolemia or hypothermia.
- Peripheral vascular disease in the leg

Somatosensory Evoked Potential

SSEP monitoring for spine procedures is useful for detecting surgical maneuvers that block sensory signals from traveling from the posterior tibial nerve to the cortex via the dorsal column. This may be caused by loss of blood supply to the spinal cord from stretching vasculature or nerve fibers in the cord while straightening the spine. However, they cannot detect an interrupted motor pathway in the anterior spinal cord. Patients with intact SSEPs may awaken in the recovery room unable to move their legs. The ventral and dorsal spinal cord have separate blood supplies with very limited collateral flow; an anterior cord syndrome (paralysis or paresis with some preserved sensory function) is a possible surgical sequela.

Transcranial Motor Evoked Potentials

TcMEP, either electrical (TceMEP) or magnetic (TcmMEP), stimulation of the cerebral cortex, can theoretically monitor the descending motor pathway in the anterior cord. TcMEP alone has been touted as being more sensitive to spinal cord injury intraoperatively than SSEP. [3,4] The combination of the 2 forms of evoked potential monitoring should provide a very powerful tool for intraoperative spinal cord monitoring.[3,4] However, there have been reports of patients waking with paraplegia after having intact MEPs intraoperatively.[5]

Summary

There is probably little justification for monitoring the plethysmogram on one toe during ALIF. If this is the only site used for SpO_2 monitoring, the extreme time delay for measuring changes in oxygen saturation in the body, as measured from the toe, probably does not justify its use. SSEPs most likely measure the ability of the spinal cord to conduct sensory information in the dorsal column of the cord, while TcMEP has the potential to measure the function of descending motor tracts in the anterior spinal cord.

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The APSF Committee on Technology

Letter to the Editor:

Breathing Bag has Faulty Connection

To the Editor:

A 76-year-old man scheduled for an open colectomy received propofol for induction of general anesthesia and vecuronium to facilitate endotracheal intubation. After loss of consciousness, positive pressure ventilation via facemask was attempted using a Uni-lim™ coaxial circuit (Westmed, Tucson, AZ, USA). This was unsuccessful, as the breathing bag (Figure 1) separated from the white retaining ring that articulates with the manual ventilation limb of the anesthesia machine (Figure 2). Department policy is to stock additional circuits in the back of the anesthesia machine, so one was opened and an intact breathing bag was immediately substituted.

After the anesthetic, the bag was examined carefully. It was noted that a piece of tape that holds the green rubber portion of the bag to the white articulation ring was missing. Other circuits from the lot were visually inspected and found to be intact. Notification of the company about this defect resulted in their rapid response to evaluate available stock and reinforce the procedure for correct construction among their assembly personnel.[1] While seemingly an isolated incident, this could have had disastrous consequences because of the inability to ventilate a patient who had just received a neuromuscular blocking drug.

Figure 1. Breathing bag.

Figure 2. Manual ventilation limb.

See "Breathing Bag," Next Page

Faulty Breathing Bag

"Breathing Bag," From Preceding Page

Of note, the machine "passed" its manual check for leaks prior to the anesthetic. However, manual ventilation using the breathing bag often involves a downward force, which could cause separation of improperly manufactured equipment. Preinduction testing of the anesthesia machine for leaks does not involve this downward force, thus the problem was not identified.

If no additional circuits had been available, alternate means of airway management would have had to include urgent tracheal intubation (without additional oxygenation and ventilation) and mechanical ventilation, the use of an Ambu bag, or the placement of the mask attached to the circuit over the patient's face (using an appropriate manual seal) and using the anesthesia workstation ventilator. This last option bypasses the manual limb of the anesthesia machine and, in essence, has the bellows act as the breathing bag.

After an equipment malfunction, steps should be taken to ensure that other practioners do not suffer the same problem (Table 1). Regardless of the options, practitioners need to remember that despite following all usual safeguards and guidelines, equipment failure can still occur, and alternate plans of rescue are paramount for safe anesthetic care.

Reference

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Table 1. Steps after equipment failure or malfunction

1. Involve the manufacturer in error or defect detection
2. Retrieve and save the failed equipment for later inspection and evaluation
3. Examine all similar equipment within the institution for comparable problems
4. Consider reporting the failure to the FDA/MedWatch Alerts

New Scientific Evaluation Committee Members

Annually, the APSF Scientific Evaluation Committee (SEC) considers the addition of new members to participate in the review of clinical and educational patient safety grants. Applicants for SEC membership should be experienced patient safety researchers with a track record of funding and peer-reviewed publication. The SEC is particularly interested in applicants with safety related expertise in informatics, simulation, or the responsible conduct of research. Interested applicants should submit their curriculum vitae and a cover letter explaining interest and qualifications to Dr. Sorin Brull at brull@apsf.org.

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In this issue:

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