Pharmacologic Properties of Novel Local Anesthetic Agents in Anesthesia Practice

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KEYWORDS

• Local anesthetics • Delivery systems • Site-1 sodium channel blockers • Adjuvants • Liposomal bupivacaine • Proliposomal ropivacaine • Tetrodotoxin • Neosaxitoxin • Bupivacaine

KEY POINTS

- Duration of traditional amide-based and ester-based local anesthetics when used in peripheral blocks is limited to a few hours.
- Several new approaches to extending the therapeutic duration of peripheral blocks are available or are currently under development.
- Naturally occurring site-1 selective sodium channel blockers can provide longer peripheral blocks, while limiting neurologic or cardiac toxicity.
- Various local anesthetics delivery systems can provide longer block duration, lower postoperative pain, lower opioid requirement, lower hospital cost, and/or repeatable triggered local anesthetics release.
- Novel adjuvants of local anesthetics, such as magnesium and dexmedetomidine, can extend peripheral block duration and lower postoperative opioid requirement.

INTRODUCTION

Local anesthetics (LAs) are part of the multimodal approach to provide intraoperative and postoperative pain management. However, the duration of traditional amide-based and ester-based LAs is normally limited to only a few hours. Techniques, such as continuous catheter placement or multiple serial injections, can be used to enhance the duration and effect of LAs for postoperative pain control. However, these

Disclosure of Relationship with Commercial Company: The authors have nothing to disclose.

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Anesthesiology Clin ■ (2017) ■–■
http://dx.doi.org/10.1016/j.anclin.2017.01.019 anesthesiology.theclinics.com

approaches increase the risk of infection, toxicity, and cost. Therefore, alternative methods of extending the clinical duration of nerve blocks have always been a topic of significant interest. This article focuses on 3 newer approaches to extending the therapeutic duration of peripheral blocks:

1. Site-1 sodium channel blockers, such as tetrodotoxin (TTX) and neosaxitoxin (NeoSTX)
2. Novel LA delivery systems
3. The adjuvants, magnesium and dexmedetomidine.

NATURALLY OCCURRING SITE-1 SELECTIVE SODIUM CHANNEL BLOCKERS

NeoSTX and TTX are selective sodium channel blockers that are naturally produced by animals such as pufferfish and shellfish. Both substances have been used for decades in laboratory as a pharmacologic tool to selectively block and study a subset of sodium channels, specifically the voltage-gated sodium channels Nav1.1, Nav1.3, Nav1.6, and Nav1.7.[1] These compounds have a different mechanism of action than lidocaine. Specifically, they interact with the extracellular aspect of the α-subunit of the voltage-gated sodium channel and thus can act in a synergistic manner with traditional LAs.[2–4] Notably, there are subtypes of the TTX-sensitive voltage-gated sodium channels that are preferentially expressed in peripheral neurons (eg, Nav1.7 in dorsal root ganglion and sympathetic neurons). This may open up the possibility of blocking peripheral pain conduction without affecting cardiac or central nervous system electrical conduction.[1] For example, patients with specific mutations in Nav1.7 show a severely impaired pain perception from birth but are otherwise normal, including having a normal proprioception, temperature sensation, and sympathetic response.[5] Selective naturally occurring sodium channel blockers, such as NeoSTX and TTX, have come into renewed attention because traditional amide-based and ester-based LAs do not reliably provide analgesia beyond 6 to 12 hours via single-shot injection.[6] Also, intravascular injection or excessive dosage of traditional LAs can cause neurologic or cardiac toxicity. In contrast, toxicities from NeoSTX and TTX are primarily due to diaphragmatic paralysis and respiratory failure, which are reversible.

Among the selective sodium channel blockers, NeoSTX has been demonstrated to be the most potent both in vitro and in vivo.[7,8] It differs from saxitoxin (STX) by the addition of 1 oxygen atom.[9] Like the other substances in this family, NeoSTX is a site-1 sodium channel blocker that selectively binds to the outer pore of the voltage-gated sodium channels, interrupting the depolarization of excitable cells and propagation of action potential.[10] Unlike traditional LAs, in studies of anesthetized animals NeoSTX seemed to be devoid of cardiotoxicity.[11] An overdose of NeoSTX produces reversible skeletal and respiratory muscle weakness, which can be treated with respiratory support until the patient makes full recovery. This lack of significant cardiac effect may be secondary to the extremely low binding affinity of cardiac Purkinje fibers to selective sodium blockers.[12] In addition, although TTX can cause substantial hypotension via direct action on smooth muscle cells and sympathetic nerves, this is less of an issue with STX-related compound.[13] Similar to LAs, the addition of vasoconstrictors, such as epinephrine, can help reduce systemic concentration levels, which results in improved potency and duration while decreasing systemic toxicity.[14]

More recently, multiple in vivo studies and randomized clinical trials have examined the LAs properties and safety profile of NeoSTX. In randomized studies of healthy male subjects, subcutaneous injection of NeoSTX produced a significantly longer effect on pain threshold compared with bupivacaine, which was increased even further by the coinjection of epinephrine. Notably, none of the volunteers reported any motor