

ACUTE PAIN MANAGEMENT REVISITED

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INTRODUCTION

Pain management is required following the majority of the 70 million surgical procedures performed annually in the United States.^{1a} As Apfelbaum et al point out in their recent survey, many more surgical procedures are now performed in an outpatient setting. The under-treatment 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.¹⁻³

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 post-operative pain management and proposed a systematic approach to doing so.⁴ The ASA has promulgated practice guidelines for acute pain management because this aspect of our contemporary practice is essential.⁵ 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.^{5a} 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 preoperative assessment of the patient,^{5b} the presentation of options and preferences for pain management techniques as well as the teaching provided and a definitive postoperative 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. Given the contemporary attention to evidence-based medicine, Todd and Brown 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?⁶ This discussion is further illuminated by Wu and Fleischer who encourage ongoing research into a broader scope of outcomes than is usually sought.^{6a}

PATHOPHYSIOLOGY OF POSTOPERATIVE PAIN

Surgery represents a form of pre-mediated 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.^{2,3,7-12} 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 other 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.^{7,8,10-12} The threshold for activation and the activity of these receptors are modified by the local release of chemical mediators of inflammation and sympathetic amines released within the surgical stress response. Substances such as bradykinin, serotonin and histamine both sensitize and stimulate the receptors whereas arachidonic acid derivatives only sensitize them. Interleukins, notably IL-6, are pro-inflammatory cytokines that are released in correlation with the magnitude of the tissue injury, as is IL-1RA (as a marker for IL-1B).^{12a} It may be through substances such as these, and others such as tumor necrosis factor-alpha (TNF-alpha), that the sympathetic nervous system becomes involved in the acute phase response. **Problem #1** in postoperative pain is this peripheral sensitization which 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 (ie, 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*.

Ordinarily, A-delta and c-fibers transmit nociceptive information from the periphery to the CNS.^{2,7,8,10} The input from A-delta fibers is associated with sharp, localized pain which is rapidly conveyed (due to these fibers being myelinated) whereas that related to the c-fibers is usually aching, throbbing, diffuse and more slowly transmitted (due to these fibers being unmyelinated). A-delta 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-alpha and A-beta fibers can be induced to carry nociceptive input to the CNS when peripheral sensitization occurs. This input does not necessarily undergo the usual inhibition in the dorsal horn, as does A-delta or c-fiber input, because A-alpha and A-beta fibers do not terminate in the same levels of the dorsal horn, i.e., the substantia gelatinosa, as do the A-delta and c-fibers. An ancillary problem that is a consequence of #1 and #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 plasticity in the CNS response.¹³

Problem #3 occurs when the noxious input begins to be processed by the central nervous system.^{9,13} 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.^{7, 7a} Regional anesthesia and analgesia do not inhibit the local (traumatized tissue) release of stress mediators into the bloodstream. Brodner et al have highlighted that blocking the systemic SSR results in faster recovery and decreased cost.¹⁴ They studied patients undergoing abdominothoracic esophagectomy surgery. Group 1 was a retrospective cohort of patients who had an epidural placed at T₆₋₉ preoperatively, followed by general anesthesia. An epidural infusion of bupivacaine and sufentanil not titrated to analgesia was provided postoperatively for five days. Group II patients had a pre-induction 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 most likely blocked 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.^{1,2,3,5,7,11,14} Brodner et. al. have recently reported the benefits of multi-modal therapy in patients who underwent radical cystectomy.^{14a}

To be fair, there is some literature that proposes a more muted view.^{14b} Peyton et al 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.^{14b} In performing sub-group 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 this particular study, de Leon-Casasola critiques their findings that seem to so severely contradict our conventional wisdom.^{14c} He highlights 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.^{3,4,7,15} Every body system can be negatively affected by inadequately treated pain, and there is the potential for multisystem failure as more individual systems are over-stressed. 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.

The original benefit of epidural anesthesia was documented in patients undergoing hip replacement¹⁶ and lower extremity vascular surgery.^{17,18} 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. have demonstrated the benefits of effective pain management with epidural analgesia in patients with a history of cardiac disease¹⁹, and Loick et al. have presented the positive impact of thoracic epidural anesthesia on lessening myocardial ischemia.²⁰ Von Dossow et al have recently provided commentary on the benefits of thoracic epidural anesthesia combined with general anesthesia in patients with cardiopulmonary disease undergoing thoracic surgery.²¹ Ballantyne et al. performed a telling meta-analysis on seven post-operative analgesic therapies as to their impact on pulmonary outcome.²² Epidural analgesia had a significant effect on decreasing pulmonary morbidity. Groudine et al. showed that intravenous 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.²³ Hahnenkamp et al 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.^{7a} Steinbrook provides a thorough review of the positive consequences that epidural analgesic techniques have on recovery of gastrointestinal function.²⁴

As if the above enumeration of problems alone isn't impressive enough, the noxious input from acute injury also triggers a state of sensitization of the CNS response, called wind-up (problem #5).^{2,7,8,10,12} 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-alpha and A-beta input is "painful," and secondary hyperalgesia occurs due to 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.²⁵⁻²⁷ The process of wind-up is not prevented by general anesthesia but is modified by opioid administration in experimental animal paradigms.²⁸ The primary excitatory neurotransmitters in the spinal cord are glutamate and aspartate. The intensity and/or the constancy of the noxious input recruit NMDA receptor activation among other receptors (AMPA, ACPD). Knowing this about the neuropharmacology of the spinal cord has 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 NMDA receptors have in the induction and maintenance of central sensitization as well as the mediation of peripheral receptor sensitization and visceral pain continue to evolve.^{28a}

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 and contemporary reviews have been provided by Schmid et al and De Kock et al.^{29,29a,29b} Less postoperative pain was documented when epidural ketamine was administered by Choe et al³⁰ in patients having upper abdominal

surgery, Wong et al³¹ in patients undergoing total knee replacement, and Chia et al³² in patients using patient controlled epidural analgesia (PCEA) following major intrathoracic or upper abdominal surgery, whereas Kucuk et al did not identify a preemptive analgesic effect in patients following abdominal surgery.³³ Aida et al offered data that epidural morphine and IV ketamine had a preemptive effect in patients undergoing gastrectomy (although subsequent letters to the editor debate the issue)^{33a}, and Menigaux et al provide data about the utility of low-dose ketamine in an orthopedic surgery model.^{33b} 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 al³⁴ and Weinbroum et al^{34a} - positive, Grace et al³⁵ - negative). 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 and Hollmann et al provide contemporary data concerning the modulation of NMDA receptor function by ketamine and magnesium and the potential augmentation of the effect by volatile anesthetic agents.^{35a,35b} Thus, the use of up to two grams of magnesium IV and up to 0.5mg/kg ketamine IV every 4-6 hours of operating time appears to be a beneficial adjunct therapy to anesthesia in terms of modifying the CNS response to operative pain.

The entire concept of preemptive analgesia fostered by the above realities is predicated upon "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.³⁶⁻³⁸ Though the concept of pre-emptive 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. Kissin eruditely notes that "proving" preemptive analgesia can be expected to be difficult because of the necessity to meet a number of criteria: a pre-established, universal definition of what preemptive analgesia is, assurance of complete afferent input blockade, partial preemptive effects in control groups, standardizing the intensity of the noxious input, and agreeing upon appropriate outcome measures.³⁹ Numerous studies have proposed pre-emptive effects of epidural analgesia.^{31,32,36,37,40-41} Gottschalk et al continued the notion of preemptive analgesia in their study of patients who had undergone radical prostatectomy surgery.⁴² Patients who received epidural fentanyl or bupivacaine prior to the surgical incision had less pain while hospitalized postoperatively and at follow-up 9.5 weeks later and were (understandably) more active and sooner so 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.^{42a,42b,42c} Gottschalk provides a contemporary commentary that advocates a broader and longer application of pre-emptive therapies since the effectiveness of same will more likely be manifested when the intensity and the duration of the noxious stimuli are recognized and more thoroughly dealt with.^{42d}

The sophisticated goal of preemptive analgesia is to achieve a differential effect on physiologic and clinical pain.^{7,36} 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 post-surgical 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 doesn't "heal as fast as the incision does"!

APPLYING WHAT WE KNOW TO POSTOPERATIVE PAIN MANAGEMENT

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.⁷⁻¹² One can't 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. NSAIDs are another example of drugs that should alter peripheral responses, but there is weak evidence that this occurs in a preemptive way. Actually, the central (ie., spinal) effects of the NSAIDs may be more clinically significant than the peripheral anti-inflammatory effects.⁴³⁻⁴⁵ Zhu et al have provided an evolution of the concept of the significant action of COX-1 in the spinal cord.^{44a} 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 non-specific 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 for the S(+) isomer of ibuprofen^{44b}, and an evolving application of this concept is predicted by White.^{44c}

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.^{45,45a} Gajraj 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.^{45b}

Wound infiltration with local anesthetics has obvious merit.^{46,46a} However, the anti-inflammatory effect of local anesthetics in this application may be more prominent than neural blockade in some cases.⁴⁷ 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.⁴⁸ To present a balanced view, there may be reasons for not infiltrating all wounds with local anesthetics, as Brower and Johnson have collected data that document the interference on local anesthetics on the first and second stages of wound healing.^{48a} The potentially negative impact of this on the subsequent third and fourth stages of healing and wound strength and any relationship of this to incisional hernias is not known, but certainly requires further investigation.

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.^{2-6,14,20,46} Many applications of this concept are already in practice, such as ilioinguinal/iliohypogastric blocks in hernia patients,⁴⁹ penile nerve blocks in circumcision patients, intercostal blocks in thoracotomy patients, peripheral nerve blocks in knee surgery patients,^{50-52c} and interscalene and continuous brachial plexus blocks in patients having upper extremity surgery.^{53,53a} The study of Capdevila et al. 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.⁵² 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!^{2,3,6,6a,51,52}

One of the most fantastic discoveries in medical science in recent decades has been that of the opioid receptors.^{7,9,10} 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.^{9,53b} 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 pre-synaptically to decrease neurotransmitter release and post-synaptically to hyperpolarize dorsal horn neurons. Once central sensitization is established, doses that exceed those capable of preventing wind-up are needed.

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.²⁻⁵ 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 showed that patients having more intense pain preoperatively used more PCA morphine in the first 24 hours after surgery.⁵⁴ 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/hr morphine given intravenously. Thus, patients using such drugs prior to a definitive operative procedure will require this maintenance dose plus dosing to treat the "new" postoperative pain. Stacy et al. demonstrated that the focused guidance of PCA dosing by an acute pain service (APS), as compared to surgeon-directed PCA, resulted

in more effective pain control with fewer side effects, even though more opioids were used.⁵⁵ Gagliese et al. have recently shown that age is not an impediment to patients using PCA effectively.⁵⁶ Javery et al have advanced the utility of PCA by showing that adding 1mg/mL ketamine to morphine PCA enhances the analgesic effect and lessens opioid side effects.⁵⁷ Additional 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.^{57a,57b} Peng and Sandler extol the virtues of fentanyl PCA in their review article (on the many routes for providing analgesia with fentanyl).⁵⁸

The clinical use of opioids in either the intrathecal or the epidural space has brought unquantifiable comfort to many patients.^{2-4, 14-24, 41, 42} There are innumerable protocols that detail the continuous infusion of local anesthetics, opioids and the combination thereof into patients with acute pain.^{2-5,9} 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.^{58a} Patients receiving perispinal opioids alone should be able to ambulate. Epidural administration is still the most common technique. The broader use of subarachnoid opioids, as given in a CSE technique in OB anesthesia or given concurrently with a subarachnoid anesthetic, is now being manifested as clinical reports validate this practice.^{59, 60} Perispinal local anesthetics may cause sympathectomy, sensory and/or motor changes, or urinary retention.^{2-4,7} 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 (see table 2).^{1-5,9-11,14-22,41,42,61} Niemi and Breivik have advocated the concurrent use of epinephrine in epidural infusions both to augment analgesia and to decrease the adverse consequences of thoracic epidural analgesia.^{61a} Bernards et al provide significant data not only about the discrepancy between epidural, CSF, and plasma concentrations of various opioids given by the epidural route but also the variety of effects of adding epinephrine.^{61b, 61c}

Stevens et al have highlighted the progress made in the last 10 years of acute pain management using epidural analgesia.⁶² 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.^{61b, 62} They point out that morphine and hydromorphone exhibit definitive spinal analgesic action as compared to 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. has documented such clinical effectiveness of epidural analgesia in patients who underwent major colon surgery that discharge from the hospital was possible in 48 hours provided a fast-track protocol was followed.⁶³ Clinically this means establishing an effective epidural pre-induction, 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 only overnight. A related report 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!⁶⁴

The sentinel report by Liu et al on the use of patient controlled epidural analgesia (PCEA) techniques (with 0.05% bupivacaine and 4 µg/mL fentanyl) is clinically relevant.⁶⁵ The study includes over 1000 patients having a variety of surgical procedures and documents that PCEA is 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.⁶⁶ They compared intermittent opioids to IV PCA opioids to PCEA in patients after abdominal surgery. They demonstrated that significant markers of the immune response were less impaired with PCEA use.

Contemporary investigation strives to identify the ideal epidural analgesic infusion. Hodgson and Liu have updated their comparison of ropivacaine with fentanyl to bupivacaine with fentanyl in PCEA for pain control in patients with following abdominal surgery.⁶⁷ Scott et al identified 0.2% ropivacaine with 4 µg/mL fentanyl as the optimal postoperative infusion in patients having had major abdominal surgery.⁶⁸ As studies comparing ropivacaine to the more commonly used bupivacaine appear, an appropriate question to ask is, what is the dose equivalence between these two drugs?⁶⁹

CONCLUDING COMMENTS

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 or ambulating or homebound, rather than simply at rest.^{2,3,7,9} This acknowledges the potential benefit of postoperative pain control from peripheral and central nerve blocks 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. The benefits of these techniques are being extended as, for example, the use of regional anesthesia/analgesia techniques in pediatric patients is being advocated and gaining favor.^{69a} Our challenge then remains that of providing effective analgesia for longer periods of time and doing so with as few drug- or procedure-related side effects as possible, while also surveying for infection related to indwelling catheters⁷⁰ and bleeding in patients receiving ever-changing thromboprophylactic regimes.⁷¹ Diversifying our techniques, based upon evidence-based medicine and randomized controlled trials, will enhance clinical care. We can appreciate that the "anatomically correct" location of epidural catheters, as shown by Kahn et al. in patients who had thoracoabdominal esophagectomy, enhances benefit.⁷² We should consider the ease of providing

paravertebral blocks when other options are less desirable.^{52c,73-76a} The search for adjuncts and additives to perispinal injectates (i.e., clonidine, ketamine, neostigmine, and epinephrine) must continue.^{57-57b, 61b,77-79} Perhaps the use of low-dose intravenous ketamine to enhance opioid effects will gain broader favor.^{29a,29b,33a,33b,57-57b,80} Maybe we should simply follow established guidelines for more conscientious pain management.^{4,5,5a,81} Perhaps we can appreciate the development of refined postoperative pain guidelines that are unique by being site-specific for the operative location.^{81a, 81b} The approach should streamline the number of options considered by bringing focus to the clinical care and allow more involved in the patient's care to actively participate.

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.^{7,7a,8,10,42c,66,81c,81d} 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 three to seven days of postoperative care, as we guide the transition of the patients from regional techniques to oral analgesics? Ginsberg et al⁸² predicted the benefit of providing *reputable* conversions of IV PCA doses used to long-acting oral opioids, and Reuben et al⁸³ and Sunshine et al⁸⁴ have validated this concept. Sustained release hydromorphone becoming available will add another option for continuous pain control.^{84a} 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 inadequate pain control, as is common in the chronic pain model.^{81a} This step will help one achieve the highest quality pain control, given the attention to physical and non-physical factors, and will help one to meet the new standards for pain control and patient satisfaction that are upon us. Kotani et al provide intrigue with their study results detailing the benefits of preoperative intradermal acupuncture on postoperative pain, nausea, vomiting and the sympathoadrenal responses.^{84b} Wang et al have documented that most patients receiving in-patient 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.^{84c}

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.^{81,84d,84e} Because local anesthetics and opioids can't "do-it-all," other drugs and non-medication techniques must become available.^{81a} 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 acknowledgement that part of the pathology present is the facilitated responses in the CNS as to the processing of noxious input. Since we understand that acute pain that is not consistently treated can provoke CNS sensitization, trials using AEDs preoperatively

are appearing. Dirks et al have shown an opioid-sparing effect by neurontin given to patients prior to mastectomy.^{84f} The question posed by Gilron in the accompanying editorial, "Is neurontin a broad-spectrum analgesic?", raises an intriguing issue that awaits further clarification through research.^{84g}

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.^{1-3,85,85a} The Warfield and Kahn survey of 300 USA hospitals (of varying size) revealed that only 42% had acute pain management programs as of 1994.⁸⁵ 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 initiates the discussion about the need for acute pain services to evolve to the next level of patient care, close clinical follow-up and data collection, and provision of quality data about patient outcome.⁸⁶ Dahl et al provide data supporting the use of a protocol by institutions to effect pain management with improvements shown in the documentation of pain levels with contemporary pain scales and the use of non-pharmacological strategies.^{86a} Interestingly, as there were no documented differences in pain outcomes, further analysis is warranted.

Because so many anesthesiologists do nerve blocks, Tetzlaff and Yoon provide practitioners a valuable lesson.⁸⁷ They reported that orthopedic patients for whom regional anesthesia would be an excellent option refused such anesthesia because of an associated adverse personal event during a previous procedure or one that involved a friend or relative. If neither of these reasons were applicable, media information was found to be cautionary. Thus, as we learn more about the tremendous benefits of acute pain management, and because so many of them are needle-based, we must remain compassionate, patient, and technically proficient at all times, so that our patients are recruited to contemporary care rather than being unaccepting. We have so much to offer - let's keep doing it!

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TABLE 1 PATHOPHYSIOLOGIC CONSEQUENCES OF PAIN

| | |
|-------------------------|---|
| <u>cardiovascular</u> | tachycardia, hypertension, increased SVR, increased cardiac work |
| <u>pulmonary</u> | hypoxia, hypercarbia, atelectasis; decreased cough, VC, FRC; V/Q mismatch |
| <u>gastrointestinal</u> | nausea, vomiting, ileus, NPO |
| <u>renal</u> | oliguria, urinary retention |
| <u>extremities</u> | skeletal muscle pain, limited mobility, thromboembolism |
| <u>endocrine</u> | vagal inhibition; increased adrenergic activity, increased metabolism, oxygen consumption |
| <u>CNS</u> | anxiety, fear, sedation, fatigue |
| <u>immunologic</u> | Impairment |

TABLE 2 EPIDURAL LOCAL ANESTHETICS AND/OR OPIOIDS

- the most common LA is bupivacaine (0.0625%, 0.125%, 0.1%)
- ropivacaine is an alternative (0.05%, 0.1%, 0.2%)
- the most common opioids are:
 - 1) morphine - bolus 1-4 mg and infusion 25-50 ug/mL at 5-15 mL/hour
 - 2) fentanyl - bolus 25-100 ug and infusion 1-10 ug/mL at 5-15 mL/hour
 - 3) dilaudid - bolus 0.1-0.3 mg and infusion 3-12 ug/mL at 5-15 mL/hour

- 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

