Current Methods of Controlling Post-Operative Pain

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Until recently, the clinical significance of post-surgical pain and its undertreatment were for the most part unappreciated. Recognition that inadequate analgesia adversely affects the patient’s cardiovascular, pulmonary, and emotional status has spurred development of new and highly effective methods of controlling pain. With the introduction of spinal opioid and patient-controlled analgesia (PCA) came the realization that, while such forms of therapy provided superior pain relief, they were not without their own unique and occasionally serious side effects. For this reason, both techniques are more safely provided by highly trained members of a dedicated acute/post-surgical pain service.

Although spinal opioid (epidural, intrathecal) techniques are invasive and require patient cooperation, they have a high degree of safety in low-risk populations (ASA 1 and 2). The major therapeutic advantage of spinal opioids is their ability to prevent pain from being perceived.

PCA permits patients to titrate intravenous opioids in proportion to their particular level of pain intensity. Although PCA provides effective pain “relief,” the technique is incapable of preventing pain from being appreciated. A number of studies have observed that pain scores in patients successfully employing PCA were significantly higher than those noted in individuals treated with epidural opioids. Nevertheless, the control gained by self-administration, uniformity of analgesia, and low level of adverse results associated with PCA provides higher patient satisfaction and decreased sedation when compared with traditional intramuscular dosing. The effectiveness of PCA may be improved by adjusting for patient variables, utilizing opioids having rapid onset, the addition of a basal infusion, and supplementation with non-steroidal anti-inflammatory agents.

Interpleural analgesia represents an important therapeutic option in patients sensitive to opioid-induced respiratory depression. The technique is more effective when local anesthetic solutions are continually infused. Analgesic efficacy may be further enhanced by the addition of “low-dose” PCA.

INTRODUCTION

Although pain is among the most common of symptoms encountered by the hospital staff, it remains one of the most poorly treated. In a well-documented post-operative study, 32 percent of patients reported severe pain and 41 percent experienced moderate pain in the post-surgical period [1]. It is now apparent that with traditional as-required (PRN) dosing, a number of variables, including patient age, ASA status, site and extent of injury, and coping skills, must be accounted for in the algorithm of providing adequate analgesia. Most patients are either intentionally (fear of adverse drug effect, respiratory depression, addiction, and the like) or unintentionally (poor understanding of onset, minimal effective plasma concentra-
tion, half-life of analgesic effect) undermedicated [2]. Many are prescribed analgesic dosages that are less than half of what is required to relieve pain adequately. In addition, nurses may further reduce dosage, leading to the patient’s accurate perception that analgesics were not administered in a high enough dose or as frequently as was required [2,3]. Some workers have shown that the amount of pain medication a patient receives is directly related to the number of nurses on duty [1,2].

During the last decade, the medical community has become increasingly concerned over the significant morbidity associated with poorly controlled post-surgical pain. The importance of reducing emotional, hormonal, and neural stress responses associated with moderate to severe discomfort has emphasized the need for clinical specialists trained to formulate strategies that provide more uniform and effective levels of analgesia. The anesthesiologist, having a thorough understanding of opioid pharmacology, and skilled in regional forms of drug administration, is uniquely qualified for this role. Workers in this specialty have long recognized that there are more similarities than differences between numerous opioid derivatives, and that what was necessary for more effective pain management was the development of more appropriate methods of drug delivery [3]. In this regard, departments of anesthesiology have made significant contributions toward the clinical utilization of three new methods of pain control: namely, the “selective” analgesia provided by spinally acting opioids, the “demand” analgesia offered by patient-controlled administration of intravenous opioids, and interpleural catheter techniques utilizing local anesthetics.

In an effort to improve the availability and appropriate follow-up of patients treated with these new techniques, Ready and co-workers [4] have inspired development of physician (usually anesthesiology-based) “Acute Pain Services.” Acute pain services offer in-house individuals trained to provide both nursing and patient education, individualized epidural opioid and PCA dose, assess the effectiveness of and adjust ongoing therapy, and treat associated side effects. New methods of providing post-operative analgesia via organized pain services are becoming increasingly widespread and have been found to be more effective and safer than traditional forms of opioid delivery.

TRADITIONAL METHODS OF PAIN CONTROL

Intramuscular administration of opioid analgesics, repeated every three to four hours, remains the most widely used method of pain control. While most physicians are comfortable with the ease and simplicity of PRN or by-the-clock dosing, the onset of analgesia is often delayed, and clinical effectiveness may be unpredictable. When a parenteral analgesic is administered [either intramuscularly (IM) or subcutaneously (SC)] every three to four hours, concentrations in plasma may equal or exceed minimal analgesic concentration during only 35 percent of the dosing interval [3]. Moreover, peak plasma concentrations vary between three- and fivefold, and time to reach peak activity, seven- to fifteenfold among individuals [5]. Thus, it is understandable why attempts at predicting the amount of opioid needed for an individual patient have met with little success. Many authors [3,4,6] have shown that older patients require less opioid; however, whether this finding is related to alterations in pharmacokinetics (smaller volume of distribution) or pharmacodynamics (changes in central nervous system access, opiate receptor density, binding affinity, and so on)
remains unclear. Other investigators have shown that obese individuals require more post-operative analgesics, yet attempts at demonstrating relationships among height, weight, and body surface area have provided little success [6]. The reason for failure may be in part due to the manner in which the drugs are administered but is also related to large inter-individual variation regarding perceived intensity of the painful stimulus over time [3].

As noted in Fig. 1, the traditional PRN every three-to-four-hour dosing involves an elaborate sequence of events which inevitably delays administration by at least 30 minutes to an hour. In addition, one typically notices the repetitive cycle of increases in pain followed by excessive sedation-narcosis after absorption of the opioid.

When a patient initiates a request for medication, a variable delay occurs before the nurse arrives. Because pain may not be considered an emergency, the length of time patients wait is dependent upon the situation on the ward (and nursing workload) at the time of the request. Once the nurse has responded, he or she usually initiates a “screening” of the complaint to assess whether the patient really needs additional pain medication. Despite published research indicating that physical dependence occurs in fewer than 0.1 percent of hospitalized patients, this screening is done presumably in order to avoid opioid abuse [2,3,7].

When the level of pain is deemed appropriate and requiring treatment, a long sequence of events occurs before the patient actually achieves relief. The nurse must sign out the medication, prepare an injection, and administer the dose. The drug must then be absorbed from the IM or SC site of administration, achieve effective plasma concentration, and interact at central nervous system (CNS) receptor sites. Since the dose administered is relatively large and absorption is erratic and prolonged, the initial analgesic effect is often followed by sedation and some degree of respiratory depression. In point of fact, the presence of sedation is often equated with a satisfactory analgesic effect [1,2].

Other traditional delivery options include PRN boluses of intravenous opioids in which the advantage of rapid onset must be coupled with shorter analgesic duration and increased labor intensity. Timed-release oral morphine and “depot” methadone offer advantages of prolonged duration (but because dosage is high, possibly greater side effects) and deserve further study.
CLINICAL USE OF SPINAL OPIOIDS

Pharmacology

The identification of specific opioid binding sites, receptor subtypes, and the discovery of the endogenous opioid peptides has helped to clarify how and where these useful agents interact with the nervous system; nevertheless, considerable controversy has existed regarding the effects of opioids at the spinal level. Earlier investigators favored the view that systemically administered opioids had major impact on supraspinal centers or activated descending pathways, which inhibited transmission of nociceptive information at the spinal level, rather than having direct effects at the cord [3,5]. Follow-up studies presented evidence of significant opioid suppression of spinal nociceptive neurons. Kitahata and Collins [8] had reasoned that small amounts of opiate receptor binding in a strategic location (dorsal horn) could have major effect on pain modulation since nociceptive input could be effectively blunted at the first synapse in the CNS. These investigators were first to demonstrate a dorsal horn suppressive effect of morphine upon nociceptive cells in laminae I and V. This effect was quite selective, since the activity of neurons of laminae IV and VI, which respond to non-noxious cutaneous and proprioceptive stimuli, was unaffected. Similar opioid suppressive effects reported by Duggan et al. [9] were related to specific receptor binding, which could be reversed by iontophoretically administered naloxone.

Autoradiographic techniques, in which radiolabeled opioids are employed to localize sites of activity, have demonstrated a remarkable correlation between the above-mentioned neurophysiology and those regions having highest binding. Autoradiographs prepared by Pert et al. [10] revealed that specific opioid binding in spinal cord was restricted to the dorsal horn. In a more detailed study, dorsal horn binding density was found to be highest in laminae I and II. Autoradiographs made following spinal application of radiolabeled morphine show that, as the front of radioactivity penetrating dorsal horn reaches laminae II and V, the discharge of neurons to noxious stimuli begins to decrease [11].

Attempts have been made to carry the localization of opiate receptors one step further and determine whether they are located pre- or post-synaptically with respect to the primary afferent fibers in the spinal cord. Evidence exists for both a pre- and a post-synaptic location. A study by LaMotte et al. [12] showed a significant reduction in stereospecific opiate binding in the dorsal horn of monkeys following rhizotomy, suggesting a pre-synaptic receptor location. In cats, morphine depressed nociceptive responses when injected into the substantia gelatinosa but not at more ventral sites where cell bodies are located. Enkephalin depresses cell firing at either location, suggesting that receptors for morphine may be restricted to pre-synaptic terminals, while enkephalin may also act upon post-synaptic dendrites [13].

Behavioral Studies

While the above studies demonstrated clear evidence of opioid receptor binding and activity at the spinal level, it was not clear whether spinal opioids would provide useful analgesia in the intact organism. This question was answered by administering small amounts of opiates through chronically implanted catheters into the spinal

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1Unless specifically described, the term “spinal opioids” is used to identify the site of action and analgesic effect provided by intrathecal or epidurally administered agents.
space of intact animals [14–16]. Utilizing this model, Yaksh and Rudy [14] showed that small doses (40–160 μg) of intrathecal morphine produced behaviorally defined naloxone-reversible analgesia of prolonged duration. These investigators have provided evidence that two or more distinct opioid receptor systems may be involved in modulating pain at the spinal level [15,16]. Intrathecally administered nalbuphine, a kappa receptor agonist, had no antinociceptive effect in rats exposed to thermally evoked stimuli (tail flick, hot plate), but had a powerful suppressive effect against visceral-chemical stimuli (acetic acid writhing test). Morphine, a mu-kappa agonist, was found to be effective against both cutaneous-thermal and visceral/chemical stimuli [16]. In a follow-up study, Schmauss and Yaksh [17] were able to characterize further spinal opioid binding by showing that delta receptor agonists (metkephamid, DADL) attenuated thermally evoked responses but were less effective in blunting visceral stimulation. Table 1 outlines present understanding of opioid receptor subtypes in spinal cord.

From the above discussion, the following picture begins to emerge. Noxious stimuli relayed to the dorsal horn by unmyelinated nociceptive afferents (C fibers) result in the release of substance P at synapses with second-order neurons [substantia gelatinosa (SG) cells]. The SG cells in turn drive neurons of laminae VII and VIII whose axons ascend as the spinoreticular-spinothalamic tract and synapse in the periaqueductal grey and medial thalamus. Such input is modulated by two distinct mechanisms. The first is mediated by local release of endogenous opioids from spinal interneurons that bind mu, kappa, and delta receptors at pre- and post-synaptic sites [15–17]. Receptor activation inhibits further transmission of nociceptive impulses by blocking substance P release or by stabilizing second-order SG cells. The second mechanism is mediated by descending inhibition from the brain stem reticular formation, periaqueductal grey, and nucleus raphe magnus [14,17,18]. These descending adrenergic, enkephalinergic, and serotonergic axons either inhibit pre- and post-synaptic membranes directly or facilitate release of endogenous spinal opioids. Both mechanisms have close association with the paleospinothalamic tract [9,12], which is responsible for transmission of slow-dull pain, and have little relationship to the neospinothalamic tract, responsible for mediating sharp pain.

In the clinical setting, intravenous opiates activate both mechanisms in dose-dependent fashion, while intrathecally administered opioids maximally activate spinal receptor sites and have less impact on descending pathways. Figure 2 illustrates mechanisms whereby nociceptive input is modulated in the dorsal horn.
Physiochemical Properties

The complex pharmacokinetics that follow opioid deposition into the epidural space have been outlined [18] and must be appreciated in order to understand the benefits and potential complications of spinal analgesia. Although many factors including dose, volume of injectate, molecular weight, and shape are considered important variables, lipid solubility appears to play the key role in determining onset, dermatomal spread, and duration of analgesia [18]. In this regard, delayed analgesic onset noted with morphine has been related to its low lipid solubility, which reduces dural permeability and, more important, retards penetration into spinal tissue [19]. Following administration, significant amounts of drug become sequestered in cerebrospinal fluid (CSF) for relatively long periods of time. This aqueous "depot" of unbound morphine molecules may provide analgesia of prolonged duration, but is the major causative factor underlying delayed respiratory depression [18,19].

Spinal administration of opioids produces dose-dependent analgesia of greater potency than similar doses administered parenterally. This potency gain is inversely related to lipid solubility as the blood-brain barrier is bypassed [18]. A second major advantage noted with spinally administered opioids is the "selectivity" of analgesic effect, which occurs in the absence of motor or sympathetic blockade, potentially allowing patient ambulation and the avoidance of cardiovascular collapse.

Initial Clinical Studies

The efficacy of spinal opioids in animal studies, coupled with established techniques for administering drugs into the spinal and epidural spaces, provided a new and potentially useful method of controlling pain in a variety of clinical settings. Although intrathecal morphine may have been used clinically over 80 years ago, Wang and colleagues in 1979 were the first to report a double-blind, controlled study of spinally administered opioids in humans [20]. In six out of eight patients suffering from intractable cancer pain, intrathecal morphine (0.5–1.0 mg) produced complete
TABLE 2

Analgesic Efficacy and Frequency of Adverse Effects with Epidural, PCA, and IM Morphine

| Study No. | Epidural | PCA | IM | Epidural | PCA | IM | Epidural | PCA |
|-----------|----------|-----|----|----------|-----|----|----------|-----|
| I         | 65       | 40  | 25 | 85       | 60  | 35 | NA       | NA  |
| II        | 85       | 60  | 50 | 72       | 38  | 17 | NA       | NA  |
| III       | 95       | 50  | NA | 73       | 35  | NA | 53       | 18  |

Study I, from [24]; Study II, from [23]; Study III, from [25]

relief for 12–24 hours without evidence of significant sedation, respiratory depression, or impairment of neuromuscular function. This report was soon followed by other clinical studies noting remarkable analgesic efficacy and prompting the statement that “never in the history of medicine has a concept progressed as rapidly from laboratory experimentation to clinical application in man” [21]. Thousands of literature citations [18–34] have since confirmed the remarkable efficacy of epidural opioids, and such techniques have gained considerable popularity in settings of post-surgical, obstetrical, and chronic pain.

Spinal Analgesia: Morphine

Morphine was first to receive FDA approval for epidural and intrathecal use and remains the most widely investigated and extensively used spinal opioid. Morphine has been employed to control post-operative pain following a variety of surgical procedures, appears to improve post-operative respiratory function [18,27], and encourages earlier ambulation [18,31,32]. While it has been found to be effective in management of post-operative and cancer pain, morphine is less efficacious in controlling labor pain, especially during second stage [18]. Epidural morphine is usually administered at lumbar sites in doses ranging from 3 to 10 mg [22–24]. In patients recovering from gynecological surgery, epidural morphine requirements appeared to be inversely related to patient age, with 24-hour dose requirement in milligrams equivalent to: 18 – age × (0.15) [22]. Thoracic sites of administration may be employed for control of upper abdominal or thoracic pain [27]. Onset and duration of epidural morphine analgesia following single-dose administration vary according to the surgical stimulus, dose, and site of administration. Onset is usually appreciated in 30–60 minutes, peak effect at 90–120 minutes, and duration of analgesia ranges from 12 to 24 hours [24,25]. The superiority of epidural morphine analgesia (as determined by descriptive and visual analogue scores) over pain relief offered by parenteral opioids has been demonstrated following a wide variety of post-surgical settings [18,23,25,31,32]. Epidurally administered morphine effectively relieves visceral pain following abdominal or pelvic surgery [18,29,30,31] as well as somatic pain associated with orthopedic procedures [25,26]. Three recent studies noted that the quality and uniformity of post-operative analgesia provided by epidural morphine was significantly better than that offered by IM morphine or patient-controlled analgesia with morphine, while requiring only 1/5 the parenteral dose over the 24-hour study period [23–25] (Table 2).
Following upper abdominal and major orthopedic surgery [26], epidural morphine provided similar pain relief to that observed with 0.5 percent bupivacaine; however, duration of analgesia was more prolonged, and there was a reduced incidence of hypotension. A recent trend is to utilize continuous epidural morphine infusions and combination infusions of low-concentration bupivacaine and morphine for the more severe pain associated with upper abdominal and thoracic surgery. El-Baz et al. [27] evaluated the effectiveness of epidural bolus doses of morphine or bupivacaine and continuous infusion of morphine for post-thoracotomy analgesia. They noted that continuous infusion (0.5 mg/hour) provided excellent analgesia yet avoided the systemic side effects observed with intermittent epidural dosing.

Improvements in post-surgical physiological parameters observed with epidural morphine may be more important than reductions in pain scores. Using improvements in respiratory effort as an index of pain relief, Bromage et al. [28] noted significant benefit in patients receiving epidural morphine \( \text{FEV}_1 = 67 \) percent of baseline versus 45 percent noted with intravenous (IV) morphine. Following gall bladder surgery, epidural morphine provided a more uniform level of analgesia and more effective respiratory effort than that noted with intramuscular opioids or intercostal nerve block [29]. Rawal et al. [30] noted faster return of peak expiratory flow and fewer pulmonary complications in grossly obese patients treated with epidural morphine. Other investigators have demonstrated improved \( \text{PaO}_2 \), reduced incidence of pneumonia, earlier extubation, and decreased ileus in patients treated with epidural morphine [26,30–32]. Two potentially important benefits, of reduced post-surgical hospital stay [18,30,31] and improved post-operative course in high-risk patients [32] with intrathecal and epidural morphine, remain to be confirmed in large-scale, multi-center evaluations.

Improved post-operative analgesia and pulmonary function have been reported with intrathecally administered morphine in patients recovering from orthopedic [18] and upper abdominal surgery [33]. Intrathecal morphine appears to be particularly useful in gall bladder surgery, as doses of 0.2 mg provided up to 24 hours of complete analgesia with minimal risk of precipitating sphincter of Oddi spasm [33]. With the development of 28- and 32-gauge catheters, the future role of continuous intrathecal morphine analgesia looks especially promising. Continuous administration of intrathecal morphine offers the advantage of potent, highly selective analgesia (100-fold reduction in morphine dose requirement over 24 hours) and improved versatility in dosing.

Benefits of prolonged and selective analgesia noted with epidural morphine have nevertheless been tempered by the considerable delay or latency noted in onset and peak activity, inter-patient variability in duration of action, and reports of significant adverse effects, including pruritus, nausea, vomiting, urinary retention, and, most important, respiratory depression. Such morbidity has had a negative effect upon patient and physician satisfaction, possibly delaying overall acceptance of the technique [18].

**Adverse Events Associated with Morphine**

Respiratory depression associated with epidurally administered morphine occurs at two different intervals [18,19]. An early phase observed soon after administration reflects rapid systemic absorption and is of similar magnitude as that noted following
parenteral dosing. A later, more insidious depression occurring between 8–12 hours after administration has been related to rostral flow of CSF and delivery of morphine molecules to the brain stem respiratory centers [18,28]. Risk factors underlying delayed respiratory depression include high doses of morphine (over 5 mg, epidurally), thoracic epidural administration, age over 60, patients with pulmonary disease, and perhaps greatest risk associated with concomitant administration of parenteral opioids (Table 3).

Several large prospective evaluations have reported that mild depression of CO₂ responsiveness is common following epidural administration of morphine (3–5 mg) [18,34]. Even in the absence of the above-mentioned risk factors, the incidence of clinically significant respiratory compromise has been found to range between 0.1 and 0.4 percent [34]. While delayed respiratory depression is usually gradual in onset and reversible with small doses of IV naloxone, it nevertheless requires frequent respiratory checks and increased nursing supervision. The picture becomes further complicated by the fact that respiratory rate is often a poor indicator of ventilatory depression. Increasing somnolence may provide a more reliable warning of respiratory compromise [4] and should be evaluated frequently. Frequent level-of-consciousness checks often interrupt normal sleep, however, and may lead to increased patient anxiety and dissatisfaction.

A high incidence of nausea and vomiting [18,28] noted with epidurally administered morphine is also believed related to rostral CSF flow with transport of molecules to the chemoreceptor trigger zone (area postrema) in the brain stem. Severe pruritus is another common and especially troublesome side effect that further complicates therapy. Following epidural administration of morphine, the incidence of pruritus requiring treatment may approach 70 percent in younger individuals and in patients post-cesarean section, and is often of such severe magnitude that it may compromise benefits of superior analgesia [23,24]. Pruritus observed early after administration may be related to systemic histamine release and responds to H1 antagonists; however, late pruritus involving the face and upper trunk may be related to spinal reprocessing of afferent input whereby interrupted nociceptive impulses are interpreted as itch [18,28]. Late pruritus does not respond to antihistamine but is antagonized by small doses of naloxone [35] (refer to treatment protocol below). A final serious side effect that adds to the morbidity of epidurally administered morphine is urinary retention. This complication occurs most often, but not exclusively, in young males and has been related to relaxation of the bladder detrusor muscle [18]. Its occurrence is particularly disturbing to both patient and surgeon, especially when frequent catheterization is required. Intravenous naloxone and apomorphine may be effective antagonists in selected cases.

### Table 3

| Bupivacaine | Fentanyl | Morphine | Meperidine |
|-------------|----------|----------|------------|
| 0.05–0.1%   | 0.0005–0.001% | 0.005–0.01% | 0.1% |

*Concentrations most commonly employed in post-surgical patients by the Yale University Acute Pain Service.
Factors Predisposing to the Development of Respiratory Depression Following Administration of Epidural Opioids

| Drug-Related Factors: | Hydrophilic opioids |
|-----------------------|---------------------|
|                       | Large dose (mg)     |
|                       | Large volume (ml)   |
|                       | Repeated doses      |
|                       | Concomitant administration of parenteral opioids |
| Patient-Related Factors: | Age greater than 60 years |
|                       | Debilitated individuals |
|                       | Co-existing respiratory disease |
|                       | Intrathecal administration |
|                       | Raised intrathoracic pressure |
|                       | Shock wave lithotripsy |
|                       | Position |

*Summarized from [18,28,41]

Spinal Analgesia: Lipophilic Opioids

The morbidity associated with intrathecal and epidural morphine has reduced the widespread application of "selective" spinal analgesia and has mandated investigation and utilization of other opioids having pharmacology better suited for this application. Two classes of opioids have been considered as attractive alternatives and include the lipophilic phenylpiperidines (fentanyl, sufentanil) and mixed agonist-antagonists (butorphanol, buprenorphine).

The recognition that delayed respiratory depression (and other side effects) was related to the retention and rostral spread of hydrophilic morphine molecules [18,19,28] led investigators to turn their attention toward more lipid-soluble agents that would theoretically leave the aqueous CSF and rapidly bind to lipid-rich spinal tissue. A number of lipophilic opioids have been employed for control of acute post-operative pain and chronic pain syndromes [36-54]. In general, these agents provide a more rapid onset but shorter duration of analgesia than morphine [36,37,40,49]. Unlike local anesthetics, the addition of epinephrine or dextran does not significantly influence the quality or extend the duration of analgesia provided by lipid-soluble opioids [18,40]. The lipophilic opioids are not associated with a high incidence of pruritus or delayed respiratory depression. On the other hand, "early-onset" respiratory depression, usually occurring within 30 minutes of administration, has been observed [37,46,52].

Early-onset respiratory depression is believed to result from significant vascular uptake (at epidural or subarachnoid venous plexi) of lipophilic agents and rapid delivery via the systemic circulation to brain stem respiratory centers [18,19]. Early-onset depression, while measurable, is usually of lesser significance than delayed respiratory compromise observed with morphine and is more likely to occur in high-visibility, controlled settings (operating room, recovery room, intensive care unit) with the anesthesiologist present or immediately available.

Commonly utilized lipophilic agents include the phenylpiperidine derivatives meperidine, fentanyl, and, most recently, sufentanil. The physiochemical properties of meperidine, including its moderately high lipid solubility, mu receptor specificity, and local anesthetic properties, suggested a useful agent for analgesia in this setting.
In an initial evaluation, Glynn et al. [36] reported that the onset of post-surgical analgesia following epidural administration (100 mg) was extremely rapid. Benefits were noted at five minutes, peaked at 30 minutes, and lasted eight hours. Analgesic onset paralleled an equally rapid rise in CSF meperidine levels. In this regard, peak levels noted between 15 and 45 minutes occurred significantly sooner than the 60-120-minute latency in the CSF peak reported with morphine. These investigators noted few side effects and no evidence of delayed respiratory depression, findings that have since been confirmed in larger controlled trials. Early-onset respiratory depression has been reported following epidural administration of meperidine, usually with doses exceeding 75 mg [18,36].

Fentanyl has surpassed meperidine as the lipophilic opioid of choice for epidural analgesia. While not FDA-approved for administration into the epidural space, its high analgesic efficacy and superior safety profile have withstood the test of time, and it is commonly employed for control of post-operative and obstetrical pain [37-40]. Early animal studies indicated that epidurally administered fentanyl had an extremely rapid onset, was equally effective as morphine in blocking responses to pain, and had no neurotoxic effects [15,17]. These properties, together with the fact that fentanyl is marketed in a preservative-free solution, led investigators to evaluate its usefulness in a variety of settings. Naulty and associates [37] reported that epidurally administered fentanyl (50–100 μg) provided excellent post-cesarean section analgesia of rapid onset and three to four hours’ duration. In patients recovering from thoracotomy [38,39], epidural fentanyl provided rapid and effective analgesia and improved both respiratory volume and flow rate. Fentanyl’s reliability, rapid onset, and short duration made it ideally suited for continuous epidural infusion techniques where the level of analgesia can be carefully titrated to the level of pain stimulus and rapidly terminated if problems should occur [18,38-40].

Several clinical reports [37-40] support the impression that epidurally administered fentanyl is a very safe form of therapy and that significant respiratory depression is unusual. While mild depression of CO₂ response curves can be expected within minutes of a fentanyl bolus (50–100 μg) or following prolonged continuous infusion therapy [41], only one case of life-threatening respiratory depression has been reported. Wells and Davies [41] observed CNS depression and bradypnea in an obese male following extra-corporeal shock-wave lithotripsy. It is unclear whether shock waves associated with this procedure may have caused cephalad spread of fentanyl. In the usual clinical setting, it is often difficult to promote rostral spread of fentanyl. Gourlay et al. [42] noted that fentanyl, in contrast to morphine and meperidine, did not migrate to the C7-T1 interspace following lumbar epidural administration. This lack of rostral spread presumably reflects fentanyl’s rapid clearance from epidural and spinal sites of deposition (across capillary endothelium and into the systemic circulation) and helps explain its “segmental” analgesic properties. Since the rate of dural penetration and dermatomal spread of lipophilic agent appears to be directly related to the surface area in contact with the drug [43], fentanyl’s effectiveness in blunting pain associated with upper abdominal and thoracic surgery may be improved when administered in larger volumes of solution [44].

Fentanyl is an extremely versatile epidural analgesic. For this purpose, it may be combined with lower-than-normal doses of epidural morphine to minimize delays in analgesic onset and reduce morphine’s dose-dependent side effects [18]. Epidural
fentanyl has also been combined with subtherapeutic doses of bupivacaine [45] to achieve “supra-additive” analgesia that may effectively blunt pain associated with first and second stage of labor, while having minimal effect on sympathetic tone or motor strength. Modification of this technique may be useful in patients requiring an effective anesthetic block, yet who, because of pulmonary or cardiac disease, cannot tolerate intercostal muscle weakness or the extensive sympathectomy that follows high dermatomal blockade with more concentrated solutions of local anesthetic [39].

Small amounts of intrathecal fentanyl appear to increase the efficacy of spinal anesthesia while providing one to two hours of post-operative analgesia [46]. This technique is also indicated for use in debilitated patients who cannot tolerate high levels of dermatomal blockade or extensive spinal sympathectomy.

The high lipid solubility and potency of fentanyl’s chemical cousin, sufentanil, suggested optimal characteristics for use as an epidural analgesic. In theory, large numbers of sufentanil molecules should easily penetrate the dura and bind to spinal tissues (resulting in rapid onset), while its high affinity for mu receptors would result in a moderately prolonged duration of activity [47]. These characteristics were noted in preliminary animal studies [48] and evaluations in human volunteers [49] where epidural administration of sufentanil resulted in segmental analgesia without evidence of significant rostral spread.

Sufentanil is currently in the final phase of evaluation prior to FDA approval for use as an epidural analgesic. A review of the medical literature has identified 28 studies, involving 900 adults and 15 children, investigating the safety and efficacy of epidural sufentanil as a post-operative analgesic [50]. Sufentanil administered as a single bolus, repeat bolus, and continuous infusion appears well suited for relief of post-surgical pain, pain following cesarean section, and for use as an analgesic during labor and delivery [51–60]. When one summarizes the results of the above studies, it becomes obvious that sufentanil provides extremely rapid and effective analgesia without evidence of delayed respiratory depression; however, dose requirements are surprisingly high, early-onset ventilatory depression can occur, and its duration of action (while dose-dependent) appears to be no greater than that observed with fentanyl.

In a well-designed double-blind study [51], the onset of post-operative analgesia was more rapid with epidurally administered sufentanil (50 μg) than with morphine (5 mg). With sufentanil, pain at rest was alleviated at five minutes, while pain associated with movement was absent after ten minutes. This speed of onset was three to five times faster than that noted in the morphine group. On the other hand, the duration of morphine analgesia was twice as long as that observed with sufentanil.

After cesarean section, patients who received epidural sufentanil doses of 30 to 60 μg experienced effective analgesia that ranged between 3.9 and 5.6 hours’ duration [52] (Table 5). The addition of epinephrine did not significantly prolong the duration of analgesia in this study; however, research by Naulty and co-workers [53] suggests that epinephrine may increase the duration of small epidural doses (25 μg) of sufentanil while having little effect on doses above 50 μg.

Epidural analgesia following abdominal surgery appears to be of relatively short duration, despite administration of sizable doses of sufentanil. Graf et al. [54] noted that doses between 25 and 70 μg resulted in extremely effective analgesia; however, duration of pain relief (in which patients were totally pain-free) ranged between 140
and 224 minutes. These investigators caution against using higher bolus doses to extend duration, as a serious respiratory arrest occurred within seconds of administering 70 μg of sufentanil. Other “immediate” onset respiratory arrests have been reported following administration of large boluses or repeat boluses [55,56]. Immediate respiratory depression may be related to inadvertent puncture of epidural vein with intravascular administration or may simply reflect vascular uptake of sufentanil. In this regard, peak plasma levels of sufentanil are achieved within two minutes and approach 0.31 ng/ml [49]. For this reason, we take similar precautions administering sufentanil as we would any local anesthetic; that is, a test dose of 5 μg is followed by slowly administered incremental doses. Rapid removal of sufentanil from epidural and subarachnoid vessels is also responsible for the surprisingly high dosage required for epidural analgesia and reflects the decreased gain in specificity and potency noted with opioids of increasing lipophilicity [48,57]. If one measures the subcutaneous-to-epidural analgesia potency ratio, one finds a linear relationship with lipid-to-water partition coefficient (i.e., selective gains in spinal analgesic effectiveness are reduced as the agent administered increases in lipid solubility) [48].

Perhaps the most effective method of administering sufentanil is via continuous infusion. This method takes advantage of sufentanil’s rapid onset yet short duration and minimizes respiratory risks associated with large bolus doses. Cheng et al. [58] reported that continuous lumbar infusions of 0.3 μg/kg/hour provided rapid and sustained analgesia with minimal side effects in patients recovering from intra-abdominal surgery. We have noted similar effectiveness with lower doses (0.1–0.2 μg/kg/hour) following administration via thoracic catheters or when larger volumes of dilute solution are infused at lumbar sites [59]. Sufentanil’s rapid onset of analgesia may also be used to advantage when combined with morphine. We have also observed that the epidural combination of sufentanil (30 μg) and morphine (3 mg) provides extremely rapid analgesic onset while significantly reducing 24-hour parenteral opioid requirements in patients recovering from major gynecological surgery [60].

In conclusion, lipophilic opioids offer excellent spinal/epidural analgesia without many of the liabilities observed with morphine. Their favorable attributes include improved titratability (i.e., rapid and predictable analgesic onset) and lack of significant rostral spread. Liabilities include short duration and respiratory compromise associated with large-bolus doses. Lipid-soluble opioids outlined in this review and new agents, possibly alfentanil and lofentanil, will play an increasingly important role in controlling acute post-operative and labor pain [18]. As mentioned above, their safest and most efficacious method of administration will be as a continuous

| TABLE 5 | Onset and Duration of Analgesia with Epidural Morphine and Sufentanil |
|----------------------------------|----------------------------------|
| Morphine Sulfate 5 mg | Sufentanil 30 mcg | Sufentanil 45 mcg | Sufentanil 60 mcg |
| Onset of 50% pain relief (minutes) | 52* | 15 | 15 | 15 |
| Onset of 90% pain relief (minutes) | 90* | 30 | 30 | 15 |
| Duration of analgesia, first dose (hours) | 26* | 3.9 | 4.5 | 5.6 |

*Significant difference
From [52]
TABLE 6
Epidural Opioid Pharmacology/Pharmacokinetics

| Opioid            | Molecular Weight | Lipid<sup>a</sup> Solubility | Epidural Dose | Onset (minutes) | Duration (hours) |
|-------------------|------------------|-------------------------------|---------------|-----------------|-----------------|
| Morphine          | 285              | 1.4                           | 3-5 mg        | 60-90           | 12-24           |
| Dihydro Morphone  | 287              | 8                             | 1-2 mg        | 20              | 8-12            |
| Diacetyl Morphone | 369              | 17                            | 1-3 mg        | 15              | 6               |
| Meperidine        | 247              | 39                            | 50-75 mg      | 10              | 4-8             |
| Methadone         | 309              | 116                           | 50-75 mg      | 15              | 8-10            |
| Buprenorphine     | 468              | 200                           | 300-500 mcg   | 15              | 5-7             |
| Alfentanil        | 452              | 126                           | 200-300 mcg   | 10              | 2               |
| Fentanyl          | 528              | 813                           | 50-100 mcg    | 10              | 2-3             |
| Sufentanil        | 578              | 1,778                         | 40-50 mcg     | 5               | 3-3.5           |

<sup>a</sup>From [18,59]
<sup>b</sup>Octanol: water partition coefficient

infusion, either alone or in combination with smaller doses of epidural morphine or other adjunctive agents.

The mixed agonist-antagonist class of opioids have certain theoretical advantages for spinal application, namely, the presence of spinal kappa receptors (mentioned above), which modulate visceral nociception, and the so-called "ceiling effect" for respiratory depression, which would limit reductions in respiratory drive even if molecules spread rostrally to the brain stem. Butorphanol, which is formulated in a preservative-free solution, has been shown to provide up to 12 hours of effective analgesia in patients recovering from cesarean-section delivery [61]. Other than sedation (which lasted four to six hours), 5 mg of epidurally administered butorphanol was not associated with significant respiratory depression, nausea/vomiting, or pruritus. Table 6 outlines epidural opioid doses commonly employed at our institution.

Adverse Effects Associated with Spinal Opioids

Side effects associated with epidural and intrathecally administered opioids [18,28,62] may be treated effectively and should not be allowed to persist, as patient jeopardy and dissatisfaction will soon outweigh the benefits of selective analgesia. Patients treated with morphine or continuous opioid infusions should have respiratory rates monitored (every hour) by nursing staff and apnea-monitoring devices. Increasing level of sedation is also monitored as a premonitory sign of impending respiratory depression [4]. Patients in high-risk groups are best observed in an intensive care unit setting, with naloxone at the bedside. Continuous oxygen saturation and/or serial arterial blood gases should be followed in all high-risk patients. Respiratory rate less than ten per minute or evidence of diminished tidal volume is treated promptly with naloxone (40–80 µg IV) followed by a naloxone infusion (300–400 µg/liter of crystalloid every eight hours). This dose will quickly reverse respiratory depression yet will maintain spinal analgesia [35]. Table 7 outlines the usefulness of naloxone infusion in patients treated with epidural morphine. Early-onset generalized pruritus observed with morphine responds to diphenhydramine (50–100 mg); however, late-onset truncal/facial itching may only respond to nalox-
one administered as above. Similarly, the early occurrence of nausea is often well controlled with compazine (10 mg) or droperidol (1.25 mg), while delayed nausea [62] (4–12 hours past administration) associated with facial pruritus is best treated with naloxone infusion or transdermal scopolamine patch. Urinary retention [18,62] may respond to urocholine but may also require treatment with naloxone. Recent evidence [18] suggests that small doses of nalbuphine (10 mg every four hours) antagonize opioid side effects with less danger of reversing useful analgesia [35,63]; however, this mixed agonist/antagonist may increase the level of sedation. Side effects appear to be infrequent and of lower magnitude in patients treated with lipophilic opioids.

In summary, spinally administered opioids provide an excellent analgesic alternative to parenteral narcotics or epidural local anesthetics. This application is a new one for an old family of drugs [21], yet these agents appear ideally suited to block pain selectively as it first enters the CNS. Nevertheless, potential advantages of spinal/epidural analgesia must be carefully balanced on a case-by-case basis against the above-mentioned side effects and the greater invasiveness of the technique. We have not considered the endogenous opioid peptides; however, the enkephalin analogues (metkephamid, DADL), serotonin, alpha-2 agonists, and the family of enkephalinase inhibitors may offer even more selective spinal analgesia with minimal systemic side effects [15,16,18]. These agents administered separately or in combination represent the future of spinal/epidural pain suppression.

**PATIENT-CONTROLLED ANALGESIA**

**Background**

Patient-controlled analgesia (PCA) is a relatively new technique that permits patients to treat pain by directly activating doses of intravenous opioids. The patient is allowed to control the rate of drug administration (within prescribed limits), based upon his or her appreciation of the degree of pain, and thereby correct for individual differences in tolerance, variability in pharmacokinetics, or inappropriate “screening” by house staff. PCA with intermittent intravenous doses of opioid analgesics was first described by Sechzer in 1968 [64]. While its main use during its first decade of application was experimental (i.e., the evaluation of equianalgesic dosing in drug trials), PCA has since taken on a greater role in the analgesic management of post-operative and labor pain.

**TABLE 7**

Influence of Naloxone Infusion on Pain Relief and Adverse Effects of Epidural Morphine (4 mg)

|                       | Naloxone Infusion 10 mcg/kg\(\cdot\)hour\(^{-1}\) | Naloxone Infusion 5 mcg/kg\(\cdot\)hour\(^{-1}\) | Saline Infusion |
|-----------------------|--------------------------------------------------|-------------------------------------------------|----------------|
| Duration of analgesia (hour) | 13.7*                                             | 17.8                                             | 18.5           |
| Urinary retention (%)   | 33                                                | 53                                               | 67             |
| Severe pruritus (%)     | 0                                                 | 7                                                | 7              |
| Nausea/vomiting (%)     | 7                                                 | 13                                               | 20             |
| Pulmonary complications (%) | 7                                               | 7                                                | 20             |

*Significant difference

From [35]
It is well recognized that, with appropriate titration of drug, marked variation in opioid requirement may be evident among populations of patients recovering from the same operative procedure; however, PCA allows individuals to maintain adequate analgesia regardless of changes in pharmacokinetic parameters, or changes in pain intensity over time. PCA systems work under a number of assumptions [3,5,65], the first assumption being that opioid side effects occur at higher brain concentrations than those needed to produce analgesia [5,65]. While massive opioid doses could theoretically eliminate all pain (but with unacceptable levels of respiratory depression), an adequate level of analgesia usually represents a compromise between tolerable pain and troublesome side effects. A second assumption is that pain intensity is rarely constant. Post-operative pain is intensified by movement and coughing and seems to have a circadian rhythm, with increasing pain at night [4,6]. A final assumption is that the entire spectrum of pain relief occurs within a narrow range of plasma analgesic concentration subject to individual variation [3,4,65,66].

Presently, several patient-controlled analgesia systems are sold in this country and include devices manufactured by Abbott, Bard, and Pharmacia. These systems all incorporate a microprocessor that allows the patient to interact with an infusion pump connected to his or her established intravenous line. Patients usually activate the pump by pressing a button connected to the apparatus. A pre-programmed amount of opioid is then administered over 10–30 seconds. A lockout interval is simultaneously begun after each injection, thereby preventing a second dose from being delivered within a preset time interval (usually between 5–15 minutes, depending upon dose and agent selected). Potential overdosage is prevented by limiting the amount of opioid delivered per bolus and limiting the number of injections over a given time interval. In addition, increasing patient sedation usually decreases pump activation enough to prevent overdosage.

Several delivery options are available with second-generation PCA systems. The most popular and simple is the bolus dose-on-demand system. This system simply responds to the patient’s activation with a pre-programmed dose and lockout interval. A more sophisticated delivery system incorporates a minimal (basal) constant-rate infusion plus patient-activated bolus doses on demand. This system may be best utilized with rapid-acting, short-duration agents.

By utilizing smaller boluses and more frequent dose intervals than IM PRN dosing, PCA more closely approximates a continuous infusion (Fig. 3). Like continuous infusions (which could be described as having infinitely small doses and inter-
PCA has the advantage of minimizing fluctuations in plasma drug concentration. Unlike continuous infusions, PCA plasma levels do not depend to as great a degree on drug elimination remaining constant [3,4]. Since PCA is precisely titrated by the patient, very stable steady-state plasma levels and optimal analgesic concentration are maintained. This condition is important since, in the case of opioids, analgesia is associated with a narrow range of plasma concentration, above which there is no increase in pain relief and side effects begin to dominate. In this respect, the minimum effective plasma concentration (MEC) of morphine has been calculated to be 20 ng/ml or 2 mg/hour in a 70 kg patient [65,66]. It should be appreciated that MEC is a dynamic definition, influenced by patient tolerance and level of pain intensity. An MEC of 80–90 ng/ml is safely tolerated, and plasma morphine concentrations are severalfold higher than this amount following IM administration. As a rule, patients over 60 years of age require one-third to one-half less PCA opioid than healthy adults aged 20 to 40 years [6].

Finally, when administering opioid analgesics, the optimal plasma concentration must be rapidly achieved, and the natural accumulation time of four half-times must be bypassed with the administration of a “loading” dose. The loading dose is a relatively large bolus of drug (10–15 mg morphine), preferably administered in divided IV doses, which enables plasma concentrations to reach a level where maintenance PCA doses can maintain a steady state [3,4,65,66].

Objectives of PCA

The objectives of PCA have been described as: (1) to achieve effective analgesia as rapidly as possible with the minimum dose of opioid; and (2) to maintain continuously effective analgesia for extended periods, during which the patient should be able to maintain a normal sleep pattern [3,64,65]. As listed below, PCA offers several practical and theoretical advantages over traditional dosing regimes.

1. Superior pain relief with less medication
2. Less sedation during daytime hours
3. Decreased delay between request for analgesic and relief
4. Improved respiratory function
5. Minimized inappropriate screening
6. Accommodation for diurnal changes
7. Accommodation for inter-individual analgesic requirements
8. Ability to titrate analgesic in response to need (i.e., movement)

While there have been few well-controlled studies comparing PCA with traditional IM PRN dosing, the impression from investigators utilizing this modality is that it offers not only superior pain relief, but also reduces total opioid requirements and need for associated medications [23,24]. Patients inevitably find themselves titrating pain against sedation or other opioid side effects. They are usually willing to accept some amount of pain in order to have a clear sensorium. At the same time, they are comforted with the fact that, if they choose to, they can suppress an even greater amount of their pain [3,23,24]. By administering small amounts of opioid intravenously without being dependent upon the house staff, the series of events described in Fig. 1 is eliminated, and the interval between a request for analgesia and relief is markedly reduced.
A superior level of analgesia may contribute toward an improved post-operative course, especially in higher-risk patients. Improved post-operative forced vital capacity and an overall decrease in pulmonary complications have been reported in patients utilizing PCA with morphine following thoracic and upper abdominal surgery [3,6]. Obese patients utilizing PCA following gastric bypass surgery had improved post-operative pulmonary function and required significantly less total medication than weight-matched controls [5,6]. Although mild respiratory depression is commonly reported with PCA (or any form of opioid analgesic therapy, for that matter), only two cases of severe depression have been reported. In both instances, drug overdose was secondary to house staff-nursing error rather than patient misuse or pump malfunction [67].

Variables Influencing PCA

The amount of medication (mg) administered during each PCA bolus dose is important and must be adjusted in relation to patient age, weight, site, and extent of surgery (i.e., there is no “cookbook” dose; each patient must be assessed individually). If the size of the bolus dose is too small, patients will tend to fail PCA, as they often experience incomplete analgesia. If, on the other hand, the dose is too high, patients tend to fail PCA as they experience a high incidence of side effects (nausea, sedation, dysphoria) [68]. When patients associate the appearance of side effects shortly after pressing the PCA button, they tend to reduce self-administration and begin to experience very high pain scores. On our PCA service, nausea and vomiting appear to be the most common (45 percent in gynecological surgical patients, 15 percent in orthopedic surgical patients) and troublesome side effects. In a recent study, we noted that application of transdermal scopolamine (Transderm Scop®) significantly reduced the incidence and severity of nausea in patients recovering from major gynecological surgery [69]. We also observed that the addition of Phenergan® (hydroxyzine) to PCA morphine (12.5 mg Phenergan® added to every 30 mg morphine) reduced the severity of nausea and vomiting, while not increasing the level of sedation following gynecological surgery [70].

While PCA and epidural administration of opioids appear to provide a superior level of analgesia [3,23–25], it was necessary to compare these new methods with traditional IM dosing in patients recovering from the same surgical procedure. In a controlled randomized study reported by Harrison et al. [23], 60 patients recovering from cesarean-section delivery were treated with either epidural morphine (5 mg), PCA morphine (2 mg/eight-minute lockout), or IM morphine (10–15 mg/three hours). In contrast to previously mentioned PCA studies [3,5,7], we were unable to demonstrate significant differences in quality of analgesia or total opioid requirement when patients treated with PCA were compared with the IM group. Patients in the epidural group, while benefiting from a significantly improved level of analgesia during the first 16 post-operative hours, were troubled by a high incidence of pruritus (70 percent, 40 percent requiring treatment). Thus, despite higher pain scores than those observed in the epidural group, patient satisfaction with the level of relief provided by PCA was comparable. Factors responsible for the lack of correlation between pain scores and high patient satisfaction in the PCA group may be related to the uniform level of analgesia, lack of troublesome side effects, and an awareness that reliable analgesia was only a button press away [23].
Despite the high patient satisfaction noted above, it appeared that patients were more pleased with the independence and control PCA afforded than with the analgesic agent administered. While morphine remains the PCA drug of choice in the United States, it is probably not the ideal opioid analgesic to be used in this setting [71,72]. An agent having faster onset, less sedation, and fewer adverse effects might further increase patient satisfaction and increase analgesia to levels comparable to that seen with epidural morphine. Oxymorphone, hydromorphone, and meperidine are semisynthetic opioid agonists that have many attributes considered useful in the setting of PCA, including high analgesic efficacy, rapid onset of effect, a lower level of sedation, and minimal histamine release at clinically useful doses. Two recent studies [71,72] have documented the effectiveness of oxymorphone and meperidine for use in PCA. Oxymorphone provided effective analgesia when administered by patients recovering from cesarean delivery [71]. In this prospective evaluation, self-administered incremental doses (4 µg/kg every eight minutes) were given as required over the next 24 hours. During this interval, mean oxymorphone dose requirements were 16 mg per patient or ½ the average morphine dose required in this patient population. Although the majority of patients reported mild pain, even those occasionally reporting moderate pain (viselinear pain scores of 4–6 on a scale of 10 = worst pain) expressed complete satisfaction with their level of analgesia and lack of side effects.

In a follow-up double-blinded randomized evaluation [72], patients recovering from cesarean delivery received an analgesic base of either morphine (6 mg), meperidine (60 mg), or oxymorphone (1 mg), and were then allowed to self-administer incremental opioid doses as required over the next 24 hours. Incremental doses were morphine (1.8 mg), meperidine (18 mg), or oxymorphone (0.3 mg) with a lockout interval of eight minutes between administrations. While all three treatment groups reported excellent analgesia, those receiving oxymorphone and meperidine tended to report lower pain scores at rest, less sedation, and higher patient satisfaction than patients treated with morphine. Analgesia appeared to be more rapid in onset and more uniform in patients self-administering oxymorphone. An important finding was that the oxymorphone group had significantly less pain with movement. This useful quality suggested superior drug efficacy in patients who were attempting to ambulate or to hold and nurse their newborns. Also important was the fact that patients treated with meperidine had minimal sedation and the lowest incidence of side effects. In summary, both oxymorphone and meperidine in doses listed above may be more preferable PCA agents than morphine in the post-cesarean-section delivery patient. These findings will be re-examined in patients recovering from general surgery or suffering from the pain associated with malignancy.

One disadvantage of meperidine in the obstetrical setting is the fact that its metabolite, normeperidine, tends to concentrate in breast milk. In a recent evaluation of nursing mothers [73], we noted slightly depressed neonatal Brazelton scores in infants whose mothers were utilizing PCA meperidine for post-cesarean delivery analgesia. In contrast, scores in infants exposed to morphine (PCA) were normal. Normeperidine levels in breast milk remained elevated during a five-day sampling period, while concentrations of morphine and its major metabolite, morphine-6-glucuronide, were low. For this reason, we avoid meperidine in parturients attempting to breast feed following cesarean delivery.

In a final study [74], oxymorphone and morphine were administered in a continu-
ous (basal) infusion plus superimposed PCA infusion mode in patients recovering from cesarean delivery. Using a second-generation PCA pump (Abbott Lifecare II) capable of providing this dual form of narcotic administration, we noted significantly improved pain scores associated with movement and ambulation. Unfortunately, the incidence of side effects (nausea/vomiting) was increased. We are about to repeat this study with the addition of Transderm Scop® or placebo patches to determine whether we can maintain this excellent level of pain relief while minimizing nausea and vomiting.

Work directed at improving PCA therapy continues, and investigators are beginning to document earlier patient ambulation, decreased overall morbidity (reduced thrombophlebitis and pneumonia, improved wound healing, reduced opioids and adjunctive medication requirement), and possibly earlier hospital discharge [3,75]. These findings are of critical importance to hospital administrators and third-party insurance carriers, as they evaluate the overall cost-effectiveness of newer analgesic techniques.

INTERPLEURAL CATHETERS

Since the description of interpleural analgesia by Reiestad and Stromskag [76], a number of investigators have modified and improved the safety and efficacy of the technique for management of post-operative pain following cholecystectomy, thoracic surgery, and breast reconstruction surgery [76–78]. Kambam et al. [77] demonstrated the efficacy of the technique in managing post-operative pain in patients recovering from lateral and posterior thoracotomies.

Interpleural injection of local anesthetic is able to block indirectly intercostal nerves, splanchnic nerves, and blunt directly irritation of the parietal pleura [76–78]. In our experience, the technique effectively blunts both visceral and abdominal wall pain but may have to be supplemented with low doses of parenteral opioid or anxiolytic agents in order to achieve best results. Interpleural catheter placement is frequently associated with clinically insignificant side effects such as small hematoma, non-leaking lung puncture, or small pneumothoraces. The risk for serious complications such as tension pneumothorax is low but exists irrespective of technique, needle, or syringe used [79].

A 19-gauge open-tip epidural catheter is inserted at the anterior axillary line via a 17-gauge Touhy epidural needle [76–79]. A distinct click is noted following penetration of the parietal pleura and is associated with a loss of resistance noted in a saline-filled syringe. The catheter is carefully inserted 3–5 cm (toward the shoulder) and taped in place; 2 ml increments of bupivacaine 0.5 percent are injected every two to three minutes until a total of 15–20 ml has been administered. Pain relief is noted within five to ten minutes following administration. At this time, the epidural catheter may be connected to an infusion pump set to deliver bupivacaine 0.25 percent at a rate of 8–10 ml/hour⁻¹ [80,81].

A number of studies [78,80,81] indicate that the technique provides maximum analgesic benefit when local anesthetic is continuously infused, rather than by intermittent boluses administered in response to patient complaint of pain. The interval between intermittent doses varies but can be as frequent as every four hours (this rate obviously becomes very labor-intensive and is associated with risk of high plasma bupivacaine concentrations immediately following re-bolus). Laurito et al. [81] recently compared the efficacy and safety of continuous infusion versus bolus
injections in providing post-operative analgesia following cholecystectomy and noted a more uniform level of pain relief and reduction in PCA (morphine) requirements in the continuous infusion group. Continuous interpleural analgesic technique has also provided effective analgesia in pediatric patients recovering from thoracotomy [82].

Patients receiving interpleural analgesia often benefit from superior intraoperative and post-operative cardiovascular stability. While such stability was initially attributed to superior analgesia, recent studies [77–79] suggest direct blockade of the sympathetic chain and splanchnic outflow, causing a sympathetic denervation. Such modification of endocrine and stress responses needs to be studied in greater detail.

Finally, interpleural analgesia may provide effective therapy in non-surgical patients suffering from upper abdominal visceral pain. Durrani et al. [83] recently noted that long-lasting relief of upper abdominal pain secondary to pancreatic cancer was achieved by injections of 8 ml 0.5 percent bupivacaine. They suggest that the technique may also be useful in patients suffering from pancreatitis.

CONCLUSION

The preceding pages have commented on deficiencies associated with traditional analgesic regimens, described new and highly effective methods of controlling pain, and provided rationale for their use in the post-surgical period. Spinally administered opioids provide the most significant gain in analgesic potency (as compared with traditional IM dosing); however, the technique is labor-intensive and associated with a higher risk of adverse events. Nevertheless, the higher intensity of pain relief noted with continuous epidural opioid infusions is capable of providing “pain prevention” or lack of pain perception. Pain prevention is an important goal in high-risk and debilitated individuals, as it is associated with greater cardiovascular stability and improved pulmonary function in the immediate post-surgical period [32].

Although the intensity of pain relief provided by PCA is of lower magnitude than that observed with spinal opioids, the incidence of adverse effects is also lower; moreover, the uniformity of relief and patient satisfaction with therapy is superior to that provided by traditional therapy.

Optimal delivery of spinal opioids, PCA, and interpleural analgesic therapy is best provided by a dedicated Acute Pain Service. The role of the service includes: (1) 24-hour availability of trained personnel who can assess and treat adverse events; (2) availability of personnel who could, if necessary, modify analgesic therapy, thereby maximizing overall effectiveness; (3) provision of quality assurance and continual improvement in therapy. Pain services in academic settings are also obliged to provide education and training of future clinicians skilled in pain management and to initiate research protocols. Such investigations have not only optimized analgesic delivery but have developed effective treatment protocols to reduce adverse effects.

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