THE anesthesia research community has contributed enormously to the development of modern pharmacokinetic and pharmacodynamic methodologies. For example, pharmacokinetic studies defined the plasma concentration profile during the first minute after bolus administration (demonstrating the flaw in assuming that plasma concentration peaked at time 0, then decreased monotonically); other studies disproved relevance of the traditional “elimination half-life” (demonstrating that duration of administration of anesthetic drugs markedly influenced washout after administration); pharmacodynamic studies introduced the concept of an effect compartment (i.e., that the effect of a drug might not be explained by its plasma concentration), thereby reconciling the observation that shortly after bolus administration, plasma concentrations are decreasing yet the effect of most drugs is increasing. Yet, as science evolves, new methodologies might be flawed, yielding specious conclusions. Such could have been the case in an article in the current issue of ANESTHESIOLOGY.5 had the authors not maintained any financial interest in, any commercial activity that may be associated with the topic of this article. Such could have been the case in an article in the current issue of ANESTHESIOLOGY. Struys et al. did not measure plasma drug concentrations, but rather estimated them from the target-controlled infusion and assumed they were correct. Such assumptions may be hazardous and in this case directly affected the potential validity of the conclusions. A reviewer asked the authors to perform another experiment in which propofol concentrations were measured; this was necessary to validate conclusions based on simulated data. This was not an insubstantial undertaking, requiring additional institutional review board application and review, investigator effort, subject recruitment and study, plasma and data analysis, and resources with which to accomplish the effort. The result was a richer data set and more robust conclusions. Moreover, the investigators then discussed their new data with the reviewer (who had identified himself in his review); this discussion yielded further data analysis and even more important conclusions. Peer review is not perfect, but an internal review of this process in ANESTHESIOLOGY indicates that constructive interactions between authors and reviewers result in improved articles, at least as judged by their likelihood of being cited. Although there is no substitute for scientific analysis of the peer review process, we nonetheless provide an illustrative anecdote and celebrate its success.

Evan D. Kharasch, M.D., Ph.D., Editor, ANESTHESIOLOGY
James C. Eisenach, M.D., Editor-in-Chief, ANESTHESIOLOGY

Take It to the Limit1 (One More Time)

Editor’s Note: The peer-review process is a foundation of scientific scholarship and publication. The goals are to (1) identify manuscripts acceptable for publication and (2) provide feedback to authors and improve manuscript quality and clarity, whether accepted by ANESTHESIOLOGY or for future research and submission. The editorial below describes the remarkable success of this process in an article in the current issue. In their original manuscript, Struys et al. did not measure plasma drug concentrations, but rather estimated them from the target-controlled infusion and assumed they were correct. Such assumptions may be hazardous and in this case directly affected the potential validity of the conclusions. A reviewer asked the authors to perform another experiment in which propofol concentrations were measured; this was necessary to validate conclusions based on simulated data. This was not an insubstantial undertaking, requiring additional institutional review board application and review, investigator effort, subject recruitment and study, plasma and data analysis, and resources with which to accomplish the effort. The result was a richer data set and more robust conclusions. Moreover, the investigators then discussed their new data with the reviewer (who had identified himself in his review); this discussion yielded further data analysis and even more important conclusions. Peer review is not perfect, but an internal review of this process in ANESTHESIOLOGY indicates that constructive interactions between authors and reviewers result in improved articles, at least as judged by their likelihood of being cited. Although there is no substitute for scientific analysis of the peer review process, we nonetheless provide an illustrative anecdote and celebrate its success.

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THE anesthesia research community has contributed enormously to the development of modern pharmacokinetic and pharmacodynamic methodologies. For example, pharmacokinetic studies defined the plasma concentration profile during the first minute after bolus administration (demonstrating the flaw in assuming that plasma concentration peaked at time 0, then decreased monotonically); other studies disproved relevance of the traditional “elimination half-life” (demonstrating that duration of administration of anesthetic drugs markedly influenced washout after administration); pharmacodynamic studies introduced the concept of an effect compartment (i.e., that the effect of a drug might not be explained by its plasma concentration), thereby reconciling the observation that shortly after bolus administration, plasma concentrations are decreasing yet the effect of most drugs is increasing. Yet, as science evolves, new methodologies might be flawed, yielding specious conclusions. Such could have been the case in an article in the current issue of ANESTHESIOLOGY. had the authors not maintained any financial interest in, any commercial activity that may be associated with the topic of this article. In 1980, Toner et al. administered single bolus doses of thiopental to healthy subjects and measured thiopental concentrations. Larger doses were associated with higher venous concentrations at awakening, leading the authors to conclude that there was acute tolerance to thiopental. Subsequently, Hudson et al. demonstrated that this conclusion was an artifact—modeled brain concentrations of thiopental did not vary with dose, i.e., there was no evidence to support acute tolerance. Thus, the use of venous concentrations as a biomarker for effect compartment concentration led to a flawed conclusion.

A second example involved a similar conclusion: that different doses of a muscle relaxant resulted in different concentrations producing 50% twitch depression (C50). In that case, Bergeron et al. administered cisatracurium and applied accepted pharmacokinetic–pharmacodynamic models to estimate C50. They reported a 1.5-fold change in C50 over a 4-fold range of doses. I thought that their result could be an artifact of the analysis method; specifically, their flawed assumption that Cp peaked instantly, and then decreased monotonically, would have a different impact depending on the magnitude of the dose administered (because larger doses suppressed twitch markedly more rapidly than smaller doses). Paul and I used simulation to demonstrate that the results of Bergeron et al. were likely to be artifactual. Ironically, the importance of proper characterization of the plasma concentration profile during the first few minutes after bolus administration had been championed earlier by some of Bergeron’s coauthors.

Both of these examples (and there are more) show that
applying accepted methodologies may yield spurious outcomes, especially when the new studies "take it to the limit." Struys et al. encounter a similar situation. They were interested in the inconsistent published values for the half-life for effect site equilibration \((t_{1/2,e0})\) for propofol. Previous studies suggested that this half-life differed when propofol was administered by bolus compared with rapid infusion. Was this an artifact? Or did it represent a true phenomenon that should be accounted for if one administered propofol by target-controlled infusion?

To address this question, Struys et al. administered 2.5 mg/kg propofol as either a bolus or a rapid infusion (duration of 1, 2, or 3 min) to healthy subjects who received no other drugs; spectral edge encephalograph was measured as the effect. Instead of measuring plasma concentrations of propofol, they estimated plasma concentrations using a "validated" set of pharmacokinetic parameters. Their initial analysis indicated that equilibra- tion half-life differed twofold between the two modes of administration. The authors could have accepted this as a plausible result: Ludbrook et al.\(^{11}\) had reported that high concentrations of propofol constrict cerebral vessels, which might delay blood–brain equilibration.

Fortunately, Struys et al. did not stop there. When challenged that their results could be artifactual, a result of misspecifying the plasma concentration profile during the first minutes after bolus administration, Struys et al. attempted to validate their plasma concentration estimates by sampling propofol frequently after bolus administration in a new cohort. To their surprise, measured plasma concentrations during the first minutes were severalfold lower than the values they estimated. Perhaps they should not have been surprised: Data from Doufas et al.\(^{12}\) suggest a similar phenomenon.

Struys et al. then evaluated additional models to determine the impact of these new plasma concentration values. Interestingly, most of the difference in equilibration half-life between the bolus and infusion groups disappeared. Thus, their initial conclusion—that mode of administration affected equilibration half-life—was no longer tenable. Had Struys et al. not studied the additional cohort, they would have published an article containing a flawed conclusion, creating the opportunity for a future study to refute their findings. Alternatively, a flawed conclusion might have gone unchallenged, potentially for a lengthy period.

Science evolves constantly. We benefit from investigators taking studies to the limits of the available methodologies. And we also benefit when mistakes are made, acknowledged, and corrected.

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Continuous Local Anesthetic Wound Infusion to Improve Postoperative Outcome

Back to the Periphery?

EFFECTIVE postoperative analgesia is a prerequisite to enhance the recovery process and reduce morbidity. The use of local anesthetic techniques is well documented to be effective, but single-dose techniques (infiltration, peripheral blocks, neuraxial blocks) have been of limited value in major operations because of their short duration of analgesia. Continuous administration of local anesthetics at various segments in the nociceptive pathway has therefore been introduced and where the relatively demanding continuous peripheral nerve blocks and epidural techniques have proven effective, although with a small risk of complications and relatively high costs. From a theoretical point of view, administration of local anesthetics at the wound site is the most rational approach to reduce the afferent nociceptive barrage and thereby pain and stress responses with their secondary risks of organ dysfunction and morbidity. Therefore, an improved understanding of the analgesic efficacy of continuous wound infusion of local anesthetics and its consequences on outcome is important as reported by Beaussier et al. In their double-blind randomized setup, patients undergoing colonic surgery received continuous ropivacaine at 0.2%/10 ml/h for 48 h or saline through a multiholed wound catheter placed in the preperitoneal space. The study has important clinical implications because they assessed in detail relevant outcomes such as patient-controlled analgesia—quantified opioid sparing, level of dynamic analgesia, sleep quality, and recovery of gastrointestinal function, all of which were significantly improved, and duration of hospitalization was reduced (115 vs. 147 h) as well. No wound morbidity or ropivacaine toxicity was observed.

Hitherto, no analgesic technique has fulfilled all requirements of optimal efficacy—no side effects, low costs, high patient compliance, and improvement in outcome—and consequently, multimodal analgesic techniques have been introduced with a focus on opioid sparing to improve analgesia and recovery. As documented by Beaussier et al. as well as in randomized studies with different continuous local anesthetic wound infusion techniques, the available data have almost consistently shown improved analgesia across a range of procedures and with a very low (approximately 1%) technical failure rate and zero reported toxicity. Most importantly, wound infection rates have not increased, and patient compliance is acceptable. Unfortunately, the studies previously reported in the literature have not allowed sufficient analyses on postoperative recovery of different organ functions (pulmonary, ileus, mobilization, etc.), or a potential reduction in morbidity as well as duration of hospitalization will require further studies because of a lack of well-defined discharge criteria and standardized care and rehabilitation programs according to the concept of fast-track surgery. The report by Beaussier et al. therefore represents an important example of how to optimize design for an improved assessment of local anesthetic wound infusion to enhance the postoperative recovery process.

The important question is whether we have enough evidence to more widely recommend continuous local anesthetic wound infusion techniques in our perioperative care programs. The primary risk from peripheral infusions of local anesthetics is direct tissue toxicity such as myotoxicity. Although there are supportive laboratory data, the clinical experience is that such injuries are rare. So far, the benefits clearly outweigh the risks, and the only drawback of the technique is catheter equipment costs, which amount to approximately US $250 per patient. However, this may be acceptable in certain major procedures such as abdominal surgery, provided that the significant improvements in outcome as demonstrated by Beaussier et al. can be confirmed by others. The cost of this technique may be further offset by its

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simplicity. Because the equipment is basic and risk of serious complications is minimal, it is likely that these patients can be treated on the floor without involvement and subsequent cost of an acute pain service. This would not only save charges to the patient, but also allow the acute pain service to focus on patients with more complicated pain management techniques. On the other hand, continuous local anesthetic wound infusion in minor procedures such as inguinal herniorrhaphy may not be cost effective despite proven efficacy.3 Instead, in such minor procedures we should strive to implement effective oral multimodal nonopioid analgesia,2 which is more simple to manage and can be continued for a longer period where necessary than the usual wound infusion regimens with 2–3 days’ duration.1,3

However, as is so often the case, introduction of new analgesic techniques also raises several important questions: What is the optimal concentration and volume of the local anesthetic? (no conclusive procedure-specific dose response studies available); what is the optimal site of placement of the wound catheter? Beaussier et al.1 used preperitoneal placement, which may be rational, and probably the placement should be close to the muscle-facial layer and not in the subcutaneous layer, as demonstrated in one of the few comparative studies.6 Furthermore, we should not be overoptimistic that these newer techniques alone will provide sufficient dynamic analgesia, and therefore the opioid-sparing effects should be assessed in more detail in different procedures (postoperative nausea and vomiting, sedation, sleep disturbances, etc.)1,2 and combined with other nonopioid analgesics. In addition to these patient-reported outcomes, it will be interesting to examine impact on patient safety from opioid sparing. The Anesthesia Patient Safety Foundation has recently released a position statement highlighting potential risks of respiratory depression with systemic and central neuraxial opioid analgesia.6 Use of continuous local anesthetic wound infusion techniques, especially with concomitant use of several nonopioid analgesics,2 may thus directly improve patient safety. Importantly, the optimal duration of wound local anesthetic infusion must be evaluated together with the effect on relevant outcomes. So far, the literature on the effect of different types of perioperative analgesia on outcome is controversial,7 most probably because the analgesic techniques have not been sufficiently incorporated into multimodal rehabilitation programs to take advantage of the provided analgesia.4 Finally, there is a need for comparative studies with other local anesthetic techniques such as epidural analgesia,7,8 predominately to assess potential differences in technical failures, costs, and side effects. Comparison with continuous paravertebral blocks and epidural analgesia in thoracic procedures is a good example,3,9 as well as comparison with peripheral nerve blocks in major orthopedic procedures.10,11 Therefore, recent data from high-volume incisional multimodal local anesthetic infiltration/infusion12 is of major interest because of its simplicity, efficacy, and safety, but additional studies are required to assess the relative role of incisional versus intraarticular administration in major joint replacement.12 Other areas of interest could be comparison with systemic administration of local anesthetics.13

So far, the promising data on continuous wound infusion of local anesthetics call for a balanced assessment of practicality versus other benefits versus side effects with other analgesic techniques and agents. This balanced approach to evaluation may become especially valuable because multiple new peripheral analgesics are being developed for postoperative analgesia. Sustained duration local anesthetics may provide up to 96 h of analgesia after a single injection and would further improve on simplicity by removing the requirement for any infusion pump equipment.14 Additional peripheral pharmacologic agents are also being examined, such as a TRPV1 (capsaicin) agonist for sustained postoperative analgesia after total knee replacement15 and possible application of peripheral tricyclic antidepressants.16 All of these represent new, exciting, and potentially valuable means to provide nonopioid analgesia directly to the periphery. However, all must be comprehensively evaluated.

In summary, the peripheral use of continuous wound infusion of local anesthetics represents an effective analgesic technique that, because of its simplicity, may find its way to be an important instrument in our analgesic armamentarium across several major surgical procedures. It is hoped that future research will document in more detail other extra-analgesic benefits on outcomes, such as reduction of postoperative organ dysfunctions and enhanced recovery when integrated into multimodal rehabilitation programs,4 patient safety, and quality of life and health economics.

**References**


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**Glucocorticoids for Acute and Persistent Postoperative Neuropathic Pain**

**What Is the Evidence?**

PERSISTENT neuropathic postoperative pain is a major health problem. It is highly important to find therapies that prevent or reduce chronic neuropathic postoperative pain. The current issue of *Anesthesiology* contains an animal study by Li et al.\(^1\) that examines the role of a systemic glucocorticoid (triamcinolone acetonide) on aspects of pain and inflammation using the spinal nerve ligation model. This model is traditionally considered a neuropathic pain model, but involves surgery and evokes an inflammatory response linked to pain behavior. In their study, Li et al.\(^1\) demonstrate that systemic injections of a glucocorticoid reduce apparent pain behavior, proinflammatory cytokines, overall neuronal firing rate, incidence of bursting activity, and abnormal sympathetic sprouting in dorsal root ganglia.

Proinflammatory cytokines secreted at or near the site of a nerve injury are involved in the development and maintenance of central sensitization and neuropathic pain.\(^2,3\) Glucocorticoids suppress proinflammatory cytokines and induce expression of antiinflammatory cytokines.\(^1,2,4–6\) They also reduce the prostaglandin synthesis by inhibiting phospholipase A\(_2\) and by blocking the expression of cyclooxygenase-2 messenger RNA.\(^4,6\)

Spinal glial activation stimulates nuclear factor κB, which induces cyclooxygenase-2, release of prostaglandins, and production of proinflammatory cytokines, excitatory amino acids, and growth factors establishing pathologic pain.\(^5,7,8\) By inhibiting glial activation and the activation of nuclear factor κB in animal models, glucocorticoids prevent the development of neuropathic pain behavior.\(^5,7\)

Reduced release of neuropeptides from nerve endings, inhibition of signal transmission in nociceptive C fibers and ectopic discharge from traumatized nerves,\(^9–11\) reduced mechanically induced dysesthesis after nerve injury,\(^12\) improved nerve recovery and regeneration,\(^12–14\) and a dose-dependent rapid inhibitory effect on the voltage-dependent calcium currents in dorsal root ganglion neurons\(^15\) are all documented effects of glucocorticoids that may contribute to analgesia.

Rapid antihyperalgesic effects of glucocorticoids have been demonstrated in animals and humans.\(^2,16–17\) Reduction in neural discharge within seconds to a few minutes due to nongenomic steroid effects on membrane receptors has been observed.\(^18\) These rapid nongenomic effects of glucocorticoids are due, at least in part, to decreased glutamate release and increased release of γ-aminobutyric acid and endocannabinoids.\(^19,20\) By decreasing glutamate and increasing γ-aminobutyric acid, glucocorticoids would be expected to rapidly cause a marked reduction in excitability of nerve cells.\(^21\) A theoretic possibility is that both nongenomic and genomic steroid actions are responsible for the analgesic and antihyperalgesic effect, where the nongenomic mechanisms lead to the rapid analgesia and antihyperalgesia (minutes) and the genomic mechanisms give a sustained analgesia and antihyperalgesia (hours to days).

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The study by Li et al. confirms previous animal and human studies that have found analgesic effects of glucocorticoids on acute postoperative pain, and proposes effects on persistent neuropathic pain after surgical procedures that involve nerve injury. In sharp contrast to the current study by Li et al. and other experimental and clinical trials, several studies have demonstrated that glucocorticoid receptors in the spinal cord are up-regulated after constriction nerve injury, and indicate that glucocorticoids can exacerbate neuropathic pain behavior. Therefore, at present, results from animal studies on the effect of glucocorticoids after nerve injury are conflicting. The direct relevance of the animal models as predictors of human clinical pain response is difficult to entangle. So far, animal studies on this field need verification in human models before clinical implementation. Regarding glucocorticoid use in humans, there are already convincing evidence for acute analgesic and antihyperalgesic effects of glucocorticoids after surgery and experimental injuries.

Even if human studies are less equivocal than animal studies, the effects on pain after surgery have not been convincing in all clinical studies. Differences in anesthetics methods, surgical technique, use of other analgesics (such as paracetamol or nonsteroidal antiinflammatory drugs in the placebo group), main outcome measures other than pain (usually postoperative nausea and vomiting), and small studies with low power may all be confounding factors in such studies. The dose of glucocorticoid and the extent of the surgical trauma may also influence the analgesic effect. Major surgery may cause such high levels of endogenous cortisol that the benefit of additional exogenous glucocorticoids on pain may be small. But even after major surgery, benefits have been demonstrated, such as reduced inflammatory response, improved pulmonary function, less fatigue, less postoperative nausea and vomiting, appetite stimulation, and more rapid convalescence.

Acute postoperative pain is usually considered as inflammatory and nociceptive, but neurogenic mechanisms also contribute, and reversible neuropathic pain may dominate from the late acute phase. When postoperative hyperalgesic or allodynic pain persists beyond the usual time of healing, or 3–6 months, it is defined as “chronic postoperative pain” and may persist for months or years. This process is probably initiated by peripheral nerve injury and central sensitization occurring at an exaggerated degree causing dysfunctional adaptations of the neurons in the pain-regulating system. Chronic neuropathic pain occurs in 10–50% of patients after surgery and always has components of hyperphenomena and/or hypophenomena indicating nerve damage and central sensitization. Steroids given after oral and orthognathic surgery prevent sensory hypersensitivity. Preincisinal administration of methylprednisolone attenuated hyperesthesia at 6 weeks and 1 yr after breast augmentation surgery. The same study demonstrated that hyperesthesia 6 weeks after surgery is a risk factor for persisting pain after 1 yr. A recent study in male volunteers demonstrated that methylprednisolone rapidly suppresses central sensitization, shown as reduction of burn-induced secondary hyperalgesia, suggesting a role for glucocorticoids in preventing long-term sensitization.

Sustained postoperative opioid sparing and pain relief continuing for 3 days after one single dose of glucocorticoids (methylprednisolone or dexamethasone) have been reported. This cannot be explained by the duration of the biologic antiinflammatory effect (36 h for methylprednisolone). Reduction in central sensitization reducing postoperative hyperalgesia may contribute to this prolonged analgesic and opioid-sparing effect.

The objection to the use of glucocorticoids perioperatively has been a presumed risk for side effects. However, one single dose of a glucocorticoid (1–2 mg/kg methylprednisolone or 0.2–0.4 mg/kg dexamethasone intravenously) is enough to give a prolonged analgesic and opioid-sparing effect (for 72 h) after surgery. A systematic review of data from more than 1,900 patients concluded that perioperative methylprednisolone up to 30 mg/kg, as a single dose, was not associated with any adverse effects. However, it is important to be aware that glucocorticoids can give a marked but transient elevation in blood glucose.

Sustained analgesic and antihyperalgesic effect, no problems with bleeding or allergy, no renal or respiratory adverse effects, no increase in infection risk, no increase in wound dehiscence, potent antiemetic effects, and a more rapid convalescence are all arguments for a perioperative single dose of a glucocorticoid. However, not all studies investigating glucocorticoids after major surgery have found analgesic effects. And although we believe it is safe to give one dose of a glucocorticoid, what happens when we combine it with nonsteroidal antiinflammatory drugs or coxibs? We suppose that it is safe, but safety data on drug combinations perioperatively are lacking.

In summary, there is evidence that glucocorticoids alleviate acute and continued postoperative pain by suppressing inflammatory mediators, glial activation, reducing neural activity, sympathetic sprouting, and central neuroplastic changes such as central sensitization. Li et al. have revealed mechanisms of glucocorticoid action indicating that they may have a role in reducing chronic postoperative neuropathic pain. Although experimental studies on rats are conflicting, there is evidence supporting the perioperative use of glucocorticoids for the relief of acute and sustained postoperative pain. What we now need is properly sized studies investigating long-term effects of perioperative glucocorticoids on human postoperative pain.
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