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Intrathecal oxybuprocaine and proxymetacaine produced potent and long-lasting spinal anesthesia in rats

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ABSTRACT

Proxymetacaine and oxybuprocaine were clinically used for topical ocular anesthesia but never for spinal anesthesia, and therefore spinal anesthetic effects of proxymetacaine and oxybuprocaine were performed and compared with bupivacaine and lidocaine. After rats were injected intrathecally with proxymetacaine, oxybuprocaine, bupivacaine, and lidocane, dose–response curves were constructed. We evaluated the potencies (ED_{50}) and durations (time to full recovery) of proxymetacaine and oxybuprocaine on spinal blockades of motor function, proprioception, and nociception and compared with bupivacaine and lidocaine in rats. We found that proxymetacaine and oxybuprocaine acted like bupivacaine or lidocaine and produced dose-related spinal blockades of motor function, proprioception and nociception. On the ED_{50} basis, the ranks of potencies in motor, proprioception, and nociception were proxymetacaine > oxybuprocaine > bupivacaine > lidocaine ($P < 0.01$ for the differences). On an equipotent basis (ED_{20}, ED_{50}, ED_{80}), oxybuprocaine and bupivacaine produced similarly longer spinal blockades than did proxymetacaine or lidocaine ($P < 0.05$ for the differences). Intrathecal proxymetacaine, oxybuprocaine, and bupivacaine also produced longer sensory blockade than motor blockade. These data demonstrated that oxybuprocaine and proxymetacaine produced more potent spinal blockades, when compared with bupivacaine or lidocaine. Oxybuprocaine and bupivacaine with a more sensory-selective action over motor blockade produced longer spinal blockade than did proxymetacaine or lidocaine.

Topical anesthesia began in 1884, when Koller introduced the use of cocaine as a topical ocular anesthetic [17]. Since then, numerous topical anesthetics have been developed, including the amide- and ester-linked local anesthetic agents [10]. Until now, topical ocular anesthesia has been part of ophthalmology for more than a century. The most commonly used drugs today are proparacaine (proxymetacaine), tetracaine, benoxinate (oxybuprocaine), cocaine, lidocaine and bupivacaine. Oxybuprocaine and proxymetacaine, two ester-linked local anesthetics, are commonly used drugs today for topical ocular anesthesia because of its easy administration and fewer side effects [20]. Clinically, ocular anesthesia practiced with topical 0.4% oxybuprocaine for penetrating trabeculectomy [26], repair of a ruptured globe [1], and cataract surgery [28] and with topical 0.5% proxymetacaine in patients undergoing strabismus surgery [16] and posterior vitrectomy [3]. Many publications have reported the successful treatment of trigeminal neuralgia by topical anesthetic oxybuprocaine [33] or proxymetacaine [33,29] instilled in the eye of the affected side. In vivo nonophthalmological trials and more recently in vitro and in vivo ophthalmological studies have provided consistent evidence demonstrating the antibacterial activity of topical anesthetic oxybuprocaine and proxymetacaine [2,23,24,27].

Intrathecal anesthesia is a relatively simple technique, which produces adequate surgical conditions by injecting a small amount of local anesthetic with easy landmarks, giving a wide popularity to this practice [5]. Dr. August Bier first described spinal administration of cocaine to render large part of the body insensitive to pain for surgical purposes in 1899 [5]. Until now, intrathecal lidocaine in doses ranging from 50 to 100 mg is widely used for surgical procedures lasting up to 1 h [19,11]. Long-acting agents, such as bupivacaine (with doses ranging between 10 and 20 mg of either plain or hyperbaric solutions), are widely used to give spinal anesthesia for surgical procedures lasting up to 2–2.5 h [6,32]. Besides, lidocaine 2% gel, bupivacaine 0.5% drops, proxymetacaine 0.5% drops and oxybuprocaine 0.4% drops were effective topical anesthetic agents in cataract surgery [28,24]. However, to the best of our

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knowledge, no study of intrathecal oxybuprocaine and proxymetacaine has been reported to date. In this study, we compared spinal anesthesia of oxybuprocaine and proxymetacaine with bupivacaine and lidocaine.

Male Sprague–Dawley rats weighting 300–340 g were obtained from the National Laboratory Animal Centre, Taipei, Taiwan. They were housed in groups of three, with food and water freely available until the time of testing. The climate controlled room maintained at 24°C with approximately 50% relative humidity on a 12-h light/dark cycle (6:00 AM–6:00 PM). The experimental protocols were approved by the animal investigation committee of China Medical University, Taiwan, and conformed to the recommendations and policies of the International Association for the Study of Pain. Proxymetacaine HCl, oxybuprocaine HCl, bupivacaine HCl, and lidocaine HCl were purchased from Sigma Chemical Co. (St. Louis, MO). All drugs were freshly prepared in 5% dextrose as solution before intrathecal injections.

The drugs were intrathecally injected into conscious rats as previously described [7,8]. In brief, a 27-gauge needle attached to a 50-μL syringe (Hamilton, Reno, Nevada) was inserted into the midline of the lumbar 4-5 (L4-5) intervertebral space and 25 μL of drugs were injected. Rats were then observed for paralysis of two hind limbs, indicative of a spinal blockade [7,8]. Rats that showed unilateral blockades were excluded from the study and killed using an overdose of sevoflurane. All rats were injected intrathecally one time in this study. Before behavioral tests, the rats were handled to familiarize them with the experiments and to minimize stress-induced analgesia [7,21]. After intrathecal injections, motor function, proprioception, and nociception were evaluated as previously described [7,8,31]. In brief, the motor function was evaluated by measuring 'the extensor postural thrust' of the right hind limb of each rat on a digital scale. The pre-injection control value was considered a 0% motor block or 0% MPE, and a force less than 20 g was interpreted as a 100% motor block or 100% MPE (maximal possible effect). Proprioceptive evaluation was based on the resting posture and postural reactions ('tactile placing' and 'hopping') [7,8,31]. The functional deficit was graded as 3 (normal or 0% MPE), 2 (slightly impaired or 33% MPE), 1 (severely impaired, 67% MPE), and 0 (completely impaired or 100% MPE). The nociception was evaluated according to the withdrawal reflex or vocalization elicited via pinching a skin fold on each rat's back at 1 cm from the proximal part of the tail, the lateral metatarsus of the two hind limbs, and the dorsal part of the mid-tail. The nociception was graded as 0 (absent or 100% MPE), 1 (75% MPE), 2 (50% MPE), 3 (25% MPE), and 4 (normal or 0% MPE) [7,8,31]. For consistency, one experimenter (Dr. Hung) was responsible for handling all the rats and behavioral evaluations.

After rats were injected with different doses of each drug ($n = 8$ for each dose of each drug) intrathecally, dose–response curves were constructed from the % MPE of each dose of each drug. The curves were then fitted using a computer-derived SAS Nonlinear (NLIN) Procedures (version 9.1, SAS Institute, Cary, NC), and the values of ED_{50}, defined as the doses that caused 50% spinal blockades of motor function, proprioception, and nociception, were obtained [8,21]. Drug potencies were compared via ED_{50}s, constructed from dose–response curves.

The blockade duration caused by each drug was also evaluated on an equipotent basis. The ED_{20} and ED_{80} of drugs were obtained using the same computer-derived curve-fitting (SAS NLIN analysis) that was used to derive the ED_{50} [21]. The rats were intrathecally injected with different doses of ED_{20}, ED_{50}, and ED_{80} drugs ($n = 8$ rats for each dose of each drug), and the duration of each spinal blockade, defined as the interval from injection to full recovery, were measured and compared. In this study, the onset time of each spinal blockade, defined as the first detectable block (%PE) from injection, was evaluated at the dose of ED_{80}.

Values are presented as mean ± SEM or ED_{50} values with 95% confidence interval (95% CI). The differences in potencies (ED_{50}s) between medications were evaluated using a one-way analysis of variance (ANOVA) and then the pairwise Tukey's honestly significant difference test. The differences in durations among drugs were evaluated by a two-way ANOVA followed by the pairwise Tukey's HSD test. In the control groups, a one-way ANOVA followed by the Dunnett test was used to evaluate the effects of medications. SPSS for Windows (version 12.0) was used for all statistical analyses. Statistical significance was set at $P < 0.05$.

The time courses of spinal blockade of proxymetacaine, oxybuprocaine, bupivacaine, and lidocaine in motor function, proprioception, and nociception have been performed. Due to the similarities of the figures, only the figures obtained from bupivacaine and oxybuprocaine were shown (Fig. 1). At the dose of 1.14 μmol/kg, bupivacaine showed 38%, 64%, and 75% of blockades (% MPE) in motor function, proprioception, and nociception with duration of action of about 11, 32, and 44 min, respectively. Oxybuprocaine at 0.38 μmol/kg showed 31%, 39%, and 58% of blockades in motor function, proprioception, and nociception with duration of action of about 8, 12, and 30 min, respectively.

After intrathecal injections (6–7 doses in each group), the dose–response curves of proxymetacaine, oxybuprocaine, bupivacaine, and lidocaine were constructed (Fig. 2). ED_{50}s of motor function, proprioception, and nociception of drugs were obtained from dose–response curves (Table 1). On the ED_{50} basis, the ranks of potencies in motor function, proprioception, and nociception were proxymetacaine > oxybuprocaine > bupivacaine > lidocaine ($P < 0.01$ for the differences between drugs; Table 1). The nociceptive blockades (ED_{50}) were more potent than the motor blockades

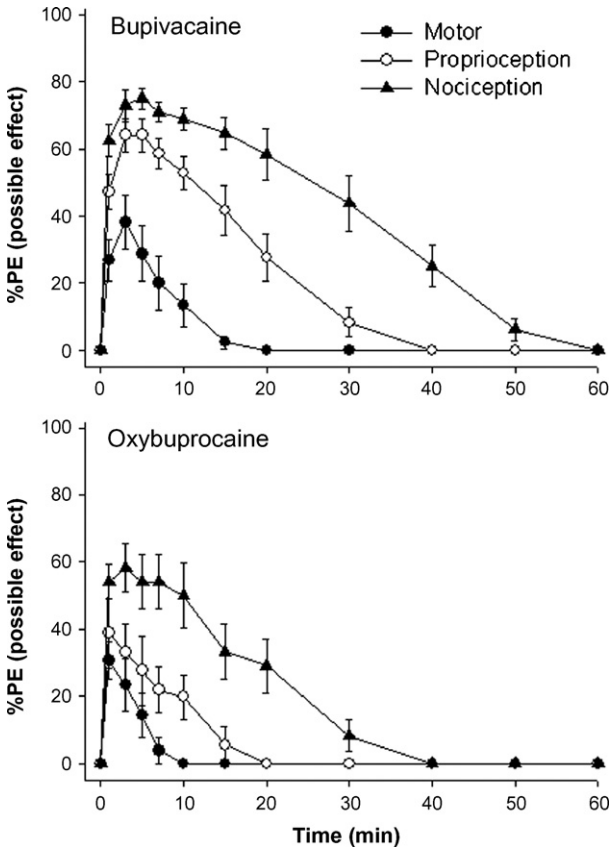

Fig. 1. Time courses of spinal blockade (% PE) of oxybuprocaine at 0.38 μmol/kg and bupivacaine at 1.14 μmol/kg in motor function, proprioception, and nociception. Neurological evaluation was constructed after drug injection. Data are presented as mean ± SEM; each group, $n = 8$.

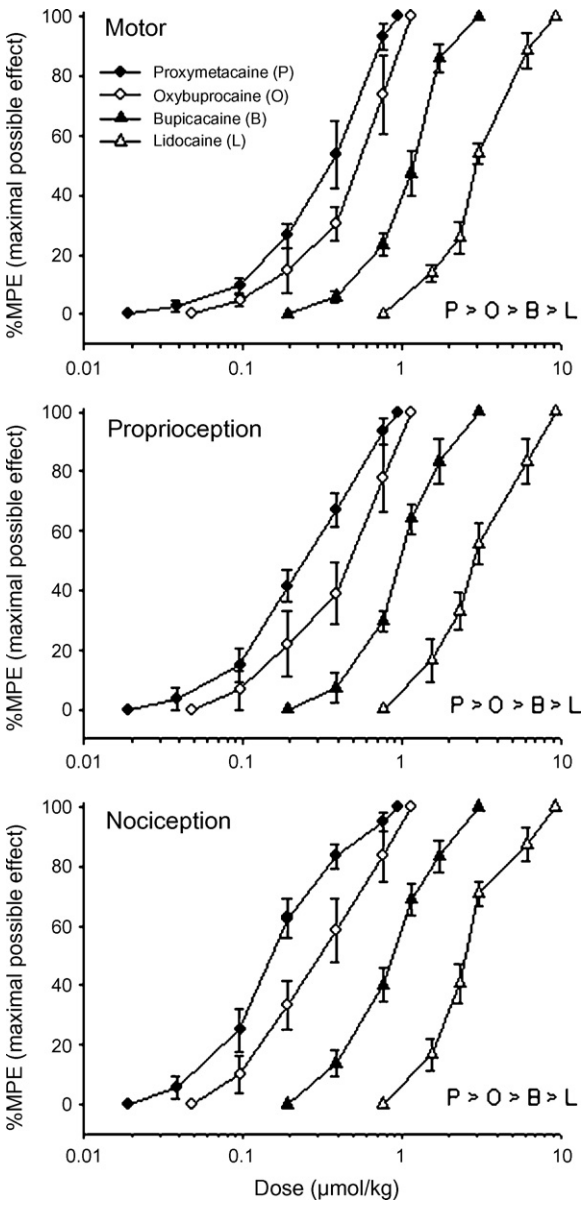

Fig. 2. The dose–response curves of proxymetacaine, oxybuprocaine, bupivacaine, and lidocaine on spinal blockades of motor, proprioception, and nociception (% MPE) in rats ($n = 8$ at each testing point). Data are shown as mean ± SEM.

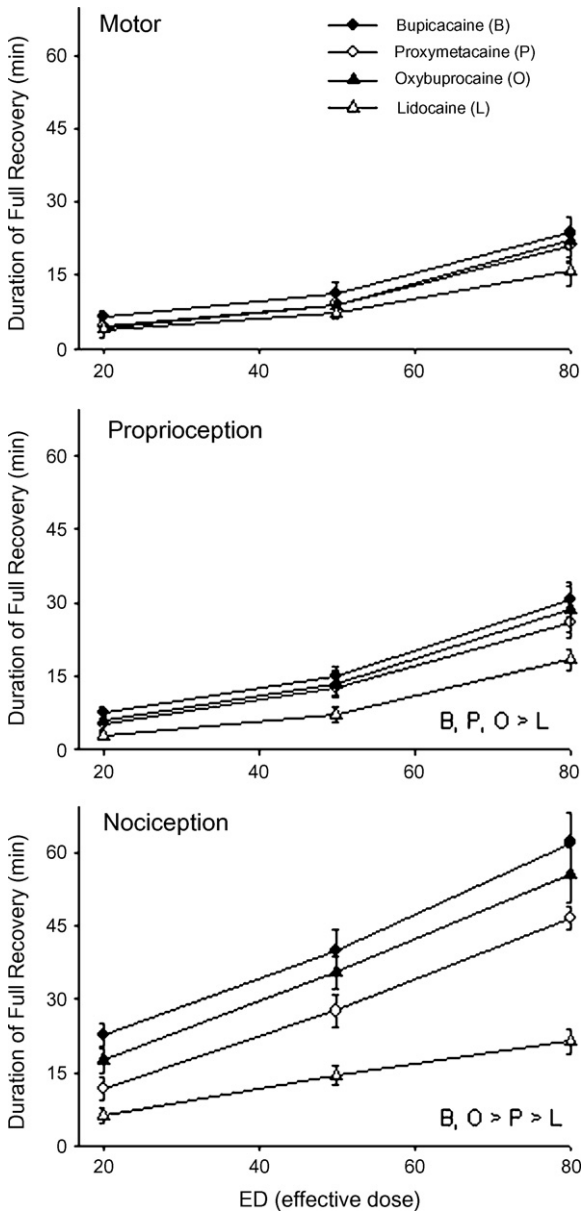

Fig. 3. The duration of full recovery of drug effects on spinal blockades of motor, proprioception, and nociception (% MPE) at doses of ED_{20}, ED_{50}, and ED_{80} ($n = 8$ at each testing point). Data are means ± SEM. The differences in duration were evaluated using a two-way ANOVA and then the pairwise Tukey's honestly significant difference test.

for bupivacaine, proxymetacaine, and oxybuprocaine but not lidocaine ($P < 0.05$ for the differences between drugs; Table 1).

Durations were measured as an interval from the time zero at the time of injection to the time of complete functional recovery. On an equipotent basis (ED_{20}, ED_{50}, and ED_{80}), all drugs tested produced motor blockades of similar duration, but the blockades of nociception caused by oxybuprocaine and bupivacaine were longer than those caused by proxymetacaine or lidocaine (Fig. 3). At these given doses, the blockade duration of proprioception for lidocaine was shorter than those for bupivacaine, proxymetacaine, and oxybup-

Table 1
The 50% effective dose (ED_{50}) of drugs with 95% confidence interval (95% CI) on spinal blockades of motor function, proprioception, and nociception in rats.

Drugs	ED_{50} (95% CI)			Mean		
	Motor	Proprioception	Nociception	ED_{20}	ED_{50}	ED_{80}
Bupivacaine (B)	1.13 (1.04–1.22)	0.98 (0.91–1.06)	0.87 (0.79–0.96)	0.65	0.99	1.54
Lidocaine (L)	3.03 (2.81–3.26)	2.93 (2.61–3.29)	2.52 (2.33–2.81)	2.09	3.16	4.77
Proxymetacaine (P)	0.32 (0.28–0.37)	0.24 (0.21–0.27)	0.16 (0.14–0.18)	0.13	0.24	0.46
Oxybuprocaine (O)	0.50 (0.43–0.59)	0.43 (0.36–0.53)	0.31 (0.25–0.38)	0.24	0.41	0.73

The ED_{20}s, ED_{50}s, and ED_{80}s of drugs (μmol/kg) were obtained from Fig. 2 using SAS Nonlinear (NLIN) Procedures. The potency ranks (ED_{50}) of the spinal blockades of motor, proprioception, and nociception of the tested drugs were P > O > B > L ($P < 0.05$ for the differences) using a one-way ANOVA and then the pairwise Tukey's honestly significant difference test.

rocaine (Fig. 3). The onset time of oxybuprocaine, proxymetacaine, bupivacaine, and lidocaine at the dose of ED_{80} in motor function, proprioception, and nociception was all 1 ± 0 min (data not shown). In our studies, all rats recovered completely after intrathecal injections of drugs.

This study demonstrated that intrathecal injections of oxybuprocaine, proxymetacaine, bupivacaine, and lidocaine produced dose-related spinal anesthesia. Among these drugs, proxymetacaine was the most potent local anesthetic. On an equipotent basis, spinal block duration of oxybuprocaine was similar to bupivacaine and longer than that of proxymetacaine or lidocaine.

Bupicacaine, lidocaine, proxymetacaine and oxybuprocaine are local anesthetics that produce neural blockade through a direct blocking effect on the voltage-gated Na+ channels of the nervous tissues [9,25,30,18,4]. In this study, we also showed that intrathecal injections of oxybuprocaine, proxymetacaine, bupivacaine, and lidocaine produced dose-related spinal anesthesia. Lower doses of proxymetacaine 0.125% and oxybuprocaine 0.2% would be effective in topical anesthesia [14], and therefore they may produce more potent spinal anesthesia than bupivacaine 0.5%. According to dose–response curves of intrathecal proxymetacaine, oxybuprocaine, bupivacaine, and lidocaine, our study showed that proxymetacaine was more potent than oxybuprocaine, bupivacaine, and lidocaine (Fig. 2 and Table 1). Proxymetacaine and oxybuprocaine produced almost 4.1- and 2.4-folds higher potency than did bupivacaine in spinal anesthesia, respectively. Therefore, in human and animal studies, a lesser dose of proxymetacaine is similar to a higher dose of oxybuprocaine to produce spinal or topical ocular anesthesia. The lipid solubility depends upon the heptane-buffer partition coefficient and has been shown to correlate well with local anesthetic potency [18]. Highly lipid soluble agents such as bupivacaine require lower concentrations (0.1–0.75%), compared to less lipid soluble agents such as lidocaine, which require the use of higher concentrations (1–4%) [18]. We presumed that the partition coefficient between drugs might be proxymetacaine > oxybuprocaine > bupivacaine > lidocaine, and this must be confirmed in the future.

Administration of long-acting local anesthetics for surgery and postoperative pain control is frequently performed [15]. The duration of spinal blockade, defined as the interval from injection to full recovery, was evaluated for spinal anesthesia (e.g. ambulatory surgery for predicting readiness for discharge). In this study, we also tested oxybuprocaine and proxymetacaine for long-acting local anesthetics. Intrathecal proxymetacaine, oxybuprocaine, bupivacaine, and lidocaine at equipotent doses (ED_{20}, ED_{50}, and ED_{80}) were performed. Our study showed that the duration of spinal blockade caused by oxybuprocaine and bupivacaine was longer than those caused by proxymetacaine or lidocaine on an equipotent basis (Fig. 3). Protein binding (%) has been shown to correlate well with duration of local anesthetic action [18]. It can be related to highly protein binding agents such as bupivacaine, compared to less protein binding agents such as lidocaine [18].

Bupivacaine produced a longer duration of sensory blockade than the motor blockade (Figs. 1 and 3). This is in resemblance to the clinical impression that bupivacaine is the drug of choice when a more sensory-selective action over motor blockade [12,13,22]. Intrathecal proxymetacaine and oxybuprocaine also produced a longer duration of sensory blockade than the motor blockade (Figs. 1 and 3). We also found that the potencies (ED_{50}s) of proxymetacaine, oxybuprocaine, and bupivacaine in nociceptive blockades were more potent than those in motor blockades (Table 1). The sensory/nociceptive blockades in proxymetacaine, oxybuprocaine, and bupivacaine were almost 2.0-, 1.6-, and 1.3-folds higher potencies (ED_{50}) than the motor blockades, respectively. Bupivacaine is rarely noted the sensory/motor potency in clinical practice because complete blockades are performed. We showed that intrathecal proxymetacaine, oxybuprocaine, and bupivacaine produced more dominant sensory/nociceptive than motor blockade in potencies (%MPE) and duration of action.

We did not evaluate whether proxymetacaine and oxybuprocaine had neurotoxicity, however, it is noteworthy that in neurobehavioral studies we detected no apparent side effects or behavioral abnormalities after intrathecal drug injection. All rats recovered completely. Histologic studies must be performed in the future before further consideration of these agents for clinical trials.

In conclusion, intrathecal oxybuprocaine and proxymetacaine produced more potent spinal blockade than bupivacaine or lidocaine. Oxybuprocaine and bupivacaine produced similarly duration of spinal blockade and a more sensory-selective action over motor blockade.

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