Elsevier Editorial System(tm) for European Journal of Pharmacology
Manuscript Draft

Manuscript Number:

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Article Type: Research Paper

Section/Category: Neuropharmacology and analgesia

Keywords: propranolol; spinal anesthesia

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Abstract: To prevent cardiovascular effects of peripherally administered propranolol, the aim of this study was to evaluate the spinal anesthetic effect of intrathecal propranolol, a sodium channel blocker. After rats were injected 5 doses of propranolol intrathecally, the dose—response curve of spinal anesthesia was obtained. Then the spinal block potency and duration of propranolol was compared to lidocaine, which is known to produce local anesthesia. We found that propranolol produced a dose-dependent spinal blockade in motor, proprioception, and nociception. On a 50% effective dose (ED50) basis, the spinal anesthetic effect of propranolol was equal to lidocaine. On an equipotent basis (0.5, 1.0, and 2.5 μmol), the block duration on spinal anesthesia caused by propranolol was longer than that caused by lidocaine ($p < 0.01$ for each comparison). These preclinical findings reported that propranolol produced similar spinal anesthesia to lidocaine. Propranolol with a more sensory-selective action over motor blockade produced longer spinal blockade than did lidocaine.

Intrathecal propranolol displays long-acting spinal anesthesia with a more sensory-selective action over motor blockade in rats

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Conflicts of interest: There is no conflict of interests for all authors.

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ABSTRACT

To prevent cardiovascular effects of peripherally administered propranolol, the aim of this study was to evaluate the spinal anesthetic effect of intrathecal propranolol, a sodium channel blocker. After rats were injected 5 doses of propranolol intrathecally, the dose—response curve of spinal anesthesia was obtained. Then the spinal block potency and duration of propranolol was compared to lidocaine, which is known to produce local anesthesia. We found that propranolol produced a dose-dependent spinal blockade in motor, proprioception, and nociception. On a 50% effective dose (ED_{50}) basis, the spinal anesthetic effect of propranolol was equal to lidocaine. On an equipotent basis (0.5, 1.0, and 2.5 μmol), the block duration on spinal anesthesia caused by propranolol was longer than that caused by lidocaine ($p < 0.01$ for each comparison). These preclinical findings reported that propranolol produced similar spinal anesthesia to lidocaine. Propranolol with a more sensory-selective action over motor blockade produced longer spinal blockade than did lidocaine.

Key Words: propranolol; spinal anesthesia

1. Introduction

Propranolol is discovered in 1964 and its introducing to the clinical practice has been essential for the clinical usefulness in the therapy of cardiovascular diseases (Frullani et al., 1970; Matthews and Baker, 1982). Propranolol was the first clinically useful β-adrenergic receptor antagonist which was introduced by Sir James W. Black. It revolutionized the medical management of angina pectoris and is considered to be one of the most important contributions to clinical medicine and pharmacology in the 20th century (Zimmermann et al., 2010). Indications for the use of propranolol are numerous, including the treatment of angina pectoris (Frishman et al., 1989; Zimmermann et al., 2010), hypertension (Frishman et al., 1989), cardiac arrhythmias (Matthews and Baker, 1982), hyperthrophic obstructive cardiomyopathy (Hess et al., 1983), migraine (Linde and Rossnagel, 2004), and in the therapy of many neuropsychiatric disorders (Tchivileva et al., 2010).

Recently, propranolol has been introduced as a novel modality for the treatment of proliferating haemangiomas (Buckmiller, 2009; Maturo and Hartnick, 2010; Zimmermann et al., 2010) and dental anxiety (Heaton et al., 2010). The response of infantile haemangiomas to propranolol reported in the New England Journal of Medicine by Léauté-Labréze et al. (Leaute-Labreze et al., 2008) catapulted the use of this therapy to first-line status among physicians managing this disease (Siegfried et

al., 2008). In *in vitro* study, propranolol (100 μM) performed 78% inhibition of veratridine-stimulated Na^+ influx in a concentration-dependent manner in rat cerebrocortical synaptosomes.(Chidlow et al., 2000) It is accepted that local anesthetics reversibly block the conduction of electrical impulses in nerves by blocking voltage-gated Na^+ channels (Scholz, 2002; Sheets and Hanck, 2003). Because propranolol can inhibit Na^+ currents (Chidlow et al., 2000), it therefore has been known to have a local anesthetic (termed topical) effect (Frullani et al., 1970; Leszczynska and Kau, 1992; Zimmermann et al., 2010).

Spinal 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 (Hung et al., 2009). However, to the best of our knowledge, no study of spinal anesthesia of propranolol following intrathecal puncture has been reported. The aim of this study was to evaluate the spinal anesthetic effect of propranolol but also duration of action of drugs. Lidocaine, a common local anesthetic, was used as control. Our results demonstrate that intrathecal propranolol produces the spinal anesthetic effect.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats weighting 300-350 g were obtained from the National Laboratory Animal Centre in Taiwan, and then housed in a climate controlled room maintained at 22℃ with approximately 50% relative humidity. Lighting was on a 12-h light/dark cycle (light on at 6:00 AM), with food and water available *ad libitum* up to time of testing. 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 (IASP).

2.2. Drugs

(±)-Propranolol HCl and lidocaine HCl were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). All drugs were freshly prepared in 5% dextrose as solution before intrathecal injections.

2.3. Experimental protocol

Three experiments were carried out. In experiment 1, the potencies of propranolol (0.27, 0.50, 1.00, 1.75, 2.50 μmol) and lidocaine (0.25, 0.50, 0.75, 1.00, 2.50 μmol) on spinal anesthesia were evaluated (n=8 rats for each dose of each drug). In experiment 2, the %MPE, duration of drug action, area under curves (AUCs) of the

spinal blockade of propranolol at the dose of 2.5 μmol was compared to lidocaine (n=8 rats for each dose of each drug). In experiment 3, on an equipotent basis (0.5, 1.0, and 2.5 μmol), the spinal block duration of propranolol was compared with that of lidocaine. (n=8 rats for each dose of each drug).

2.4. Spinal anesthesia

2.4.1. Intrathecal drug injection

Intrathecal injections of drugs were performed in conscious rats. Following an optimal flexion of the rat lumbar spine under prone position, each 50-μL of 1% lidocaine was injected into the right and left side of paraspinal space (0.5 cm in depth) which was 0.5 cm away from the mid-point of the longitudinal line of L4–5 intervertebral space. Two minutes later, a 27-gauge needle attached to a 50-μL syringe (Hamilton, Reno, Nevada) was inserted into the mid-line of the L4–5 intervertebral space and advanced at a slightly caudal angle until a tail-flick indicated entrance into the intrathecal space. Twenty-five microliters of drug were injected and the rat was observed for the development of spinal blockade, indicated by paralysis of both hind limbs (Chen et al., 2007; Leung et al., 2010). Rats, which showed unilateral blockade, were excluded from the study and sacrificed by using an over dose of isoflurane. All rats were injected intrathecally one time in this study.

2.4.2. Neurobehavioral evaluation

After intrathecal drug injection, three neurobehavioral examinations, which consisted of evaluations of motor, proprioception, and nociception, were conducted (Chen et al., 2010a; b; Hung et al., 2009). For consistency, one trained examiner was responsible for handling of all rats and behavioral evaluations. The magnitude of spinal blockade (motor, proprioception, and nociception) was described as the percentage of possible effect (% PE). The maximum blockade in a time course of spinal anesthesia of drugs was described as the percent of maximum possible effect (% MPE). 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 evaluation of proprioception was based on the resting posture and postural reactions (‘tactile placing’ and ‘hopping’). The functional deficit was graded as 3 (normal or 0% MPE), 2 (slightly impaired), 1 (severely impaired), and 0 (completely impaired or 100% MPE). The nociception was evaluated using 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 right hind limb, and the dorsal part of the mid-tail.

2.5. The 50% effective dose (ED_{50})

After intrathecally injecting the rats with different doses of each drug (n = 8 for each dose of each drug), the dose—response curve was constructed by the % MPE of

each dose of each drug, The curve was then fitted using a computer-derived SAS NLIN analysis (SAS Institute Inc., Carey, NC), and the values of 50% effective doses, defined as the doses that caused 50% spinal anesthesia, were obtained (Hung et al., 2010; Chen et al., 2010a; Chen et al., 2010b).

2.6. The spinal block duration

The blockade duration (n = 8 rats for each dose of each drug) caused by each drug was also evaluated on an equipotent basis (0.5, 1.0, and 2.5 μmol). The duration of each blockade, defined as the interval from drug injection to full recovery, was measured and compared. In this study, the area under curve (AUC) of motor, proprioception, and nociception of propranolol and lidocaine at the same dose of 2.5 μmol was estimated using Kinetica version 2.0.1 (InnaPhase Corporation, Philadelphia, PA).

2.7. Statistical Analysis

Values are presented as means ± SE or ED_{50} values with 95% confidence interval (95% CI). Data were evaluated by either student-t test (experiment 1 and 2) or 2-way (experiment 3) analysis of variance (ANOVA) followed by pairwise Tukey's honest significance difference (HSD) test. The full recovery time and AUCs of motor, proprioception, and nociception was evaluated by 1-way (experiment 2) ANOVA followed by pairwise Tukey's HSD test. A statistical software, SPSS for Windows

(version 17.0, SPSS, Inc, Chicago, IL, USA), was used, and a *P* value less than 0.05 was considered statistically significant.

3. Results

3.1. The spinal blockade of propranolol

Intrathecal propranolol, as well as lidocaine, produced dose-dependent effects on spinal anesthesia in rats (Fig. 1). The ED_{50}s of propranolol and lidocaine in motor, proprioception, and nociception are shown in Table 1. On the ED_{50} basis, the spinal blockade of propranolol in motor, proprioception, and nociception is similar to lidocaine (Table 1).

3.2. The spinal blockade of propranolol and lidocaine at the dose of 2.5 μmol

The time course of spinal blockade of propranolol and lidocaine in motor function, proprioception, and nociception has been demonstrated in Figure 2. At this given dose of 2.5 μmol, propranolol showed 100, 100, and 100% of blockades (% MPE) in motor function, proprioception, and nociception with duration of action of about 24, 38, and 114 min, respectively. At the same given dose, lidocaine performed 94, 92, and 94% of blockades in motor function, proprioception, and nociception with duration of action of about 22, 25, and 30 min, respectively (Fig. 2 and Table 2). Of note, propranolol at the dose of 2.5 μmol performed complete blockade (100% MPE) of motor function, proprioception, and nociception, but not lidocaine (Fig. 2 and Table 2).

3.3. The full recovery time and AUCs of propranolol and lidocaine on spinal

anesthesia

The full recovery time and AUCs of nociceptive blockade are longer than the motor or proprioceptive blockade for propranolol, but not lidocaine ($P < 0.001$ for the differences; Fig. 2 and Fig. 3). The full recovery time and AUCs of spinal blockade of propranolol significantly are greater than those of lidocaine in nociception (Fig. 2 and Table 2). However, the duration of complete spinal blockade of propranolol is similar to that of lidocaine in motor function, proprioception, and nociception (Fig. 2 and Table 2).

3.4. On an equipotent basis, the spinal block duration in nociception caused by propranolol was longer than that caused by lidocaine

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 (0.5, 1.0, 2.5 μmol), the spinal block duration in nociception caused by propranolol was longer than that caused by lidocaine (Fig. 3). All rats recovered completely after intrathecal drug injections.

4. Discussion

This study indicated for the first time that intrathecal propranolol produced a dose-dependent spinal anesthesia in rats. Propranolol was similar to lidocaine at producing spinal anesthesia. On an equipotent basis, propranolol showed the longer action of spinal blockade than lidocaine.

The adrenergic system is a prime controller of blood pressure. Though we have made no study about the known cardiovascular effects, the previous study showed that centrally active propranolol ($\beta_{1+2+[3]}$, 44 μmol/kg) had little effect on blood pressure, cardiac output, heart rate, and total peripheral vascular resistance in normotensive rats (Berg et al., 2010). Furthermore, our study performed the lower dose of 7.7μmol/kg of centrally administered propranolol to produce spinal anesthesia. We suggest that the lower dose of intrathecal propranolol may have no effect on cardiovascular baselines (e.g. blood pressure), and it is worth studied in the future.

Adrenergic antagonists have long been known to affect nerve function. Beta-blockers inhibit nerve conduction at millimolar-range concentrations (Sada and Ban, 1981). The high concentrations of adrenergic antagonists markedly potentiate the duration of block of tetrodotoxin, by an effect that does not appear to be adrenergic receptor-specific (Kohane et al., 2001). Co-injection with 20 mM propranolol prolonged tetrodotoxin block to 486 min in sciatic nerve blockade of rats (Kohane et

al., 2001). Local anesthetics produce neural blockade via blocking the Na^+ currents in the nervous tissues through the voltage-gated Na^+ channels (McLure and Rubin, 2005). The beta-blockers propranolol blocks, moreover, Na^+ current in a manner similar to the blocking of local anesthetic drugs (Bankston and Kass, 2010), and propranolol efficacy is dependent on the inactivated state of the channel and blocks late non-inactivating current more effectively than peak Na^+ current (Bankston and Kass, 2010). These data can support that propranolol produced spinal anesthesia in rats and propranolol administration into the sciatic nerve area produced neuromuscular blocking activity and local anesthesia (Leszczynska and Kau, 1992) in mice. In this report, we also demonstrated that propranolol produced the similar potency of spinal blockades to lidocaine.

Propranolol contains both hydrophobic and hydrophilic groups. In addition, it contains a secondary amine, and the same chemical characteristic exists in some local anesthetics. We demonstrated that intrathecal propranolol showed motor, sensory and proprioceptive blocking effects, suggesting the local anesthetic characteristics of propranolol. Intrathecal propranolol (2.5 μmol) produced complete spinal anesthesia with drug action of about 5-8 min and duration of spinal blockades with drug action of about 24-114 min.

Treatment with long-acting local anesthetics for surgery or postoperative pain

control is frequently practiced (Gurlit et al., 2004). The duration of spinal blockade is defined as the interval from drug injection to full recovery of blockades. Intrathecal propranolol and lidocaine at equipotent doses (0.5, 1.0, and 2.5 μmol) were studied. Our results showed that the duration of spinal blockade in nociception caused by propranolol was longer than that caused by lidocaine on an equipotent basis (Fig. 3). Besides, sensory block duration of propranolol was longer than that of lidocaine on an equivalent dose (2.5 μmol) (Fig. 2 and Table 2). Treatment with long-acting local anesthetic propranolol for surgery and postoperative pain control is worth studied in the future.

Intrathecal propranolol produced a longer duration of sensory blockade than the motor blockade, but not lidocaine (Fig. 2 and Fig. 3). This is in resemblance to the clinical impression that lidocaine is not the drug of choice when a more sensory-selective action over motor blockade. Besides, the AUC of propranolol in nociceptive blockade was almost 5.0-folds larger than that in motor function. We suggested that the pharmacokinetic differences, such as absorption, distribution and metabolism of propranolol and lidocaine, may account for the differences in the duration of action of the two drugs.

We did not evaluate whether propranolol had spinal nerve toxicity, however, it is noteworthy that in neurobehavioral studies we detected no apparent side effects after

intrathecal drug injection. Furthermore, there is no an emerging sedative effects of centrally administered propranolol. All rats recovered completely. Histologic studies must be performed in the future before the possible use of propranolol as spinal analgesic in humans.

In conclusion, intrathecal propranolol produced similar potency to lidocaine on spinal anesthesia, and propranolol showed longer spinal anesthetic action with a more sensory-selective action over motor blockade than lidocaine in rats.

Acknowledgements

The authors gratefully acknowledge the financial support provided for this study by the National Science Council of Taiwan (NSC 98-2314-B-006-017-MY3; NSC 99-2314-B-039-013-MY3).

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Table 1. The 50% effective doses (ED_{50}s) of propranolol and lidocaine on spinal blockades of motor, proprioception, and nociception

	ED_{50} (95% CI)		
	Motor	Proprioception	Nociception
Propranolol	1.16 (1.01 – 1.34)	1.10 (0.92 – 1.31)	1.05 (0.89 – 1.24)
Lidocaine	1.03 (0.94 – 1.13)	0.95 (0.84 – 1.07)	0.87 (0.79– 0.96)

ED_{50}s of drugs (μmol) were obtained from Figure 1. CI = confidence interval. The differences between propranolol and lidocaine on ED_{50}s of motor, proprioception, and nociception are not significant.

Table 2. The %MPE, duration, and AUCs of intrathecal propranolol and lidocaine

	%MPE	Duration (min)		AUCs (%MPE x min)
		Complete blockade	Full Recovery	
Motor				
Propranolol	100 ± 0	4.8 ± 0.5	24.4 ± 2.2†††	1178 ± 90†††
Lidocaine	94 ± 3	5.9 ± 1.6	21.7 ± 3.4	1151 ± 204
Proprioception				
Propranolol	100 ± 0	4.8 ± 0.5	37.5 ± 4.9†††	1752 ± 222†††
Lidocaine	92 ± 4	6.1 ± 1.6	25.4 ± 3.6	1347 ± 231
Nociception				
Propranolol	100 ± 0	7.9 ± 2.0	114.4 ± 8.5***	5832 ± 708***
Lidocaine	94 ± 3	9.9 ± 3.4	30.0 ± 3.4	1862 ± 278

Percent of maximal possible effect (%MPE), duration of drug action, and area under curves (AUCs) of motor, proprioception, and nociception (means ± SE) for propranolol and lidocaine at the same dose of 2.5 μmol (n = 8). Of note, all of the rats in the propranolol group showes complete blockade (100% MPE) of any function tested. Symbols (***) indicate $P < 0.001$ when propranolol compared to lidocaine; Symbols (†††) indicate $P < 0.001$ when nociception compared to motor or proprioception.

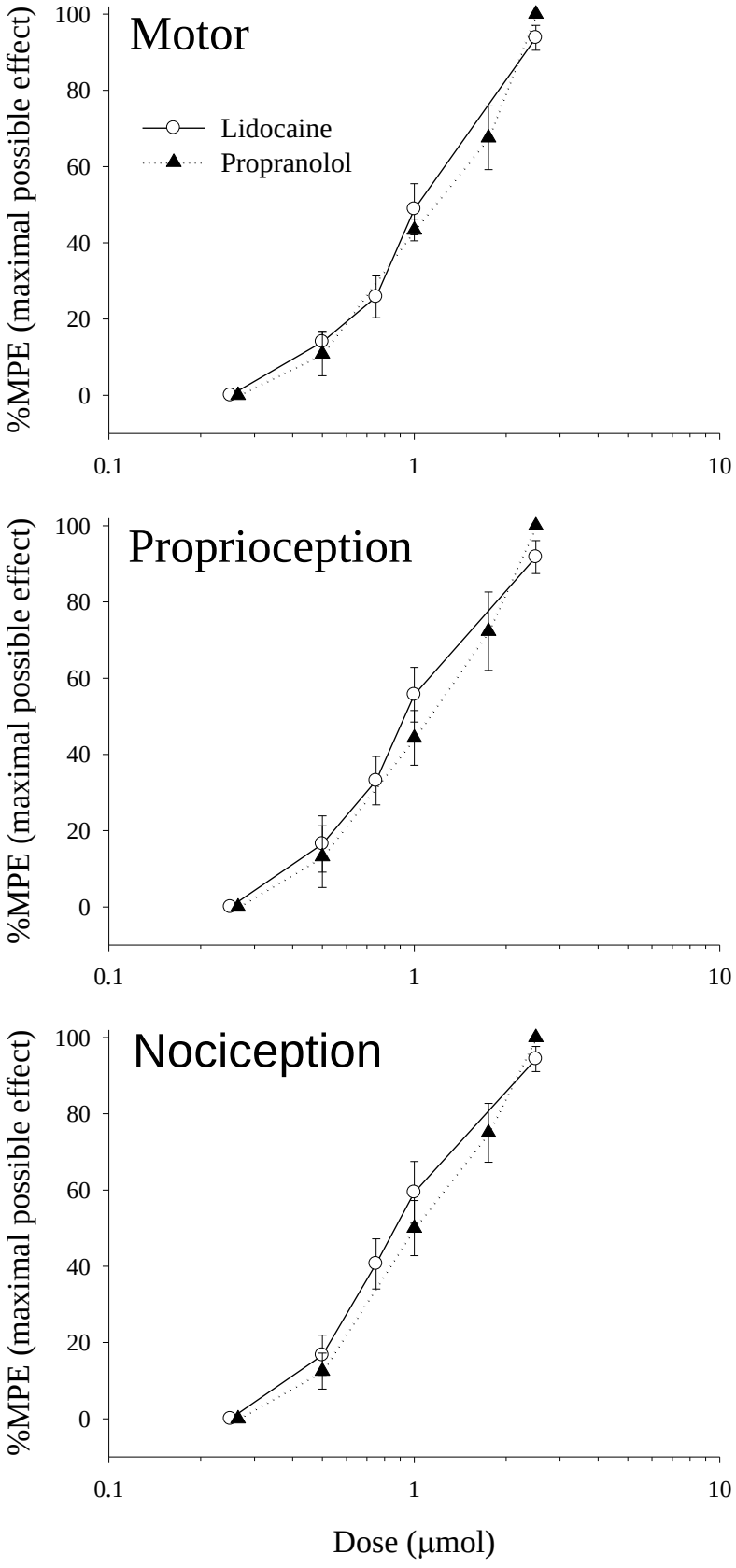
Motor
Lidocaine
Propranolol
Proprioception
Nociception
%MPE (maximal possible effect)
100
80
60
40
20
0
0.1
1
10
Dose (μmol)

Fig. 1.

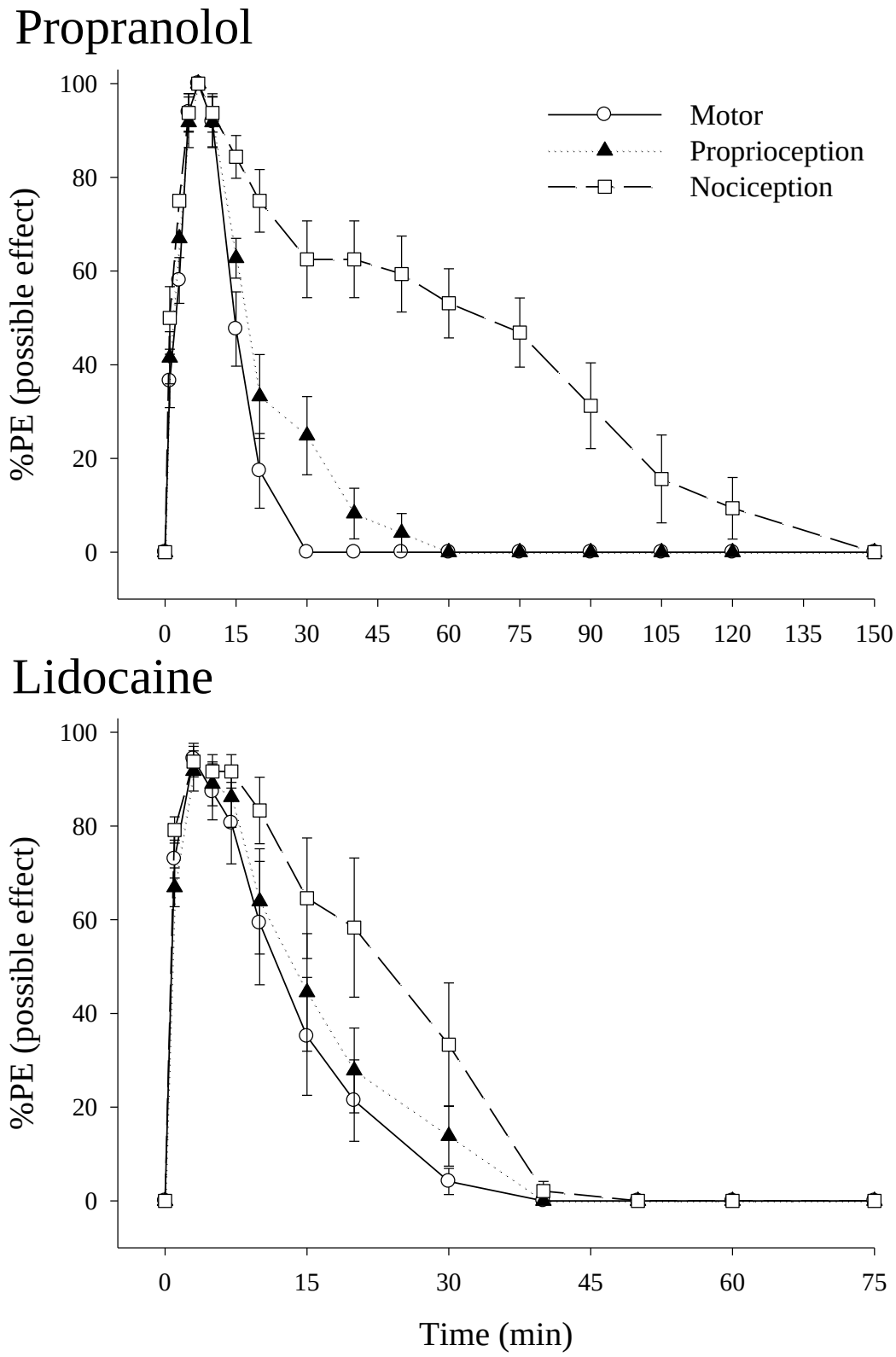
Propranolol
Motor
Proprioception
Nociception
%PE (possible effect)
100
80
60
40
20
0
0
15
30
45
60
75
90
105
120
135
150
Lidocaine
%PE (possible effect)
100
80
60
40
20
0
0
15
30
45
60
75
Time (min)

Fig. 2.

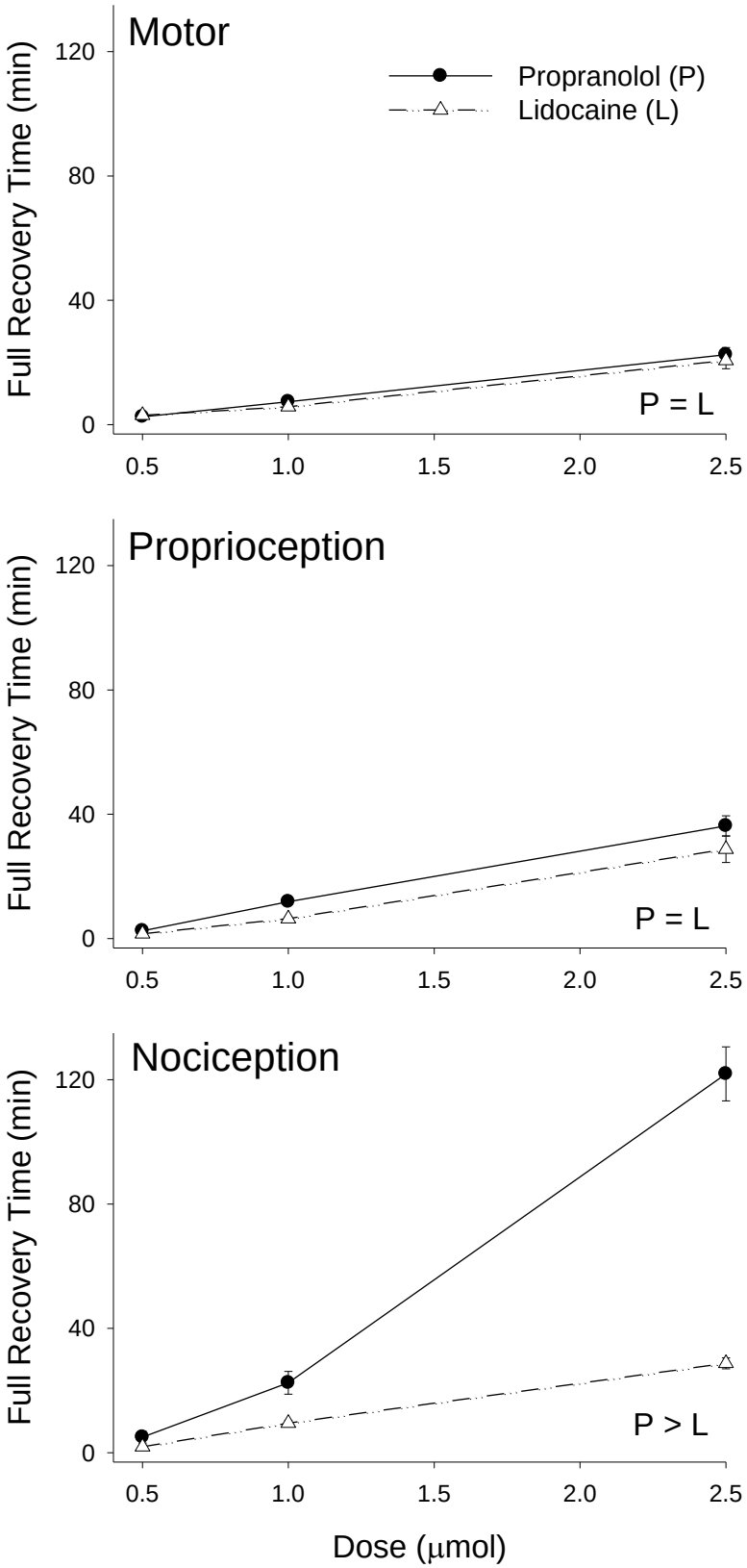
Motor
Propranolol (P)
Lidocaine (L)
Full Recovery Time (min)
120
80
40
0
P = L
0.5
1.0
1.5
2.0
2.5
Proprioception
Full Recovery Time (min)
120
80
40
0
P = L
0.5
1.0
1.5
2.0
2.5
Nociception
Full Recovery Time (min)
120
80
40
0
P > L
0.5
1.0
1.5
2.0
2.5
Dose (μmol)

Fig. 3.

Figure Legends

Fig. 1. The dose—response curves of propranolol and lidocaine on spinal blockades of motor, proprioception, and nociception (% MPE) in rats (n = 8 at each testing point). Data are means ± SE.

Fig. 2. Time courses of spinal anesthesia of propranolol and lidocaine at the same dose of 2.5 μmol in rats. Values are expressed as means ± SE. Each testing point of the time course study contained eight rats.

Fig. 3. Full recovery time of drug action on spinal blockades (% MPE) of motor, proprioception, and nociception at three doses of 0.5, 1.0, and 2.5 μmol (n = 8 at each testing point). Values are expressed as means ± SE.