Update on Acute Pain Management

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A growing number of the 75 million surgical procedures performed annually in the United States will require the use of pain management strategies postoperatively. As Apfelbaum et al. (1) pointed out in their survey, many more surgical procedures are now performed in an outpatient setting. The undertreatment of postoperative pain results in a significant, negative impact on patient satisfaction, clinical and functional outcomes, and quality of life. The potential for these effects can only be greater when the patients are physically removed from the traditional hospital environment. Indeed, their survey showed that 80% of patients said they had moderate to severe pain, yet we have a potent arsenal of modalities that can effectively minimize a patient's postoperative or post-trauma pain. Doing so prevents unnecessary patient discomfort, lengthy hospital stays, undue medical expenses, poor clinical outcomes, and extensive utilization of already overburdened healthcare resources (1–4). Aubrun (5) has raised these same issues in relationship to postoperative pain control in the elderly. The population is constantly gaining a higher percentage of elderly people, and this group has a fourfold higher incidence of surgery than younger people. Reasons listed for inadequate pain management in the elderly include the impression that their pain threshold is higher; the assessment for pain is difficult and the results may be unreliable; the perception that they need lower doses of drugs, especially because the risk of adverse drug interactions is high given their use of a significant number of medications for concurrent medical conditions; and, the ever-present concern of inducing addiction to opioid drugs.

The clinical practice guidelines promulgated by the Agency for Health Care Policy and Research (AHCPR) from 1992 encouraged clinicians to focus on providing effective, aggressive acute postoperative pain management *and* proposed a systematic approach to doing so (6). The ASA promulgated and has revised practice guidelines for acute pain management because this aspect of our contemporary practice is essential (7). So significant are the benefits from treating pain effectively that the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) commanded that all institutions develop pain management programs as a criterion for regaining certification (8). The proposed guidelines identify the responsibilities of *both* the institution and the clinical staff, as well as delineate the patient's rights. The JCAHO standards change the emphasis to patient satisfaction as the crucial element that drives the clinical activity of healthcare professionals. The documentation of the *pre*operative assessment of the patient (9), the presentation of options, the declaration of the patient's preferences for pain management techniques as well as the teaching provided, and a definitive *post*operative evaluation protocol become paramount in establishing hospital policy and clinical care. Into this milieu, we must blend our skills as a practicing pharmacologist, capable provider of regional anesthesia/analgesia, and compassionate physician.

Pathophysiology of Postoperative Pain

Peripheral Events

Surgery represents a form of premediated injury to the body. We understand that surgical and traumatic injury provoke changes in the peripheral *and* the central nervous system that must be dealt with therapeutically to define effective care and to positively influence outcome (3,4,10–16). Many patients believe that there will be no escape from the pain that follows their surgery and for some this attitude actually becomes a coping strategy. What the patient believes and understands about "the pain" are crucial factors that influence his/her reaction to all of the therapy provided and this emphasizes how important are educating the patient about the impending care and involving them in clinical care decisions.

The physical processes of incision, traction, and cutting of tissues stimulate free nerve endings and specific nociceptors (10,12,14–16). The threshold for activation and the activity of these receptors are modified (lowered) by the *local* release of inflammatory mediators and sympathetic amines. Substances such as bradykinin, serotonin, and histamine *both* sensitize and

stimulate the receptors whereas arachidonic acid derivatives only sensitize them. Interleukins (IL), notably IL-6, are proinflammatory cytokines that are released in correlation with the magnitude of the tissue injury, as is IL-1RA (as a marker for IL-1B) (17). It may be through substances such as these and others such as tumor necrosis factor (TNF)-α that the sympathetic nervous system becomes involved in the acute phase response. **Problem #1** in postoperative pain is this *peripheral sensitization* that is characterized by the decreased activation threshold of receptors, a shortened response latency to the point that there can be spontaneous pain (pain without an obvious stimulus), and an exaggerated response within the peripheral nervous system to a given stimulus (i.e., the patient stays in pain long after the surgeon has examined the healing incision). Clinically, the patient manifests primary hyperalgesia, meaning that even gentle stroking of the *incisional area* causes exquisite pain. Secondary hyperalgesia results when the elaborated chemicals and vascular response sensitize adjacent receptors such that pain "spreads," i.e., the patient's skin is painful and sensitive to even light touch *away from the incision*. Primary and secondary hyperalgesia involve both peripheral and central nervous system changes. The chemical events at the site of injury gain expression as an electrical signal through a process called transduction. What follows is transmission to the central nervous system (CNS).

Transmission to the CNS

Ordinarily, A-δ and c-polymodal fibers transmit nociceptive information from the periphery to the CNS (3,4,12,14). The input from A-δ fibers is associated with sharp, localized pain that is rapidly conveyed (as a result of these fibers being myelinated), whereas that related to the c-polymodal fibers is aching, throbbing, diffuse, and more slowly transmitted (as a result of these fibers being unmyelinated). A-δ and c-fibers make up about 70%–90% of a peripheral nerve. What percentage function under normal circumstances and what percentage act as "reserve cabling" (so called "silent" primary afferent fibers) is not known**. Problem #2** relates to the reality that A-α and A-β fibers can be *induced* to carry *nociceptive input* to the CNS when peripheral sensitization occurs. This input does *not* undergo the usual inhibition in the dorsal horn, as does A-δ or c-polymodal fiber input, because A-α and A-β fibers do *not* terminate in the same levels of the dorsal horn, i.e., the substantia gelatinosa, as do the A-δ and c-polymodal fibers. An ancillary problem that is a consequence of problem #1 and problem #2 is that there is a *constant bombardment* of the CNS with noxious input; this overwhelms the CNS's innate capability to filter/ameliorate painful input and fuels ongoing neuroplasticity in the CNS response (18). Neuroplasticity can be thought of as a process by which tissue injury increases the responsiveness of the sensory system so that subsequent stimuli produce a greater effect.

Central Nervous System Events

Problem #3 occurs when the noxious input begins to be processed by the central nervous system (13,18). Spinal reflexes (which require no integration of input within the CNS) such as muscle spasm and sympathetic stimulation are provoked. Supraspinal reflexes that involve the integration of nociceptive input from a few spinal segments incite the mediators of the stress response. The *surgical stress response* (SSR) peaks in the postoperative period and has major effects on the cardiac, coagulation, and immune systems of the body (10,11). Regional anesthesia and analgesia do *not* inhibit the *local* (traumatized tissue) release of stress mediators into the bloodstream. Brodner et al. (19) have highlighted that blocking the *systemic* SSR results in faster recovery and decreased cost. They studied patients undergoing abdominothoracic esophagectomy surgery. Group 1 was a retrospective cohort of patients who had an epidural placed at T_{6-9} preoperatively, followed by general anesthesia. An epidural infusion of bupivacaine and sufentanil *not titrated* to analgesia was provided postoperatively for 5 days. Group II patients had a preinduction level of analgesia established at T4 with an epidural bupivacaine/sufentanil mixture and an intraoperative infusion via the epidural was maintained. Postoperatively, Group II patients had the epidural infusion rate varied to achieve effective analgesia. Patients in Group II demonstrated superior pain relief, faster extubation, earlier mobilization, earlier achievement of ICU and step-down unit discharge criteria, and less metabolic disturbance. The authors concluded that this multimodal approach to pain management that substantially blocked the ramifications of the SSR improved patient outcome and decreased the cost of care. This *multimodal therapy concept* has been touted as being essential to gaining the potential benefits of regional anesthesia/analgesia (1,3,4,7,10,15,19). Brodner et al. (20) have recently reported similar benefits of multimodal therapy in patients who underwent radical cystectomy.

To be fair, there is some literature that proposes a more muted view. Peyton et al. (21) did further analysis of the MASTER Anesthesia Trial database to elaborate on the possibility that epidural analgesia did not manifest the published benefits in all groups of postoperative patients. In performing subgroup analyses of specific groups of patients, these authors were unable to uncover evidence that perioperative epidural analgesia significantly influenced cardiac or pulmonary morbidity or mortality in patients who had undergone major abdominal surgery. Commenting on

Table 1. Pathophysiologic Consequences of Pain

Cardiovascular	Tachycardia, hypertension, increased SVR, increased cardiac work
Pulmonary	Hypoxia, hypercarbia, atelectasis; decreased cough, VC, FRC; V/Q mismatch
Gastrointestinal	Nausea, vomiting, ileus, NPO
Renal	Oliguria, urinary retention
Extremities	Skeletal muscle pain, limited mobility, thromboembolism
Endocrine	Vagal inhibition; increased adrenergic activity, increased metabolism, oxygen consumption
CNS	Anxiety, fear, sedation, fatigue
Immunologic	Impairment

this particular study, de Leon-Casasola critiqued their findings that seem to severely contradict the conventional wisdom (22). He highlighted aspects of their protocol design and statistical analyses of data, plus the changing emphasis on what outcomes are regarded as significant as explanations for the apparent discrepancies.

The summation of the adverse effects described so far generates the *pathophysiological consequences* of acute pain listed in Table 1 (**Problem #4**). As each of these consequences can detrimentally influence postoperative morbidity and mortality, Table 1 is also a compelling listing of reasons why postoperative pain *must be* treated effectively (4,7,10,23). Every body system can be negatively affected by inadequately treated pain, and there is the potential for multisystem failure as more individual systems are overstressed. Contemporary literature provides insight into the physiologic impact of epidural analgesia used to clinical advantage. The most painful incisions include those on the chest wall, the upper abdomen, the back, the major joints, and the anorectal area. All are regions of the body we can "block" with regional anesthesia/analgesia. Given the contemporary attention to evidence-based medicine, Todd and Brown (24) add real-world awareness to this discussion in raising the timely question: how can we most firmly establish the true advantages of the incredible regional anesthesia/analgesia techniques we have at hand? This discussion is further illuminated by Wu and Fleischer (25), who encourage ongoing research into a broader scope of outcomes than is usually sought.

The original benefit of epidural anesthesia was documented in patients undergoing hip replacement (26) and lower extremity vascular surgery (27,28). Presumably because of the increased blood flow from the technique (and perhaps the effect of local anesthetics on the rheology of the blood), lower rates of deep venous thrombosis were manifested. Beattie et al. (29) have demonstrated the benefits of effective pain management with epidural analgesia in patients with a history of cardiac disease, and Loick et al. (30) have presented the positive impact of thoracic epidural anesthesia on lessening myocardial ischemia. Von Dossow et al. (31) have provided commentary on the benefits of thoracic epidural anesthesia combined with general anesthesia in patients with cardiopulmonary disease undergoing thoracic surgery. Ballantyne et al. (32) performed a telling meta-analysis on seven postoperative analgesic therapies as to their impact on pulmonary outcome. Epidural analgesia had a significant effect on decreasing pulmonary morbidity. Groudine et al. (33) showed that IV lidocaine was effective in speeding the return of bowel function and shortening a patient's hospital stay, but, at that time, one could not directly correlate the blood levels of local anesthetic from this study with those encountered during continuous epidural infusions. Hahnenkamp et al. (11) provide a different view in stating that the levels of local anesthetic in the systemic circulation associated with epidural analgesia can have positive effects on coagulation, inflammation, and the microcirculation, all of which have beneficial consequences and therapeutic potential. Steinbrook (34) provides a thorough review of the positive consequences that epidural analgesic techniques have on recovery of gastrointestinal function.

The Augmented CNS Response

As if the above enumeration of problems alone is not impressive enough, the noxious input from acute injury also triggers a state of sensitization of the CNS response, called *wind-up* (**Problem #5**) (3,10,12,14,16). The neurotransmitter release at the dorsal horn that is precipitated by *repetitive* nociceptive input conditions the central nervous system such that there is enhanced responsiveness, i.e., A-α and A-β input is "painful" and secondary hyperalgesia occurs as a result of an expansion of receptive fields in the area of the primary incision. Experimental evidence shows that the duration of "wind-up" of the CNS response long outlasts that of the provocative stimulus, although the exact correlation is still a matter of debate (35–37). The process of wind-up is *not* prevented by general anesthesia but is modified by opioid administration in experimental animal paradigms (38). The primary excitatory neurotransmitters in the spinal cord are glutamate and aspartate. The intensity and/or the constancy of the noxious input provokes NMDA receptor activation among other receptors (AMPA, ACPD). Knowing this about the neuropharmacology of the spinal cord led to research aimed at modifying or blocking NMDA receptors to effect pain control *and* to the concept of

preemptive analgesia. Our understanding of the major role that NMDA receptors have in the induction and maintenance of central sensitization as well as the mediation of peripheral receptor sensitization and visceral pain continues to evolve (39).

Most research efforts have devoted attention to the blockade of NMDA receptors with ketamine. A nice review of the evolution of the change in our use of this drug is provided by Kohrs and Durieux (40), and contemporary reviews have been provided by Subramanian et al. (41), Himmelseher et al. (42), and Elia and Tramer (43). It is fair to say that the exact role for ketamine in the perioperative period remains to be clarified. Elia and Tramer (43) reviewed 53 clinical trials from 25 countries that included 2839 patients. The distillation of these data to firm, practical guidelines proved difficult secondary to the variation in doses of ketamine used, the timing relevant to the surgical stimulation, and the different technologies for drug administration.

More recent research has pursued the use of dextromethorphan, another NMDA receptor blocker, for its preemptive effect, with mixed results reported thus far: Kawamata et al. (44) and Weinbroum et al. (45). found positive results; Grace et al. (46) found negative results). Given the redundancy in the neurotransmitter-receptor systems in the CNS, it is of little surprise that blocking one component of the system in a variety of clinical situations does not result in uniform effects. Liu et al. (47) and Hollmann et al. (48) have provided data concerning the modulation of NMDA receptor function by ketamine and magnesium and the potential augmentation of the effect by volatile anesthetic agents. Thus, the use of up to 2 g of magnesium IV and up to 0.5 mg/kg ketamine IV every 4–6 h of operating time appears to be a beneficial adjunct therapy to anesthesia in terms of modifying the CNS response to operative pain.

Preemptive Analgesia

The entire concept of *preemptive analgesia* fostered by the above realities is predicated on "treating" the pain before it is provoked by anticipating the mechanism of its causation and preventing the peripheral and central sensitization with carefully chosen therapy (49–51). Though the concept of preemptive analgesia is very appealing and electrophysiologic and whole animal studies support the use of pre-emptive techniques to prevent peripheral and central sensitization, clinical benefit in humans has been only variably achieved thus far. Aida (52) updates the discussion by pointing out that three critical criteria must be met to approach preemptive analgesia: all nociception must be blocked, the treatment must be extensive enough to cover the surgical field, and the therapy must be prolonged enough to last through the surgery and the postoperative period. Numerous studies have proposed preemptive effects of epidural analgesia (49,50,53,54). Gottschalk et al. (55) continued the notion of preemptive analgesia in their study of patients who had undergone radical prostatectomy surgery. Patients who received epidural fentanyl or bupivacaine before the surgical incision had less pain while hospitalized postoperatively *and* at follow-up 9.5 wk later and were (understandably) more active sooner than patients in the other study group. Debate continues over the reality of preemptive treatment and the direction in which research and conceptual development needs to go to gain more advocates (56–58). Gottschalk (59) provides a contemporary commentary that advocates a broader and longer application of preemptive therapies because their effectiveness will more likely be manifested when the intensity and the duration of the noxious stimuli are recognized and more thoroughly dealt with.

The sophisticated goal of preemptive analgesia is to achieve a differential effect on physiologic and clinical pain (10,49). The former is characterized by high-threshold criteria, being well-localized, having a stimulus-response relationship, and serving to warn the organism of harm. Clinical pain (which is induced following acute [inflammatory] injury and chronic [neuropathic] injury) is characterized by low-threshold criteria because of the subsequent sensitization that follows injury such that allodynia, hyperesthesia, and hyperpathia are present. If we avoid total analgesia and can block only the clinical pain, the physiologic system will remain functional to herald the onset of any painful postsurgical complications. This is an admirable goal of our therapeutic interventions but not one that we can always realize. Suffice it to say, a key point to acknowledge is that the induced sensitivity in the nervous system outlasts the stimulus (**Problem #6**). Put another way, conceptually, the nervous system does not "heal as fast as the incision does!"

Applying What We Know to Postoperative Pain Management

Treatment at the Site of Injury

Given that numerous chemicals are elaborated at the site of tissue injury, it would make sense to use specific antidotes/antagonists to modify postoperative pain caused by these various agents. The main goal would be to prevent the sensitization and/or stimulation of peripheral receptors (10–16). One cannot help but wonder if the old-fashioned idea of giving antihistamines to "boost" the analgesia of concurrently

administered opioids worked in some patients because of a peripheral antihistamine effect. Nonsteroidal antiinflammatory drugs (NSAIDs) are also drugs that should alter peripheral responses, but there is weak evidence that this occurs in a preemptive way. Actually, the central (i.e., spinal) effects of the NSAIDs may be more clinically significant than the peripheral antiinflammatory effects (60–62). Zhu et al. (63) have provided an evolution of the concept of the significant action of cyclooxygenase-1 (COX-1) in the spinal cord. In an animal model, they showed that COX-1 plays an important role in spinal cord pain processing and the related sensitization of the CNS. They predict that the intrathecal use of specific COX-1 inhibitors may become a treatment of the future. In the ongoing search for other, non-opioid analgesic adjuncts, the NSAIDs have long been utilized, yet the traditional drugs have nonspecific effects on the COX enzymes and subsequent side effects relevant to renal function, stomach acid protection, and platelet function. As with the use of other adjunctive drugs such as ketamine, the use of specific isomers has enhanced analgesic effects with fewer drug-related side effects. This has been shown by Bonabello et al. (64) for the S(+) isomer of ibuprofen, and an evolving application of this concept is predicted by White (65). This line of research would seem to be important because Kehlet (66) summarizes a recent article by Marret et al. (67) by noting that although the use of NSAIDs and selective COX-2 inhibitors (as well as acetaminophen, ketamine, gabapentin/pregabalin and regional anesthesia techniques) results in a 20%–50% opioid-sparing effect, there is not a concordant decrease in opioid-related side effects. Marret et al. (67) performed a meta-analysis of 22 randomized controlled trials to assess the risk of morphine side effects in patients also treated with NSAIDs. They reported a decrease in PONV and sedation but no influence on the incidence of urinary retention, pruritus, or respiratory depression.

The clinical use of selective COX-2 inhibitors is another step in the provision of medicinal therapy, aimed at a specific pathological cause for pain, with an eye towards reducing the drug-related side effects. Thus, there may be a specific role for the COX-2 inhibitors, as they might express a preemptive effect as well as the expected analgesic effects postoperatively (62,68). Gajraj (69) has presented a contemporary review of the COX-2 inhibitors and their vital role in analgesia plus the potential positive health benefits in other disease processes, whereas White (70) queries whether the projected benefits of these drugs will be realized.

Wound infiltration with local anesthetics has obvious merit (71,72). However, the antiinflammatory effect of local anesthetics in this application may be more prominent than neural blockade in some cases (73). Having said that, once wind-up is established, the application of local anesthetic *at the wound* would *not* be expected to be so immediately effective. Wound lavage is a variation on the local anesthetic infiltration theme that may be useful, and there are now commercial systems to facilitate this therapy (74). To present a balanced view, there may be reasons for *not* infiltrating all wounds with local anesthetics, as Brower and Johnson (75) have collected data that document the interference of local anesthetics on the first and second stages of wound healing. The potentially negative impact of this on the subsequent third and fourth stages of healing and wound strength and any relationship to incisional hernias is not known, but certainly requires further investigation.

Peripheral and Neuraxial Blocks

The neural blockade achieved with peripheral nerve blocks diminishes or eliminates the bombardment of the CNS with nociceptive input, which minimizes the stress response, adverse spinal reflexes, and wind-up (3–9,19,24,30,66,71). Many applications of this concept are already in practice, such as ilioinguinal/iliohypogastric blocks in hernia patients (76), penile nerve blocks in circumcision patients, peripheral nerve blocks in knee surgery patients (77–82), and interscalene and continuous brachial plexus blocks in patients having upper extremity surgery (83,84). The study of Capdevila et al. (79) is intriguing because it demonstrates emphatically that the use of a regional anesthetic technique for a short period of time postoperatively resulted in long-term benefit, as manifested by the faster achievement of rehabilitation goals in patients after total knee arthroplasty. Peripheral nerve block applications are so effective in some cases that patients can avoid hospital admission postoperatively. This must result in a significant saving of healthcare costs—which is worth emphasizing to third-party payors, administrators, and legislators whenever possible (3,4,24,25,78,79)! The evolution of acquired skill among clinicians and the availability of technology have led to a growing practice of sending patients home with peripheral nerve infusions (85).

One of the most fantastic discoveries in medical science in recent decades has been that of the opioid receptors (10,13,14). The realization that the primary site of opioid action is in the substantia gelatinosa of the dorsal horn of the spinal cord led quickly to the clinical application of subarachnoid and then epidural opioids for pain management (13,86). This is still not common knowledge shared by practitioners outside of anesthesiology, so repeatedly sharing the message is vital to fostering the understanding of use of these classic drugs. Opioids work presynaptically to decrease neurotransmitter release and postsynaptically to hyperpolarize dorsal horn neurons. Once central sensitization is established, doses that exceed those capable of preventing wind-up are needed.

Table 2. Epidural Local Anesthetics and/or Opioids

The most common LA is bupivacaine	(0.0625%, 0.125%, 0.1%)
Ropivacaine is an alternative	(0.1%, 0.2%)
The most common opioids are:	1) morphine-bolus 1–3 mg and infusion 25–50 μg/mL at 5–15 mL/h 2 fentanyl-bolus 25–100 μg and infusion 1–10 μg/mL at 5–15 mL/h 3) dilaudid-bolus 0.1–0.3 mg and infusion 3–12 μg/mL at 5–15 mL/h
Advantages of the combination = synergistic effect, lower opioid doses, and fewer overall side effects	
Disadvantages of the combination = infusion required, risk of local anesthetic toxicity, risk of catheter migration, risk of sympathetic block and orthostatic hypotension, potential problems with ambulation, risk of opioid-related side effects	

LA = local anesthetic.

There are many routes of administration for the opioids. When IV opioids are used, they are now commonly provided using patient-controlled analgesia (PCA) technology (3–7,87). Essentials in the successful use of this modality include loading the patient to comfort with IV dosing before initiating the PCA action, assuring the patient wants control of the treatment, using appropriate PCA dose and lockout settings, and considering using a basal rate. Slappendel et al. (88) showed that patients having more intense pain preoperatively used more PCA morphine in the first 24 h after surgery. The conventional use of ordinary doses (2 tablets up to four times a day) of moderate strength analgesics, i.e., oxycodone and hydrocodone, may be equivalent to as much as 1 mg/h morphine given IV. Thus, patients using such drugs before a definitive operative procedure will require this maintenance dose *plus* dosing to treat the "new" postoperative pain. Stacy et al. (89) demonstrated that the focused guidance of PCA dosing by an acute pain service (APS), as compared with surgeon-directed PCA, resulted in more effective pain control with fewer side effects, even though more opioids were used. Gagliese et al. (90) have recently shown that age is not an impediment to patients using PCA effectively. Javery et al. (91) have advanced the utility of PCA by showing that adding 1 mg/mL ketamine to morphine PCA enhances the analgesic effect and lessens opioid side effects. Further clinical studies with a positive analgesic result, as well as a notable incidence of ketamine-related side effects, have been presented by Burstal et al. and Reeves et al. (92,93). One of the most effective advances in PCA technology may prove to be the development of the patient-controlled transdermal fentanyl delivery system (94). This device does not deliver a basal rate as does the classic fentanyl patch system. Rather, when the patient presses the activation mechanism, a metered dose of fentanyl is delivered, assisted by iontophoretic technology. This therapy has been found to be as effective as PCA morphine.

The clinical use of opioids in either the intrathecal or the epidural space has brought unquantifiable comfort to many patients (3–6,19–34,54,55,95,96). There are innumerable protocols that detail the continuous infusion of local anesthetics, opioids, and the combination thereof into patients with acute pain (3–7,13). It is now clearly understood that each drug type and route of administration has its own risks and benefits. Patients being given perispinal opioids will not be immune to side effects (pruritus, nausea, vomiting, urinary retention, and respiratory depression) related to the use of these drugs by any route (95). Patients receiving perispinal opioids alone should be able to ambulate. Epidural administration is still the most common technique (96). The broader use of subarachnoid opioids, as given in a CSE technique in obstetric anesthesia or given concurrently with a subarachnoid anesthetic, is now being manifested as clinical reports validate this practice (97,98). Perispinal local anesthetics may cause sympathectomy, sensory and/or motor changes, or urinary retention (3–6,10). Excellent analgesia can often be provided with concentrations that minimize these physiological consequences. It is exceedingly common to use low concentrations of both classes of drugs (opioids and local anesthetics) to achieve maximal analgesia with few side effects (Table 2) (1–7,13–15,19–32,54,55,96,99). Niemi and Breivik (100) have advocated the concurrent use of epinephrine in epidural infusions both to augment analgesia and to decrease the adverse consequences of thoracic epidural analgesia. Bernards et al. (101,102) provide significant data not only about the discrepancy among epidural, CSF, and plasma concentrations of various opioids given by the epidural route but also the variety of effects of adding epinephrine.

Stevens et al. (103) highlighted the progress made in the second decade of acute pain management using epidural opioid analgesia. It is now well-recognized that the lipid solubility of the chosen opioid impacts the incidence of opioid-related side effects and the onset and duration characteristics (101,103). They point out that morphine and hydromorphone exhibit definitive spinal analgesic action as compared with lipid-soluble opioids such as fentanyl and sufentanil, that the use of lower doses of epidural opioids alone and combinations of dilute opioids and local anesthetics make the therapy safe enough to be used in other than an ICU environment, and that improved patient outcome is the worthy goal of such therapy. A recent study by Basse et al. (104) has documented such clinical effectiveness of epidural

analgesia in patients who underwent major colon surgery that discharge from the hospital was possible in 48 h provided a fast-track protocol was followed. Clinically, this means establishing an effective epidural preinduction, using an analgesic infusion throughout the operation, giving ketorolac and ondansetron intraoperatively, infiltrating the incision with local anesthetic, not using a nasogastric tube, requiring out-of-bed if not ambulation time the evening of surgery, permitting per os intake of (at least) liquids the day of surgery, and using a Foley catheter only overnight. A related report (105) documented the lesser need for persistent urinary drainage in patients receiving epidural analgesia in such a protocol, news which could be heartening to many patients! Data continue to accumulate that critically tabulate the benefits of epidural analgesia by meta-analytic review (106–108). The recent availability of an encapsulated liposomal sustained-release morphine preparation for epidural use manifests the zeal to create newer and better products (96). The drug is delivered by a single injection and can provide analgesia for up to 48 h.

The sentinel report by Liu et al. (109) on the use of patient controlled epidural analgesia (PCEA) techniques (with 0.05% bupivacaine and 4 μg/mL fentanyl) is clinically relevant. The study included over 1000 patients having a variety of surgical procedures and documented that PCEA was both effective and safe even when provided to patients on non-ICU wards. Their realistic data concerning the therapy-related side effects and risk factors are invaluable. Scientific insight into the biochemical consequences of PCEA are illuminated nicely by Beilin et al. (110) They compared intermittent opioids to IV PCA opioids with PCEA in patients after abdominal surgery. They demonstrated that significant markers of the immune response were less impaired with PCEA use. So the sophistication of benefit analysis is exceeding the more clinical realm.

Contemporary investigation strives to identify the ideal epidural analgesic infusion. Hodgson and Liu (111) have updated their comparison of ropivacaine with fentanyl and bupivacaine with fentanyl in PCEA for pain control in patients after abdominal surgery. Scott et al. (112) identified 0.2% ropivacaine with 4 μg/mL fentanyl as the optimal postoperative infusion in patients having had major abdominal surgery. As studies comparing ropivacaine with the more commonly used bupivacaine appear (113), an appropriate question to ask is "what is the dose equivalence between these two drugs?"

Other Considerations in Pain Control

Concepts to Ponder

The practice of postoperative pain control is especially significant when patient satisfaction is elevated and patient outcomes are improved. The *contemporary standard* for pain relief is achieving analgesia while the patient is active, i.e., coughing, ambulating, or homebound, rather than simply at rest (3,4,10,13,66). This acknowledges the potential benefit of modern-day postoperative pain control from peripheral and central nerve blocks and intellectual medication use and advances the practice of pain medicine in concert with progress in clinical care. The quality of analgesia using epidural techniques exceeds that of systemic opioids in most cases. The use of epidural local anesthetic, opioid, or, more commonly, the combination, is consistently superior to routine IM analgesia and PCA (86,87,106). The benefits of these techniques are being extended as, for example, the use of regional anesthesia/analgesia techniques in pediatric patients (114). Our challenge then remains that of providing effective analgesia for longer periods of time and doing so with as few drug-related or procedure-related side effects as possible, while also surveying for infection related to indwelling catheters (115) and bleeding risks in patients receiving ever-changing thromboprophylaxic regimes (116). Diversifying our techniques, based on evidence-based medicine and randomized controlled trials, will enhance clinical care (117). We can appreciate that the "anatomically correct" location of epidural catheters, as shown by Kahn et al. (118) in patients who had thoracoabdominal esophagectomy, enhances benefit. We should consider the ease of providing paravertebral blocks when this proves difficult or when other options are less desirable (82,119–123). The search for adjuncts and additives to perispinal injectates (i.e., clonidine, ketamine, neostigmine, and epinephrine) must also continue (91–93,101,124–126). We should follow established guidelines for more conscientious pain management that have been developed by reputable agencies (6–8,127). Perhaps we can appreciate the development of refined postoperative pain guidelines that are unique by being site-specific for the operative location (128,129). The approach should streamline the number of options considered by bringing focus to the clinical care and allowing more active patient participation.

An Eye to the Future

It is now perceived that treatment must be continued until the inflammatory reaction that fuels the nociceptive input is minimized lest the patient become vulnerable to a postoperative chronic pain syndrome (10–12,14,58,110,130,131). A fundamental lesson learned in the management of acute (and chronic) pain is that even when the obvious, peripheral source of pain is gone, the underlying nervous system may not have "healed," i.e., recovered from sensitization. Thus, we

need to participate in the extended "analgesic" planning for our patients. For instance, should we advocate the use of sustained release opioids for the first 3 to 7 days of postoperative care, as we guide the transition of the patients from regional techniques to oral analgesics? Ginsberg et al. (132) predicted the benefit of providing *reputable* conversions of IV PCA doses to long-acting oral opioids, and Reuben et al. (133) have validated this concept. What is getting a great deal of press these days is the management of breakthrough pain (134). This is described as a transient increase in pain that has otherwise been controlled. Effective strategies revolve around the use of appropriate medications and relevant nonpharmacologic modalities to rapidly contain the pain.

Another example of extended care would be the consideration of a consultation with a pain psychologist to help gain control of pain in patients with extreme cases of pain, as is common in the chronic pain model (128). This step will help one achieve the highest quality pain control, given the attention to physical *and* nonphysical factors, and will help one to meet the new standards for pain control and patient satisfaction that are upon us. Kotani et al. (135) provide intriguing study results detailing the benefits of preoperative intradermal acupuncture on postoperative pain, nausea, vomiting, and the sympathoadrenal responses. Some of these benefits and more are elaborated in a review of perioperative acupuncture and related techniques by Chernyak and Sessler (136). Wang et al. (137) have documented that most patients receiving inpatient and ambulatory surgery care use some form of complementary or alternative medicine (CAM) therapy and are willing to continue to do so in a perioperative pain management program. White's recent review on the changing role of non-opioid analgesia (138) is an expansive, enlightening treatise that encourages a program of treatments for postoperative pain.

Conclusion

It is best to avoid intense, single modality therapy in acute pain management. The more modern motif is to strive for an approach that balances the application of a number of therapies, each aimed at counteracting "the pain" in a different way (66,117,127,138–140). Because local anesthetics and opioids cannot "do it all," other drugs and non-medication techniques must become available (127). We stand to benefit from progress made on many fronts in pain management. For example, the use of antiepileptic drugs (AEDs) is exceedingly common in the management of neuropathic pain, given the acknowledgment that part of the pathology present is the facilitated responses in the CNS as to the processing of noxious input. Because we understand that acute pain that is not consistently treated can provoke CNS sensitization, trials using AEDs preoperatively are appearing. Dirks et al. (141) have shown an opioid-sparing effect by neurontin given to patients prior to mastectomy. The question posed by Gilron (142) in the accompanying editorial "Is neurontin a broad-spectrum analgesic?" raises an intriguing issue that awaits further clarification through research.

The institution and elaboration of acute pain services as a mechanism to address the logistical, administrative and service demands for the delivery of effective postoperative care, has been a boon to pain management (1–4,143,144). The Warfield and Kahn survey of 300 United States hospitals (of varying size) (143) revealed that only 42% had acute pain management programs as of 1994. An acute pain service must strive to be both a clinical as well as a research vehicle for anesthesiologists to remain crucial contributors in the fascinating field of pain management. Rawal (145) initiates the discussion about the need for acute pain services to evolve to the next level of patient care, provide close clinical follow-up and data collection, and assure the provision of quality data about patient outcome. Dahl et al. (146) provide data supporting the use of a protocol by institutions to affect pain management with improvements shown in the documentation of pain levels with contemporary pain scales and the use of nonpharmacological strategies. Interestingly, as there were no documented differences in pain outcomes, further analysis is warranted.

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