Patient-Controlled Analgesia

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One of the most common methods for providing postoperative analgesia is via patient-controlled analgesia (PCA). Although the typical approach is to administer opioids via a programmable infusion pump, other drugs and other modes of administration are available. This article reviews the history and practice of many aspects of PCA and provides extensive guidelines for the practice of PCA-administered opioids. In addition, potential adverse effects and recommendations for their monitoring and treatment are reviewed.

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Patient-controlled analgesia (PCA) is commonly assumed to imply on-demand, intermittent, IV administration of opioids under patient control (with or without a continuous background infusion). This technique is based on the use of a sophisticated microprocessor-controlled infusion pump that delivers a preprogrammed dose of opioid when the patient pushes a demand button. Although this article focuses on IV-PCA, it is important to note that PCA is a conceptual framework for administration of analgesics (1). The broader concept of PCA is not restricted to a single class of analgesics or a single route or mode of administration. Nor should PCA imply the mandatory presence of a sophisticated and expensive infusion device. Any analgesic given by any route of delivery (i.e., oral, subcutaneous, epidural, peripheral nerve catheter, or transdermal) can be considered PCA if administered on immediate patient demand in sufficient quantities. In this context, first reviewed is the "traditional" system, then IV-PCA, beginning with an historical perspective, followed by a discussion of the PCA paradigm. Then presented is a comprehensive review of clinical management issues, patient characteristics influencing effective use, safety considerations, benefits, and limitations. Subsequently, alternative routes of PCA delivery and future directions in PCA technology and management are presented.

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An Historical Perspective

Gross undertreatment of acute pain has been well chronicled over the last quarter century and likely continues today. The traditional approach of IM opioids given *pro re nata* (prn) results in at least 50% of patients experiencing inadequate pain relief after surgery. Marks and Sachar's landmark 1973 publication (2) ignited a philosophical revolution in practitioners' perception of the adequacy of conventional analgesic practices. Not only did this study document that a large proportion of hospitalized patients were undertreated, it also exposed that physicians and nurses are misinformed and lack sophistication regarding the effective use of opioid analgesics. This began the shift in intellectual milieu from the quest for the "perfect" analgesic (with an ever-expanding opioid pharmacopoeia) towards optimizing the mode of administration and delivery system for the (perfectly adequate) analgesic drugs that already existed.

Roe (3) was the first to demonstrate, in 1963, that small IV doses of opioids provide more effective pain relief than conventional IM injections. Subsequently, Sechzer (4)—the true pioneer of PCA—evaluated the analgesic response to small IV doses of opioid given on patient demand by a nurse in 1968 and then by machine in 1971 (5). Obviously, frequent administration of IV doses of opioid by nurses to large numbers of patients is impractical and cost prohibitive. Thus, the late 1960s witnessed development of PCA technologies. Prototypic devices were developed by Sechzer (5), Forrest et al. ("Demand Dropmaster") (6), and Keeri-Szanto ("Demanalg") (7). In 1976, the first commercially available PCA pump, the "Cardiff Palliator," was developed at the Welsh National School of Medicine (8). Since then, PCA devices have evolved enormously in technological sophistication, ease of use,

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Table 1. Points of Concern in Evaluation of Patient-Controlled Analgesia Devices

- Machine-user interface
  - Programmability
  - Flexibility
  - Standard terminology
  - Ability to eliminate programmable drug concentrations
  - Customizable rate and dosing limit variables
  - Adequate, easy to access and interpretable reports
  - Report download capability (paper, Personal Digital Assistant, Personal Computer)
  - Tamper protection
  - Ease of ambulation
- Machine operability
  - Pump mechanism
  - Operational modes
  - FDA approved for epidural and intrathecal delivery
  - Fail-safe mechanisms
  - Alarms and indicators
  - Upstream and downstream occlusion sensors
  - Free flow impedance protection
  - Memory
  - Mounting
  - Disposables
    - Reservoir type and capacity
    - Infusion tubing (distinction of IV *versus* epidural)

Adapted from (1).
FDA = Food and Drug Administration.

flexibility, and portability. Although a discussion of PCA device technology is beyond the scope of this review, issues concerning evaluation of PCA devices are presented in Table 1.

The PCA Paradigm

Austin et al. (9) deserve credit for elucidating the pharmacologic principles that are the basis for IV-PCA. They administered small increments of meperidine, measured plasma concentrations, and assessed pain scores in patients to demonstrate the steepness of the concentration-effect curve for opioid analgesics (Fig. 1). A minimal increase in meperidine concentration (as little as 3%–5%) more than the maximum concentration associated with severe pain dramatically decreased pain. The smallest concentration at which pain was relieved was termed the "minimum effective analgesic concentration" (MEAC). Minimal analgesia is achieved with titration of opioid until the MEAC is achieved, which marks the difference between severe pain and analgesia. Furthermore, these investigators found a discrete concentration of opioid within an individual to consistently provide effective analgesia, whereas the discrete concentration that provided analgesia varied considerably among individuals, thus

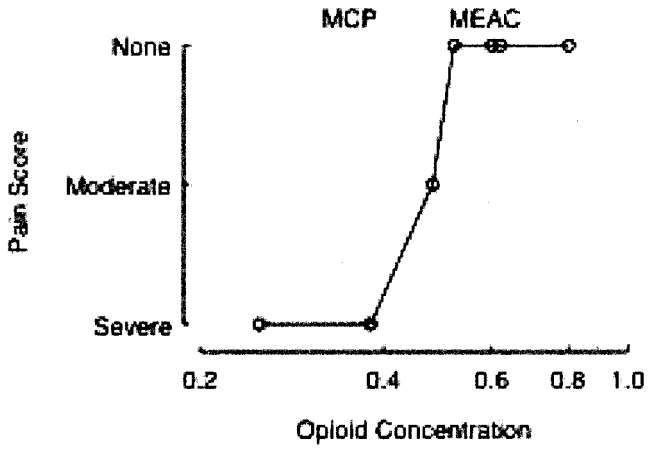

Figure 1. A theoretical representation of the steepness of the concentration/response curve for opioids is shown. The x-axis is plasma opioid concentration; the y-axis is pain rated from severe (bottom) to none (top). Circles represent sequential measurements of opioid concentration and the corresponding pain values during an interval when opioid concentration is increasing. With increasing opioid concentrations, progressive increases in concentration initially produce no change in pain, then over a finite range of concentrations, pain is attenuated, then further increases in opioid concentration produce no additional effect. MCP or "maximum concentration pain" is the maximum concentration of opioid associated with severe pain. MEAC or "minimum effective analgesic concentration" is the smallest opioid concentration at which pain is relieved. Adapted from Austin et al. (9).

establishing that pharmacodynamic variability in response to opioids accounts for individual differences in dose requirements. Tamsen et al. (10) and Dahlstrom et al. (11) subsequently studied the contribution of pharmacokinetic and pharmacodynamic factors on analgesic requirements of other opioids. Pharmacokinetic variables (volume of distribution, rates of distribution and elimination) consistently failed to correlate with dose requirement; in contrast, an individual's hourly opioid dose and their plasma opioid concentration did correlate. Further work by Tamsen et al. (12) suggested that the individual's MEAC may be determined by preoperative cerebrospinal fluid (CSF) endogenous opioid content: patients with larger CSF endogenous opioid content required smaller MEACs to establish and maintain analgesia.

Two prerequisites for effective opioid analgesia were thus established: 1) individualize dosage and titrate to pain relief response to achieve the MEAC and establish analgesia, and 2) maintain constant plasma opioid concentrations and avoid peaks and troughs (13). These requirements cannot be achieved with prn or around-the-clock IM injections. Figure 2 depicts the PCA paradigm and its inherent pharmacologic superiority over IM injections. After titration to achieve the MEAC and establish analgesia, patients use PCA to maintain plasma opioid concentrations at or just above their individual MEAC ("optimal plasma concentration"). In contrast, patients receiving IM bolus

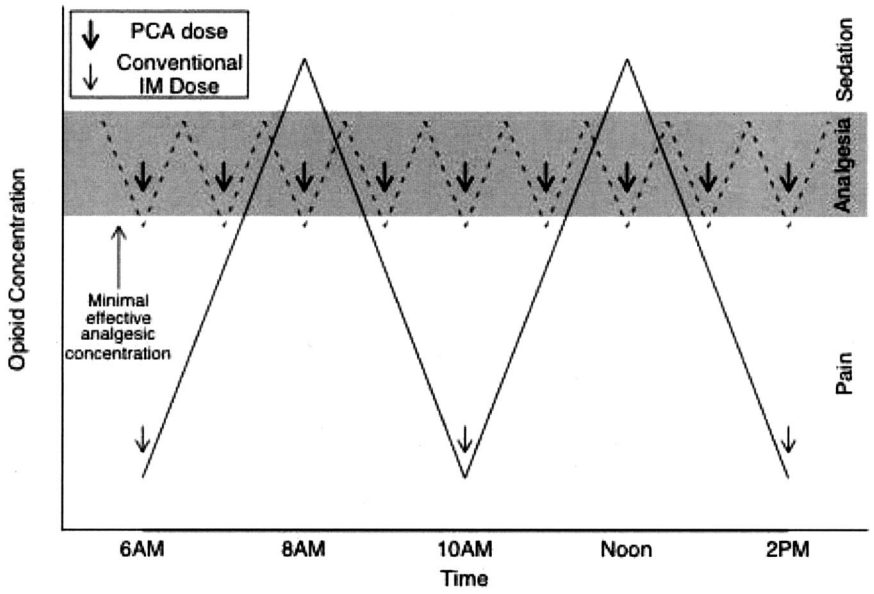

Figure 2. This graphic compares analgesia achieved with two different analgesic regimens: intermittent bolus administration (nurse-administered analgesia) or frequent small doses (patient-controlled analgesia, PCA). The shaded area represents the target analgesic concentration. With intermittent bolus administration, there are frequent periods with concentrations more than and less than the target range. In contrast, PCA results in the opioid concentration being in the target range for a large percentage of the time. Adapted from Ferrante and Covino (13).

injections experience significant periods of severe pain with their plasma opioid concentrations less than their individual MEAC, followed by periods of "overshoot" more than the optimal plasma concentration resulting in excessive sedation, possible respiratory depression, and no better pain relief.

PCA Modes and Dosing Variables

PCA has several modes of administration. The two most common are demand dosing (a fixed-size dose is self-administered intermittently) and continuous infusion plus demand dosing (a constant-rate fixed background infusion is supplemented by patient demand dosing). Nearly all modern PCA devices offer both modes. Less commonly available and less studied modes of administration include infusion demand (in which successful demands are administered as an infusion), preprogrammed variable-rate infusion plus demand dosing (in which the infusion rate is preprogrammed on an internal clock to vary or turn off altogether by time of day), and variable-rate feedback infusion plus demand dosing (in which a microprocessor monitors demands and controls the infusion rate accordingly) (1).

For all modes of PCA, there are the following basic variables: initial loading dose, demand dose, lockout interval, background infusion rate, and 1-h and 4-h limits. The initial loading dose allows for titration of medication when activated by the programmer (not the patient). The initial loading dose can be used by nurses in the postanesthesia care unit (PACU) to titrate opioid to the MEAC or by postsurgical nurses to give "breakthrough" doses. The demand dose (sometimes called incremental or PCA dose) is the quantity of analgesic given to the patient on activation of the demand button. To prevent overdosage by continual demand, all PCA devices use a lockout interval (or delay), which is the length of time after a successful patient demand during which the device will not administer another demand dose (even if the patient pushes the demand button). The background or continuous infusion is a constant rate infusion that is administered regardless of whether the patient activates demand doses. Some devices allow entry of 1-h and/or 4-h limits, with the intent of programming the device to limit the patient over either 1-h or 4-h intervals to less total cumulative dose than were they to successfully activate the demand button at the end of each lockout interval. Use of these 1-h and 4-h limits is controversial. Proponents argue that these limits provide additional safety, whereas detractors argue that no data demonstrate enhanced safety. Moreover, if a patient uses enough demand doses to reach the 1-h or 4-h limit, they probably require more analgesic instead of being locked out from further access for the balance of the interval. The alarm on most devices is nonspecific and nurses typically do not recognize if this condition has triggered the alarm. Most modern microprocessor-driven PCA devices allow for programming in the "PCA mode" (in which a continuous infusion is not offered) or the "PCA + continuous

Table 2. Common IV-Patient Controlled Analgesia Regimens for Opioid-Naive Patients

Opioid	Demand dose	Lockout (min)	Continuous basal*
Morphine	1–2 mg	6–10	0–2 mg/h
Hydromorphone	0.2–0.4 mg	6–10	0–0.4 mg/h
Fentanyl	20–50 μg	5–10	0–60 μg/h
Sufentanil	4–6 μg	5–10	0–8 μg/h
Meperidine†	10–20 mg	6–10	0–20 mg/h
Tramadol	10–20 mg	6–10	0–20 mg/h

* Continuous basal infusions are not recommended for initial programming; † Meperidine should only be used in patients intolerant to all other opioids.

mode." Whereas earlier PCA devices allowed for entry of parameters in units of "mL" or "mg," many newer devices also allow for entry in "μg" units, thereby reducing the potential for programming error when using fentanyl or sufentanil.

The demand dose and lockout interval (as well as the background infusion—see the hazards of continuous background infusions with IV-PCA under the safety section below) deserve further discussion. Owen et al. (14) originally hypothesized that patients would demand analgesia until pain was controlled, regardless of how small the demand increment. However, in practice, most patients have an inherent maximum frequency of demands. Thus, if the demand dose is too small, they refrain from making demands and may become frustrated with PCA, resulting in poor pain relief (15). For PCA to be successful, the demand dose should produce appreciable analgesia with a single demand (15). However, if the demand dose is too large, plasma drug concentration may eventually reach toxic levels. There is an optimal range of doses for each opioid, albeit a wide enough dose range to accommodate the pharmacodynamic variability in response to opioids among individuals. It is possible to coach patients to increase the demand rate (16). If the demand dose is changed during PCA treatment, patients will alter their demand rate to accommodate the change, thus maintaining a consistent plasma opioid concentration (15).

The lockout interval is designed to prevent overdose. Ideally, it should be long enough for the patient to experience the maximal effect of one dose before another is permitted, thus preventing "stacking" of doses. Therefore, speed of onset of analgesia is paramount in setting the lockout interval. Based on this rationale, one might consider using a slightly shorter lockout interval when using the "fentanyl family of opioids" compared to morphine or hydromorphone. However, once titration to MEAC has been achieved, there appears to be no clinically appreciable major differences in time of onset of analgesia among the opioids commonly used for PCA (17). Owen et al. (18) suggested that the rate of drug distribution (flux) between plasma and brain is a useful concept in determining the lockout interval. While drug flux is positive, there is net movement of drug from plasma to brain and drug effect increases. The next dose should be administered when net flux becomes negative, i.e., when drug is leaving the brain and effect has peaked (17). The change from positive to negative flux occurs over a similar length of time for diverse opioids. Upton et al. (19) examined the relative brain and spinal cord central nervous system (CNS) concentration profiles of opioids. CNS concentration was expressed as a percentage of its maximum value. Relative onset was defined as the time that the relative CNS concentration first reached 80% of maximum and relative duration was defined as the period during which the concentration remained more than 80%. For an IV bolus dose of all the common opioids, relative onset varies from approximately 1 min for alfentanil to 6 min for morphine, and relative durations are ~2 min and 96 min, respectively. They concluded that, although all of the common opioids (except alfentanil) have kinetic and dynamic properties suitable for IV-PCA, the relatively long duration of morphine makes it particularly suited for a gradual titration approach. Furthermore, titration is improved by frequent administration of small doses after the initial "loading" period. Thus, there appears to be pharmacokinetic rationale for the empirically derived use of 5–12 min lockout intervals for the opioids commonly used for IV-PCA.

Of greater importance is the relationship between size of demand dose and lockout interval. At present, there are few comparisons of the efficacy of small demand doses with short lockout intervals versus large doses with longer lockout doses. Badner et al. (20) compared varying doses and lockout intervals with IV-PCA morphine in 75 patients. Patients were randomly assigned to 1 of 3 groups: Group 1–6 received a dose (D) of 1 mg with a 6-min lockout interval (LI); Group 1.5–9 received D = 1.5 mg with LI = 9 min; and Group 2–12 received D = 2 mg with LI = 12 min. There was no difference among groups in 24-h morphine consumption, analgesia, or incidence of side effects. Two patients, 1 in each of the 1.5–9 and 2–12 groups, required naloxone for respiratory depression. The authors concluded that, although the number of PCA attempts, missed attempts, successful demands, and the need to increase the dose were all significantly more frequent for the 1–6 group, use of an initial 1-mg dose with a 6-min lockout may represent the most appropriate and perhaps safest dose titration. However, despite equivalent analgesia, the increased number of PCA attempts and missed attempts may translate into less satisfaction for some patients if the 1–6 regimen is not adjusted in a timely fashion.

Table 3. Commonly Available Parenteral Opioids

μ-agonists	Agonist-antagonists	Partial agonists
Morphine	Butorphanol	Buprenorphine
Fentanyl	Nalbuphine	Dezocine
Hydromorphone	Pentazocine	
Meperidine		
Sufentanil		
Alfentanil		
Remifentanil		

Clinical Management of IV-PCA

Choice of Opioid

All of the common opioids have been used successfully for IV-PCA (Table 2), with morphine having been studied the most (21–23). Whichever opioid is chosen for IV-PCA, knowledge of its pharmacology is prerequisite for setting the dosing variables of the PCA device. A brief review of the practical clinical pharmacology of opioids, as it pertains to management of IV-PCA, is essential.

Parenteral opioids have three profiles of μ opiate-receptor binding capacity: pure agonists, agonist-antagonists, and partial agonists (Table 3). Pure agonists are mainstays of acute pain management because they provide full μ-receptor binding, i.e., there is no analgesic ceiling (e.g., titration of more opioid results in better pain relief). However, there is a "clinical ceiling" in that side effects such as sedation, specifically respiratory depression, often prevent further dosing before achieving adequate pain relief. The μ agonists are equally effective at equianalgesic doses (e.g., 10 mg of morphine = 2 mg of hydromorphone = 100 mg of meperidine). Similarly, there are no differences in side-effect profile, although individual patients may experience reproducible nausea and vomiting or pruritus with one drug but not another. All μ-agonists reduce propulsive gut activity and coordination, contributing to postoperative ileus. Contrary to surgical myth, no individual μ-agonist has less effect on gut motility: in conventional IV-PCA doses, morphine, meperidine, and fentanyl have similar effects on the bile ducts and sphincter of Oddi (24). There is evidence that agonist-antagonists share this activity to a lesser degree (24). Metabolites and routes of elimination differ markedly between μ-agonists, providing one rationale for choosing an opioid for IV-PCA.

The agonist-antagonist opioids provide κ-receptor activation and μ-receptor antagonism. Although they are marketed as having a ceiling effect on respiratory depression, thereby providing a greater margin of safety, this effect appears only at very large doses relative to μ-agonists. Most importantly, the agonist-antagonists possess an analgesic ceiling, rendering them unable to reliably provide a level of pain relief comparable to the μ-agonists. Thus, although the successful use of an agonist-antagonist for IV-PCA has been described for gynecologic surgery (25), they are not commonly used in clinical practice and would not reliably provide adequate analgesia for moderate-to-severe pain conditions. Furthermore, agonist-antagonists can provoke an acute withdrawal response in patients who have already received a μ-agonist or are maintained on one chronically. As a result of σ-receptor activation, they also have a frequent incidence of disturbing psychotomimetic side effects. Interestingly, there appears to be a major gender difference in response to agonist-antagonists. Although women consistently experience dose-dependent analgesia, an antianalgesic response with increased pain compared with placebo was observed in men receiving nalbuphine (26). Partial agonists produce only a partial response in binding to μ receptors, thereby limiting the analgesia that can be achieved. They are not used commonly for IV-PCA.

Morphine remains the "gold standard" for IV-PCA, as the most studied and most commonly used IV-PCA drug in the United States. It is important to note that morphine has an active metabolite—morphine-6-glucuronide (M6G)—that also produces analgesia, sedation, and respiratory depression. Whereas morphine is eliminated mainly by glucuronidation, its active metabolite relies predominantly on renal excretion for elimination. Prolonged and profound delayed onset respiratory depression has been reported in patients with renal failure receiving parenteral morphine (27). Sear et al. (28) studied the disposition and kinetics of morphine in patients with renal failure compared with healthy controls. There were no differences between the two groups in morphine elimination half-life (renal failure, 290 min versus controls, 286 min). However, peak concentration of M6G was significantly larger in the renal failure patients ($P = 0.01$), as was the area under the concentration-time curve (AUC) ($P = 0.002$). Therefore, the increased AUC for M6G accounts for the prolonged effect and potential for delayed onset respiratory depression seen with morphine in patients with impaired renal function. The authors recommend avoiding morphine for IV-PCA (and avoiding repeated cumulative dosing of parenteral morphine) in patients with serum creatinine >2.0 mg/dL.

Hydromorphone is a good alternative for morphine-intolerant patients or those with altered renal function because it is metabolized primarily in the liver and excreted primarily as an inactive glucuronide metabolite (29). Because it is approximately six times as potent as morphine, a demand dose of 0.2 mg is considered equianalgesic to 1.0 mg of morphine. Because hydromorphone is more potent than morphine and is commonly used in PCA pumps at a

concentration of 0.5 mg/mL or 1 mg/mL, it is ideally suited for opioid-tolerant patients, increasing the interval between refilling the drug reservoir.

Fentanyl is considered 80–100 times as potent as morphine with single doses or brief periods of administration. However, because of its short duration of action, particularly in the early phase of administration (owing to redistribution pharmacokinetics), double-blind IV-PCA comparator trials have suggested 25–30 μg fentanyl to be equianalgesic to 1 mg morphine as an IV-PCA demand dose (29), i.e., 33–40 times as potent as morphine. Because of its lipophilicity, fentanyl has a quicker onset than morphine, perhaps making it better suited for IV-PCA. Fentanyl has been used successfully for IV-PCA (30,31). It is an excellent alternative for morphine-intolerant patients and is suitable for patients with renal failure because it does not rely on renal excretion for elimination.

Although meperidine has traditionally been the second most common μ-agonist opioid prescribed for IV-PCA, its routine use for IV-PCA is strongly discouraged (22). Meperidine has a neurotoxic metabolite, normeperidine, that possesses no analgesic property and relies mostly on renal excretion for elimination. Normeperidine accumulation causes CNS excitation, resulting in a range of toxic reactions from anxiety and tremors to grand mal seizures. Unwitnessed seizures with loss of airway reflexes can result in severe permanent anoxic brain injury or death. One review (32) concluded "IV-PCA meperidine can be used with a reasonable margin of safety." The authors reviewed 355 medical records of patients receiving IV-PCA meperidine, finding a 2% incidence of toxic CNS reactions. They recommend 10 mg/kg per day (a relatively small dose) as a maximum safe meperidine dose by an IV-PCA device for no longer than 3 days. The problem with this recommendation is that because of the pharmacodynamic variability in response to opioids, some patients require >10 mg/kg per day. Using meperidine for IV-PCA invites adverse outcomes in some patients while offering no advantage over alternative opioids. Meperidine is absolutely contraindicated for IV-PCA in patients with renal dysfunction, seizure disorder, and in those taking monoamine oxidase inhibitors because of the potential for a lethal drug interaction causing malignant hyperpyrexia syndrome. For these reasons, the Agency for Healthcare Policy and Research Acute Pain Guideline (22) recommends that meperidine be used for short durations in carefully monitored doses and only in patients who have demonstrated intolerance to all other μ agonists. Meperidine is $1/10^{th}$ as potent as morphine and a 10-mg demand dose is equianalgesic to 1 mg of morphine.

Use of sufentanil, alfentanil, and remifentanil for IV-PCA has been reported, with sufentanil studied the most (33). With sufentanil, an initial demand dose of 4–6 μg appears to be most appropriate. In contrast to the longer-acting opioids discussed above, a small background infusion may be necessary to sustain analgesia with sufentanil. Owen et al. (34) could not identify an optimal dose and administration rate for alfentanil, concluding that it is not a useful drug for IV-PCA. Because of its ultra-short duration, remifentanil is probably only appropriate for IV-PCA use in short duration, severe episodic pain conditions such as labor pain (35).

Tramadol is used extensively for IV-PCA in some European countries. It is a centrally-acting analgesic with opioid and non-opioid analgesic mechanisms. Tramadol hydrochloride (Ultram; Ortho-McNeil, Raritan, NJ) is currently available only in the oral form in the United States. Tramadol binds to the μ receptor approximately 6000-fold less than morphine and has a weaker affinity for the κ- and σ-receptors. The mono-O-desmethyl metabolite of tramadol (M1) has a greater affinity for opiate receptors and is thought to contribute to its analgesic effects. Tramadol also inhibits central uptake of norepinephrine and serotonin. Thus, tramadol antinociception is mediated by both opioid and non-opioid (inhibition of monoamine uptake) mechanisms, which interact synergistically to relieve pain.

Safe and effective use of tramadol for IV-PCA has been documented in clinical trials (36–38). Tramadol is $1/6^{th}$ to $1/10^{th}$ as potent an analgesic as morphine when both intensity and duration of effect are considered (36–38). A demand dose of 10 mg tramadol is equianalgesic to 1 mg morphine; demand doses of 10–20 mg and 5–10 min lockout intervals have been used in clinical trials. Although there was no difference in sedation, quality of analgesia, and patient satisfaction, two clinical trials concluded that the use of tramadol for IV-PCA after lower abdominal surgery (36) and breast reconstruction (37) is associated with more nausea and vomiting compared with morphine. A third tramadol versus morphine IV-PCA comparator trial after thoracotomy found a similarly infrequent incidence of nausea and vomiting in both groups (38).

Initial Dosing Regimen and Adjustment for Inadequate Pain Relief

There is no established superior dosing scheme for IV-PCA (i.e., 2 mg morphine demand with a 10-min delay versus 1-mg morphine demand with a 5-min delay). I prefer to start with an equianalgesic demand dose of either 1 mg morphine or 0.2 mg hydromorphone or 25–30 μg fentanyl with a 6–8 min lockout interval, in opioid-naïve patients (Fig. 3). I do not start with a basal infusion in any opioid-naïve patient (see below) nor do I use a cumulative 1-h or 4-h lockout. A

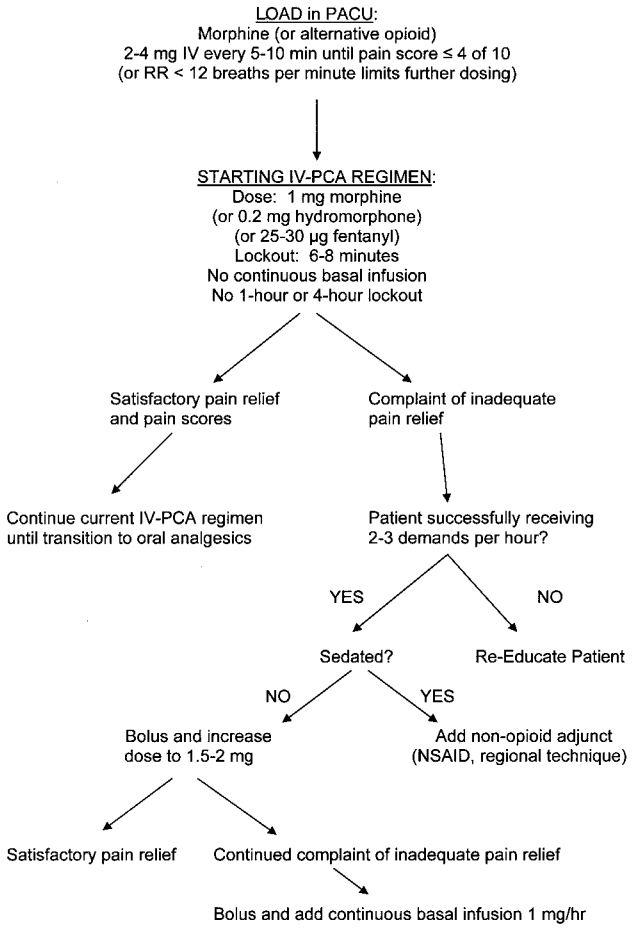

Figure 3. Simplified algorithm for management of IV patient-controlled analgesia (IV-PCA) in opioid naïve patients. RR = respiratory rate; NSAID = nonsteroidal antiinflammatory drug; PACU = postanesthesia care unit.

key component of effective PCA therapy is appropriate titration to establish initial analgesia. Initial loading doses of 2–4 mg morphine (or equianalgesic amounts of alternative opioids) should be administered every 5–10 min in the PACU until the pain score is ≤4 of 10 or a respiratory rate of <12 breaths/min limits further loading. One should always consider using a multimodal therapy approach to optimize analgesia and reduce opioid requirements, thereby reducing the potential for side effects and respiratory depression.

If the patient complains of inadequate pain relief and/or has repeated pain scores >4 of 10, one should consider administering a bolus dose and increasing the demand dose. First, determine if the patient is successfully pushing the button to obtain medication. Many patients simply require re-education regarding use of PCA. Occasionally, the remote PCA cord and activation button become nonfunctional (or other delivery system problems, such as kinking of the tubing proximal to the pumping mechanism, occur) so the patient receives no medication. Once the clinician has confirmed that the patient is actually receiving at least 2–3 doses per hour, and the patient is not excessively sedated, administer a bolus dose of 3–4 mg morphine and increase the demand dose to 1.5–2 mg morphine (or an equianalgesic bolus and demand dose increase of an alternative opioid). A demand dose increase should be discussed with the patient because many patients will opt to trade less effective pain relief in return for fewer side effects, specifically nausea and sedation or mental clouding. Only after first increasing the demand dose for a period of at least 4 h should the clinician consider adding a basal infusion for an opioid-naïve patient. With the dose at 2-mg morphine (or an equianalgesic equivalent), concurrent administration of a nonsteroidal antiinflammatory drug (NSAID) or cyclooxygenase-2 inhibitor (unless contraindicated), and continued inadequate pain relief, I then add a continuous infusion of 1 mg/h morphine (or an equianalgesic equivalent). I caution against the use of basal infusions >1 mg/h morphine (or an equianalgesic equivalent) in opioid-naïve patients, as they are rarely required and markedly increase the risk of respiratory depression. Also, it is important to titrate off the basal infusion as the patient's opioid requirements diminish during recovery. A simple rule is that the continuous infusion should supply no more than 50% of total opioid requirement (i.e., demand dosing should constitute >50% of all opioid administration).

These simple guidelines for IV-PCA management do not apply to patients who are opioid-tolerant, those on chronic opioids, or those with chronic pain, particularly cancer pain. Use of IV-PCA in cancer pain is beyond the scope of this review. However, typically the goal in this setting is to provide most (>80%) of the opioid requirements with continuous infusion delivery, while reserving large doses with long lockout intervals to treat breakthrough pain. Patients who are opioid-tolerant and/or are maintained on chronic opioids, particularly sustained-release opioids, should receive a continuous infusion as part of IV-PCA treatment in the acute pain setting. A simple guideline is to convert the patient's baseline total daily opioid consumption to an IV equivalent and administer this amount divided by 24 h as the hourly rate of infusion. A larger demand dose should be used in accordance with the patient's opioid tolerance, with consideration of a slightly longer lockout of 8–10 min, so that an appreciable effect of the larger demand dose is achieved before the patient can access the next dose.

Management of Side Effects

The common side effects of IV-PCA are the same side effects seen with opioid administration by any route or method of delivery; specifically, nausea and vomiting, pruritus, sedation, and, less commonly, respiratory depression (discussed below) and confusion.

Nausea and Vomiting. Postoperative nausea and vomiting (PONV) is the most common and most bothersome side effect of IV-PCA. Accordingly, pharmacologic strategies to reduce PCA-PONV associated with IV-PCA, including adding antiemetics directly to the IV-PCA opioids, have been studied extensively.

Anesthesia & Analgesia has published Consensus Guidelines for managing PONV (39). The Consensus Guidelines promote a risk stratification approach to identifying patients at increased risk for PONV. These risk factors include female sex, a history of motion sickness or PONV, nonsmoking status, and use of postoperative opioids (39). Certain surgical procedures, drugs used during anesthesia, pain, anxiety and dehydration are associated with increased incidence of PONV (40). Administration of a single antiemetic acting on one receptor site reduces the incidence of PONV by approximately 30% (40). A combination of antiemetics acting on different receptors reduces this incidence further. Antiemetic combinations, most often a serotonin antagonist with a dopamine antagonist or a corticosteroid (dexamethasone), have been studied extensively (41). The combination of ondansetron and droperidol can achieve at least a 90% response rate, defined as no nausea, vomiting, or rescue antiemetics (42). Similar effectiveness is achieved when a serotonin antagonist is combined with droperidol or dexamethasone (43). Thus, the Consensus Guidelines (39) recommend single-drug prophylaxis for patients with mild-to-moderate risk (1–2 risk factors present) and combination prophylaxis with droperidol plus a serotonin antagonist or dexamethasone plus a serotonin antagonist for patients at moderate-to-high risk (3–4 risk factors present). For very high risk patients, the Consensus Guidelines recommend combination antiemetics plus consideration of total IV anesthesia with propofol or regional anesthesia. These guidelines can logically be applied to management of nausea and vomiting in patients receiving IV-PCA. A recent warning by the Food and Drug Administration (FDA) has severely limited use of droperidol in the United States (44).

Several studies have specifically examined antiemetic prophylaxis efficacy in the setting of IV-PCA therapy. The antiemetic efficacy of adding droperidol directly to a morphine IV-PCA mixture has been the most studied (45–48). Each of these double-blind clinical trials concluded that droperidol added to the morphine IV-PCA mixture reduced the incidence and severity of nausea and decreased the need for rescue antiemetics. Some trials found a less frequent incidence of vomiting. Tramer and Walder (48) published a systematic review of all randomized trials published through May 1998 that compared prophylactic antiemetic interventions with placebo or no treatment in the postoperative IV-PCA setting with opioids. Fourteen placebo-controlled trials involving 1117 patients with different regimens of droperidol, ondansetron, hyoscine transdermal therapeutic system, tropisetron, metoclopramide, propofol, and promethazine were analyzed. One IV-PCA study was with tramadol; all others were with morphine. The authors concluded that evidence supports the efficacy of droperidol, but evidence is lacking for all other antiemetics. Droperidol (0.017–0.17 mg per 1 mg morphine; 0.5–11 mg per day droperidol) was significantly more effective than placebo in preventing nausea and vomiting (48). Although there does not appear to be a dose-response for antiemetic efficacy, the incidence of minor adverse effects (sedation and dysphoria) increased with doses >4 mg per day (47). Individual dose-finding studies suggest that the optimal dose of droperidol ranges from 15–100 μg (0.015–0.1 mg) per 1 mg of morphine (45–47).

Ondansetron does not appear to offer any advantage over droperidol as an antiemetic additive to IV-PCA and is significantly more expensive (49). Recently, Han et al. (50) emphasized the importance of using a risk stratification approach to antiemetic prophylaxis. They randomized 374 patients using morphine IV-PCA but otherwise considered to be at low risk for PONV to receive ondansetron (4 mg IV plus 16 mg added into the PCA pump) or saline (control). The only difference between the two groups was a more frequent incidence of headaches in the ondansetron group.

Transdermal scopolamine, applied on arrival in the PACU in women receiving morphine IV-PCA after intraabdominal gynecologic surgery, was assessed in a double-blind placebo-controlled trial (51). Incidence and severity of both nausea and vomiting and need for rescue droperidol were reduced beyond 2 h after scopolamine application. Promethazine, when given either preoperatively or postoperatively in a dose of 0.1 mg/kg, was shown in a placebo-controlled trial to reduce the incidence of PONV by 50% in women undergoing total abdominal hysterectomy and receiving morphine IV-PCA (52). In a study designed to determine the minimum dose of dexamethasone for preventing PONV associated with morphine IV-PCA, Lee et al. (53) randomized 240 women to receive 2, 4, 8, or 12 mg dexamethasone IV before induction of anesthesia versus droperidol 0.1 mg per 1 mg morphine demand in the PCA pump versus saline placebo control. Complete response (defined as no PONV for 24 h) rates for dexamethasone 8 mg (72%) and 12 mg (79%) were significantly more than for saline (43%) ($P < 0.05$) and similar to those for droperidol. Two double-blind, placebo-controlled trials have shown clonidine to reduce PONV associated with morphine IV-PCA (54,55). One trial (54) used oral clonidine (0.5 μg/kg), whereas the second infused clonidine 4 μg/kg at the end of surgery followed by PCA clonidine 20 μg per 1 mg morphine (55).

Continuous infusion of subhypnotic doses of propofol reduced PONV in female patients receiving fentanyl IV-PCA after major gynecological or orthopedic surgery (56). One hundred women were randomized to receive either propofol 10 mg or placebo followed by an infusion of propofol 5, 10, 15, or 20 $\mu g/\cdot kg^{-1} \cdot min^{-1}$ versus Intralipid 1 mL/h as a placebo. Significantly more of the women given propofol 15 and 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ experienced no PONV versus placebo (65% and 70% versus 25%; $P < 0.05$); the 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ group reported more sedation than did all other groups. In contrast, addition of propofol directly to morphine IV-PCA (5 mg propofol per 1 mg morphine) did not reduce PONV in a double-blind, randomized, placebo-controlled trial after major gynecological surgery (57).

Use of an opioid antagonist is another novel approach to preventing IV-PCA associated side effects. Gan et al. (58) randomized 60 women undergoing total abdominal hysterectomy followed by morphine IV-PCA to receive either 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ naloxone (small dose), 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (large dose) or saline (placebo) as a continuous infusion. The naloxone doses were equally effective in significantly reducing the incidence of nausea, vomiting, and pruritus compared with placebo. Not only was there no increase in morphine consumption with large-dose naloxone, cumulative morphine use at 24 h was significantly less in the small-dose naloxone group. The authors cite animal studies in which ultra-small doses of naloxone (0.001–0.1 μg/kg) produce analgesia in animal models, although any proposed mechanism is purely speculative. Other studies in which naloxone was administered intermittently along with morphine in the IV-PCA have not shown an opioid-sparing effect (59,60). Sartain et al. (59) randomized 92 women undergoing hysterectomy to receive morphine 1 mg on demand versus morphine 1 mg combined with naloxone 26.7 μg (0.8 mg in 30 mL) on demand with a 5-min lockout. Not only was there no difference in pain scores, morphine use, or sedation, there was no benefit in reducing side effects. At 24 h, the incidence of nausea was 84.8% in each group; the incidence of pruritus was 56.5% with naloxone and 58.7% with placebo. The median dose of naloxone was 0.38 $\mu g \cdot kg^{-1} \cdot h^{-1}$. In contrast, in a study involving 265 patients, Cepeda et al. (60) found the combination of ultra-small dose naloxone and morphine IV-PCA (naloxone 0.6 μg/mL and morphine 1 mg/mL) decreased the incidence of nausea and pruritus but did not affect analgesia or opioid requirements. Joshi et al. (61) evaluated the influence of nalmefene, a pure opioid antagonist with a longer duration of action, on opioid-related side effects with morphine IV-PCA. One-hundred-twenty women undergoing lower abdominal surgery were randomized to receive saline, 15 μg nalmefene, or 25 μg nalmefene. Both doses of nalmefene significantly decreased the need for antiemetics and antipruritic medications. Overall, small doses of pure opioid antagonists appear to be effective in reducing IV-PCA related PONV and pruritus without affecting opioid consumption and quality of analgesia.

Although a number of clinical trials have evaluated efficacy of mixed agonist-antagonists to prevent or treat neuraxial morphine-related side effects, no studies have evaluated the potential role of these drugs for treating IV-PCA related side effects. Because agonist-antagonists can cause significant reversal of μ-agonist analgesia, use of these drugs for IV-PCA related side effects is not recommended.

Pruritus. Although pruritus is a common side effect of IV-PCA, no clinical studies, other than the pure antagonist trials discussed above, have evaluated efficacy of antipruritic drugs commonly used in clinical practice. Common treatments for IV-PCA related pruritus that are empirically effective include diphenhydramine 12.5–25 mg IV, hydroxyzine 50 mg IM, and alizapride 50 mg IV. None of these drugs typically abolishes pruritus completely and each (especially diphenhydramine) can be quite sedating. Although there is no evidence that opioids differ with regard to incidence of pruritus, nausea and vomiting, or sedation, there is clearly intra-subject variability in response to different opioids, particularly regarding side effects.

Woodhouse et al. (62) conducted an interesting study in which patients were treated with morphine, pethidine, and fentanyl in random sequence, finishing with the first-administered opioid. There were no differences among opioids in the overall analgesic effectiveness and satisfaction. However, the response of individual patients to opioids varied markedly. Some patients tolerated all three opioids, some were intolerant to all, and some were sensitive to one or two of the opioids but preferred the others. These findings support the clinical practice of changing from one opioid to another (with good result) when patients experience intolerable side effects that do not respond to initial treatment.

Sedation and Confusion. There is no evidence to suggest that opioids differ in sedation in patients with normal renal function. However, individual patients differ in the magnitude of sedation in response to particular opioids (62). Patients with altered renal function experience sedation with accumulation of morphine active metabolites (see above). Some clinicians contend that fentanyl causes less sedation than morphine, perhaps because it does not have active metabolites. Opioid-sparing strategies, such as coadministration of around-the-clock NSAIDs, may reduce sedation.

Postoperative confusion (or delirium) is relatively common, particularly in elderly patients, and often has no clearly defined etiology. Although IV-PCA often contributes, other potential etiologies should be

investigated fully. Conversely, undertreatment of pain can cause confusion in elderly patients (63). Lynch et al. (63) interviewed daily a large population of patients undergoing noncardiac surgery to measure their level of pain and development of delirium. Higher pain levels at rest correlated the development of delirium, whereas method of postoperative analgesia, type of opioid, and cumulative opioid dose were not associated with an increased risk of delirium.

Patient Characteristics Influencing PCA Use

Age, Gender, Weight

Individual patient characteristics such as age, gender, and body weight are often assumed to be important factors influencing any pharmacologic therapy. Age affects opioid dosing whereas gender and body weight do not.

Burns et al. (64) confirmed the influence of age on IV-PCA requirements. One-hundred patients undergoing upper abdominal surgery received IV-PCA programmed to deliver incremental morphine doses of 0.02 mg/kg, with a lockout interval of 2 min (with no continuous infusion). Morphine consumption decreased with age for both males and females ($P < 0.00005$): over 24 h, the typical morphine dose was 75 mg at 20–30 yr of age versus 30 mg at 60–70 yr. Macintyre and Jarvis (65) similarly found the best predictor of IV-PCA morphine requirement in the first 24 h after surgery (the amount required in the 24 h after the initial loading dose) was patient age. The expected morphine requirement during the first 24 h for patients ≥20 years of age can be estimated by the following equation: morphine requirement (mg) = 100 − age (yr). Although significantly less opioid is required for the elderly, Aubrun et al. (66) showed that IV morphine titration loading regimens are similar in elderly and younger patients.

Burns et al. (64) found no correlation between morphine consumption and patient weight across a weight range of 40–100 kg. Despite common belief, there is presently no evidence supporting adjusting analgesic dosage for body weight in adults. Hourly morphine consumption appeared to follow a diurnal rhythm, with demand peaking at 9 AM and 8 PM. Although this study (64) found that men require significantly more morphine than women, other studies have failed to show an effect of gender on analgesic requirement (10,11).

Opioid Tolerance and Chronic Pain

Opioid tolerance and chronic pain increase IV-PCA opioid requirements. Although IV-PCA can be used successfully in the postoperative setting in opioid-tolerant patients, use of regional analgesia techniques and adjuvant therapies should be considered in these patients. Attention must be given to supplying patients who have been on chronic opioids at least that same dose before beginning to consider their additional postoperative analgesic requirements. Patients with chronic pain consistently report higher pain scores in the postoperative setting than patients without chronic pain (67).

Psychological Factors

The individual's decision to press the PCA button remains paramount to successful use of PCA. Fear, confusion, or other psychological factors may override pharmacodynamic considerations so that patients may accept worse pain or be unable to attain maximum benefit from PCA (68).

The basic tenet of PCA is that analgesia is better when the patient, as opposed to the nurse or physician, is in control. This may not apply to all individuals. "Locus of control" is a psychological concept that refers to a set of beliefs about the relationship between behavior and subsequent reinforcement (69). Individuals with an internal locus of control perceive reinforcement to result from their own actions. Individuals with an external locus of control perceive that reinforcement results from luck, chance, fate, or the intervention of powerful people. Individuals with an internal locus of control adopt a more active (controlling) posture towards their environment and therefore would be expected to be successful in their use of PCA: they push the demand button when they experience pain. In contrast, patients with an external locus of control believe that they exercise little control over their environment. In support of this, Johnson et al. (70) found that patients with an external locus of control had worse pain and greater dissatisfaction with PCA, whereas an internal locus of control predicted better pain scores and increased satisfaction.

Some patients have certain characteristics of the psychological construct of "learned helplessness" (71) that may predict poor results with PCA (68). Learned helplessness is a behavioral pattern characterized by emotional, motivational, and cognitive deficits in coping, associated with the belief that no effective solutions are available to ameliorate a source of stress such as pain.

Safety of IV-PCA

Safety of IV-PCA relies on a negative feedback control system. Inherent to safety of IV-PCA is the concept that the patient will become too sedated to physically push the button to receive more opioid before reaching a critical point of severe respiratory depression. Concurrent use of a continuous background infusion

bypasses this safety feedback loop, obligating the patient to receive additional continuous medication despite progressive respiratory depression.

IV-PCA has achieved widespread acceptance over the last quarter century and is generally perceived as more effective and safer than conventional IM injections of opioids (72). IV-PCA is also perceived as being safer and having fewer logistic problems in monitoring and patient management than intraspinal opioid or epidural analgesia (72). Nonetheless, critical respiratory depression events occur with IV-PCA. Some believe that these events are underreported and perhaps underrecognized. The possibility of causing respiratory depression by injudicious dosing is a legitimate concern. Another legitimate concern is that equipment failures put patients at risk. To place the incidence of respiratory depression with IV-PCA into perspective, one must first understand the incidence of respiratory depression with other routes and modalities of opioid delivery.

Respiratory Depression with Opioid Delivery

The reported incidence of respiratory depression with opioids administered by different routes depends on definitions (72). A large survey of Swedish practice found that only 0.25%–0.4% of patients receiving epidural morphine required naloxone for respiratory depression (73). Although data are lacking regarding the incidence of respiratory depression using intermittent IM opioids postoperatively, the rate of this complication in the general surgical population is probably approximately 0.9% (74). Continuous IV infusions of opioids without the capability of PCA demand dosing are now rarely used except in critical care wards. Two published series highlight the considerable risks of this technique. In one small series, 10 of 16 patients who received a continuous infusion of morphine postoperatively (mean dose, 0.76 mg/h) experienced episodes of severe desaturation ($Sao_2 < 80\%$) (75). In a larger series, 62 of 247 patients given 1 mg/h morphine after abdominal surgery had their infusions discontinued because of respiratory rates <8 breaths/min (76).

Hazards of Continuous Background Infusions with IV-PCA

When a background infusion is used with IV-PCA in opioid-naïve patients, the incidence of respiratory depression is frequent (77). Schug and Torrie (78) reported an incidence of respiratory depression comparable to that with continuous infusion alone (1.65%) and significantly more frequent than that with PCA alone in a large, acute pain service, observational series. Notcutt and Morgan (79) also reported a disproportionately more frequent incidence of respiratory depression in patients in whom background infusions were used (2.5% versus 1%). Moreover, most studies have failed to demonstrate any benefits when PCA is combined with a background infusion (80–82). In the largest study (230 women undergoing abdominal hysterectomy) assessing a concurrent opioid infusion, Parker et al. (80) assessed basal infusions of 0.0, 0.5, 1.0, or 2.0 mg/h morphine. None of the basal infusions improved pain relief and patients in all groups used the same amount of supplemental demand morphine, which resulted in larger opioid consumption in the 2 mg/h group. Patients receiving 2 mg/h had to be discontinued from the study much more frequently for nausea and vomiting and excessive sedation. In a subsequent study (81), the same authors found no benefit of a nighttime opioid infusion with morphine IV-PCA, including no better quality of sleep. Three of 78 patients receiving the nighttime infusion had prolonged episodes of hypoxemia, compared with no episodes in the PCA alone group (81). Continuous basal infusion plus PCA is best reserved for opioid-tolerant patients and those who need it as judged by a management algorithm described above.

Safety of IV-PCA Alone

There is good evidence that IV-PCA alone (without continuous basal infusion) causes little respiratory depression (77). From the studies summarized in Table 3 (78,83–87), an overall incidence for respiratory depression with PCA can be estimated as 0.25%. This compares favorably with the 0.9% incidence estimated for intermittent IM injections and is probably slightly better than the incidence with neuraxial opioids. Brose and Cohen (88) found that although patients are prone to mild desaturation with IV-PCA, they are less likely to progress to severe respiratory depression when compared with intermittent IM injection of opioids. This study reinforces the safety feedback loop inherent in PCA.

Risk Factors for Respiratory Depression and Mishaps with IV-PCA

Several authors have summarized the risk factors for respiratory depression with IV-PCA (72,77,86). These risk factors can be categorized as "patient/disease related" and "technique/equipment" related. The patient/disease related risk factors apply regardless of route of opioid administration and include advanced age, head injury, sleep apnea syndrome (89), obesity, respiratory failure, concurrent use of sedative medications, especially benzodiazepines, hypovolemia, and renal failure (72). Unfortunately, avoidable instances of critical events continue to occur when IV-PCA alone is used (77). Some of the reasons include operator errors: programming errors (the most frequent mishap) (90), accidental bolus administration during syringe change (90), inappropriate dose prescription or

lockout interval (78), drug errors (wrong drug or wrong concentration), inappropriate drug selection (i.e., morphine or meperidine in a patient with renal failure), and misconnection or absence of Y-connector (allowing for accumulation of opioid in the IV tubing followed by intermittent bolus delivery). Common patient errors include activation of the PCA pump by others (i.e., family members) (78,91), and failure to understand the device (92). Possible equipment problems include siphoning of drug (pump placed above patient without flow restriction valve or cracking of a glass syringe) (93) and equipment failure resulting in spontaneous activation of drug delivery (79).

A case report illustrates how IV-PCA can result in a lethal mishap. Vicente et al. (94) describe a 19-yr-old woman who underwent uneventful cesarean section delivery, after which morphine IV-PCA was ordered. A drug cassette containing 1 mg/mL was unavailable, so the nurse substituted a cassette that contained 5 mg/mL. The patient was found dead 7.5 h later in her postpartum room. The available evidence was consistent with a programming error wherein morphine 1 mg/mL was entered instead of 5 mg/mL, thereby causing the pump to deliver a demand dose of 10 mg instead of 2 mg. Based on a search of the FDA Medical Device Reporting database and other sources and on a denominator of 22,000,000 PCA uses provided by the PCA device manufacturer, the authors estimated that mortality from user programming errors with this device is a small likelihood event (ranging from 1 in 33,000 to 1 in 338,800) but that it is relatively numerous in absolute terms (ranging from 65–667 deaths in the history of the use of the device) (94). Clearly, mishaps with IV-PCA, mostly resulting from human error, remain a problem.

To minimize the occurrence of these hazards, hospitals need to incorporate standard safety features into practice. Nursing staff on every ward must be trained in the safe use of PCA pumps and recognition and management of complications (77). Initial programming and setup of the pump and changes in programming require great care to prevent errors. It is common practice in most hospitals for a second nurse to witness and verify the initial programming and any changes in programming. Hospital pharmacies should formulate standard solutions of drug and send only those standard solutions to the wards. Patient and family education is important for safety, particularly instruction that only the patient should activate the PCA button (78,91).

Benefits of IV-PCA

The benefits of IV-PCA in comparison to intermittent IM injection delivery of opioids have been best summarized in two published systematic reviews (95,96). Both of these evidence-based reviews concluded that IV-PCA offers better analgesic efficacy (albeit only an average of 5 mm on a 0–100 mm pain scale) as well as superior patient satisfaction. However, both reviews concluded that there is no evidence to support reduced opioid consumption or a difference in opioid-related side effects. Walder et al. (96) concluded that PCA reduces postoperative pulmonary complications, whereas Ballantyne et al. (95) concluded that there is no difference in pulmonary outcomes. Both reviews agree that cost-effectiveness data are currently lacking and there is no evidence to support decreased length of hospital stay.

Limitations of IV-PCA

Although IV-PCA offers superior analgesia compared with IM injections of opioids, patients still experience an equivalent profile of bothersome opioid side effects (i.e., nausea, vomiting, pruritus, sedation, confusion). Even though IV-PCA has a very acceptable safety profile, life-threatening mishaps do occur. Furthermore, there is no evidence to support a decrease in morbidity and mortality with IV-PCA, except perhaps some mild decrease in pulmonary complications (96). IV-PCA is clearly inferior to epidural analgesia and other peripheral nerve block techniques for pain relief after most severely painful surgical procedures (97). In addition, the encumbrances of IV-PCA (being tethered to an IV pole) may impede postoperative mobilization.

Cost-Effectiveness Analysis of IV-PCA

Although conclusive cost-effectiveness data are lacking (95,96), some investigators have concluded that IV-PCA is more costly in comparison with IM injections, even when accounting for nursing time. Colwell and Morris (98) randomized 184 patients undergoing elective joint replacement to receive IV-PCA versus IM injections as needed. The average cost per day (in 1995 US dollars) for both nursing time and materials was $58.58 for IV-PCA and $22.45 for IM injections. Choiniere et al. (99) randomized 126 women undergoing abdominal hysterectomy to receive IV-PCA versus regularly timed IM injections of morphine. With more frequent adjustments in the IM group, they were able to achieve analgesia comparable to IV-PCA. Their economic analysis concluded that IV-PCA is more expensive than IM injections, despite PCA pump costs being excluded. Cost differences in nursing time favoring IV-PCA were offset by drug and material costs. Current dollar estimates for the daily cost of IV-PCA in nursing time and materials range from $65–$105. However, one must place the cost of providing IV-PCA or epidural analgesia into the overall perspective

of health care costs. Macario and McCoy (100) concluded that the pharmacy cost of delivering postoperative analgesia to patients undergoing joint replacement surgery represents only 1% of the total costs of surgery.

A number of factors must be considered in a cost analysis of PCA. Direct medical costs include the PCA pump itself (which can be purchased, leased, or used with no capital purchase with an agreement to use a quota of disposables), the drug, and the disposables. Although IV-PCA probably reduces nursing time allocated to analgesia administration and assessment in comparison with IM injections (99), nursing time is still a considerable cost consideration in the overall cost of IV-PCA. Well-conducted time-motion studies are needed to more accurately quantify total time devoted to PCA management. There are also direct nonmedical costs associated with PCA, many of which are hidden costs. These include storage and inventory management, transport and distribution, pharmacy personnel time, preventive maintenance, and repair by biomedical engineering, indirect morbidity and mortality costs (management of mishaps and resulting litigation), and costs of treating side effects. Clearly, more sophisticated, all-encompassing cost analyses must be performed before we can make conclusions regarding the costs and cost-effectiveness of PCA

Strategies to Improve Efficacy of Opioid IV-PCA

For most postoperative pain conditions, IV-PCA should not be conceived of as a "stand alone" therapy. Benefits of a multimodal approach to acute pain management are detailed elsewhere in this supplement. Around-the-clock administration of NSAIDs clearly improves analgesia and reduces IV-PCA opioid requirements. Local wound infiltration, peripheral nerve blocks, and continuous catheter techniques can all be used effectively in conjunction with IV-PCA.

Interestingly, a number of investigators have examined adding (potentially) analgesic drugs directly to the IV-PCA mixture. Cepeda et al. (101) evaluated a possible opioid-sparing effect of IV lidocaine in a double-blind clinical trial involving 195 patients after abdominal surgery. They concluded that adding lidocaine 10 mg/mL or 20 mg/mL to morphine 1 mg/mL yielded no differences in opioid use, pain levels, side effects, or speed of recovery. Chia et al. (102) conducted a similar double-blind trial in which they randomized 50 patients undergoing abdominal surgery to receive morphine 1 mg versus morphine 1 mg plus 16 mg lidocaine on demand. They also found no difference in pain intensity, cumulative morphine dose, and morphine-associated nausea, vomiting, and pruritus. Furthermore, lightheadedness and dry mouth were more frequent in the lidocaine group.

Three studies evaluated adding small doses of ketamine to morphine IV-PCA. Burstal et al. (103) randomized 70 women undergoing hysterectomy to receive IV-PCA with morphine 1 mg/mL or morphine 1 mg/mL plus ketamine 2 mg/mL. There were no differences in pain scores, morphine consumption, patient satisfaction, nausea scores, or antiemetic use. Patients in the ketamine group had a more frequent incidence of side effects, including dysphoria, resulting in early withdrawal from the study (10 versus 1; $P = 0.006$). In contrast, Unlugenc et al. (104) found adding ketamine 1 mg/mL to morphine 0.4 mg/mL (administered in a demand dose based on 0.0125 mg/kg morphine with a 20-min lockout) to significantly reduce pain scores and reduce 24-h cumulative morphine consumption in patients undergoing abdominal surgery. These investigators also found that adding magnesium 30 mg/mL to morphine 0.4 mg/mL also improved analgesia and reduced morphine consumption (104). These same investigators also found that adding small-dose ketamine or magnesium to tramadol IV-PCA improved pain relief and reduced the amount of tramadol required after major abdominal surgery (105). Sveticic et al. (106) used a novel optimization methodology to systematically evaluate 12 different combinations of morphine and ketamine in a PCA solution of 0–2 mg/mL and a lockout interval range of 5–12 min in 102 patients undergoing lumbar spine or hip surgery.

The optimization procedure converged to provide the lowest mean pain scores with an infrequent incidence of side effects with a morphine-to-ketamine ratio of 1:1 and a lockout interval of 8 min. Ketamine administered as a small-dose continuous infusion (0.5 mg/kg followed by an infusion of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) has been shown to reduce morphine IV-PCA consumption in intensive care unit patients after major abdominal surgery (107). Ketamine clearly has an evolving role in acute pain management. However, one must consider the logistics, costs and potential for medication error before considering routinely adding it to an IV-PCA mixture.

Alternative Routes of PCA Delivery

The fundamental concept of PCA is drug administration on patient demand. Alternative routes of PCA delivery that have been described in the literature include: subcutaneous (108), oral transmucosal (109), nasal (110), intrathecal (111), epidural, via peripheral nerve catheter, and transdermal. The latter three have received the most clinical attention, have been the most studied, and deserve brief further discussion.

Epidural PCA

Epidural PCA or patient-controlled epidural analgesia (PCEA) is the second most frequently used and second

most studied route of PCA delivery for acute pain management. PCEA has been extensively reviewed elsewhere (112). Similar to IV-PCA, PCEA optimizes analgesic efficacy by titrating delivery of epidural analgesic drugs to a patient's individual requirements while attempting to minimize side effects. PCA theoretically offers several advantages over continuous epidural infusion (CEI), including superior analgesia, greater patient satisfaction, and less epidural analgesic use, ideally resulting in fewer side effects such as sympathetic and motor block. Large observational studies suggest PCEA is an effective technique that can safely be used on routine postoperative wards (113,114).

The optimal PCEA delivery variables (demand dose, lockout interval, and continuous or background infusion) have not been clearly determined. For postoperative analgesia, the PCEA demand dose is most commonly set at 2–4 mL (using the concentrations of local anesthetic described below combined with small concentrations of opioid) with a lockout of 10–20 min. Continuous infusions at a rate of 3–10 mL/h are commonly used with the smaller demand doses and rates of continuous infusion for thoracic level catheters and in elderly patients. In contrast to IV-PCA, most experts agree (112–114) that a continuous infusion should be used with PCEA, particularly when a local anesthetic is used, to optimize the potential physiologic benefits of epidural analgesia and to maintain continuous neural blockade. The optimal PCEA analgesic solution is also uncertain. PCEA analgesic solutions are generally a combination of a local anesthetic and a lipid-soluble opioid (fentanyl or sufentanil), although hydrophilic opioids (morphine and hydromorphone) have also been used extensively (114). Use of small-concentrations of long-acting local anesthetics (bupivacaine 0.05%–1.25%, levobupivacaine 0.05%–1.25%, and ropivacaine 0.1%–0.2%) results in reasonable analgesia while minimizing local anesthetic-related side effects. Combining an opioid and local anesthetic results in superior analgesia compared with either administered alone. When compared with CEI, PCEA provides comparable analgesia for a variety of surgical procedures, may offer superior patient satisfaction, and likely results in need for fewer interventions by the acute pain service and nursing staff.

Peripheral Nerve Catheter PCA

Perineural and incisional catheter techniques are increasingly being used to manage postoperative pain in hospitalized and ambulatory surgery patients. Catheter techniques have been studied most extensively with brachial plexus block, especially in patients undergoing shoulder surgeries (115). The most commonly used technique has been a continuous infusion of local anesthetic. However, patient-controlled regional analgesia (PCRA) may allow the patient to correct for individual variations in intensity and duration of postoperative pain and to minimize bothersome motor and sensory blockade. Local anesthetic brachial plexus PCRA has been used successfully to provide analgesia after hand surgery (115) and shoulder surgery (116). Femoral nerve catheter PCRA can provide analgesia for most surgeries involving the femur, the knee, and skin of the anterior, lateral, and medial thigh, as well as the distal medial leg (117). Singelyn and Gouverneur (118) found that a smaller dose continuous infusion and PCRA boluses, in comparison with a continuous infusion alone, reduces local anesthetic consumption without compromising pain relief. PCRA *via* a continuous popliteal sciatic nerve catheter inserted in the popliteal fossa has also been shown to be safe and effective for treating pain after foot and ankle surgery (119).

Transdermal PCA

A new noninvasive method of PCA may offer logistic advantages for patients and nursing staff, eliminating the need for venous access and complicated programming of pumps. Iontophoresis (electrotransport) delivers ionizable drugs, such as fentanyl HCl, through the skin by application of an external electrical field (120) and allows on-demand drug administration. Using this technology, a fentanyl HCl patient-controlled transdermal system (PCTS) has been developed that is a preprogrammed, self-contained, self-adhesive, on-demand drug-delivery system. The system uses a non-detectable low electrical current technology (E-TRANS®; ALZA Corp, Mountain View, CA) to deliver 40-μg fentanyl over a 10-min period. The device allows for up to 6 demand doses per hour and up to 80 demand doses over 24 h, at which point the device shuts off and can be replaced. To activate a demand dose, the patient presses a demand button twice in 1 s. An LCD display informs the patient when the next dose is available for demand and quantifies the number of doses delivered. Preliminary trials led to the selection of the 40-μg fentanyl demand dose: when patients were randomized to IV-PCA of 20, 40, or 60 μg of fentanyl infused over 10 min, the 40-μg and 60-μg doses controlled pain better than the 20-μg dose (121). However, the 60-μg dose was associated with an increase in adverse respiratory events compared with the 40-μg dose.

Safety and efficacy of the on-demand fentanyl HCl PCTS 40 μg were compared against a placebo device for postoperative pain up to 24 h after major abdominal, orthopedic, or thoracic surgery in 205 patients (122). Use of fentanyl HCl PCTS 40 μg resulted in lower Visual Analog Scale pain scores and higher mean patient and investigator global assessment

scores compared with placebo. No patient experienced clinically relevant respiratory depression. This study demonstrated that the fentanyl HCl PCTS 40 μg for PCA is superior to placebo and is well tolerated for the control of moderate to severe pain after major surgery.

Viscusi et al. (123) recently published a randomized controlled, multicenter clinical trial to assess the fentanyl HCl PCTS 40 μg versus standard morphine IV-PCA for postoperative pain. Six-hundred-and-thirty-six adult patients were randomized to receive the fentanyl HCl PCTS 40 μg versus morphine IV-PCA (1 mg demand every 5 min; maximum of 10 mg/h). Ratings of good or excellent pain relief after 24 h of treatment were given by 73.7% of patients (233 of 316) who used transdermal fentanyl PCA and 76.9% of patients (246 of 320) who used IV-PCA. Early discontinuations, pain intensity scores, and opioid-related side effects were similar between the groups. With continued treatment for up to 48 or 72 h, more than 80% of patient assessments in each group were good or excellent. The authors concluded that the fentanyl HCl PCTS 40 μg provided postsurgical pain control equivalent to that of a standard morphine IV-PCA delivered by a PCA pump.

The fentanyl PCTS offers the advantages of needle-free, preprogrammed operation in a small, self-contained unit. It should allow patients greater mobility, may reduce nursing time in administering PCA, and will reduce the chance of potentially life-threatening PCA pump programming errors. In contrast, the device only offers a single fixed dose of opioid and cannot be adjusted to add a basal infusion or to administer additional bolus doses.

Future Directions in PCA Development

Novel routes of PCA delivery will continue to evolve and become more commonplace in clinical practice. In particular, PCRA will likely flourish as anesthesiologists gain better training in regional anesthesia, particularly peripheral continuous catheter techniques. Transdermal iontophoretic delivery holds great promise for simplified preprogrammed opioid delivery and one can envision different doses of fentanyl and other opioids being delivered by this system.

Evolution of PCA device technology represents a great paradox; as clinicians strive for greater sophistication and more complex capabilities in the devices, a greater complexity of human operation and greater potential for devastating programming errors and other mishaps are introduced. Anesthesiologists, surgeons, nurses, pharmacists, human factors engineers, and device manufacturers must work together to enhance the safety of PCA pumps by redesigning user interfaces, drug cassettes, and hospital operating procedures to minimize programming errors and to enhance their detection before patients are harmed. PCA pumps should have the capability of eliminating programmable drug concentrations not used by the institution and the capability to customize rate and dosing limit variables. Bar coding to assure the correct drug cassette corresponds to the concentration and dosing variables programmed into the PCA device would be optimal. PCA pump terminology should be standardized across all manufacturers' devices to streamline health care provider education and to reduce the chance for dangerous programming errors. Pump reports should provide adequate information regarding dosing variables, dosing history, and total drug consumption; they should be easy to access and interpret. Graphical interfacing with demand/dose trend analysis and the capability of personal digital assistant downloading are under development.

Conclusion

IV-PCA has become entrenched in, and moreover has revolutionized, acute pain management over the last quarter century, spawning greater attentiveness to effective postoperative pain control and facilitating the proliferation of other modalities, including neuraxial analgesia techniques. Although this review article has focused mainly on the intricacies of IV-PCA, PCA is really a conceptual framework for the administration of analgesics. The broader concept of PCA is not restricted to a single class of analgesics or single route or mode of administration. It is likely that the future direction of PCA will be the evolution and refinement of alternative routes and drugs (other than opioids) for analgesic delivery. Whereas IV-PCA has a well-established safety track record as a method of opioid delivery, I challenge the PCA device industry and health care providers to work together to enhance the safety of PCA devices and PCA delivery to eliminate the harmful and even fatal mishaps that continue to occur.

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