Anesthesiology 2003; 99:1037–8

The Right Dose of Succinylcholine

SUCCINYLCHOLINE is considered to be endowed with two great qualities: It provides intense paralysis rapidly, and its effect is likely to wear off before an adequately preoxygenated patient becomes hypoxic. However, this claim was challenged because calculations showed that at the recommended dose, 1 mg/kg, preoxygenated patients were likely to become hypoxic before spontaneous breathing resumed.[1] Two articles in this issue of the Journal address the questions that come next: Would a smaller dose be just as effective, and if so, would this dose have a short enough duration of action? Naguib *et al.*[2] suggest that acceptable intubating conditions can be obtained in 95% of patients with just 0.56 mg/kg of succinylcholine. Kopman *et al.*[3] report that decreasing the dose by 40% from 1.0 to 0.6 mg/kg decreases the duration of action by approximately 90 s.

Succinylcholine is used to facilitate tracheal intubation, especially in emergency situations when the risk of aspiration of gastric contents is present. In this context, manual ventilation can increase the risk of aspiration, so it is important to limit the duration of paralysis so the patient can breathe again in case of failure to intubate. The question of the right dose to obtain adequate intubating conditions has not been addressed until now, probably because the problem is not as simple as it appears. Monitoring the twitch response at the adductor pollicis is of limited use because of different onset times, intensities of blockade, and duration of action at different muscles. In addition, depth of anesthesia affects the quality of intubating conditions.

Thus, the only way to determine the best dose is to assess intubating conditions in a large number of patients. The assessor must be blinded and must follow a well-accepted scoring system, such as the one proposed by the 1994 Copenhagen consensus conference.[4] Ideally, a group not receiving any neuromuscular blocking agent should be included, to take into consideration the effect of the anesthetic. Still, many variables must be fixed by the investigators, and the choices should be adapted to the drug and situation to be studied. The dose and timing of administration of narcotics, the dose of induction agent, and the interval between injection of the neuromuscular blocking agent and intubation are all important.[5] Succinylcholine is meant to be used for rapid-sequence intubation. Therefore, Naguib *et al.*[2] quite appropriately chose a relatively light anesthetic and a short induction-intubation interval, 60 s. The authors chose not to give any nondepolarizing drug to prevent fasciculations. Doing so would have increased the dose of succinylcholine required,[6] so the results of the study do not apply to the situation when a defasciculant is given.

As expected, the quality of the intubating conditions increased with dose. Acceptable conditions were found in only 30% of patients receiving no succinylcholine, but in 98% of subjects administered 1 mg/kg. From their data, the authors concluded that 0.56 mg/kg was expected to provide acceptable conditions in 95% of patients. However, the 95% figure and the definition of *acceptable* were picked arbitrarily. If one is content with acceptable conditions 9 times out of 10, then 0.3 mg/kg is more than enough. However, if one aims for 99% of patients with acceptable conditions, more than 1 mg/kg is needed. The term *acceptable* is also arbitrary, as it includes excellent *and* good conditions. Only those with excellent conditions do not move at all, and this occurs in only 55% and 60% with doses of 0.3 and 0.5 mg/kg, respectively. The proportion increases to 80% with 1 mg/kg, but this is not perfect. Despite the subjective nature of intubation quality assessment, it is interesting to note that all large-scale studies agree on the conditions provided by succinylcholine, 1 mg/kg (Table 1).

Clearly, high doses should be chosen, unless the associated duration of action is too long. Benumof *et al.*[1] calculated that preoxygenated healthy adult patients can withstand an 8-min period of apnea until desaturation to 90% occurs, but the average duration to 90% twitch height recovery after succinylcholine, 1 mg/kg, is greater (10 min). They concluded that "significant-to-life threatening hemoglobin desaturation will occur before functional recovery"[1] if an airway fails to be secured. Kopman *et al.*,[3] in this issue of the Journal, obtained a similar recovery value (9.3 min), longer than the 8-min critical period. A 40% reduction in dose to 0.6 mg/kg corresponded to a 7.6-min duration, which at first sight brings the patient into the safe zone.

But before we all adopt the 0.6-mg/kg dose, let us look at the duration of apnea and not the twitch height at the thumb. At least two studies demonstrated that, *on average*, breathing resumes before the subject becomes hypoxic after a 1-mg/kg dose. Heier *et al.*[7] obtained a mean duration of apnea of 5.2 min in 12 volunteers. Hayes *et al.*[8] measured a mean time to first diaphragmatic move-

◆ This editorial view accompanies the following articles: Naguib M, Samarkandi A, Riad W, Alharby SW: Optimal dose of succinylcholine revisited. ANESTHESIOLOGY 2003; 99:1045–9; and Kopman AF, Zhaku B, Lai KS. The "intubating dose" of succinylcholine: The effect of decreasing doses on recovery time. ANESTHESIOLOGY 2003; 99:1050–4.

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Table 1. Intubating Conditions after Succinylcholine, 1 mg/kg

Study	Anesthetic	Intubating Conditions		
		Excellent (%)	Good (%)	Poor/Failed (%)
Andrews *et al.*[11] (n = 139)	Propofol	74	23	3
Sparr *et al.*[12] (n = 156)	Fentanyl/propofol or thiopental	73	24	3
Blobner *et al.*[13] (n = 200)	Fentanyl/thiopental	63	29	8
Fleming *et al.*[14] (n = 112)	Fentanyl/propofol	65	28	7
Naguib *et al.*[2] (n = 50)	Fentanyl/propofol	80	18	2

All doses of fentanyl were 3 μg/kg or less; n represents the number of patients receiving the drug at that dose.

ment of 4.7 min in 100 patients. These are much shorter than the 9- to 10-min duration at the adductor pollicis, probably because the diaphragm recovers before the adductor pollicis does.[9] Upper airway muscles might recover later, but in the case of a failed intubation, the anesthesiologist is expected to be present to maintain patency of the airway. On the basis of these results, it is tempting to recommend a dose of 1 mg/kg, which provides excellent intubating conditions in 80% of subjects, more often than the lower doses, and a safe duration of apnea.

Careful inspection of the data suggests that although this is true, on average, not all patients are average. Functional residual capacity may be reduced and/or oxygen consumption increased and/or preoxygenation not optimal.[1] Also, succinylcholine does not have the same effect in all subjects, even if their plasma cholinesterase activity is within the normal range. Kopman *et al.*[3] found a 5-min range for all levels of recovery. In Hayes *et al.* 's study,[8] manual ventilation had to be applied in 11% of cases to prevent hypoxia, and in Heier *et al.* 's study,[7] one subject was apneic for 9 min! The safety of succinylcholine is limited by these relatively sensitive patients, and interestingly, a decrease in dose does not have a marked effect on the upper range of duration (10, 10.5, and 11 min in Kopman *et al.* 's study[3] for 0.4, 0.6, and 1 mg/kg, respectively). This is not unexpected, because the half-life of succinylcholine is less than 1 min.[10] Doubling the dose of any drug should prolong its duration of action by one half-life, because it takes one half-life for the concentration to decrease by 50%, that is, to bring it down to that corresponding to a single dose.

What should we conclude? The traditional 1-mg/kg dose is not a bad choice, after all. It is perfect in average patients, providing excellent intubating conditions, and oxygenation can be maintained during the apnea period. But not all patients are average. A reduction of dosage, to 0.5–0.6 mg/kg, will not compromise intubating conditions dramatically, but neither will it shorten the period of apnea below the safe level in all subjects. Succinylcholine has limitations because of its variability. No single dose is perfect.

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Target-controlled Infusions for Intravenous Anesthetics

Surfing USA Not!

IN this issue of the Journal, Avram and Krejcie examine one of the conundrums that confront the design of target-controlled infusion (TCI) systems: The "standard" models used in pharmacokinetic and pharmacodynamic analyses are wrong.[1] Specifically, such models assume that the plasma concentration peaks at the instant a bolus of drug is administered. Obviously, the concentration in the plasma is zero at the moment the drug is administered, because the drug must move through the veins, get mixed in the heart and great vessels, and ultimately flow through the aorta to the sampling site. All of this takes 30–45 s. Those of us who write software for TCI systems or study these devices have dismissed these 30–45 s of time delay as a minor nuisance, but Avram and Krejcie demonstrate that the way this error is handled by the model can measurably affect performance of TCI systems.

The international reader of ANESTHESIOLOGY, accustomed to routine use of TCI systems, will doubtless find these results of interest. The North American reader, by contrast, will probably have no clue why these results are interesting, because exactly 0 of the estimated 13 million propofol anesthetics administered worldwide with TCI (written personal communication from James B. Glen, Ph.D., Glen Pharma, Knutsford, Cheshire, United Kingdom, June 2003) since the introduction of the Diprifusor (AstraZeneca, Macclesfield, Cheshire, United Kingdom) in Europe, Asia, the South Pacific, South America, and Africa have been performed in North America. The reason, at least in part, is that the U.S. Food and Drug Administration (FDA) has expressed a variety of concerns about computer-based drug delivery that have discouraged manufacturers from developing these systems, despite that the devices deliver approved drugs by approved routes at approved doses for approved indications. The specific concerns expressed by individuals within the FDA include "important health implications" that are not otherwise defined, "significant incremental risk" of anesthetic controllers (again undefined), concerns that "the use of high level languages, general-purpose computers, and complex operating systems results in products that are too elaborate for the product developer to verify entirely," and a hesitation to accept the extensive literature supporting the clinical use of TCI on the basis that published reports "emphasize positive outcomes."[2]

At the time these concerns were published (1995), AstraZeneca submitted regulatory documentation on the Diprifusor TCI system to FDA. Eight years later, there has been no discernible progress. In AstraZeneca's view, the primary problem has been the lack of regulatory precedent for a drug-device combination (written personal communication from James B. Glen, Ph.D., Glen Pharma, Knutsford, Cheshire, United Kingdom, August 2003). They have at various times been told that TCI would be regulated as a device (which it is), or as a drug. If regulated as a drug (the current FDA view), approval would require additional clinical studies and a revised package insert. The requirement for a change in the drug product labeling makes introduction of TCI drug delivery systems by device companies impossible, because device companies do not control the drug labeling.

Over the course of the 8-yr review, the FDA has demonstrated a poor understanding of the underlying scientific basis of TCI. Specifically, the FDA has not recognized that TCI devices can neither increase nor decrease underlying pharmacokinetic variability. As a result, the FDA has expressed unfounded concerns that the TCI mode of administration may lead to a greater frequency of adverse events. AstraZeneca performed a detailed review of sponsored TCI studies and the worldwide safety database on propofol, including propofol delivery by TCI, and found no evidence of increased risk of adverse events with TCI. This is consistent with the dozens of published manuscripts on the Diprifusor.

For the North American reader who is unfamiliar with these devices, we could perhaps explain them as the intravenous equivalent of a vaporizer, where one sets the desired concentration and a computer model, rather than physicochemical equilibration across the alveolus, aligns the plasma (and effect site) concentrations to the target concentration.[3] However, we will instead explain the concept using a popular North American sport: surfing. The concentration *versus* response curves of anesthetic drugs are typically fairly steep, like a wave approaching the shore. Surfing the steep portion of the concentration–effect relationship makes it possible to produce the therapeutic drug effect while preserving

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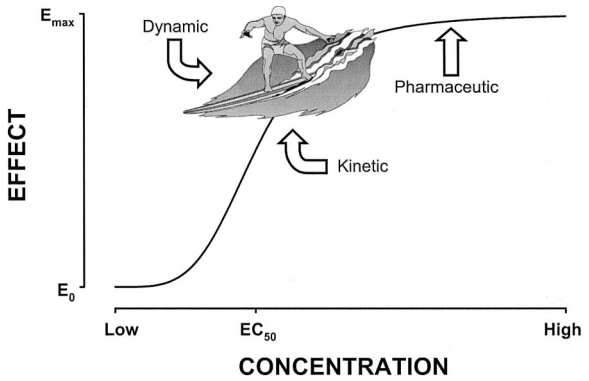

Fig. 1. A surfing analogy as a graphical explanation of how anesthesiologists use a combination of three approaches to administer anesthetics to maintain the anesthetic effect while making rapid recovery possible. Anesthesiologists target the upper portion of the "steep" part of the concentration–effect relationship so that small decreases in concentration translate into large decrements in drug effect at the end of the anesthetic; this can be visualized as a surfer riding the crest of a wave. The pharmacodynamic approach relies on the measurement of effect to guide drug administration. The pharmacokinetic approach relies on knowledge of a drug's disposition to deliver the drug to a specified target concentration. The pharmaceutic approach makes use of pharmacokinetically responsive agents, rendering the need to have exactness in the measurement of drug effect or drug delivery less important. E_{max} = maximal drug effect, E_0 = effect at zero drug concentration, EC_{50} = concentration that produces 50% of maximal drug effect.

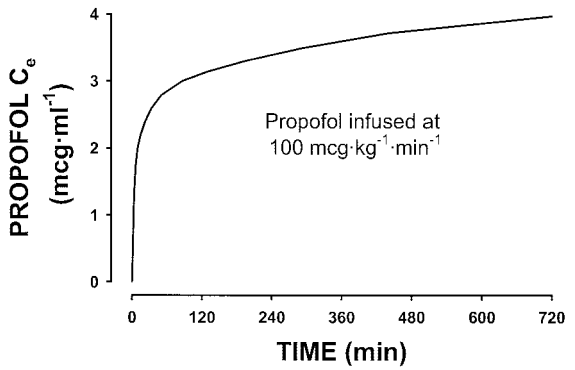

Fig. 2. The predicted concentrations resulting from a continuous infusion of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, based on the pharmacokinetic/pharmacodynamic model of propofol reported by Schnider *et al.*[5,6] Note that the relationship between infusion rate and concentration in the effect site changes with time until a steady-state is reached; the changes are particularly pronounced during the first several hours. C_e = effect site concentration.

the ability to decrease the level of effect rapidly at the end of the anesthetic with a small decrease in concentration. Figure 1 shows the anesthesiologist surfing near the crest of a wave. Surfing beyond the crest (*i.e.*, the flat portion of the concentration–effect relationship) offers no clinical advantage; it only results in prolonged recovery and increased adverse effects with no measurable increase in therapeutic effect.

Anesthesiologists simultaneously use three techniques to stay on the crest (*i.e.*, the steep portion of the concentration–effect relationship). They start with pharmacokinetic guidance, the cookbook. In our view, most physicians dose commonly used drugs within a narrow range, reflecting a fundamental trust in pharmacokinetics to yield the desired target concentration and drug effect. For example, how far do your propofol infusions (combined with reasonable doses of opioid) differ from something like: 2–2.5 mg $\cdot$ kg^{-1} bolus, then 100–150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 15 min, then 80–100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min, then 70–90 $\mu g \cdot kg^{-1} \cdot min^{-1}$ thereafter? Standard dosing guidelines such as these are based on the typical dose–concentration relationship (*i.e.*, pharmacokinetics). These standard dosing regimens represent a starting point in riding the wave's crest.

Inevitably, the initial attempt at riding the crest of the wave requires adjustment based on feedback from the patient. Perhaps the heart rate or blood pressure is higher than would be expected were the patient adequately anesthetized. Perhaps the Bispectral Index scale is 35, somewhat lower than clinically necessary. Pharmacodynamic guidance, the second technique used by anesthesiologists to stay on the crest of the wave, allows refining of the dose initially guided by pharmacokinetic knowledge to reflect the individual patient's unique pharmacologic characteristics.

The third guidance technique is pharmaceutical: choosing drugs with the right kinetic and dynamic properties to suit the patient and the duration of surgery, and to provide adequate safety margins between therapeutic and toxic doses.[4] Currently, implementing the pharmaceutical technique to target the crest of the wave often means choosing drugs with responsive pharmacokinetic profiles (*e.g.*, propofol, remifentanil) so that if the initial pharmacokinetic guidance results in an overdose (or under-dose) as suggested by pharmacodynamic feedback, the levels can be quickly decreased (or increased) to an appropriate range.

In the context of this surfing analogy, TCI can be viewed as a tool to explore the wave while riding it. With a standard infusion pump, the "wave" that the anesthesiologist sees is not the concentration *versus* effect curve, shown in figure 1; rather, it is an infusion rate *versus* effect curve. Unfortunately, this wave changes constantly. A rate of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of propofol translates to an effect site concentration of 0.5 $\mu g \cdot ml^{-1}$ at 1.5 min, 1.0 $\mu g \cdot ml^{-1}$ at 2.9 min, 2.0 $\mu g \cdot ml^{-1}$ at 9.9 min, 3.0 $\mu g \cdot ml^{-1}$ at 87 min, and 4 $\mu g \cdot ml^{-1}$ at 747 min (fig. 2).[5,6] The relationship between what is set on the device (the infusion rate) and what occurs in the patient changes every second. Thus, the wave the anesthesiologist is trying to surf constantly changes shape. If one suddenly needs to increase or decrease the concentration, the wave one was surfing has abruptly ceased to exist. So it becomes very difficult to characterize the wave, other than perhaps recognizing that "this patient needs more or less drug than average."

With TCI, the wave is the concentration *versus* response relationship shown in figure 1. Admittedly, it is the predicted concentration, not the true concentration (which is unknowable), but the critical point is that the wave doesn't change shape during the ride to shore. When the anesthesiologist finds that a certain effect site concentration yields a given effect at 10 min into the anesthetic, that same predicted concentration should produce the same effect at 600 min. More than 220 peer-reviewed articles in MEDLINE on TCI (as of June 2003, including 40 articles on the Diprifusor alone) attest to the ability of TCI to preserve the shape of the wave and assist the clinician in exploring the wave and riding it to shore. Moreover, constant advances, such as those described by Avram and Krejcie in this issue of the Journal, continue to refine the technology.

Thirty-five years have elapsed since Kruger-Thiemer first proposed using computers to deliver drugs based on pharmacokinetic models,[7] and more than 20 yr have elapsed since Helmut Schwilden first outlined the algorithm for anesthetic drugs.[8] Although these developments began in Germany, American investigators added fundamental contributions as well.[9–11] How ironic, therefore, that America, the country that brought the world surfing,[12] continues to deny physicians access to the fundamental tools to surf the concentration response curves of intravenous anesthetic agents.

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Anesthesiology 2003; 99:1041–3

Sepsis and Hypothermia

Call in the Granulocytes?

DELIBERATE hypothermia is used in a variety of therapeutic settings. Clinical applications of hypothermia include cerebral protection for out-of-hospital cardiac arrest and traumatic brain injury.[1,2] Hypothermia is also widely used intraoperatively, primarily for cerebral protection during neurosurgical procedures.[3] The rationale for hypothermia is to protect ischemic cells from injury by decreasing their metabolic demands, and, secondarily, to inhibit inflammatory mediator production.[4] Whereas this is laudable in areas of focal ischemia, the global implications of hypothermia are significant. Myriad processes are adversely affected by hypothermia, including increased rates of wound infection,[5] coagulopathy with increased blood loss,[6] adverse cardiac events,[7] and even prolonged hospital length of stay.[8] In this issue of the Journal, Torossian *et al.* examine the effects of hypothermia in a rodent model of abdominal sepsis.[9] Sepsis was induced with peritoneal contamination and infection with human stool bacteria. The primary outcome measure was survival, and in this clinically relevant model, hypothermia substantially increased mortality. Pretreatment of the rats with granulocyte colony-stimulating factor (G-CSF) completely reversed the hypothermia-induced mortality effect, actually improving survival beyond that seen with normothermia.

Whereas the benefits of decreasing cellular oxygen demands in ischemia are easily understandable, sorting out the implications of hypothermia on complex processes such as wound infection, inflammation, and he-

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mostasis is much more difficult. These processes rely on the coordinated interaction of multiple proteins, whose conformations may be altered by relatively subtle changes in temperature. It is the nature of this interaction that determines the balance between adequate host defense on the one hand, and overwhelming inflammation and multiple organ damage on the other. For example, significant coagulopathy results from even minor degrees of hypothermia.[10] The consequences of systemic hypothermia are profound. In patients with trauma, hypothermia is part of the grim prognostic triad of hypothermia, coagulopathy, and metabolic acidosis, and is associated with mortality, independent of fluid administration.[11] Therefore, hypothermia in the setting of nonneurologic trauma is clearly harmful, despite that massive trauma represents a clinical entity of global tissue ischemia—further evidence that hypothermia provides benefit primarily in areas of focal ischemia.

Sepsis is the systemic inflammatory response to infection. Like coagulation, the systemic response relies on the complex interaction of multiple proteins. Fever is a characteristic sign of infection, but sepsis may also present as hypothermia, as emphasized in the 2001 International Sepsis Definitions Conference (Washington, D.C., December 8–9, 2001).[12] The prognosis of patients with sepsis presenting with hypothermia, like those presenting with leukopenia, is thought to be worse than those presenting with leukocytosis and fever, respectively. Fever, clearly, is an important adaptive response that should be preserved. For example, it has long been clinical practice to treat fever in patients with infection. This practice is now being questioned. Active external cooling of healthy volunteers with fever does not reduce core temperature, but it increases metabolic rate and activates the autonomic nervous system.[13] Treatment of fever from viral syndromes with nonsteroidal antiinflammatory drugs may increase viral shedding and duration of symptoms,[14] and a randomized, placebo-controlled trial of ibuprofen in patients with severe sepsis did not demonstrate efficacy.[15] These and other studies confirm the importance of maintaining host defense in the setting of infection. It is also naïve to treat the inflammatory aspects of the systemic inflammatory response syndrome with high doses of nonspecific antiinflammatory agents, which may diminish the inflammatory response, but, ultimately, cause increased mortality.[16]

What are the mechanisms for an abnormal immune response in the setting of hypothermia? Both humoral and cellular immunity are adversely affected with lower temperature. In bacterial infections, neutrophil chemotaxis is an essential component of host defense. Hypothermia inhibits both neutrophil chemotaxis and killing *via* the respiratory burst, and delays induction of proinflammatory cytokine production by macrophages.[17] Torossian *et al.* showed that circulating levels of the cytokine interleukin-6 and the chemokine macrophage inflammatory protein-2 were both increased with hypothermia and ameliorated by either G-CSF administration or normothermia. Although the mortality data are robust, it is premature to speculate on mechanisms. It is tempting to conclude that the harmful effects of hypothermia were reversed *via* G-CSF's stimulation of neutrophil function, but close examination of the data suggests caution. For example, although neutrophil counts were increased by both hypothermia and G-CSF, functional phagocytic activity was not different in any of the groups. Cytokine and chemokine levels were decreased by normothermia and G-CSF, but little is known about what levels of these proteins are appropriate. It may be that G-CSF's salutary effects were on other leukocytes or on other aspects of neutrophil function. Cytokine concentrations are difficult to interpret in any study; recent data suggest that cytokine levels must be interpreted in the context of time and space, with high levels of proinflammatory cytokines advantageous early in infection and harmful later.[18] This construct would suggest that it might indeed be *harmful* to dampen the cytokine response early in infection, when host defense is critical.

How, then, should we proceed in patients in whom induced hypothermia is contemplated and who are at risk for systemic infection? Hypothermia alone clearly results in an increased rate of wound infection, coagulopathy, and other postoperative complications[5]; therefore, it should be used sparingly. More promising therapies using focal cooling, especially for the brain, are on the horizon.[19] Is it possible to ameliorate the adverse effects of hypothermia with administration of G-CSF or other immune stimulants to these patients? The data to date do not support this practice. However, enough provocative animal and human data now exist to justify a large, randomized trial.

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A Role for Cyclooxygenase-1 in Neuropathic Pain?

CYCLOOXYGENASES (COX) and prostaglandins are key players in inflammatory diseases and contribute significantly to the accompanying pain sensitization. More than 10 yr of research have shown that, in particular, those prostaglandins that are produced by the inducible COX-2 isoenzyme trigger inflammatory reactions in the tissue. Two articles in this issue of the Journal now suggest that the constitutively expressed COX-1 might be similarly important for the development of neuropathic pain—at least in animal models. Zhu and Eisenach[1] show that spinal COX-1 expression increases early in experimental neuropathy. Hefferan *et al.*[2] provide data suggesting that inhibition of COX-1 during early stages prevents the development of two typical symptoms of painful neuropathies: allodynia, which describes a state of increased pain sensation in response to stimuli that are usually not sensed as painful, such as light touch; and hyperalgesia, which is an increased sensitivity to noxious (painful) stimuli.

Both studies were conducted in closely related standard animal models of neuropathic pain. Zhu and Eisenach[1] used the partial peripheral nerve transsection[3] and Hefferan *et al.*[2] the peripheral nerve ligation model.[4] Because both of these models involve surgical procedures, they are associated with tissue damage and trigger some inflammatory response. They are therefore not universally accepted as "good models" resembling the most frequent forms of neuropathic pain in patients, which occur in the course of metabolic diseases such as diabetes or renal failure.[5] Nevertheless, both groups have performed reasonable controls to show that the inflammatory component was, at least, not dominating.

If we assume that the results of both groups can be transferred to the clinical situation of patients, *e.g.*, after traumatic nerve injury, their results bear important consequences for the treatment or prevention of neuropathic pain. Unlike inflammatory pain, neuropathic pain is difficult to treat. Classic cyclooxygenase inhibitors as well as opioids are only marginally effective, and physicians often use anticonvulsants and drugs with unknown mechanisms of action, such as gabapentin, with variable success. The present studies may provide a rational basis for an early, or possibly even prophylactic, treatment of neuropathic pain. In light of the short time period, such a prophylactic intervention will not be possible in metabolic neuropathies. However, the present results may promote clinical studies in patients with acute nerve injuries. One might speculate that cyclooxygenase inhibitors might be given as premedication before elective surgery when the patient is at risk for the development of painful neuropathies (*e.g.*, before amputation). Cyclooxygenase inhibitors might therefore find a place in so-called preemptive analgesia in neurosurgery.

What COX inhibitor, then, should be used to prevent the development of painful neuropathies? Selective COX-2 inhibitors have gained enormous publicity over the past years as a novel class of antiinflammatory and analgesic drugs with a largely reduced risk of upper gastrointestinal bleeding, which often limits the long-term use of classic (nonselective) cyclooxygenase inhibitors.[6] The work by Hefferan *et al.*[2] points to selective

This Editorial View accompanies the following articles: Zhu X, Eisenach JM: Cyclooxygenase-1 in the spinal cord is altered after peripheral nerve injury. ANESTHESIOLOGY 2003; 99:1175–9; and Hefferan MP, O' Rielly DD, Loomis CW: Inhibition of spinal prostaglandin synthesis early after L5/L6 nerve ligation prevents the development of prostaglandin-dependent and prostaglandin-independent allodynia in the rat. ANESTHESIOLOGY 2003; 99:1180–8.

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COX-1 inhibitors, which, by the way, may also exhibit reduced gastrointestinal toxicity.[7] This question, however, is far from being settled. In the spinal cord dorsal horn, and in a number of other organs, including the kidney, COX-2 is already expressed at low levels under physiologic conditions but becomes dramatically increased after peripheral tissue inflammation. It is not clear why only COX-1 should contribute to painful neuropathy. In fact, if one looks carefully at the results by Hefferan *et al.,*[2] it is clear that the selective COX-1 inhibitor SC-560 was less effective than the nonselective S-ibuprofen. Because no dose–response relationship has been performed, this interpretation must be made with caution. If it turns out to be true, one would therefore expect that a significant inhibition would also be likely after treatment with a selective COX-2 inhibitor. So, in a prospective trial, we would suggest comparing all three classes of COX inhibitors.

Two other unresolved questions are related to the pathophysiology of neuropathic pain. How do prostaglandins promote the development of painful neuropathies, and why are they only effective early in the course of the disease? Two recent publications have shed light on the molecular mechanisms of prostaglandin E_2 in the spinal cord. Baba *et al.*[8] showed that prostaglandin E_2 directly depolarizes wide dynamic range neurons in the deep dorsal horn, and Ahmadi *et al.*[9] demonstrated that prostaglandin E_2 reduces the inhibitory tone of the neurotransmitter glycine onto neurons in the superficial layers of the dorsal horn, thereby causing a disinhibition of spinal nociceptive transmission. Both mechanisms can explain why prostaglandin E_2 facilitates pain sensation. In addition, they may both contribute to plastic changes in neurotransmission between dorsal horn neurons, which may become prostaglandin-independent and largely irreversible during the disease course. In any case, the novel results point to a new possibility to prevent neuropathic pain, which, if already established, is largely refractory to current treatment options.

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