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Patient-Controlled Analgesia in the Management of Postoperative Pain

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Abstract

Patient-controlled analgesia (PCA) is a delivery system with which patients self-administer predetermined doses of analgesic medication to relieve their pain. Since its introduction in the early 1980s, the daily management of postoperative pain has been extensively optimised. The use of PCA in hospitals has been increasing because of its proven advantages over conventional intramuscular injections. These include improved pain relief, greater patient satisfaction, less sedation and fewer postoperative complications.

All PCA modes contain the following variables: initial loading dose, demand dose, lockout interval, background infusion rate and 1-hour or 4-hour limits. Morphine is the most studied and most commonly used intravenous drug for PCA. In spite of the fact that it is the 'first choice' for PCA, other opioids have been successfully used for this option.

The most observed adverse effects of opioid-based PCA are nausea and vomiting, pruritis, respiratory depression, sedation, confusion and urinary retention.

Although intravenous PCA is the most studied route of PCA, alternative routes have extensively been described in the literature. PCA by means of peridural catheters and peripheral nerve catheters are the most studied. Recently, transdermal PCA has been described. The use of peripheral or neuraxial nerve blocks is recommended to avoid the so called opioid tolerance observed with the intravenous administration of opioids.

Numerous studies have shown the superiority of epidural PCA to intravenous PCA. The beneficial postoperative effects of epidural analgesia are more apparent for high-risk patients or those undergoing higher risk procedures. PCA with peripheral nerve catheters results in increased postoperative analgesia and satisfaction for surgery on upper and lower extremities. Serious complications occur rarely with these catheters.

With the introduction of an Acute Pain Service, management of postoperative pain can be improved. This will also help to minimise adverse effects related to PCA and to avoid lethal mishaps.

Patient controlled analgesia (PCA) is a delivery system, based on the use of a sophisticated microprocessor-controlled infusion pump, with which patients self-administer small, predetermined doses of analgesic medication to relieve their pain.

PCA started in the early 1980s.[1,2] Since its introduction, it has become widely accepted for the management of postoperative pain. The use of PCA devices in daily clinical practice has been an important step towards optimised postoperative pain management.

Currently, numerous models are used in clinical practice. All models are designed in a manner to avoid any access to the drug or the set programme unless using a key or a code by the nurse and/or physician. A Y-shaped tube is placed between the reservoir and the intravenous catheter. This tube contains an antireflux and antisyphon valve to avoid accidental overdoses.

All PCA models contain the following basic variables: initial loading dose, demand (bolus) dose, lockout interval (LI), background infusion rate and 1-hour or 4-hour limits.

The initial loading dose can be activated by either a nurse or a physician to titrate analgesic medication in order to achieve a minimal level of analgesia. Establishing initial analgesia is an important component of effective PCA therapy. Initial loading doses should be administered in the recovery room with consideration of the haemodynamic status of the patient and until the visual analogue scale is ≤4 (for a scale of 1–3 = mild pain; 4–6 = moderate pain; 7–10 = severe pain).

The demand dose is the small amount of analgesic the patient receives, each time he or she activates the system. Earlier PCA devices allowed for entry of parameters in units of 'mL' or 'mg', whereas most new devices also allow for entries in 'μg' units, thereby reducing the potential for programming errors when using drugs other than morphine. Optimal efficacy and safety depend on the selection of a demand dose small enough to minimise adverse

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effects, but large enough to achieve analgesic satisfaction.

The LI is the length of time during which there will be no drug delivery, even if the patient pushes the demand button. In general, short LIs are more likely to resolve the problem of great interpatient variability in opioid pharmacodynamics.[3] LIs between 5 and 10 minutes appear optimal regardless of the opioid used.[4,5]

The background infusion is a constant rate infusion administered regardless of whether the patient activates the system. The use of a continuous background infusion has clearly been identified as a factor for respiratory depression.[6-9] Furthermore, use of a background infusion to improve analgesia is controversial.[10,11] However, in opioid-tolerant patients, a background infusion may be added to deliver the equivalent of the usual opioid dose taken by the patient.

Some devices allow performing 1- and/or 4-hour maximal dosages. They limit the cumulative doses given within those delays, in whatever fashion; however, the use of such limits is controversial. Proponents argue that their use would provide additional safety,[12] whereas detractors argue the absence of any clinical data to demonstrate this.

Since their introduction, PCA devices have undergone technological changes. Attention has been given to devices that take into account demand history and electronically registered pain scores.[13] Other devices have been developed in which the system can be activated with a puff of air instead of pushing the button with the hand.[14] With the growing interest in ambulatory care, disposable mechanical devices have been used in common practice.[15,16]

This review is based on 20 years of local experience and an electronic search between 1980 and 2006 of the relevant literature written in English, French, German or Dutch. It reviews the efficacy and tolerability of various pharmacological agents used in PCA and practical issues concerning the management of postoperative pain in adults.

1. Opioid-Based Patient-Controlled Analgesia (PCA)

Analgesic effects of opioids are mainly a result of opioid μ-receptor binding. Because of their full μ-receptor binding, pure agonists are the first choice for acute pain management. All opioids have a similar spectrum of adverse effects, although quantitative differences are detectable. The choice of opioid depends on the clinical history of the patient and often on the protocols available in the hospital. There is no ideal PCA drug because the clinicians' and patients' perceptions of the ideal drug for PCA may be different (see table I). Woodhouse et al.[17,18] have clearly shown in two studies that patients are satisfied with PCA regardless of the opioid used and that there are few differences in analgesic use, pain scores and incidence of adverse effects between these agents.

1.1 Morphine

Morphine is the prototype opioid agonist to which all other opioids are compared. It is also the 'first choice' for intravenous PCA, since it has been the most studied and is the most commonly used intravenous PCA drug.

Plasma morphine concentrations after intravenous injections do not correlate closely with the pharmacological activity of the opioid. This discrepancy reflects a delay in penetration of morphine across the blood-brain barrier. As a result, the analgesic and ventilatory depressant effects of morphine may not express themselves during the initial high

Table I. Common opioids and their regimens for adult intravenous patient-controlled analgesia

Drug	Demand dose	Lockout interval (min)	Basal infusion rate
Morphine	1–2mg	5–10	≤0.5 mg/h
Fentanyl	10–50μg	5–10	≤50 μg/h
Sufentanil	4–6μg	5–10	≤5 μg/h
Remifentanil (labour)	0.5 μg/kg[a]	2	NA
Piritramide	0.75–1.5mg	5–10	≤0.5 mg/h
Hydromorphone	0.25–0.5mg	5–10	≤0.4 mg/h
Tramadol	10–20mg	5–10	≤10 mg/h

a Delivered over 20–30 seconds.

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plasma concentrations after intravenous administration, whereas these effects persist despite decreasing plasma concentrations.[19]

Demand drug doses of 1–2mg, 5–10 minute LIs and 4-hour maximal dosages between 20–30mg are generally used in clinical trials. If deemed necessary, a continuous infusion of 0.5 mg/h can be used.

In a prospective, randomised study, Badner et al.[20] observed 75 patients receiving PCA morphine after abdominal surgery. Their objective was to study the effects of varying doses and LIs while keeping the hourly maximum dose constant. Patients were randomly assigned to one of three groups. Group 1 – 6 received a dose of 1mg with a 6-minute LI; group 1.5 – 9 received 1.5mg with a LI of 9 minutes; and group 2 – 12 received 2mg with a LI of 12 minutes. Two patients, one each in the 1.5 – 9 and 2 – 12 groups, required naloxone for respiratory depression. The number of PCA injections, attempts, missed attempts, and the incidence of dose adjustment were all significantly higher for the 1 – 6 group. This means that the use of 1mg with a 6-minute lockout may represent appropriate dose titration because this group had equivalent analgesia, morphine use and adverse effects as did the two larger dose and lockout groups. However, the increased number of PCA attempts and missed attempts may reflect a lower patient satisfaction with PCA therapy.

The principal pathway of metabolism of morphine is conjugation with glucuronic acid in hepatic and extrahepatic sites, especially the kidneys. Approximately 75–85% of a dose of morphine appears as morphine-3-glucuronide, and 5–10% as morphine-6-glucuronide. The former is pharmacologically inactive, whereas morphine-6-glucuronide produces opioid effects via its actions at μ-receptors. In fact, its potency and duration of action are greater than that of morphine, and it is possible that the majority of analgesic activity attributed to morphine is actually attributable to its morphine-6-glucuronide metabolite.[19]

Because renal metabolism makes a significant contribution to the total metabolism of morphine, and since elimination of morphine glucuronides may be impaired in patients with renal failure, this condition causes an accumulation of metabolites and unexpected ventilatory depressant effects even when small doses of morphine are used. Therefore, it is recommended that other opioids are used in patients with chronic renal insufficiency.[21]

The adverse effects of morphine via PCA are also characteristic of other opioid receptor agonists administered by any route or method of delivery. The most common adverse effects of intravenous PCA are nausea and vomiting, pruritis, respiratory depression, sedation, confusion and urinary retention. Their management will be discussed in section 3. In contrast to other opioids, morphine causes histamine release. However, there is a large interpatient variability in the amount of histamine released.[19]

Opioid-induced hyperalgesia is a complex concept that can occur after acute or long-term intravenous opioid administration, but is beyond the scope of this review.[22]

1.2 Fentanyl

Fentanyl, a 4-amilidopiperidine compound, is a pure opioid receptor agonist and has a selective high affinity for the μ receptor. Unlike morphine, it has high lipid solubility which facilitates its transfer across the blood-brain barrier. Because of this lipophylic nature, fentanyl has a quicker onset of action than morphine and is 75–100 times more potent. However, when administered via the intravenous route, a single dose of fentanyl has a short duration of action, which reflects its rapid redistribution to inactive tissue sites such as fat and skeletal muscles.[19] Fentanyl is extensively metabolised in the liver to norfentanyl. The latter is excreted by the kidneys and can be detected in the urine up to 72 hours after a single intravenous dose of fentanyl. Animal studies suggest that norfentanyl has an analgesic potency on its own, but lower than that of fentanyl.[19]

Because of its quick onset, fentanyl is well suited for intravenous PCA. The efficacy and tolerability of fentanyl administered by PCA have been extensively evaluated.[23-25] The demand doses in these studies ranged from 10 to 50μg, and the LIs ranged

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from 0 to 15 minutes. In a randomised, double-blind, multicentre study Camu et al.[26] have compared the safety and efficacy of three administered demand-dose sizes of fentanyl (20, 40 and 60μg) in 150 patients after major surgery. In each group, a maximum of six doses per hour were allocated. The authors decided that based on combined safety and efficacy considerations, a demand fentanyl dose of 40μg was the most appropriate for PCA management of postoperative pain.

1.3 Sufentanil

Sufentanil is an analogue of fentanyl. The analgesic potency of sufentanil is five to ten times that of fentanyl. Its high tissue affinity is consistent with the lipophilic nature of sufentanil, which permits rapid penetration of the blood-brain barrier and a rapid onset of CNS effects. Sufentanil is rapidly metabolised by *N*-dealkylation and *O*-demethylation. Extensive hepatic extraction means that clearance of sufentanil will be sensitive to changes in hepatic blood flow but not to alterations in the drug-metabolising capacity of the liver.[19]

Lehmann et al.[27] have studied postoperative PCA with sufentanil. In their study patients received an individualised intravenous loading dose of 19.1 ± 35.7μg; demand doses were 6μg with a concurrent infusion of 1.15 μg/h and a maximum hourly dose of 40 μg/h; the LI was set to 1 minute. They concluded that although seldom used, sufentanil is suitable for postoperative PCA.

With sufentanil, a bolus dose of 4–6μg and LIs of 5–10 minutes appear to be most appropriate for PCA.

1.4 Remifentanil

Remifentanil is a selective μ-receptor agonist with an analgesic potency similar to that of fentanyl. Although chemically related to the fentanyl family of short-acting phenylpiperidine derivatives, remifentanil is structurally unique because of its ester linkage. Its ester structure renders it susceptible to hydrolysis by nonspecific plasma and tissue esterases to inactive metabolites. This unique pathway of metabolism imparts to remifentanil (i) brevity of action; (ii) precise and rapidly titrable effects as a result of its rapid onset and offset; (iii) noncumulative effects; and (iv) rapid recovery after discontinuation of its administration.[19] These characteristics make it a poor candidate for postoperative usage but prove interesting assets in situations where both patient autonomy and the use of a short-acting drug with predictable termination are desirable. This is the case for PCA in labour. A short-lasting but painful procedure such as extracorporeal shock wave lithotripsy is another example of such a clinical situation.

Although several drugs have already been used by PCA in labour (pethidine [meperidine],[28] tramadol,[29] fentanyl[30,31]), remifentanil may have an advantage compared with the others because of its rapid onset time and rate of hydrolysis, even in metabollically immature neonates. Remifentanil PCA in labour is especially interesting in parturients in whom epidural analgesia is contraindicated.[32,33]

In a pilot study, Thurlow et al.[34] compared remifentanil by PCA with intramuscular pethidine in parturients in labour. They used a bolus dosage of remifentanil 20μg over 20 seconds, with a LI of 3 minutes and no background infusion. They concluded that remifentanil by PCA provided better pain relief than intramuscular pethidine. They also suggested that mothers should be encouraged to activate the system at the start of contractions rather than when the contractions become painful. If pressed too late, the maximum analgesic effect will occur after the peak of the contraction, increasing the chances for adverse effects, especially ventilatory depression. This is because of the rapid onset of action of remifentanil, with a time to peak effect of 60–80 seconds.[35]

In a prospective, observational study Volikas et al.[36] observed maternal and neonatal adverse effects of remifentanil PCA in labour. Remifentanil was administered at a bolus dose of 0.5 μg/kg and a LI of 2 minutes. Maternal vein and umbilical vein cord samples demonstrated placental transfer of the drug, and small amounts were detected in umbilical artery samples. They concluded that at the bolus dose used remifentanil PCA had an acceptable level

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of maternal adverse effects and minimal effects on the neonate. Remifentanil crosses the placenta and appears to be either rapidly hydrolised or redistributed in the neonate.

Remifentanil may be an acceptable alternative to other forms of analgesia in labour. However, it is a potent respiratory depressant and adequate continuous monitoring is advisable.

As mentioned in the first paragraph of this section, remifentanil PCA can be suitable for procedures such as lithotripsy. Medina et al.[37] have used remifentanil as a single drug by mode of PCA at two different concentrations. In addition to a continuous infusion of 0.05 μg/kg/min or 0.1 μg/kg/min, a demand dose of remifentanil 10μg was used with a LI of 1 minute. None of the patients showed significant respiratory depression. They concluded that a smaller infusion rate was as effective as an infusion rate of 0.1 μg/kg/min. In addition, the smaller dose was associated with satisfactory significant fewer adverse effects, such as postoperative nausea and vomiting (PONV), dizziness and pruritis.

1.5 Pethidine (Meperidine)

Pethidine (meperidine) is a synthetic opioid agonist at opioid μ- and κ-receptors. Structurally, pethidine is similar to atropine and it possesses a mild atropine-like antispasmodic effect. Pethidine is about one-tenth as potent as morphine and a 10mg demand dose is equianalgesic to 1mg of morphine. Its duration of action is 2–4 hours, making it a shorter-acting opioid receptor agonist than morphine. Extensive hepatic metabolism of pethidine leads to norpethidine. Urinary excretion is the principal elimination route of norpethidine. This metabolite is about one-half as active as pethidine as an analgesic. In addition, norpethidine produces CNS stimulation, resulting in a range of toxic reactions from anxiety and tremors to grand mal seizures.[19]

Simopoulos et al.[38] performed a retrospective review of 355 medical records of patients receiving intravenous PCA pethidine treatment. They concluded that pethidine 10 mg/kg/day was a maximum safe dose for PCA and that its use should not exceed 3 days. However, because of the pharmacodynamic variability in response to opioids, some patients require dosages >10 mg/kg/day.

Although pethidine has extensively been used for intravenous PCA, it has been shown[39] that patients using pethidine via PCA are at a particularly high risk of experiencing adverse drug reactions based on cumulative doses and duration of treatment. Adverse drug reactions were documented in approximately 14% of patients. These include confusion, anxiety, nervousness, hallucinations, twitching and seizures.

Pethidine is absolutely contraindicated for intravenous PCA in patients with renal or hepatic dysfunction, seizure disorders and in those taking monoamine oxidase inhibitors (MAOIs) because of the potential for a lethal drug interaction causing malignant hyperpyrexia syndrome.

1.6 Piritramide

Piritramide is a synthetic opioid with μ-receptor agonist activity. Piritramide is a popular postoperative analgesic in Belgium, Germany, The Netherlands and Eastern Europe, but is not available in all countries. Clinical evidence supports the view that the potency of the drug is approximately 0.7 times that of morphine. Onset of action after intravenous injection is 2–4 minutes. Its duration of action is approximately 6 hours. Elimination is almost entirely dependent on hepatic metabolism. The nature of piritramide metabolites is not clear.[40]

Piritramide has been used successfully for PCA.[41] The influence of bolus size on efficacy of PCA with piritramide has been studied in a prospective, randomised, double-blind study.[42] The authors concluded that a PCA regimen with a bolus dose of piritramide 0.75mg (instead of the routinely prescribed 1.5 mg) and a LI of 5 minutes was effective in the treatment of postoperative pain, but did not reduce the occurrence of adverse effects.

Of clinical importance when using the drug is the elimination half-life of piritramide which appears to exceed the duration of clinically effective analgesia during the treatment of acute pain. This means that the dose of piritramide should be titrated carefully during long-term treatment to avoid accumulation

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that may lead to adverse effects.[43] Piritramide should not be used in patients with porphyria.

1.7 Hydromorphone

Hydromorphone is a derivative of morphine. It is metabolised primarily as an inactive glucuronide metabolite.[44] It seems to be six to eight times as potent as morphine.

In a prospective, randomised study, Lehmann et al.[45] have studied PCA with hydromorphone with or without dipyrone (metamizole). In the low-dose group, a demand dose of 283μg of hydromorphone was efficient. In the high-dose group, the demand dose was set at 566μg. The LI was set at 2 minutes. A background infusion of 67.9 μg/h was delivered in all groups. They concluded that hydromorphone is about 3–4 times as potent as morphine under the conditions of intravenous PCA. Because it is generally favourably accepted by patients, hydromorphone can be a suitable alternative for morphine-intolerant patients or those with altered renal function.

1.8 Tramadol

Tramadol, a synthetic opioid of the aminocyclohexanol group, is a centrally acting analgesic with weak opioid receptor agonist properties.[46] It binds to the μ-receptor approximately 6000-fold less than morphine and has a weaker affinity for the opioid κ- and δ-receptors. This explains the absence of respiratory depression with the use of clinical doses of tramadol.

Tramadol also inhibits central uptake of norepinephrine and serotonin. Thus, its analgesic actions are mediated by both opioid and nonopioid (inhibition of monoamine uptake) mechanisms, which interact synergistically to relieve pain. Main biotransformation pathways are *O*- and *N*-demethylation. *O*-Demethyltramadol is an active metabolite and contributes to its analgesic effects.[47] In humans, tramadol metabolism appears to be slow and relatively high amounts of unchanged drug are excreted renally. First-pass hepatic extraction in humans is about 20%, which explains the high oral bioavailability of about 70%.[47]

Despite the fact that tramadol is only available in the oral form in the US, it has been used extensively for intravenous PCA in some European countries.[47-49] Intravenously, it is about 1/6th to 1/10th as potent as morphine if one takes into account both intensity and duration of effect.

Demand doses of tramadol 10–20mg with of 5–10 minute LIs and a 4-hour limit between 400–500mg have been used in clinical trials.

Common adverse effects seen with tramadol are sweating, dry mouth, drowsiness, nausea, vomiting, headache and dizziness. It has been shown that there is a 30–35% incidence of nausea when tramadol is used postoperatively.[50,51] Two clinical trials comparing tramadol with morphine for intravenous PCA associated tramadol with more nausea and vomiting.[52,53] However, a third study[54] found a similarly infrequent incidence of nausea and vomiting in both groups.

2. Adjuvant Drugs

The adjunction of other drugs to opioid-based PCA has been extensively studied. It has been suggested that their addition would improve analgesia while minimising adverse effects of opioids. The drugs mostly used are ketamine, naloxone, lidocaine and clonidine.

2.1 Ketamine

Opioid tolerance is an early process favoured by a paradoxical nociceptive stimulation. *N*-methyl-*D*-aspartate (NMDA) receptors are implicated in this process.[55,56] As ketamine is a potent NMDA-receptor antagonist, it has been used to counteract the development of tolerance in perioperative pain management. A number of studies have observed the adjuvant analgesic effects of ketamine with morphine with contradictory results; however, only a few studies have used ketamine as an adjuvant drug in intravenous PCA.[48,57-59] Ketamine-morphine mixtures at a ratio of 2 : 1 and 1 : 1 have been used for PCA. In a dose-effect study, Sveticic et al.[58] found the three best combinations of morphine and ketamine to be: (i) morphine 1.0 mg/mL, ketamine 1.0 mg/mL, 8-minute LI; (ii) morphine 0.7 mg/mL,

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ketamine 0.7 mg/mL, 7-minute LI; and (iii) morphine 1.1 mg/mL, ketamine 1.2 mg/mL, 8-minute LI.

Ketamine even at small doses can provoke psychomimetic effects and cognitive impairment. Therefore, there is currently no clear evidence to suggest any benefit from the systemic combination of ketamine and morphine in PCA.

2.2 Naloxone

Naloxone is a competitive antagonist at opioid receptors. Its affinity for μ-receptors appears to be much greater than for κ- and δ-receptors. It has no significant agonist activity. The use of opioid antagonists to decrease opioid adverse effects is an attractive concept but carries the risk of reversing analgesia. It has been suggested that analgesia and opioid adverse effects have different dose-response curves, permitting the antagonism of adverse effects while preserving analgesia.[60] In their study, Gan et al.[60] have used continuous infusion of naloxone together with morphine PCA. The group receiving low-dose (0.25 μg/kg/h) naloxone showed an opioid-sparing effect. The opioid-sparing effect of naloxone could not be observed in other studies where an ultralow dose of naloxone (morphine PCA 1 mg/mL plus naloxone 0.6 μg/mL) was used.[61] In an another study,[62] adding naloxone 0.8mg to morphine 60mg in saline 30mL failed to provide any benefit. Therefore dose-effect studies should be performed to evaluate the real interest of the naloxone plus morphine mixture.

2.3 Clonidine

Clonidine is an α2-adrenocepter agonist with analgesic properties. It has been used successfully for supplementary analgesia intraoperatively[63] and postoperatively.[64] In a randomised, double-blind study, Jeffs et al.[65] observed the effects of adding clonidine to morphine PCA. In the clonidine group, patients received a bolus of clonidine 4 μg/kg at the end of the operation followed by PCA. A bolus of morphine 1mg and clonidine 20μg with a 5-minute LI was programmed. In the control group, after infusion of saline at the end of the operation, a standard morphine PCA was allowed. These authors observed an improved analgesia only for the first 12 hours postoperatively. This enhanced analgesic effect was probably achieved by the clonidine loading dose alone. However, the addition of clonidine to morphine PCA significantly decreased nausea and vomiting in a female population undergoing lower abdominal surgery.[65] The authors concluded that the use of clonidine in a PCA may represent a strategy for dealing with patients who state a history of severe postoperative nausea and vomiting resistant to treatment.

2.4 Lidocaine

Lidocaine is a local anaesthetic. It seems that local anaesthetics reduce inflammation and the perception of pain. They act peripherally, decreasing the release of inflammatory mediators, and centrally, modifying neuronal responses in the dorsal horn.[66]

The analgesic effect of lidocaine used in PCA has been studied in several trials. Except in the study completed by Cassuto et al.,[67] where patients received low concentrations of lidocaine (2 mg/min) starting 30 minutes before surgery and continuing for 24 hours postoperatively, the other trials did not show any postoperative morphine-sparing analgesic effect of lidocaine.[68-70] In one of these latter studies by Cepeda et al.,[68] patients were treated with PCA in three groups: group 1, morphine 1 mg/mL; group 2, morphine 1 mg/mL plus lidocaine 10 mg/mL; and group 3, morphine 1 mg/mL plus lidocaine 20 mg/mL. PCA parameters for the three groups were demand dose 1mL; LI, 10 minutes; 4-hour limit, 25mL. There were no differences in opioid use, pain levels or adverse effects with these different lidocaine dosages. Similar concentrations were used in another study by Chia et al.[69]

There is some evidence indicating that different types of pain have different analgesic dose-response behaviour to lidocaine. Nociceptive pain is believed to be most resistant[71] and requires higher doses than neuropathic pain. Such high doses, however, may be associated with neurotoxicity.

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3. Management of Common Adverse Effects

The most common adverse effects of intravenous PCA are nausea and vomiting, pruritis, respiratory depression, sedation and confusion and finally urinary retention.

3.1 Nausea and Vomiting

PONV is the most common adverse effect seen with intravenous PCA. Its management has been studied extensively. The degree of PONV depends on the type of surgical procedure, drugs used during anaesthesia, anxiety, pain and several other factors. Several drugs can be used to reduce the incidence of PONV. These are metoclopramide, serotonin receptor antagonists (ondansetron, granisetron, tropisetron), dexamethasone, transdermal scopolamine and droperidol. In 2003, *Anesthesia Analgesia* published Consensus Guidelines for management of PONV.[72]

Of all the antiemetics used, droperidol is the only antiemetic that has been extensively studied when given concomitantly with PCA.[73] Several studies have been carried out to find the optimal dose of droperidol for addition to PCA.[74-77] Culebras et al.[77] in a multicentre study, randomly allocated adults who received postoperative morphine PCA (bolus 1mg, 5-minute LI) to one of four regimens: no droperidol or 5, 15, or 50μg of droperidol per mg of morphine. They concluded that the optimal dose of droperidol, when added to a morphine PCA is between 15 and 50 μg per mg of morphine.

The most serious adverse effects of droperidol are QT prolongation and life-threatening arrhythmias. So far, there has been no case report of any arrhythmias when droperidol has been used in low doses for PCA.[74] Neither was it the case in a study by White et al.[78] Despite these studies, a recent warning by the US FDA has severely limited use of droperidol in the US.

3.2 Pruritis

Pruritis is an unpleasant and common adverse effect of opioids. There are no clinical trials treating intravenous PCA related pruritis. It has been shown that addition of a minimum dose of droperidol 15μg per morphine 1mg in PCA can have antipruritis effects.[77] The beneficial effect of droperidol on opioid-induced pruritis has been described elsewhere in the literature.[79]

3.3 Respiratory Depression

Several studies have documented the incidence of respiratory depression with intravenous PCA. However, there is considerable variability between all these studies in the criteria used for defining respiratory depression including respiratory rate, depth and rhythm, oxygen saturation using pulse oximetry and the need to administer an opioid antagonist.

In a meta-analysis focused on postoperative respiratory events, Cashman and Dolins[7] observed that the incidence of respiratory depression for intramuscular analgesia, intravenous PCA and epidural analgesia differed when using either hypoventilation or oxygen desaturation as indicator. They concluded that Acute Pain Services (APS) should expect an incidence of respiratory depression, as defined by a low-ventilatory frequency of <1%.

Risk factors for respiratory depression with intravenous PCA include background infusion; nurse- or physician-controlled analgesia; concomitant administration of hypnotics or sedatives; renal, hepatic, pulmonary or cardiac impairment; sleep apnoea (suspected or history) and obesity.[12]

3.4 Sedation and Confusion

Sedation with intravenous PCA is particularly seen in patients with renal dysfunction receiving morphine PCA. Opioid-sparing strategies, such as coadministration of paracetamol (acetaminophen) may reduce the incidence of sedation.[80]

Postoperative confusion or delirium is defined by widespread cerebral dysfunction and may be caused by a wide spectrum of organic factors. It has been observed in patients treated with intravenous PCA. However, undertreatment of pain may also put elderly patients at risk for confusion.[81]

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3.5 Urinary Retention

Acute urinary retention can follow all types of anaesthetics or operations. Not only surgical problems but also postoperative oedema around the bladder neck, and pain-induced reflex spasm of the external and internal urethral sphincters may play a role in the development of urinary retention. Urinary retention is also a frequent adverse effect of opioids, particularly after intrathecal and epidural administration. After reviewing 800 publications concerning the management of postoperative pain and the adverse effects of this management, Dolin and Cashman[82] found an overall incidence of urinary retention of 23% (highest with epidural analgesia).

In a prospective study of 47 men and 69 women undergoing lower limb joint replacement, O'Riordan et al.[83] assessed the factors that may be associated with urinary retention. After stepwise logistic regression analysis, three factors were recognised as significant indicators of an increased probability of urinary retention: male gender, increasing age and the use of PCA. The extensive use of an indwelling catheter can lead to urinary tract infection and urethral structure. However, it is essential to make sure the bladder empties in the postoperative period.

4. PCA versus Other Pain-Relieving Techniques

Since its introduction in the 1980s, the usefulness of PCA has been continuously compared with conventional nurse-controlled analgesia (NCA). Although PCA may have no[84] or modest clinical benefit for pain management after certain types of surgery,[85] it seems that in most of studies the analgesic efficacy endpoints are in favour of PCA (see table II).

In a systemic review, Walder et al.[4] analysed 32 trials. The authors observed several findings. PCA is slightly more analgesic than NCA, that the amount of opioids consumed is no different between the two methods, and that the incidence of opioid-related adverse reactions is similar. Although not totally satisfied, patients prefer PCA. PCA decreases a patient's anxiety in the postoperative period. On the basis of a limited amount of data, they found some evidence that there are fewer postoperative pulmonary complications with PCA compared with conventional opioid analgesia. This latter finding has been demonstrated in a randomised controlled trial of 120 patients undergoing coronary artery bypass graft surgery.[86] PCA significantly decreased postoperative pulmonary atelectasis when compared with NCA. NCA and PCA reflect two fundamentally different options in quality management of patient care. PCAs usually belong to an acute pain service centralising information, experience and progress. The quality of NCA reflects the variable quality of local nursing care.

Table II. Patient-controlled analgesia (PCA) vs nurse-controlled analgesia (NCA)

	PCA	NCA
Adverse effects	=	=
Pain relief	>	<
Anxiety relief	>	<
Satisfaction	>	<
Pulmonary outcome	>	<
Quality structure	Acute pain service	Local ward

= indicates equal; > indicates superior; < indicates inferior.

5. Non Intravenous PCA

The most important concept of PCA is drug administration on patient demand. Although intravenous PCA is the most studied route of PCA delivery, alternative routes have extensively been described in the literature. The three most known alternative routes are epidural catheters, peripheral nerve catheters and transdermal PCA (see table III).

5.1 Epidural PCA

Epidural analgesia would appear to be superior to intravenous PCA. Indeed, studies have shown that epidural analgesia with a local anaesthetic combined with an opioid provides better postoperative analgesia than epidural or systemic opioids alone,[87,88] and may improve postoperative outcome.[87,89,90] The beneficial postoperative effects of epidural analgesia are more apparent for high-risk patients or those undergoing higher risk procedures.[91,92] Reports suggest that patient controlled epidural analgesia

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(PCEA) may improve analgesia,[93] patient satisfaction[94] and safety[95] compared with conventional epidural infusion or bolus techniques.

Carli et al.[96] compared intravenous PCA with continuous epidural analgesia in patients after elective colonic resection. They showed that epidural analgesia enhanced functional exercise capacity and health-related quality of life. In this study, patients who benefited from epidural analgesia had an earlier restoration of gastrointestinal function. They were mobilised earlier and were discharged sooner than those who received intravenous PCA. These results are in agreement with earlier studies.[97,98] Wu et al.[99] performed a meta-analysis and found that PCEA provided superior postoperative analgesia than intravenous PCA. Their results correspond with previous systemic reviews of the analgesic efficacy of postoperative epidural analgesia versus systemic opioids.[100,101] Schenk et al.[102] have recently compared intravenous PCA with PCEA in patients undergoing spinal fusion surgery. In this prospective, double-blind study they showed that PCEA using intraoperatively placed epidural catheters provides superior analgesia and higher patient satisfaction.

However, the potential benefits of PCEA must be balanced against potential risks linked to the placement of a catheter, which can cause serious accidents such as epidural haematoma, infection or neurological injury.

In a large, observational study including 1030 surgical patients, Liu et al.[103] concluded that PCEA provided effective and safe postoperative analgesia on the hospital ward after various surgical procedures. However, one should keep in mind that PCEA is not suitable or more advantageous in every type of surgery. In a randomised controlled trial of 113 patients, Hansdottir et al.[104] recently showed that in elective cardiac surgery, thoracic PCEA offers no major advantage with respect to hospital length of stay, quality of recovery, or morbidity when compared with intravenous PCA.

The ideal epidural analgesic solution is not known. Usually, a small concentration of a long-acting local anaesthetic (e.g. bupivacaine, levobupivacaine and ropivacaine), along with a lipophilic opioid (fentanyl, sufentanil) are used. The ideal PCEA delivery variables are not clearly determined either. In contrast to intravenous PCA, a continuous background infusion is routinely used for PCEA. With a background infusion, a continuous neural blockade will be maintained.

The demand dose is most commonly set at 3–6mL of a local anaesthetic with or without opioids, with a LI ranging from 15 to 45 minutes. Continuous infusions at a rate of 4–8mL are commonly used. Of importance is the segmental nature of epidural analgesia. This requires better supervision with particular attention to recognition and management of hypotension and motor blockade.

Recently, a new morphine formulation has been developed to overcome problems with indwelling epidural catheters and to provide pain relief for 24–48 hours postoperatively. Extended-release epidural morphine (EREM) formulation (DepoDur™ [1]) uses DepoFoam™ technology to provide an epidural depot of morphine for up to 48

Table III. Comparison between methods allowing patient-controlled analgesia: intravenous analgesia (IVPCA), epidural analgesia (PCEA), regional analgesia (PCRA) and transdermal analgesia (PCTA).

	IVPCA	PCEA	PCRA	PCTA
Infection risks	+	+	+	−
Catheter-related problems	+	++	+++	−
Neurological adverse events	−	++	++	−
Cost	+	++	++	++++
Adjuvant drugs	Any	Any	Any	None
Duration of use	No limit	No limit	No limit	24h

− indicates no risk; + to ++++ indicate increasing risk.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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hours. DepoFoam™ is a drug-delivery system with numerous lipid particles containing the active drug.[105] This relative new system of epidural drug injection has already been successfully used in several studies.[106-108] EREM provided good postoperative analgesia in comparison with the placebo or conventional epidural morphine. The most frequently observed adverse effects were nausea, vomiting, pruritis, pyrexia, hypotension and respiratory depression. The latter was observed in elderly patients and is in accordance with a trend toward lowering opioid doses in elderly patients.[3] These studies show that EREM may provide benefits over intravenous PCA and PCEA with respect to earlier mobilisation.

5.2 Peripheral Nerve Catheter PCA

Nerve block techniques are increasingly used nowadays to manage postoperative pain. The most observed and studied blocks are the brachial plexus block, sciatic nerve block, interscalenic nerve block and femoral nerve block. Extensive discussion of each technique is beyond the scope of this review.

Peripheral nerve blocks on both the upper[109,110] and lower extremities[111,112] result in increased postoperative analgesia and patient satisfaction. Although rare, infections and neurological complications are possible. Interestingly, in contrast with central neuraxial blocks, there is less concern about interaction of anticoagulants and peripheral nerve blocks.

In a large, prospective, multicentre study,[113] 1416 patients who underwent orthopedic surgery benefited from peripheral nerve blocks with or without general anaesthesia. The postoperative analgesia was good in 96.3% of the patients, regardless of the combination with general anesthesia, which is in accordance with the majority of studies in the literature.[112,114] However, an increase in pain scores was observed at 24 hours. This phenomenon is already reported in several studies.[115-117] It is difficult postoperatively to maintain complete anaesthesia with limited continuous infusion of low concentrations of local anaesthetic. However, optimisation of pain relief can be obtained using appropriate rescue analgesia. Minor adverse effects were observed in 28% of patients. There were mostly technical problems with catheters and devices. Serious complications occured in 0.84% of the cases. In 28.7% of the cases, cultures from the catheters were positive. This was without clinical repercussion in a large number of cases.

A continuous infusion of local anaesthetics with or without a bolus dose is generally used in peripheral nerve catheter PCA. Singelyn and Gouverneur[118] found that a smaller dose continuous infusion with boluses, in comparison with a continuous infusion alone, reduces local anaesthetic consumption without compromising pain relief.

5.3 Transdermal PCA

Transdermal PCA is a new noninvasive method of PCA, which eliminates the need for venous access and many problems that compromise patient safety, such as programming errors. Recently, a fentanyl hydrochloride patient-controlled transdermal system (PCTS) has been developed which delivers small doses of fentanyl by iontophoresis. Iontophoresis is a method of transdermal administration of ionisable drugs in which the electrically charged components are propelled through the skin by an external electric field. Iontophoresis of lidocaine for analgesia before superficial surgical procedures has been reported.[119,120] Iontophoresis has also been used to deliver corticosteroids for the treatment of pain in the joints.[121,122]

The PCTS is a preprogrammed, self-contained, self-adhesive, on-demand drug-delivery system. It uses a low-intensity direct current to move fentanyl from a hydrogel reservoir into the skin, from where it then diffuses into the local circulation and is transported to the CNS. The low molecular weight, high potency and lipid solubility of fentanyl make it suitable for transdermal delivery. When the electrical current is activated by pressing the button, PCTS delivers a fixed dose of fentanyl 40μg with a fixed 10-minute LI. The device allows for up to six demand doses per hour and up to 80 demand doses over 24 hours, at which point the device shuts off and should be replaced. These key system design

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characteristics were carefully selected according to a substantial body of literature.[26,123]

Chelly et al.[124] demonstrated that fentanyl PCTS 40μg was superior to placebo for the management of acute postoperative pain after major surgery. In a multicentre clinical trial, Viscusi et al.[125] showed that fentanyl PCTS 40μg used after major surgery provided postsurgical pain control and a safety profile equivalent to that of standard intravenous morphine PCA. As the current applied is very low, patients do not feel any unpleasant sensation at the delivery site. A mild erythema at the application site can occur and resolves without any treatment.

6. Acute Pain Service

With the introduction of PCA, our knowledge of the pathophysiology and nociception of acute postoperative pain has dramatically increased. Pain management has become an important issue for healthcare providers. Anaesthesiologists have played a tremendous role to make this feasible. In an attempt to improve postoperative analgesia, and minimise complications, APS have been developed. An APS is based on the concept that management of postoperative pain can be improved by appropriate patient selection, education and training for nursing staff working in the postanaesthesia care unit and in the surgical wards. It consists of staff and resident anaesthesiologists and specially trained nurses.

It has already been demonstrated that APSs use PCA technology differently than non-APS physicians.[126] Development of an APS is certainly very important to minimise adverse effects related to PCA (drug related, device related, catheter related, patient related) and to avoid lethal mishaps. Mishaps from technical problems and programming errors continue to happen.[127-129] System errors, however, should be reported and investigated so that they can be avoided in the future.

Although an anaesthesiologist-based APS is certainly an option, it has been shown that a nurse-based, anaesthesiologist-supervised APS provides effective and safe postoperative pain management.[130] The latter overcomes an associated increase in healthcare costs since costs for a specialist physician are greater than those for other care providers.

7. Conclusion

Since its introduction, PCA has really revolutionalised acute pain management. It has helped us to understand better the difficult concept of pain. It has surely changed the attitude of physicians other than anaesthesiologists towards pain management.

Although morphine remains the most frequently used opioid in PCA, use of other drugs can be indicated in some patients. It is important to know the pharmacokinetics and pharmacodynamics of any drug used in PCA. However, it is recommended that each department chooses one single analgesic medication that will always be used at the same concentration for PCA. Indeed, the risk of errors in preparing and programming is increased by changing the usual protocols.

Although we have mainly focused on intravenous PCA in this review, other routes are of great interest and should be taken in consideration whenever possible. The use of central and peripheral neuraxial blocks is recommended to avoid any possible opioid tolerance and hyperalgesia phenomenon observed after acute or chronic administration of intravenous opioids. Larger studies are warranted to show the benefits and cost-effectiveness of other routes of PCA, such as the patient controlled transdermal system, before routine use of them.

The development of an APS is surely a step towards a better and safer management of acute (postoperative) pain. It also provides better management of the adverse effects seen with PCA.

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