

"Above All, Do No Harm"

Hippocrates

LOCAL anesthetics block voltage-gated sodium channels, thereby preventing generation of action potentials and their propagation along the nerve. However, complete sensory blockade is generally accomplished only with simultaneous sympathetic and motor blockade, thereby often leading to unwanted adverse side effects. To date, no agent or method translatable into current clinical practice has been shown to elicit usable, predominantly sensory nerve blocks. In this issue of ANESTHESIOLOGY, Brummett *et al.*[1] report the approach of combining ropivacaine with an α_2 agonist (dexmedetomidine), thereby dose-dependently increasing the duration of sensory blockade over motor blockade in a rat sciatic nerve block model. Logically, the questions of whether and how to progress to clinical studies arise.

The clinical development of several new, promising local anesthetics had to be halted because of adverse side effects, *e.g.*, failure in late clinical trials due to neurotoxicity. These local anesthetics, as well as local anesthetics currently in use, may cause histologically detectable toxicity in various animal models even when used in modest doses. Lidocaine and bupivacaine (approved by the US Food and Drug Administration in 1947 and 1963, respectively) are still the two most widely used local anesthetics. Two homologs of bupivacaine, ropivacaine and levobupivacaine, are available, but neither is genuinely less toxic, as evidenced by recurring case reports of their toxicity.

Besides reasons of neurotoxicity, development strategies for sensory-selective nerve blockade (*sensory-selective* and *differential block* are commonly used terms and are often interchanged with *pain-selective* and *nociceptor-selective*) are plagued by simple inefficacy. A major effort has taken place to develop Na^+ channel blockers for specific channel subtypes, because Na_v 1.7, $Na_v1.8$, and $Na_v1.9$ are expressed exclusively on peripheral nociceptors.

A "hot" target for nociceptive-specific blockade is $Na_v1.7$, because this channel determines the ability of a nerve to transmit pain sensation. The importance of Na_v 1.7 has become increasingly evident through genetic correlation of this channel with congenital abnormality of pain perception. Loss-of-function mutations of $Na_v1.7$ are reported in patients with associated neurologic insensitivity, in which patients have isolated lack of sensory function for pain and smell.[2] On the other hand, several gain-of-function mutations of genes related to the regulation or function of $Na_v1.7$, resulting in overactivity of this channel, are found in patients with two painful congenital disorders, erythromelalgia and paroxysmal extreme pain disorder. Both are congenital conditions whereby patients are afflicted by severe episodic pain attacks accompanied by cutaneous flushing.[3] Unfortunately, although $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ are ideal targets for developing more effective drugs, none of the existing compounds have proven suitable for clinical use, mostly due to low bioavailability.

So why does the approach of Brummett *et al.* of combining dexmedetomidine with ropivacaine seem to be a "fast-track" approach? Others have used very effective combination approaches, *e.g.*, transient receptor potential vanilloid subtype 1 channel–mediated local anesthetic delivery (*e.g.*, QX-314) into C-fibers, yielding even pain-selective nerve blockade.[4] However, the introduction of the investigational drug QX-314 will take many years, whereas dexmedetomidine is already in clinical use, although for a different indication (approved by the US Food and Drug Administration for intravenous sedation). Although the combination of ropivacaine and dexmedetomidine certainly is not intended to achieve sensory-selective blockade, current work suggests that the combination prolongs the sensory block more than the motor block, compared with ropivacaine alone.

The peripheral mechanism of dexmedetomidine is not known. Other α_2 agonists, such as clonidine, have been found to enhance sensory blockade through the hyperpolarization-activated cation current (I_h current).[5] Similarly, it has been suggested that a direct inhibition of tetrodotoxin-resistant Na^+ channels may contribute to the antinociceptive effects of clonidine and dexmedetomidine.[6,7] Laboratory studies using clonidine have been limited to examining its efficacy in combination with short-acting drugs such as lidocaine or procaine. The effect of clonidine added to a long-acting local anesthetic (bupivacaine, levobupivacaine, and ropivacaine) for peripheral nerve blocks has not been studied *in vitro*, whereas results in human studies have been mixed.[8] The favorable results by Brummett *et al.*[1,9] investigating long-acting local anesthetics combined with dexmedetomidine for peripheral nerve block, allow for cautious opti-

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mism, but only prolonged clinical trials will provide a definitive answer.

Traditionally, regulatory agencies (*e.g.*, US Food and Drug Administration) requires evidence of lack of systemic and neurotoxicity in two animal species, a small (rodent) and a large one, to grant permission for a phase 1 clinical trial. The guiding principle has to be *primum non nocere*: "first do no harm." Because of unfavorable adverse effects, most drugs never find their way to clinical trials. So, where does the combination of ropivacaine with dexmedetomidine stand?

Systemic toxicity seems not to be an issue, as long as the systemic uptake from the perineural space does not exceed that which would be seen with approved intravenous dosing. One can reasonably assume that plasma levels due to vascular absorption of perineurally injected dexmedetomidine are less than or comparable to those obtained with the approved dexmedetomidine intravenous bolus and infusion dose for sedation. The potential sedation when dexmedetomidine is used as an additive for regional anesthesia would actually be favorable in most circumstances.

Neurotoxicity clearly will be of major interest here. In a preceding study, Brummett *et al.*[9] compared 0.5% bupivacaine alone with 0.5% bupivacaine plus 0.005% dexmedetomidine in the same rat sciatic nerve model. They assessed neuropathology of harvested nerves at 24 h and 14 days, by means of hematoxylin and eosin, and Luxol fast blue for axons and myelin staining. (Of note, some neuropathologists argue that additional staining methods are potentially more sensitive for detection of toxicity. Nevertheless, in general, mild histopathologic findings do not result in detectable neurologic symptoms.) Interestingly, in terms of inflammatory parameters, and strongly supportive of potential clinical use of perineural dexmedetomidine, there was less inflammation in the bupivacaine–dexmedetomidine group compared with the bupivacaine-alone group. The finding that dexmedetomidine attenuated perineural inflammation is consistent with previous work in a rat nerve injury model using clonidine.[10] In the current study,[1] the authors performed identical neuropathologic assessment with the highest dose/concentration of the ropivacaine combined with dexmedetomidine group and did not detect any neurotoxicity. Previous studies in similar rat models have detected neurotoxicity in experimental drugs (amitriptyline[11]) and local anesthetics.[12]

In general, neurotoxicity is excluded by higher drug dosage/concentration and longer exposure than clinically assumed. The concentration of dexmedetomidine used here seems to be much larger than would be used clinically. However, a statement of neurotoxicity after prolonged drug exposure cannot be inferred by this model, because catheters, inserted into the perineural space of rat sciatic nerves, would definitely dislocate.

In summary, it appears that the current study by Brummett *et al.*[1] demonstrated *primum non nocere*, because it seems that the dosages/concentrations chosen are much higher than those to be used clinically and are lacking toxicity. Taken together, this animal work supports an application for human investigation of the combination of ropivacaine and dexmedetomidine for peripheral nerve block, but not widespread clinical use. In addition, the ethical position of modern anesthesia journals states that this investigation should be performed only after consultation with federal regulatory agencies. Hopefully, a phase 1 trial in the near future will provide an answer to whether we are getting closer to the long desired goal of achieving a predominantly sensory/nociceptive block.

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