



# Development of long-acting local anesthetics: a long way from basic research to clinical application

Yutaka Oda<sup>1</sup>

Received: 16 July 2024 / Accepted: 1 August 2024 / Published online: 9 August 2024  
© The Author(s) under exclusive licence to Japanese Society of Anesthesiologists 2024

**Keywords** Long-acting local anesthetics · QX-314 · Voltage-gated sodium channel blockers · Site-1 sodium channel blockers · Controlled-release local anesthetics

## Introduction

Management of postoperative pain remains one of the most challenging aims of modern anesthesia. Opioids have been the mainstay of postoperative pain management for decades; however, they may also lead to adverse events, e.g., respiratory depression, tolerance and hyperalgesia. Regional anesthesia techniques have shown their benefit by reducing opioid use and shortening the stay in the postanesthesia care units, thus local anesthetics represent an important alternative to the use of systemic opioids.

An ideal local anesthetic should have (1) rapid onset of dense blockade, permitting surgery under local or regional anesthesia, (2) persistence of dense and reliable blockade more than 24 h, and (3) a prolonged period of partial blockade over the next 2 or 3 days. Since the synthesis of lidocaine in 1943, numerous compounds have been developed for prolonging the duration of analgesia. However, currently available agents have a limited duration of analgesia for covering the expected time course of postoperative pain. Perineural and wound catheter infusions can extend the duration of analgesia. Conversely, catheters are sometimes more cumbersome to place compared with single-shot blocks, can dislodge and require tethering the patient to a pump. These limitations promoted the researchers to seek new long-acting local anesthetics.

During the past decades, numerous efforts were undertaken, aiming novel agents with various application strategies, with the primary goal to achieve a safe, reliable and long-lasting analgesic effect with minimal motoric

restrictions. Here, I review the current literature to outline the promising strategies and discuss their benefits and limitations.

## Quaternary lidocaine derivatives: QX-314 and QX-OH

QX-314 is a quaternary lidocaine found during the early phase of development of long-acting local anesthetics [1]. It is a permanent cationic compound without cell membrane permeability, while enters into the neuronal cells via the transient receptor potential vanilloid 1 (TRPV1) channel, predominantly expressed in unmyelinated afferent nerve fibers. TRPV1 is activated by capsaicin, resulting in long-acting analgesic effect of QX-314 with a significantly shorter duration of motor block. The current local anesthetics such as lidocaine and bupivacaine also excite the TRPV1 channel, and QX-314 in combination with these anesthetics produces a long duration of action via the TRPV1 channels. However local tissue toxicity mainly through activation of TRPV1 to mediate calcium influx, and higher systemic toxicity than lidocaine prevent QX-314 from being an ideal long-acting local anesthetic [2].

QX-OH is a hydroxylated form of QX-314 with significantly prolonged duration of sensory block compared with the corresponding concentration of QX-314. Although the onset of analgesic effect is slow, approximately 30–60 min with QX-OH alone, a combination of QX-OH and levobupivacaine significantly shortened the onset time to 10 min and extended the sensory block time to approximately 17 h without prolonging motor block time after sciatic nerve block in rats [3]. QX-OH also induces concentration-dependent local tissue toxicity. Both QX-314 and QX-OH remain in the cell

✉ Yutaka Oda  
yutakaodayutaka@gmail.com

<sup>1</sup> Department of Anesthesiology, Osaka City Juso Hospital, 2-12-27, Nonaka-kita, Yodogawa-ku, Osaka 532-0034, Japan

for longer period of time due to their non-permeability to the membrane, thus enhancing cytotoxic effects.

## Voltage-gated sodium channel antagonists

Of the nine voltage-gated sodium channels,  $Na_v1.3$ ,  $Na_v1.7$ ,  $Na_v1.8$  and  $Na_v1.9$  have been implicated in nociceptive transmission and/or contribution to the hyperexcitability characteristics of inflammatory and neuropathic pain conduction. Of note  $Na_v1.7$  is expressed predominantly in primary afferent nociceptive and sympathetic neurons. Specific mutations that lead to a loss of function in  $Na_v1.7$  are associated with a congenital indifference to pain, whereas those mutations causing a gain of function are being found in hereditary pain disorders [4]. Thus,  $Na_v1.7$  has become an important therapeutic target. Aryl sulfonamides were identified as selective  $Na_v1.7$  antagonists in animal models. They bind to the voltage-sensor region of the fourth pseudosubunit domain (VSD4) of the voltage-gated sodium channels on the external side of the plasma membrane [5]. Of those  $Na_v1.7$  antagonists, PF-05089771 provided favorable analgesic effect in subjects with inherited erythromelalgia, although its analgesic effect for diabetic peripheral neuropathy was less than that of pregabalin [6]. Vixotrigine is a recently synthesized, pyrrolidine-based sodium channel blocker, which inhibits a broad spectrum of voltage-gated sodium channel subtypes. Oral vixotrigine is effective for reducing pain scores in patients with idiopathic or diabetic-associated small fiber neuropathy in a recent clinical trial [7], although its effect on postoperative pain remains unclear.

## Site-1 sodium channel blockers

Site-1 sodium channel blockers bind to the outer pore of the voltage-gated sodium channels thereby blocking impulse generation and propagation. Saxitoxin and neosaxitoxin are small molecules known as shellfish poison. Tetrodotoxin is another site-1 toxin derived from puffer fish. These molecules have poor affinity for the cardiac isoform of the sodium channel, with reduced cardiotoxicity compared with currently available local anesthetics. Subcutaneous injection of neosaxitoxin  $\leq 40 \mu\text{g}$  in 10 ml saline decreased cutaneous sensitivity to mechanical and thermal stimuli which lasted for approximately 7 h in human volunteers [8]. However, the maximum tolerated dose is limited because of its local tissue toxicity. The intensity of cutaneous sensory block by neosaxitoxin was less than that of the same volume of 0.2% bupivacaine, and a combination with bupivacaine or bupivacaine added with adrenaline was required for intense nerve block and for prolonged effect longer than 24 h. Subcutaneous injection of tetrodotoxin  $\leq 90 \mu\text{g}$  provided favorable

analgesic effects for cancer pain and chemotherapy-induced neuropathic pain [9]. Both neosaxitoxin and tetrodotoxin are highly hydrophilic and initial rapid absorption from the injection site resulting in an increase of plasma concentration limits the dose. Perioral numbness shortly after injection of these site-1 toxins suggests the central nervous system toxicity, although they have been believed to be devoid of the central nervous system and cardiovascular side effects.

## Controlled-release local anesthetics

Drug delivery systems encapsulating currently used local anesthetics have been developed, with the goal of safely extending the duration of analgesia while reducing the risk of systemic toxicity. An effective drug delivery system requires reduced tissue reaction, efficient drug release capability, good stability, steady degradation rates of a biodegradable carrier: liposomes, polymer-based carriers, metallic particles and others have been developed for satisfying these requirements [10, 11].

Liposomal bupivacaine (Exparel<sup>®</sup>) is the first formulation approved by the US Food and Drug Administration (FDA), which is currently applied for local infiltration analgesia and for brachial plexus block. Exparel<sup>®</sup> is bupivacaine encapsulated in multivesicular liposomes (DepoFoam<sup>®</sup>), where bupivacaine is extremely slowly released from and its plasma levels last for 72 h after topical application [12]. Despite its expected analgesic effect lasting up to 72 h, its potency  $> 24$  h after application is still controversially discussed, which has decreased initial enthusiasm [13].

One of the mechanisms of local anesthetic failure is the reduction of its diffusion across the nerve cell membrane in the affected area due to tissue acidity caused by the inflammatory process from injury, infection or surgical intervention [14]. HTX-011, commercially named Zynrelef<sup>®</sup>, is an extended release, dual-acting local anesthetic formulation containing bupivacaine and meloxicam, a non-steroidal anti-inflammatory agent. HTX-011 provides simultaneous diffusion of the active ingredients in a controlled manner over 72 h with a novel biological polymer technology, and maintains physiological pH in the microenvironment in the surgical site and reduce cytokine-induced peripheral sensitization. HTX-011 can be applied to the affected tissues in the surgical incision without a needle, producing analgesic effect lasting for  $> 24$  h [15].

SABER-Bupivacaine<sup>®</sup> (Posidur<sup>®</sup>) is a sustained-release formula of bupivacaine in a matrix composed of sucrose acetate isobutyrate (SAIB) and benzyl alcohol. SABER-Bupivacaine<sup>®</sup> was approved by the FDA for subcutaneous injection under direct arthroscopic guidance during shoulder surgery [16]. SABER-Bupivacaine<sup>®</sup> significantly reduced pain and reduced the consumption of morphine over 72 h

after arthroscopic subacromial decompression in a randomized, placebo-controlled trial [17].

One of the most serious adverse effects of bupivacaine is systemic toxicity, which is most often caused by inadvertent intravascular injection during administration in liquid form, and formulation that safely deliver bupivacaine over time into the surgical site for prolonged postoperative pain is needed. XaraColl<sup>®</sup> is a bioresorbable bupivacaine collagen-matrix implant that produces extended delivery of bupivacaine directly at the site and avoids the risk of accidental injection. It is a combination of bupivacaine and a drug delivery component of bovine collagens designed to be placed in the surgical site, with analgesic duration of approximately 24 h [18]. It has been approved by FDA in 2021 for analgesia following open inguinal hernia repair in adults.

In conclusion, thus far, many promising and innovative pharmacological developments have occurred with the aim to extend the duration for regional anesthesia. Among the four categories of currently developing local anesthetics described above, only sustained-release bupivacaine encapsulated with liposomes, polymers or collagen-matrix implants is presently available for clinical use. Although the reasons for preventing other compounds from clinical application seem to be complicated, they would be summarized as follows: high systemic toxicity besides delayed onset of analgesic action requiring adjuvants such as capsaicin for quaternary lidocaine derivatives; relatively small analgesic potency compared with currently used analgesics as shown for sensory-selective analgesic agents; local tissue and nerve toxicity as reported for site-1 toxins. Increasing costs required for development of new agents will be reflected in the price of them, leading to increased hospitalization cost. Cost-effectiveness is another important theme for development new agents.

**Funding** None.

## Declarations

**Conflict of interest** None.

**Approval from the institutional review board** Not applicable.

**Informed consent** Not applicable.

## References

1. Binshtok AM, Bean BP, Woolf CJ. Inhibition of nociceptors by TRPV1-mediated entry of impermeant sodium channel blockers. *Nature*. 2007;449:607–10.
2. Wang Q, Zhang Y, Liu J, Zhang W. Quaternary lidocaine derivatives: past, present, and future. *Drug Des Devel Ther*. 2021;15:195–207.
3. Yang Y, Wang C, Liu J, Liao D, Zhang W, Zhou C. QX-OH/levobupivacaine: a structurally novel, potent local anesthetic produces fast-onset and long-lasting regional anesthesia in rats. *J Pain Res*. 2022;15:331–40.
4. Hameed S. Nav1.7 and Nav1.8: role in the pathophysiology of pain. *Mol Pain*. 2019;15:1–11.
5. Jo S, Bean BP. Lidocaine binding enhances inhibition of Nav1.7 channels by the sulfonamide PF-05089771. *Mol Pharmacol*. 2020;97:377–83.
6. McDonnell A, Collins S, Ali Z, Iavarone L, Surujbally R, Kirby S, Butt RP. Efficacy of the Nav1.7 blocker PF-05089771 in a randomised, placebo-controlled, double-blind clinical study in subjects with painful diabetic peripheral neuropathy. *Pain*. 2018;159:1465–76.
7. Faber CG, Attal N, Lauria G, Dworkin RH, Freeman R, Dawson KT, Finnigan H, Hajihosseini A, Naik H, Serenko M, Morris CJ, Kotecha M. Efficacy and safety of vixotrigine in idiopathic or diabetes-associated painful small fibre neuropathy (CONVEY): a phase 2 placebo-controlled enriched-enrolment randomised withdrawal study. *EClinicalMedicine*. 2023;59: 101971.
8. Lobo K, Donado C, Cornelissen L, Kim J, Ortiz R, Peake RW, Kellogg M, Alexander ME, Zurakowski D, Kurgansky KE, Peyton J, Bilge A, Boretsky K, McCann ME, Berde CB, Cravero J. A phase 1, dose-escalation, double-blind, block-randomized, controlled trial of safety and efficacy of neosaxitoxin alone and in combination with 0.2% bupivacaine, with and without epinephrine, for cutaneous anesthesia. *Anesthesiology*. 2015;123:873–85.
9. Gonzalez-Cano R, Ruiz-Cantero MC, Santos-Caballero M, Gomez-Navas C, Tejada MA, Nieto FR. Tetrodotoxin, a potential drug for neuropathic and cancer pain relief? *Toxins*. 2021;13:483.
10. Ma H, Pan Z, Lai B, Zan C, Liu H. Recent research advances in nano-based drug delivery systems for local anesthetics. *Drug Des Devel Ther*. 2023;17:2639–55.
11. Zheng LX, Yu Q, Li Q, Zheng CD. Targeted local anesthesia: a novel slow-release Fe<sub>3</sub>O<sub>4</sub>-lidocaine-PLGA microsphere endowed with a magnetic targeting function. *J Anesth*. 2024;38:232–43.
12. Hadzic A, Minkowitz HS, Melson TI, Berkowitz R, Uskova A, Ringgold F, Lookabaugh J, Ilfeld BM. Liposome bupivacaine femoral nerve block for postsurgical analgesia after total knee arthroplasty. *Anesthesiology*. 2016;124:1372–83.
13. Hussain N, Speer J, Abdallah FW. Analgesic effectiveness of liposomal bupivacaine versus plain local anesthetics for abdominal fascial plane blocks: a systematic review and meta-analysis of randomized trials. *Anesthesiology*. 2024;140:906–19.
14. Woo YC, Park SS, Subieta AR, Brennan TJ. Changes in tissue pH and temperature after incision indicate acidosis may contribute to postoperative pain. *Anesthesiology*. 2004;101:468–75.
15. Ottoboni T, Quart B, Pawasauskas J, Dasta JF, Pollak RA, Viscusi ER. Mechanism of action of HTX-011: a novel, extended-release, dual-acting local anesthetic formulation for postoperative pain. *Reg Anesth Pain Med*. 2020;45:117–23.
16. Gasteiger L, Kirchmair L, Hoerner E, Stundner O, Hollmann MW. Peripheral regional anesthesia using local anesthetics: old wine in new bottles? *J Clin Med*. 2023;12:1541.
17. Ekelund A, Peredistis A, Grohs J, Meisner J, Verity N, Rasmussen S. SABER-Bupivacaine reduces postoperative pain and opioid consumption after arthroscopic subacromial decompression: a randomized, placebo-controlled trial. *J Am Acad Orthop Surg Glob Res Rev*. 2022;6: e21.
18. Velanovich V, Rider P, Deck K, Minkowitz HS, Leiman D, Jones N, Niebler G. Safety and efficacy of bupivacaine HCl collagen-matrix implant (INL-001) in open inguinal hernia repair: results from two randomized controlled trials. *Adv Ther*. 2019;36:200–16.

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.