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Novel delivery systems for postoperative analgesia

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Moderate-to-severe postoperative pain is usually controlled using a multimodal approach, including opioids. Intravenously administered patient-controlled analgesia (IV PCA) with opioids, popular for over 40 years, enables patients to control their level of analgesia and has advantages over a nurse-administered approach, including more satisfied patients and improved pain relief. Unfortunately, IV PCA has drawbacks such as device programming errors, medication prescribing errors, pump malfunction, limitations on patient mobility, IV patency issues, and transmission of infection. Furthermore, the setup of an infusion pump is often complex, time-consuming, and requires witnessed confirmation. Complicating IV PCA is the problem of commonly used compounds, morphine and hydromorphone, having significantly reduced brain/effector-site permeability and active metabolites, both of which create the risk of delayed adverse events. Novel patient-controlled modalities that incorporate rapid effector site-permeating opioids and non-invasive routes of administration offer great promise to enhance both patient and caregiver experiences with postoperative analgesia systems.

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Introduction

Numerous advances have been made in postoperative pain management, including regional anesthesia techniques and multimodal approaches, which enhance the control of acute pain. Despite these improvements, the 40-year-old technology of intravenously administered patient-controlled analgesia (IV PCA) with opioids remains a commonly used modality in the treatment of moderate-to-severe postoperative pain.

IV PCA popularity over the years is likely due to some advantages this approach has over nurse-administered medications and regional anesthesia techniques. Patients "feel" better when they control their own analgesia, and by requiring self-titration of opioid doses in small increments, an inherent safety benefit is created, since the patient must be alert enough to administer the next dose of medication [1–8]. Unlike regional anesthesia techniques, implementation of IV PCA is not dependent on the technical skill of a physician. However, medication ordering and dosing errors [9], IV PCA pump programming and device errors [9], mobility constraints of being tethered to the IV tubing, pump, and pole [1], analgesic gaps due to issues with IV tubing patency [10], infection risk due to the need for venous access [11], and opioid-related adverse events [12], all serve to complicate the use of IV PCA. Issues with the use of opioids in IV PCAs for postoperative pain management will be discussed and new non-invasive approaches to the PCA paradigm will be described. These new approaches may produce specific benefits beyond being easier to use, less invasive, and less prone to error than IV PCA.

Use of IV PCA for postoperative analgesia

Issues with reduced effector-site permeability

The most commonly used opioids for IV PCA are morphine, hydromorphone, and to a much lesser extent, fentanyl, due to its short duration of action caused by rapid redistribution after IV delivery [13]. Meperidine is no longer considered a viable option for IV PCA due to potential accumulation of its toxic metabolite, normeperidine, particularly in elderly patients or those with renal impairment [9,14,15]. The fundamental concept behind PCA is to provide small, on-demand opioid doses that allow each patient to safely titrate to his or her own therapeutic plasma level of opioid. The demand dose of opioid used has a significant impact on the success of PCA; the typical demand dose is generally that which has been shown to provide the optimal balance of analgesia and safety [16]. Although less frequently used in opioid-naive patients, a constant basal rate of opioid analgesic may be administered in addition to the on-demand dose, but this approach is often problematic. Basal infusions increase the risk of respiratory depression without providing increased analgesia [17–19]. Because of these safety concerns, the American Pain Society (APS) cautions against using basal infusions except in opioid-tolerant patients [20].

An important parameter, which is often not considered when determining which opioid is optimal for PCA use, is the equilibration half-life between the plasma and the μ-opioid receptor effector site in the central nervous system (CNS), known as the $t_{½ke0}$. The $t_{½ke0}$ is experimentally determined by measuring an objective sign of an opioid CNS effect (EEG and pupillometry are two popular methods) and comparing the "kinetics" of this effect with the measured drug concentration in the venous plasma, thereby determining the time required for "equilibration" between the effector site and the plasma concentration. For opioids that are highly lipophilic and not efflux transporter substrates, such as fentanyl and sufentanil, this equilibration occurs rapidly as these drugs rapidly escape out of the aqueous plasma environment into the lipid bilayers of the CNS [21]. For hydrophilic drugs that have limited ability to transit into lipophilic environments and, in addition, are substrates for efflux transporters, such as morphine, this equilibration can take hours and the equilibration of active metabolites, such as morphine-6-glucuronide (M6G), can take even longer (Table 1). So while the theoretical benefits of IV PCA are to provide iterative dosing to allow a patient to "build" into a therapeutic window, the significantly delayed $t_{½ke0}$ of morphine and hydromorphone sets the patient up for inadequate initial analgesia followed by a possible overshoot of drug administration leading to delayed adverse events. Of greater concern is the desire to overcome this equilibration delay with larger nurse-controlled bolus dosing which can add to the potential for late-occurring side effects.