J Anesth (2009) 23:295–297
DOI 10.1007/s00540-008-0720-5

Journal of
Anesthesia

Short communications

Complex of branched cyclodextrin and lidocaine prolonged the duration of peripheral nerve block

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Abstract
Although laboratories have tried to synthesize new local anesthetics, currently available local anesthetics rarely provide prolonged regional blockade. New models of sustained-release preparations of local anesthetics with liposomes and microspheres have been studied to prolong the duration of the effects of the local anesthetics. In the present study, we examined whether a complex of a branched cyclodextrin (CD), 6-*O*-α-D-maltosyl-β-cyclodextrin (G2-β-CD) and lidocaine could prolong local nerve block when compared with plain lidocaine. The sciatic nerve in male Sprague-Dawley rats was blocked with plain lidocaine ($n = 10$), the complex of G2-β-CD + lidocaine ($n = 10$), or plain G2-β-CD ($n = 4$). Sensory block was assessed with a hotplate set at 56°C. The median duration of the block was longer in the complex group than in the plain lidocaine group (110 min; range, 70–150 min vs 55 min; range, 40–80 min; $P < 0.05$), thus demonstrating that the complex with CyD significantly prolonged the nerve block effect of lidocaine. In conclusion, the present study showed that this encapsulating technique with CyD is useful to expand local anesthetic effect in peripheral nerve blockade.

Key words Lidocaine · Drug delivery system · Local anesthesia · Cyclodextrin

Prolonged regional blockade may have useful applications for both acute and chronic pain management [1]. Although laboratories have tried to synthesize new local anesthetics, currently available local anesthetics rarely produce prolonged regional blockade, unless catheter infusions are used. New models of sustained-release preparations of local anesthetics with liposomes and microspheres have been studied to prolong the duration of the effects of local anesthetics [2–5].

Cyclodextrins (CyDs) are cyclic oligomers of glucose that can form water-soluble inclusion complexes with small molecules and portions of large compounds, and it is now well known that CyDs possess multifunctional characteristics [6,7]. For instance, drugs encapsulated with CyDs provide more balanced biological activity in oral administration and serve the purpose of prolonged therapeutic effect [6]. Also, CyDs, as drug carriers, are capable of controlling the rate and/or time profile of drug release. The encapsulation of local anesthetics into CyDs improves their solubility and stability [8]. We therefore tested whether a branched CyD, 6-*O*-α-D-maltosyl-β-cyclodextrin (G2-β-CD; Fig. 1) prepared with lidocaine could prolong the duration of nerve blockade in a rat model.

The encapsulation of lidocaine (2-diethylamino-N-(1,6-dimethylphenyl) acetamide; Nacalai Tesque, Kyoto, Japan) with CyD was organized at Bio Research Corporation of Yokohama, Japan. Our preliminary study showed that G2-β-CD formed an inclusion complex with lidocaine at a 1:5 molar ratio in aqueous solution, as assessed by solubility analysis. Thus, inclusion complexes were prepared by mixing G2-β-CD solution (124.48 g 852 ml^{-1}) and 20% mol amounts of the guest molecule, lidocaine (4 g), which is a poorly water-soluble agent. The mixture was completely solubilized with a stirrer at 37°C for 3 h. Then the mixture was filtered through a 0.2-μm membrane filter, and the filtered solution was lyophilized. The lidocaine content in the freeze-dried sample was soluble in water; we used this as the test agent (G2-β-CD-lidocaine complex).

For the animal study, the complex was freshly dissolved in distilled water; all other drugs used were freshly dissolved in 0.9% NaCl (pH range, 5.0 to 6.0). The pH was not adjusted because it was assumed that the solutions of the agents would be buffered quickly by the pH of the tissue fluid [9,10].

Male Sprague-Dawley rats were obtained from Japan SLC (Shizuoka, Japan) and maintained at our animal center. All animal experimental protocols were in accordance with the *Guide for the care and use of laboratory*

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Received: October 4, 2008 / Accepted: November 10, 2008

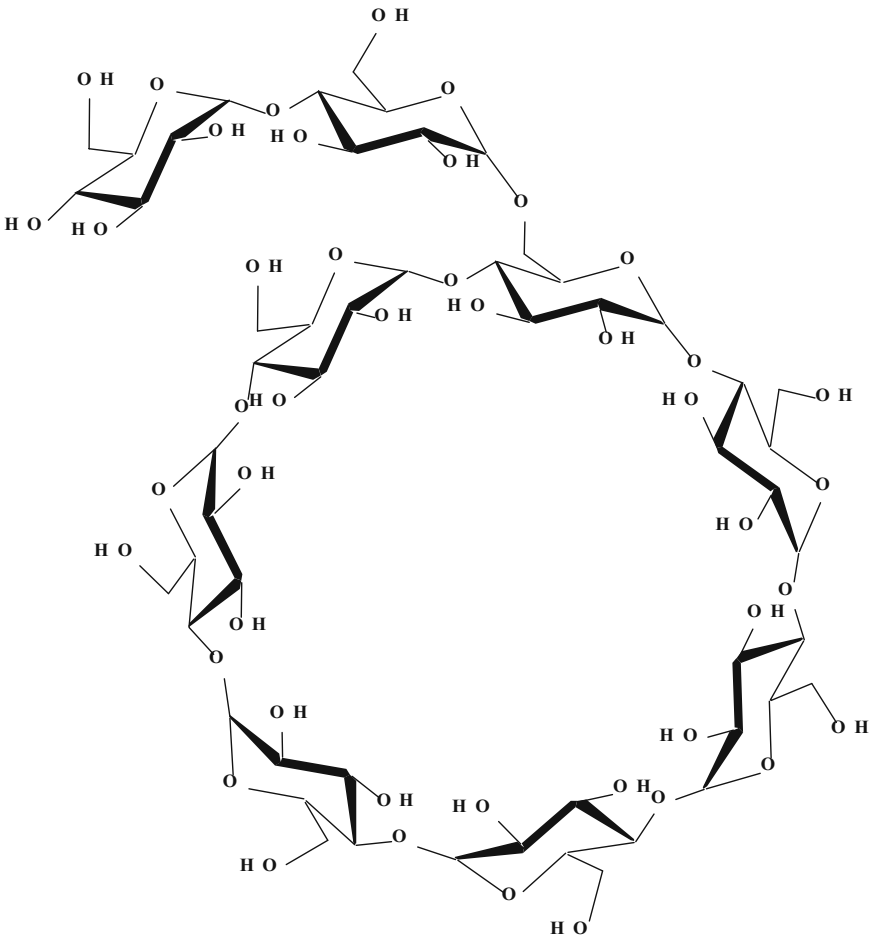

Fig. 1. A schematic diagram of 6-*O*-α-D-maltosyl-β-cyclodextrin

animals published by the United States National Institutes of Health (NIH publication no. 85–23; revised 1996) and were approved by the Ethics Committee of our university. At the time of drug injections, the animals weighed 250–300 g. The experimental animals were randomly divided into three groups: the Lido group received plain lidocaine 1 % (10 mg·kg^{-1}, 0.25–0.3 ml; n = 10); the CyD + Lido group received the complex of G2-β-CD and lidocaine (lidocaine, 10 mg·kg^{-1}, 0.25–0.3 ml; n = 10), the lidocaine concentration of which was adjusted to that of the Lido group; and the CyD group received plain G2-β-CD (0.25–0.3 ml; n = 4). For percutaneous sciatic nerve block, we used a technique reported previously [11]. In brief: under isoflurane 1.5% inspired concentration in oxygen via a face mask, rats were placed prone and the groove between the great trochanter of the femur and the ischial tuberosity was identified by palpation. A 25-gauge 45°-beveled Teflon shield needle attached to a nerve stimulator (DigiStim II; NeuroTechnology, Houston, TX, USA) was advanced into the groove while stimulating at 1 Hz, 0.2 mA. The proximity of the needle tip to the sciatic nerve was confirmed by a noticeable twitch of the hind paw, and the above solutions were injected.

Antinociception of the plantar surface of the hind paw was determined with a Life Science Model 35 D hotplate set at 56°C, using 12 s as the cutoff latency to prevent thermal injury [1]. The withdrawal latency in response to the hotplate was measured 20 min after the injection of the solution and then at 10-min intervals until the latency was less than 7 s. We defined block duration as the duration from the time of the injection to the time before the latency was less than 7 s [1].

Regarding statistical analysis, data values are presented as medians (ranges). Data were analyzed using Kruskal-Wallis one-way analysis of variance on ranks, followed by Dunn's method as a post-hoc multiple comparison test. A P value of less than 0.05 was considered to be statistically significant.

We found that the block duration in the Lido group ranged from 40 to 80 min, with a median of 55 min. Lidocaine captured with CyD prolonged the median block effect to 110 min (range, 70–150 min). There was no effect of CyD alone on nerve blockade. The difference in block duration between the lido and CyD + Lido groups was significant ($P < 0.05$). All animals tolerated the experimental conditions well, and no convulsions or

other signs of systemic local anesthetic toxicity were observed. Furthermore, no adverse reactions, such as allergic reaction to CyD, were observed.

The present study showed that the encapsulation of lidocaine with branched CyD prolonged the peripheral nerve block effect of lidocaine. Thus, CyD encapsulation could be a useful technique for the prolongation of local anesthetic effect.

Although prolonged regional blockade may have useful applications for pain management [1] and laboratories have tried to synthesize new local anesthetics [2], these local anesthetics suffer from drawbacks such as severe nerve and systemic toxicity and relatively short duration of action [5]. Various approaches, such as a mixture of local anesthetic with low-molecular weight dextran, and the use of newly designed drug-carrier glycerin or lipid solvent materials have been studied [2]. Also, microparticulate drug delivery systems have been introduced with liposomes and microspheres [1–5].

Cyclodextrins (CyDs) were first isolated in 1891 as degradation products of starch, and α-, β-, and γ-CyDs are the most common natural CyDs [6]. Recently, various kinds of CyD derivatives such as hydrophilic, hydrophobic, and ionic derivatives have been developed to modify the physical, chemical, and biological properties and inclusion capacity of CyDs. These derivatives are strong candidates for functional drug carriers to control the rate and/or time profile of drug release. In fact, hydrophilic and hydrophobic CyDs modify the release rates of drugs [6,7,12].

In the present study, we did not show the mechanism of the prolonged effect of lidocaine produced by its encapsulation with CyD. Although further research is needed to clarify how CyDs control local anesthetic release, we postulate that CyDs sustain the release of local anesthetics, thereby prolonging their nerve-blocking effect.

Although we discontinued isoflurane immediately after injection of the local anesthetic solutions, there could have been some effects of isoflurane. However, in several studies, researchers started neurobehavioral examination 10–15 min after the injection of local anesthetic solutions [9,10] and we started the examination 20 min after the injection of the local anesthetic solution. We thus believe that we do not need to consider the effect of isoflurane.

In conclusion, the inclusion complex of lidocaine with CyDs prolonged the nerve-blocking effect of lidocaine.

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