Perioperative management of opioid-tolerant chronic pain patients

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ABSTRACT

Opioids occupy a position of unsurpassed clinical utility in the treatment of many types of painful conditions. In recent years there has been a noticeable shift regarding the use of opioids for the treatment of both benign and malignancy-related pain. As acceptance of the prescribing of opioids for chronically painful conditions has grown, many more opioid-tolerant patients are presenting for surgical procedures. It is therefore imperative that practicing anesthesiologists become familiar with currently available opioid formulations, including data regarding drug interactions and side effects, in order to better plan for patients' perioperative anesthetic needs and management. Unfortunately, there is a lack of scientifically rigorous studies in this important area, and most information must be derived from anecdotal reports and the personal experience of anesthesiologists working in this field. In this review, we shall discuss current chronic pain management and the impact of opioid use and tolerance on perioperative anesthetic management.

Key words: opioids, opioid tolerance, chronic pain, perioperative, anesthesia

INTRODUCTION

Pain represents one of the most common reasons that people seek medical care.[1] In the past, most physicians were reluctant to prescribe strong opioid analgesics for chronic nonmalignant pain, and the use of opioids in such patients was considered controversial by many clinicians well into the 1990s.[2] This controversy persisted despite numerous published studies that documented the safety and efficacy of opioids in the management of a wide variety of chronic nonmalignant pain states, including those of neuropathic, myofascial, and arthritic origin.[3,4] However, following a joint consensus statement published by the American Academy of Pain Medicine and the American Pain Society[5] in 1997, *The Use of Opioids for the Treatment of Chronic Pain*, noticeable shifts in physician attitudes toward the rational use of these drugs occurred. Primary care physicians and pain specialists are prescribing opioids to a great number of patients with nonmalignant pain, in doses appropriate to their needs.[6] For example, Clark,[7] in a recent review of 300 randomly selected patient charts from a population of patients at the Veterans Affairs Palo Alto Health Care System, found that 50 percent of the patients selected suffered from at least one form of chronic pain. Of those patients with chronic pain, 75 percent were prescribed at least one analgesic drug, and most received two or more. In the group of patients who received analgesic medication, 44 percent were prescribed an opioid. It is not surprising that as a consequence of exposure to long-term opioid therapy, chronic pain patients become opioid tolerant. In this review, we shall discuss the clinical aspects of opioid use and tolerance, including the impact they may have on perioperative anesthetic management.

PREOPERATIVE CONCERNS WITH THE OPIOID–TOLERANT PATIENT

The ultimate goal of the preoperative medical assessment of a patient is to reduce the morbidity and mortality of surgery. In addition, in today's cost-conscious hospital environment there is an emphasis on reducing the cost of perioperative care and returning the patient to full functioning as quickly as possible. To achieve these ends, the anesthesiologist must perform a preoperative assessment of the patient. This traditionally includes a preoperative history, physical examination, laboratory evaluation, and risk classification of the patient. Armed with the resulting information, the anesthesiologist then formulates an individually tailored plan of care for the anesthetic management of the patient. Multiple guidelines have been published to help facilitate thorough evaluations of high-risk patients. Unfortunately, there are no specific guidelines to help anesthesiologists evaluate the unique requirements of the chronic pain patient. There are, though, several general principles

Table 1. Commonly used single opioid preparations			
Opioid name	**Preparation**	**Dosage forms**	**Comments**
Morphine			
MS Contin	Sustained-release oral tablet/capsule	15, 30, 60, 100, 200 mg	Q12 h dosing; tablets or capsules must not be broken, chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of morphine
Kadian		20, 30, 50, 60, 100 mg	
Avinza		30, 60, 90, 120 mg	
Oramorph ST	Oral liquid	10 mg/5 ml, 10 mg/2.5 ml, 20 mg/5 ml, 20 mg/ml, 100 mg/5 ml	
Roxinol		10 mg/2.5 ml, 20 mg/ml, 100 mg/5 ml	
Actiq	Transoral delivery system	200, 400, 600, 800, 1200, 1600 μg	Only indicated for the management of breakthrough pain in patients who are already receiving and who are tolerant to opioid therapy
Oralet		100, 200, 300, 400 μg	
Oxycodone			
Oxycontin	Sustained-release tablets	10, 20, 40, 80, 160 mg	Q12 h dosing; tablets or capsules must not be broken, chewed, crushed, or dissolved due to the risk of rapid release and absorption of a potentially fatal dose of oxycodone
OxyIR	Immediate-release tablets	5 mg	
OxyFast	Oral liquid	20 mg/ml	
Hydromorphone			
Dilaudid	Tablet	8 mg	Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people
Dilaudid liquid	Oral liquid	5 mg	
Methadone			
Dolphine	Tablet	5, 10 mg	Dose-dependent prolongation of the QT interval
Fentanyl			
Duragesic	Transdermal delivery system	25, 50, 75, 100 μg/hr	Apply every three days; fentanyl delivery may be altered by application of heat

that can help to guide the anesthesiologist in perioperative management of the opioid-tolerant patient.

During the initial patient assessment, the anesthesiologist should determine whether the patient is a chronic opioid user, while being careful to recognize that the terms "opioid user" or "abuser" may be considered derogatory labels by the patient. Patients are keenly aware of the significant social stigma surrounding opioid use and are entitled to privacy and the right to confidentiality. It is imperative to take a detailed history from these patients and to establish a good rapport through nonjudgmental communication. In some cases, patients may not be taking their medication as directed. A minority of these patients may be selling or trading their pain medicines. If there is concern regarding the validity of a patient's stated drug requirement, the medicine can be portioned out over a longer period of time, instead of giving a large and potentially dangerous single dose. Physicians should communicate to their patients that an improper dose of opiates can potentially result in either a life-threatening overdose or withdrawal phenomena associated with inadequate analgesia. Good rapport with the patients and a clear description of the expectations of the patients by hospital staff may help to promote an honest dialogue about drug history and medications.[8]

A preoperative medication history should include the dose, frequency of ingestion, and time of last dose. All regular medications, including opioids and adjuvants, should be reviewed with the patient. Physicians should be well versed in the commonly used opioid preparations. Opioids are available in both sustained- and immediate-release forms, and they can be administered by a number of routes, including oral, parenteral, rectal, sublingual, transdermal, and transmucosal. The prototype opioid, morphine, represents the most commonly used type of opioid. Morphine and other opioids with short half-lives require frequent administration to maintain analgesia. Immediate-release morphine products provide about four hours of pain relief and need to be dosed accordingly. Controlled-release formulations such as MS Contin provide alternatives to frequent opioid administration. Medications with longer half-lives (e.g., methadone and levorphanol) yield analgesia for six to 12 hours. Some of the more common commercially available opioids are listed in Table 1.

Tolerance to opioids is characterized by shortened duration and decreased intensity of analgesia, euphoria, sedation, and other effects caused by depression of the central nervous system. Opioid tolerance is a predictable pharmacologic adaptation. Chronic opioid exposure results in a rightward shift in the dose-response curve, and patients require increasing amounts of a drug to maintain the same pharmacologic effects. In general, the higher the daily dose requirement, the greater the degree of tolerance development. Although there are no clear gradation guidelines, individuals requiring the equivalent of 1 mg or more of intravenous (IV) morphine or 3 mg or more of oral morphine per hour for a period of longer than one month may be considered to have high-grade opioid tolerance.[9,10]

Various studies and anecdotal clinical experience suggest that tolerance to various opioid side effects develops at different rates; this is termed "selective tolerance."[11] The initial effects associated with opioid administration include analgesia, sedation, nausea and vomiting, respiratory depression, pupillary constriction, constipation, and euphoria or dysphoria. Tolerance to nausea and vomiting, sedation, euphoria, and respiratory depression occurs rapidly, while tolerance to constipation and miosis is minimal over any length of time.[12,13]

Preoperative management of the opioid-tolerant patient begins with administration of the daily maintenance or baseline opioid dose, before induction of general, spinal, or regional anesthesia. Patients should be instructed to take the usual dose of oral opioid on the morning of surgery and, if applicable, to maintain any transdermal fentanyl patches. Because most sustained-release opioids provide 12 hours or more of analgesic effect, baseline requirements will generally be maintained during preoperative and intraoperative periods. However, with shorter-acting opioids or patients who have missed a dose prior to surgery, an "opioid debt" may develop preoperatively. Opioid debt has been defined as the daily amount of opioid medication required by an opioid-dependent patient to maintain his or her usual, prehospitalization opioid level. Discontinuation of opioids in a patient who is opioid-dependent will result in a lowering of the opioid plasma level to a point below the patient's "comfort zone," leading into either early (subjective) or late (objective) withdrawal. In addition, hyperalgesia has been observed in association with opioid tolerance.[14]

A patient-controlled analgesia (PCA) pump can be used but is limited in that it is designed primarily to maintain analgesia, not to establish analgesia or overcome an opioid debt.[15] In opioid-tolerant patients, if the opioid debt is not covered, the repeated bolus doses from a PCA pump are unlikely to achieve an analgesia effect. A background infusion should be considered in opioid-tolerant patients currently on high-dose opioid therapy. One anesthesia group advocates loading the opioid-tolerant patient with opioids in the operating room as the patient is waking from surgery. Opioid-tolerant patients who undergo major surgery can receive a low dose of intraoperative ketamine (0.25 mg/kg IV, up to 20 mg) for potential reduction in opioid tolerance and improved postoperative pain control.[16,17] Unless contraindicated, patients should also be instructed to take their morning dose of cyclooxygenase-2 inhibitor to reduce inflammatory responses to surgery and to augment opioid-mediated analgesia.

Epidural and intrathecal opioid infusions delivered by internally implanted devices are generally maintained throughout the perioperative period and are used to maintain baseline pain control. The only exception to this rule applies to patients receiving intrathecal infusions of the nonopioid relaxant baclofen. It may be advisable to discontinue or reduce the intrathecal infusion rate of baclofen during the immediate perioperative period, because the central nervous system effects and peripheral skeletal muscle relaxing effects of this medication may enhance neuromuscular blockade and increase the incidence of hypotension and excessive sedation.[18]

In addition, two areas of concern in the opioid-tolerant patient that can be investigated during the preoperative interview are the risk of gastric aspiration and cardiac arrhythmias. Perioperative aspiration of gastric contents is a potentially fatal complication of anesthesia. The classic example is the patient in acute pain and with a full stomach who must have emergency surgery. Patients who are pregnant, obese, or diabetic; those with gastroesophageal reflux; or those with a hiatal hernia all may be at risk for aspiration of gastric contents and subsequent chemical pneumonitis.

Delay in gastric emptying may be caused by decreased gastric motility and gastric tone or increased pyloric tone. The tone of the pyloric sphincter regulates the outflow to the duodenum. The pylorus has a rich enkephalinergic innervation, and several studies have demonstrated that opioid administration delays gastric emptying, presumably by increasing pyloric-sphincter tone.[19] Although the exact mechanism of inhibition of gastric emptying by opioids is unclear, both central and peripheral mechanisms have been implicated.[20-22] Unfortunately, there are no studies that assess the risk of aspiration in the opioid-maintained chronic pain patient. Nevertheless, it would seem prudent to consider all chronic pain patients who have been maintained on opioids for any length of time as being at high risk for gastric aspiration, and appropriate precautions should be taken. Particular attention should be paid in those cases where the dose or formulation has recently been changed.

Recent reports have also raised concern that methadone, a commonly used medication for the treatment of chronic pain, may prolong the QT interval (QTc when corrected for heart rate). Although reviews of the literature do not provide clear evidence of the arrhythmia-inducing effects of methadone, there are a number of authors who argue that their findings suggest an effect.[14,23-28] The QT interval on electrocardiogram (EKG) has gained clinical importance, primarily because prolongation of this interval can predispose patients to potentially fatal ventricular arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes. Multiple factors have been implicated in QT prolongation and torsades de pointes, including older age, gender, reduced left ventricular ejection fraction, left ventricular hypertrophy, ischemia, slow heart rate, and electrolyte abnormalities including hypokalemia and hypomagnesemia.[29-34] However, the studies that have examined this risk in chronic methadone patients are limited, and major references differ on whether methadone should be considered a risk factor for torsades de pointes.[28,35,36] Reviews of the literature do not provide clear evidence of the arrhythmic effects of methadone, and certain sources argue that it is improbable that methadone is a cause of QT prolongation. In a mixed sample of 104 methadone-treated patients, 32 percent had QTc prolongation, but none had a QTc duration beyond the value considered a definite risk for torsades de pointes (500 msec).[36-38] Although a large percentage of patients presented with QTc prolongation, the lack of serious prolongation in a sample of patients taking as much as 1200 mg of methadone daily is reassuring and suggests that the general risk of seriously prolonged QTc and torsades de pointes may be low in these patients. In addition, there are data suggesting that a relationship between dose and cardiac effects may be complex and related to gender and duration of treatment. The data indicate that the risk of methadone-induced QTc prolongation may be greater for males, especially soon after treatment is initiated. The lack of dose-dependent cardiac effects for male patients on methadone for 12 months or more suggests that tolerance to any possible cardiac effects of methadone in males may develop over time.[39]

Further studies are needed to define the prevalence and severity of QTc prolongation and to identify predisposing factors, but at least two previous studies reported methadone-induced QTc prolongation. A widely cited retrospective case series by Krantz et al.[40] documented 17 cases of torsades de pointes in methadone-treated patients. In this review, the mean daily methadone dose was 397 mg/day, with a range of 65 to 1000 mg/day. Overall, 14 of 17 patients had at least one risk factor for arrhythmia in addition to methadone as a potential causative factor for ventricular arrhythmias. Seven patients had hypokalemia, and one patient had hypomagnesemia on initial presentation. Nine patients were receiving a potentially QT-prolonging drug (gabapentin), and one patient was taking a medication known to inhibit the metabolism of methadone (nelfinavir). Only three patients were found to have structural heart disease. The design of this study does not allow for determination of either the prevalence of QTc prolongation in patients taking methadone or the possible causal role of methadone. Moreover, seven of the patients in the study were hypokalemic, and this may have been the actual predisposing factor in these patients, rather than methadone.

Another study looked retrospectively at 190 patients treated with IV methadone and 301 treated with IV morphine over the course of 20 months. The risk appears

greatest in the following situations: oral administration of doses greater than 200 mg/day, IV administration of methadone, and medical conditions or medications that predispose patients to QTc-interval prolongation. In the 47 methadone patients who underwent at least one EKG while receiving methadone, mean QTc duration increased significantly (by 42 msec) when compared to EKGs done while the patients were off methadone. In contrast, the QTc duration increased by only 9 msec for the 35 patients treated with morphine who also had at least one EKG.[25] Some of the currently used medications known to cause QT prolongation, and which may interact with methadone, are listed in Table 2.

A recent paper by Cruciani et al.[39] examines the measurement of QTc in patients receiving chronic methadone therapy. In this study, the overall mean QTc increased significantly, from 418 to 428 msec, but there were no instances of torsades de pointes in patients receiving up to 150 mg/day of methadone. There were no significant gender-related differences, although males' QTc increased by 13 msec while females' increased by 6 msec. These results suggest the absence of serious QTc prolongation, as well as the possibility of a dose-dependent effect in male patients on methadone for less than one year. The question of whether QTc prolongation lasted substantially beyond the two-month follow-up of the methadone-maintenance patients remains. Given the limited and exploratory nature of this study, no conclusions can be drawn about the risk of prolongation related to other variables, such as structural heart disease or the dose or duration of use of medications known to prolong QTc duration or increase serum methadone levels. Further studies are needed to address these potential risk factors, as well as to confirm the importance of gender and treatment duration on the cardiac effects of methadone. Although absence of QTc prolongation above 500 msec is reassuring, the data suggest that methadone may prolong QTc in males within one year of the start of treatment.

INTRAOPERATIVE CONCERNS IN THE OPIOID–TOLERANT PATIENT

The management of anesthesia in the opioid-tolerant chronic pain patient is usually determined by the potential interactions between medications, the nature and severity of the patient's underlying disease process, and the planned surgical procedure itself. Although there may not be an ideal anesthetic technique, several areas of concern deserve special attention in this patient population.

Thermal regulation in patients using a fentanyl patch

In an effort to reduce the hypothermic effects associated with general anesthesia, it is common practice for anesthesiologists to apply forced-air warming blankets to patients about to undergo surgical procedures, and these blankets are known to be capable of generating skin temperatures up to 43°C. While there are no current studies of the effects that warming blankets may have on transdermal fentanyl patches, anecdotal case reports suggest that this practice may lead to potentially dangerous complications. In addition, recent reports have suggested that temperature and anesthetic agents may alter the pharmacokinetics of the transdermal fentanyl system.

Transdermal fentanyl patches are manufactured so that the amount of the drug released into systemic circulation is proportional to the surface area of the patch. The system comprises a drug reservoir and a rate-limiting membrane with an impermeable backing that is applied to the skin via an adhesive coating. Pharmacokinetic studies indicate that after the first application, a depot of fentanyl is present in the upper layers of the skin. From this depot, fentanyl is released into circulation, resulting in a delayed onset of clinical effect, the length of which is highly variable (1.2 to 40 hours).[41] The time necessary to achieve a steady-state concentration of the drug may not be reached until 48 to 72 hours post-application, but once reached the concentration can be maintained as long as the patches are replaced regularly. Fentanyl continues to be absorbed into the systemic circulation following removal of the patch, with a terminal half-life of 13 to 25 hours.[42]

Although fentanyl patches have proved relatively reliable in administering controlled amounts of the drug over long periods of time, recent case reports and small studies suggest that the amount of fentanyl delivered to the patient may be significantly altered in certain clinical situations.[43-48] Several factors that have been shown to influence serum fentanyl concentrations obtained from a transdermal delivery system in the perioperative period are body temperature,[46,48] anesthetic,[45] and direct or indirect warming of the transdermal delivery system itself.[43,47,48] Changes in body temperature alter skin perfusion and permeability, release of fentanyl from the drug reservoir, and total body clearance of fentanyl.[49] Because fentanyl is largely cleared by the liver, isoflurane and halothane, for example, may have different effects on the elimination of transdermally administered fentanyl due to their different effects upon hepatic function,[50] hepatic-artery blood flow,[51] and hepatic sinusoidal blood flow.[52] The vascular uptake of fentanyl from dermal depots may also vary with the choice of anesthetic inhalant agents because of the variable peripheral vasodilation induced by different volatile gases.[53] An experimental animal study by Pettifer and Hosgood[45] compared the effects of halothane versus isoflurane on the serum concentration of transdermally applied fentanyl in both normothermic and hypothermic (35°C) conditions. Results of that study

Table 2. Medications suspected to cause QT prolongation*		
Class	**Very probable**	**Probable**
Antiarrhythmics	Amiodarone, Disopyramide, Dofetilide, Ibutilide, Procainamide, Quinidine, Sotalol	
Antipsychotics	Thioridazine	Pimozide, Ziprasidone, Chlorpromazine, Haloperidol, Olanzapine, Risperidone
Anti-infectives	Clarithromycin, Erythromycin, Gatifloxacin, Pentamidine, Sparfloxacin	Fluconazole, Levofloxicin, Trimethoprin-sulfamethoxazole
Antidepressants		Amitriptyline, Desipramine, Imipramine, Sertraline, Venlafaxine
Others	Droperidol, grapefruit, grapefruit juice	Gabapentin

*Modified version based upon Al-Khatib SM et al.: What clinicians should know about the QT interval. *JAMA*. 2003; 289(16): 2120-2127.

indicated that significant decreases in serum fentanyl concentration occurred in the isoflurane group in both the normothermic and hypothermic conditions as compared to halothane. It was postulated that isoflurane produced a greater reduction in cutaneous blood flow, which resulted in reduced vascular uptake of the dermal fentanyl depot.

The effects of applied heat on transdermal fentanyl delivery have also been studied recently.[44-48] In an effort to speed up the transdermal absorption of fentanyl, Shomaker et al.[47] studied the effects of applying a heat pack to the transdermal fentanyl patch in six healthy, adult volunteers in an open, two-period, randomized, crossover study. In this study, a 25 µg/hr fentanyl patch was applied to each volunteer for a total of 240 minutes, both with and without the application of heat. The heat source used was a Controlled Heat Aided Drug Delivery (CHADD) patch (ZARS, Inc., Salt Lake City, UT), which was specifically designed to pass heat through the fentanyl patch, increasing skin temperature to 41°C, ± 1°C. Data analysis was conducted to examine the plasma concentration of fentanyl over a four-hour period in the heat versus no-heat groups. The results of this study showed that there was a four-fold difference in plasma concentrations of fentanyl between the heat group (0.39 ng/ml) and the no-heat group (0.11 ng/ml). They postulated that the use of heat drives the drug from the patch, through the subcutaneous skin depot known to be present in transdermal drug delivery, and into the systemic circulation.

Case reports now suggest that the accidental presence of a heat source near the application site of a fentanyl patch has led to adverse outcomes.[48] Frolich et al.[43] recently published a case report on how the effects of warming blankets on transdermal fentanyl patches can lead to dangerous complications. In this case, a 57-year-old woman with a past medical history of reflex sympathetic dystrophy was receiving multiple analgesic medications, including transdermal fentanyl 75 µg/hr, gabapentin 600 mg/day, baclofen 5 mg TID, sertraline 50 mg/day, and acetaminophen/oxycodone 325 mg/5 mg for breakthrough pain. She underwent an open reduction and internal fixation of a right tibial stress fracture. The patient had a lumbar epidural catheter placed at the L3-L4 interspace for intra- and postoperative analgesia. The catheter was tested with 3 ml of 1.5 percent lidocaine with epinephrine, but it was not used during the procedure. General anesthesia was induced and maintained with IV propofol, and a laryngeal-mask airway was inserted to facilitate spontaneous ventilation with a 50 percent air-oxygen mixture. The patient was noted to have a three-day-old transdermal fentanyl patch on the left side of her chest. The patch was left in place during the procedure, and an upper-body warming blanket was then placed over the patient, covering the site of the patch. Her respiratory rate at the beginning of the procedure was noted to be 16 breaths/min, with a tidal volume of 300 ml. No changes were made in the anesthetic, but over the next hour a steady decrease in respiratory rate was noted. The rate fell to three breaths/min, with a tidal volume of 800 ml, and her pupils were noted to be pinpoint bilaterally. Fortunately, following multiple doses of naloxone and close postoperative observation, the patient made an uneventful recovery. It was also interesting to note in this case that the patient's recorded core temperature had decreased to 34.9°C, with the associated exposed-skin temperature probably being lower. The authors speculated that following the application of the warming blanket significant increases in skin temperature and perfusion occurred, which were likely responsible for increased transdermal delivery of fentanyl into the systemic circulation.

This case illustrates a potentially serious adverse event that can occur with the transdermal fentanyl delivery system. While product labeling of the fentanyl patch includes a warning advising patients to avoid exposing the application site to direct heat sources, no specific recommendations or precautions are provided for the intraoperative use of fentanyl patches. Anesthesiologists need to be aware of the potential variations in systemic absorption that can occur when the fentanyl patch is exposed to a heat source.

Intraoperative analgesic requirements

The intraoperative and postoperative analgesic requirements of opioid-naïve patients, as well as those with a history of chronic opioid use and tolerance, may vary widely in terms of the dosage of opioid necessary to produce effective analgesia.[54-56] There are few published reports that can guide the anesthesiologist in determining the intraoperative opioid requirements in this population of patients. In a retrospective study, Weintraub et al.[57] contrasted the opioid requirements of 37 patients who underwent liver transplantation surgery and who were on chronic methadone maintenance therapy with a case-matched sample of 19 liver transplant recipients not receiving methadone maintenance therapy and not opioid tolerant. Intraoperative opioid requirements were determined from a review of operating room records and were analyzed by comparing mean doses of IV fentanyl. The authors found that the mean fentanyl dose in the opioid-tolerant group was significantly higher (3,175 μg) than in the opioid-naïve group (1,324 μg). In addition, they reviewed the postoperative analgesic requirements of these patients and found similar results. The mean daily postoperative analgesia requirements were significantly higher in the opioid-tolerant group (67.86 mg/day of morphine) when compared to the opioid-naïve group (12.17 mg/day of morphine). Unfortunately, the authors do not indicate how they made these intraoperative or postoperative determinations. While these findings are not surprising, they provide little guidance for determining the intraoperative analgesic requirements for individual opioid-tolerant patients.

Perhaps a more rational and quantifiable approach to the determination of individual opioid requirements in the chronic pain patient is one based upon existing data suggesting that the minimum effective plasma concentration of fentanyl necessary to provide adequate analgesia is approximately 25 to 30 percent of the concentration associated with significant respiratory depression.[58,59] A group from the University of Utah Medical Center has recently published a case report on the use of a novel technique to determine individual opioid requirements in the opioid-tolerant patient.[60] In this report, a 47-year-old female presented to the operating room for a repeat tricuspid valve replacement. The patient had a history of chronic pain and was receiving multiple analgesic medications, including sustained-release morphine 400 mg/day, two 100 μg/h transdermal fentanyl patches, and oxycodone 120 mg every eight hours. To assess the patient's response to opioids, the authors used a large-dose fentanyl infusion immediately before anesthetic induction. The goal was to determine the amount of fentanyl required to achieve clinically relevant endpoints, including apnea and/or unresponsiveness. In the operating room, standard monitors were applied and a radial artery catheter was inserted. An IV infusion of fentanyl was started at a rate of 2 μg/kg/min, based upon an ideal body weight of 69 kg. No other adjunctive anesthetics were administered during the fentanyl infusion. The infusion rate was increased incrementally until a final rate of 40 μg/kg/min had been reached and the patient was noted to be unresponsive. The total dose of fentanyl administered at the time of unresponsiveness was 24 mg (340 μg/kg). The patient was then induced with etomidate and rocuronium to facilitate endotracheal intubation. A continuous infusion of fentanyl was then started at a rate of 2 μg/kg/h and maintained throughout the surgical procedure.

The same authors then attempted to determine the opioid requirement necessary to provide subsequent analgesia. Using pharmacokinetic simulation software, the authors determined the effect-site concentration of fentanyl achieved at the time of unresponsiveness was 293 ng/ml, and to maintain a plasma level of fentanyl corresponding to 25 percent of that value an infusion rate of 33 μg/kg/min would be required. A PCA pump was programmed to allow a total hourly dose of 33 μg/kg/h by delivering fentanyl at a basal rate of 16.5 μg/kg/h with a lockout interval of 15 min and a demand dose of 250 μg. One hour after arrival in the ICU, the patient was easily awakened and able to follow commands. The patient, according to the authors, reported being satisfied with her quality of analgesia and denied any recall or pain associated with the operative procedure. She specifically commented that her experience during this perioperative course was markedly improved compared with prior surgeries. Four days after the surgery, the transition to oral and transdermal opioids was begun. By the fifth postoperative day, the patient's pain was successfully managed without IV medications, and the remainder of her postoperative course was noted to be uneventful.

Clearly, opioid-tolerant patients have analgesic requirements that are significantly higher than those of opioid-naïve patients. While the large-dose fentanyl infusion technique is a useful tool that makes it possible to accurately define the limits of a patient's opioid tolerance, it is not practical for the majority of patients encountered by anesthesiologists. Because there may be significant interpatient

variability in opioid-dose requirements, intraoperative vital signs, including heart rate, respiratory rate, and degree of pupil dilation, should be closely monitored. The amount of opioids necessary to ensure adequate analgesia in any given patient can generally be assumed to be 50 to 300 percent in excess of the opioid dose given to the naïve patient.[61] One technique that may help to gauge the adequacy of intraoperative opioid dosing is to reverse neuromuscular blockade and allow patients to breathe spontaneously at the later stages of general anesthesia. Patients with respiratory rates greater than 20 breaths/min and exhibiting slight to markedly dilated pupils generally require additional opioid dosing. IV boluses of morphine, fentanyl, or hydromorphone are titrated as needed to achieve a rate of 12-14 breaths/min and a slightly miotic pupil. The optimal intraoperative dose avoids undermedication and overmedication, both associated with adverse perioperative outcomes.[62,63]

POSTOPERATIVE CONCERNS IN THE OPIOID–TOLERANT PATIENT

Expert opinion suggests that, whenever possible, opioid-tolerant patients should be offered regional anesthesia or analgesia, particularly for surgical procedures performed on the extremities.[64,65] Techniques that may be considered include tissue infiltration and nerve and plexus blockade. Patients may be discharged with indwelling brachial plexus catheters, and local anesthetic can be infused for up to 48 hours via disposable pumps. Other interventions may include injection of local anesthetics and opioids into disc spaces or the iliac crest for spinal surgery. The goal is to minimize pain perception and reduce, but not completely eliminate, the use of oral or parenteral opioids for baseline requirements in opioid-tolerant patients.

In patients who have undergone general anesthesia with surgical procedures not amenable to regional anesthesia or analgesia, a continuous parenteral opioid infusion or IV PCA provides useful options for effective postsurgical analgesia. Initiation of IV PCA in the recovery room minimizes the risk of undermedication and breakthrough pain that may occur during patient transport to the surgical care unit. A basal infusion equivalent either to the patient's hourly oral dose requirement or one to two PCA boluses/h may be added to maintain baseline opioid requirements. Basal infusions may not be necessary in patients receiving baseline analgesia via transdermal fentanyl patches or by implanted epidural or intrathecal devices.

The importance of providing adequate analgesics in the postoperative period and understanding the physiologic adaptation that can occur with opioid administration has been underscored by a recent case report by Higa et al.[66] at the Bariatric Surgery Center in Fresno, California. They describe the case of a 27-year-old woman with a medical history significant for mild depression, for which she was treated with sertraline, who underwent uncomplicated laparoscopic Roux-en-Y gastric bypass surgery. The patient subsequently developed a chronic and unremitting course of nausea, vomiting, abdominal distention, and pain that resulted in seven readmissions to the hospital, numerous and extensive diagnostic evaluations, and five surgical procedures, all of which failed to relieve her symptoms. It was only in retrospect that the physicians involved in this case realized that the patient had become opioid tolerant during her multiple hospitalizations and that her symptoms were the result of opioid withdrawal. Following a trial of methadone 20 mg/day, her symptoms completely resolved. After that the patient did not require any hospital readmissions and her symptoms of depression were alleviated, and she has continued to do well. The physicians in this case underestimated the patient's physiological response to perioperative opioid analgesia and the level of dependence that developed during the course of her hospitalization.

DISCUSSION

Safe and effective care of the opioid-tolerant patient requires that the anesthesiologist correctly assess the patient's degree of tolerance and modify perioperative procedure accordingly. Unfortunately, scientifically rigorous studies in this important area are lacking, and most information must be derived from anecdotal reports and the personal experience of anesthesiologists. Furthermore, chronically administered opioids are often mismanaged in the perioperative setting because of unrecognized patient usage, fear of overdose, or temporary unavailability of the oral route of administration. Significant reductions in opioid dosage from preprocedural levels may lead to hyperalgesia in the perioperative period. Potentially adding to this problem is the presence of pain caused by the surgical procedure itself.

The studies and case reports described above were designed to explore the influence of chronic opioid administration on perioperative anesthetic management. Awareness of the special concerns of this patient population and administration of appropriate doses of analgesics, as well as continuous clinical monitoring, remain the keys to successful perioperative anesthetic management. The anesthesiologist plays the key role in developing and implementing a safe and effective perioperative management strategy for the opioid-tolerant patient. We have included some basic guidelines in Table 3 to aid in the formulation of an effective management plan.

Table 3. Perioperative anesthetic management guidelines for opioid-tolerant patients
Preoperative
1. Preoperative evaluation should include early recognition of possible opioid tolerance. Determine that patient received usual baseline opioid medications. Determine total opioid-dose requirement.
2. Review baseline EKG for signs of possible QT prolongation; generally 440 msec is considered the upper limit of normal. Dangerous arrhythmias have been shown to occur if the heart rate is slow (< 60) and the QT is > 600 msec. Obtain cardiology consultation if QT is prolonged.
3. Reassure the patient regarding possible fears of pain control, intraoperative awareness, etc.
4. If the patient has an implanted infusion device, continue usual dosage of opioid, but consider reducing intrathecal dose of baclofen.
5. Consider all opioid-tolerant patients as possibly having full stomachs and take usual precautions.
Intraoperative
1. Maintain all baseline opioids, including transdermal, IV, and intrathecal forms (except baclofen).
2. Avoid placing warming blankets or other warming devices over or near transdermal fentanyl patches.
3. Avoid administering any medication known or suspected to interact with patient's current analgesic and adjuvant regimen.
4. Anticipate that intraoperative analgesic requirements may be 50 to 300 percent greater than in the opioid-naïve patient. Closely monitor vital signs for indication of under- or overmedication.
5. Consider early reversal of the patient to allow for spontaneous breathing, and titrate opioid dose to achieve a respiratory rate of 12 to 14 breaths/min and a slightly miotic pupil.
Postoperative
1. Plan preoperatively for postoperative analgesia; formulate primary strategy as well as suitable alternatives.
2. Maintain baseline opioids, unless the surgical procedure is reasonably expected to reduce the patient's preoperative pain level, in which case opioid administration should be reduced by 25 to 50 percent.
3. PCA: Use as primary therapy or as supplementation for epidural or regional techniques.
4. If surgery provides complete pain relief, consult with pain service to slowly begin opioid taper; do not abruptly discontinue medications.
5. Arrange for a timely outpatient pain clinic follow-up visit.

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