Site-1 Sodium Channel Blockers as Local Anesthetics

Will Neosaxitoxin Supplant the Need for Continuous Nerve Blocks?

Laura A. Lahaye, M.D., John F. Butterworth IV, M.D.

The ideal agent for regional anesthesia would have high affinity (and be highly specific) for the target site, have a rapid onset of action, have minimal local or systemic toxicity, and would provide a long duration of analgesia. Unfortunately, traditional local anesthetics incompletely fulfill these criteria. These compounds bind the voltage-gated sodium channels responsible for producing peripheral nerve block with relatively low affinity and limited specificity. As a consequence, the relatively large doses of local anesthetics that are often required to produce regional anesthesia have an increased likelihood of systemic toxicity. Nerve blocks produced by single injections of plain local anesthetics exhibit a normal course of resolution that limits the analgesic benefit to the immediate postoperative period. Additives (e.g., dexamethasone) can modestly increase the duration of the more potent, longer-persisting local anesthetics to a maximum of about 24h. Continuous local anesthetic infusions can be used to produce prolonged analgesia but increase the complexity of the nerve block procedure. Now it appears that a neurotoxin may provide a potential alternative to local anesthetic infusions when prolonged analgesia is desired. In this issue of Anesthesiology, the articles by Lobo et al. and Templin et al. provide evidence for the safety and analgesic potential of neosaxitoxin, a site-1 sodium channel blocker.

Neosaxitoxin and similar neurotoxins have low affinity for cardiac sodium channels (Na1.5) relative to their affinity for the sodium channel isoforms (Na1.7, Na1.8, and others) found in peripheral nerves. The separation in neosaxitoxin affinities for sodium channel isoforms is at least an order of magnitude greater than that for any conventional local anesthetic. Therefore, it is not surprising that animal studies have demonstrated a reduced potential for cardiotoxicity with neosaxitoxin as compared with bupivacaine. Humans ingesting large doses of these neurotoxins have been observed to have life-threatening neuromuscular dysfunction manifesting as respiratory arrest in the notable absence of cardiotoxicity. While the safety profile is of great concern, so too are the block characteristics in the postoperative period. In many cases, the ideal agent would provide excellent analgesia while allowing use of the affected limb and providing a barrier to injury with retention of motor function and proprioception, and it remains unclear whether neosaxitoxin alone or in combination will exhibit these traits.

Although investigational studies involving human subjects are limited, we know that neosaxitoxin provided prolonged analgesia when infiltrated at port sites during laparoscopic surgery in humans. When given in combination with bupivacaine, neosaxitoxin had a duration of action outlasting either drug alone when injected subcutaneously in healthy volunteer subjects. Studying cutaneous neosaxitoxin injections in volunteers, Lobo et al. have described safety and adverse event profiles by using rating scales and comprehensive physiologic monitoring. Although a prior clinical investigation supported the safety of neosaxitoxin, the current study’s use of measured negative inspiratory force, grip strength and vital capacity measurements, correlated with detailed drug concentration data provide greater reassurance regarding safety. Both neuromuscular and respiratory function remained stable at the doses studied and symptoms were correlated with administered dose.

---

*Image: Micrograph of cyanobacteria (blue-green algae), from which neosaxitoxin is derived. From Sinclair Stammers/Science Photo Library.*

Corresponding articles on page 873 and page 886.

Accepted for publication July 2, 2015. From the Department of Anesthesiology, Virginia Commonwealth University, Richmond, Virginia.

Copyright © 2015, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. Anesthesiology 2015; 123:741-2
Given the relative potency of neosaxitoxin and its apparent ability to provide prolonged sensory blockade with limited cardiotoxicity when administered alone, one may wonder if its advantages are not offset with the addition of a traditional local anesthetic such as bupivacaine. Previous work has demonstrated that to maximize block duration while minimizing toxicity, a combination of neurotoxin, local anesthetic, and vasoconstrictor may best be used.11 When either local anesthetic or neurotoxin is administered alone in small doses, incomplete or unreliable sensory blockade may result. However, the combination at similarly small doses may provide excellent block characteristics. These findings suggest that in combination, the favorable characteristics of each drug are enhanced while minimizing undesirable side effects.

If clinical studies have begun, why is there need for further animal investigations before regulatory approval? The models of systemic toxicity used by Templin et al. provide greater detail regarding the safety profile of neosaxitoxin in rodents. Specifically, there was no enhancement of neosaxitoxin toxic effects when it was combined with bupivacaine, despite considerable prolongation of analgesia when the two drugs were given together. While local anesthetic systemic toxicity is of great concern, so too is localized tissue toxicity. The histologic evaluation of rat sciatic nerves showing low injury scores after perineural injection provides another element in the mounting case for further clinical trials of neosaxitoxin (especially with bupivacaine) in humans.

Despite these promising findings, much remains unknown about the safety and clinical utility of neosaxitoxin. Questions yet unanswered include the following: What is the maximum safe dose when injected at typical regional anesthetic sites? How do comorbid medical conditions influence dosing and safety? How closely will the reported pharmacokinetic data mimic the drug concentrations that would be achieved when the drug is injected at typical sites for regional anesthesia?

In summary, the findings by Lobo et al.3 and Templin et al.4 provide substantial new knowledge, which should guide further investigations of neosaxitoxin as a local anesthetic. We look forward to future work addressing the safety of neosaxitoxin when administered for regional analgesia at a greater range of doses to patients undergoing surgery.

Competing Interests
The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence
Address correspondence to Dr. Lahaye: llalahaye@mcvh-vcu.edu

References