# Lidocaine for prolonged and intensified spinal anesthesia by coadministration of propranolol in the rat

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## Abstract

Although the coadministration of lidocaine with propranolol interferes with the metabolic profile (pharmacokinetics), its pharmacodynamics is still unclear. In this report, we investigate whether propranolol can potentiate the effect of lidocaine, a conventional local anesthetic. After intrathecal injections of drugs in rats, three neurobehavioral examinations (motor function, proprioception, and nocicception) were performed. Rats received spinal anesthesia with lidocaine co-injected with propranolol. We showed that lidocaine and propranolol elicited a spinal blockade in motor function, proprioception, and nociception. Propranolol at the dose of 0.82 μmol/kg produced no spinal anesthesia. Co-administration of lidocaine [50% effective dose ($ED_{50}$) or $ED_{95}$] and propranolol (0.82 μmol/kg) produced greater spinal anesthesia than lidocaine ($ED_{50}$ or $ED_{95}$), respectively. These preclinical findings demonstrated that propranolol and lidocaine displayed spinal anesthesia. When combined with propranolol, lidocaine elicited a supra-additive effect of spinal anesthesia.


**Key Words:** Lidocaine; Propranolol; Supra-Additive Effect; Spinal Anesthesia

Propranolol, a β-adrenergic receptor antagonist, is considered to be one of the most important contributions to pharmacology and clinical medicine in the 20th century [29]. Indications for the treatment of propranolol are numerous, including the therapy of angina pectoris [10, 29], cardiac arrhythmias [21], hypertension [10], migraine [20], hyperthrophic obstructive cardiomyopathy [13], and in the treatment of many neuropsychiatric disorders [27]. Recently, propranolol has been introduced as a novel modality for the therapy of dental anxiety [12] and proliferating haemangiomas [3, 22, 29]. The response of infantile haemangiomas to propranolol reported in the New England Journal of Medicine by Léauté-Labréze et al. [17] catapulted the use of this therapy to first-line status among physicians managing this disease [26].

It has been shown that co-injection with high concentrations of propranolol prolonged tetrodotoxin block to 486 min in rat sciatic nerve blockade [16]. In addition, Saranteas et al. described that the concurrent administration of lidocaine with propranolol increases the concentration of the local anesthetic (lidocaine) in serum [24]. We suggest that the pharmacokinetic interactions may be significant for the effects of the pharmacodynamics (local anesthesia) of lidocaine in clinical applications. The goal of this study was to determine the pharmacodynamic interaction of lidocaine and propranolol. Lidocaine remains the most commonly used local anesthetic agent and is most often used to produce spinal anesthesia, local

infiltration, peripheral nerve block, epidural anesthesia, and topical anesthesia [2, 8]. Therefore, the spinal anesthetic effect of coadministration of lidocaine and propranolol was compared with the same dose of lidocaine or the same dose of propranolol alone. Our results reported that propranolol as adjuvant for lidocaine has a significant action in improving the quality and duration of spinal anesthesia.

Eighty-eight male Sprague-Dawley rats (300-350 g) were obtained from the National Laboratory Animal Centre in Taiwan, and then housed in groups of three 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 the experiment. The experimental protocols were approved by the Institutional Animal Care and Use Committee of China Medical University, Taiwan, and conformed to the recommendations and policies of the International Association for the Study of Pain (IASP).

Lidocaine HCl and (±)-Propranolol 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.

Three experiments were carried out. In experiment 1, the dose-dependent effects of lidocaine (1.54, 3.08, 6.15, 9.23 μmol/kg) and propranolol (0.82, 1.63 μmol/kg) on spinal anesthesia were performed (n=8 rats for each dose of each drug). In experiment

2, the spinal anesthetic effect of co-administration of lidocaine at $ED_{50}$ (2.92 μmol/kg) and propranolol (0.82 μmol/kg) was compared with lidocaine (2.92 μmol/kg) alone (n=8 rats for each dose of each drug). In experiment 3, the spinal anesthetic effect of co-administration of lidocaine at $ED_{95}$ (7.46 μmol/kg;) and propranolol (0.82 μmol/kg) was compared with lidocaine (7.46 μmol/kg) alone (n=8 rats for each dose of each drug).

Spinal anesthesia was practiced 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 [4, 19]. Rats, which showed unilateral blockade, were excluded from the study and sacrificed by using an over dose of isoflurane.

After intrathecal injection of drug, three neurobehavioral examinations, which consisted of evaluations of motor function, proprioception, and nociception, were

conducted [5, 6, 15]. For consistency, one trained examiner was responsible for handling of all rats and behavioral evaluations. 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 reduction in force, resulting from extensor muscle tone, was considered motor deficit. A force <20 g (also referred to a weight of the ‘flaccid limb’) was considered absence of extensor postural thrust or 100% motor block or 100% maximal possible effect (MPE). Nociception was evaluated using the withdrawal reflex or vocalization elicited by pinching a skin fold on each rat's back at 1 cm from the proximal part of the tail, the lateral metatarsus of both hind limbs, and the dorsal part of the mid-tail. Nociceptive block was graded as 0 (absent or 100% MPE), 1 (75% MPE), 2 (50% MPE), 3 (25% MPE), and 4 (normal or 0% MPE) [11]. 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 or 33% MPE), 1 (severely impaired or 67% MPE), and 0 (completely impaired or 100% MPE).

After injecting rats with four doses of lidocaine (n = 8 for each dose of each drug) intrathecally, the dose—response curve was constructed by the % MPE of each dose of lidocaine. The curve was then fitted using SAS NLIN Procedures (SAS Institute Inc., Carey, NC), and the values of $ED_{50}$ and $ED_{95}$, defined as the doses that caused

50% and 95% spinal anesthesia, respectively, were obtained [5, 6, 14].

The complete block duration of drug was defined as the interval between times of 100% blockade (100% MPE) of drug. The full recovery time of each blockade, defined as the interval from drug injection to full recovery, was measured and compared. In addition, the AUCs of spinal blockades of drugs were estimated by Kinetica version 2.0.1 (InnaPhase Corporation, Philadelphia, PA).

Experimental data are presented as mean ± SEM or $ED_{50}$ values with 95% confidence interval (95% CI). All data were evaluated by 2-sided Student *t* test with unequal variances. 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.

The spinal block effects of propranolol and lidocaine in motor function, proprioception, and nociception has been demonstrated in Figure 1. The $ED_{50}$s of lidocaine in motor, proprioception, and nociception are shown in Table 1. At the dose of 1.63 μmol/kg (Fig. 1), propranolol showed 8.5, 12.4, and 15.6% of blockades (% MPE) in motor function, proprioception, and nociception with duration of action of about 2.5±0.9, 2.8±1.1, and 5.9±1.8 min, respectively. Intrathecal injection of 5% dextrose or propranolol at the dose of 0.82 μmol/kg elicited no spinal blockades in motor, proprioception, and nociception (Fig. 1). Of note, lidocaine at the dose of 9.23

μmol/kg produced complete blockade (100% MPE) of motor function, proprioception, and nociception (Fig. 1).

We have known that propranolol at the dose of 0.82 μmol/kg showed no spinal anesthesia (Fig. 1). Co-administration of lidocaine at $ED_{50}$ (2.92 μmol/kg) and propranolol (0.82 μmol/kg) demonstrated greater motor, proprioceptive, and nociceptive blockade (55% MPE, 67% MPE, and 81% MPE; $P < 0.05$) than that of the same dose of lidocaine alone (44% MPE, 50% MPE, and 66% MPE) (Fig. 2 and Table 2). The time to full recovery and AUCs of co-administration of lidocaine (2.92 μmol/kg) and propranolol (0.82 μmol/kg) also displayed greater motor, proprioceptive, and nociceptive blockade than that of the same dose of propranolol alone (Fig. 2 and Table 2).

Lidocaine at the dose of 7.46 μmol/kg ($ED_{95}$) co-injected with propranolol (0.82 μmol/kg) caused similar motor, proprioceptive, and nociceptive blockade (100% MPE, 100% MPE, and 100% MPE) to that of the same dose of lidocaine alone (98% MPE, 96% MPE, and 97% MPE) (Fig. 3 and Table 3). The time to full recovery and AUCs of lidocaine at the dose of $ED_{95}$ with propranolol (0.82 μmol/kg) were greater ($P<0.05$) than those of lidocaine ($ED_{95}$) in Figure 3 and Table 3. All rats recovered completely after intrathecal drug injections.

This study reported that propranolol was similar to lidocaine at producing spinal

anesthesia in rats. Propranolol dramatically improves the spinal blocking effect and duration by lidocaine.

Local anesthetics are agents that elicit neural blockade via a direct blocking effect on the voltage-gated $Na^+$ channels of the nervous tissues [2, 8]. Because propranolol has been known to have a blocking effect of veratridine-stimulated $Na^+$ influx in rat cerebrocortical synaptosomes [7], theoretically, it may have a local anesthetic effect. In this study, we did find that the beta-blocker propranolol displayed a spinal (local) anesthetic effect. Similarly to propranolol spinal anesthetic effect in rats, propranolol administration into the sciatic nerve area produced the local anesthetic effect and neuromuscular blocking activity [18] in mice.

The coadministration of lidocaine with propranolol resulting in pharmacokinetic interactions that may be significant for the determination of the correct dose of lidocaine in clinical practice [24]. Furthermore, both the reduced concentrations and the protein-binding of lidocaine in mandible after the coadministration with propranolol may result in decreased depth and duration of local anesthesia [24]. In addition, Tesseromatis et al. reported that propranolol can displace lidocaine from liver proteins and therefore the co-administration of these two drugs may increase the free fraction of lidocaine excreted by the liver [28]. However, we showed that co-injection with propranolol enhanced and prolonged the spinal anesthetic effect of

lidocaine.

Tetrodotoxin is also a local anesthetic agent in that it does not cause seizures, arrhythmias or local neurotoxicity [23]. Interestingly, it has been demonstrated that co-injection with the high concentrations of adrenergic antagonists (e.g. propranolol) markedly prolong the duration of block of tetrodotoxin in rat sciatic nerve blockade, by an effect that does not appear to be adrenergic receptor-specific [16]. This report is agreement in our data showed that adding propranolol at 0.82 μmol/kg to lidocaine, a common local anesthetic, produced a supra-additive effect in spinal anesthesia (Figs. 2 and 3).

It is well known that the adrenergic system is a prime controller of blood pressure. In *in vitro* binding assays, propranolol shows high affinity for β1- and β2-adrenoceptors [9, 25]. Though we have made no study about the known cardiovascular effects, Berg et al. demonstrated that centrally active propranolol ($\beta_{1+2+[3]}$, 44 μmol/kg) in rats had little effect on blood pressure, heart rate, cardiac output, and total peripheral vascular resistance [1]. In this study, we only evaluated the doses of propranolol between 1.63 and 0.82 μmol/kg. Besides, spinal anesthesia is a relatively simple method, which supplies competent surgical conditions by administrating a small amount of local anesthetics [15]. In addition to the spinal anesthetic effect of propranolol, this study also indicated that co-administration of

lidocaine and propranolol elicited greater spinal blockades than that of the same dose of lidocaine alone.

In conclusion, our results showed that propranolol and lidocaine produced spinal anesthetic effects in rats. Co-injection with propranolol markedly potentiated the spinal anesthetic effects of lidocaine.

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**Table 1.** The 50% effective doses ($ED_{50}$s) of lidocaine with 95% confidence interval (95% CI) on spinal blockades of motor, proprioception, and nociception in rats

| Drug | $ED_{50}$ (95% CI) | | | Mean | |
|---|---|---|---|---|---|
| | Motor | Proprioception | Nociception | $ED_{50}$ | $ED_{95}$ |
| Lidocaine | 3.11 (2.89 – 3.38) | 2.89 (2.62 – 3.23) | 2.77 (2.52 – 3.05) | 2.92 | 7.46 |

The $ED_{50}$s of lidocaine (μmol/kg) were obtained from Fig. 1. by using SAS Nonlinear (NLIN) Procedures.

**Table 2.** The %MPE, duration, and AUCs of lidocaine at $ED_{50}$ (2.92 μmol/kg) or co-administration of lidocaine (2.92 μmol/kg) and propranolol (0.82 μmol/kg) in rats

| | %MPE | Duration (min) | | AUCs (%MPE x min) |
|---|---|---|---|---|
| | | Complete block time | Time to full recovery | |
| Motor | | | | |
| Propranolol+Lidocaine | 55 ± 2* | – | 10.0 ± 1.3** | 310 ± 48*** |
| Lidocaine | 44 ± 5 | – | 4.8 ± 0.5 | 83 ± 19 |
| Proprioception | | | | |
| Propranolol+Lidocaine | 67 ± 0* | – | 15.9 ± 2.2*** | 625 ± 96*** |
| Lidocaine | 50 ± 6 | – | 5.8 ± 0.5 | 139 ± 21 |
| Nociception | | | | |
| Propranolol+Lidocaine | 81 ± 4* | 1 ± 1 | 31.3 ± 2.3*** | 1327 ± 79*** |
| Lidocaine | 66 ± 5 | – | 9.8 ± 1.2 | 330 ± 47 |

Percent of maximal possible effect (%MPE), duration of drug action, and area under curves (AUCs) of motor, proprioceptive, and nociceptive blockades (mean ± SEM) for lidocaine alone or co-administration of lidocaine and propranolol (n = 8 in each group). Symbols (*,**,***) indicate $P < 0.05$, $P < 0.01$, $P < 0.001$, respectively, when co-administration of propranolol and lidocaine compared to lidocaine alone.

**Table 3.** The %MPE, duration, and AUCs of lidocaine at $ED_{95}$ (7.46 μmol/kg) or co-administration of lidocaine (7.46 μmol/kg) and propranolol (0.82 μmol/kg) in rats

| | %MPE | Duration (min) | | AUCs (%MPE x min) |
|---|---|---|---|---|
| | | Complete block time | Time to full recovery | |
| Motor | | | | |
| Propranolol+Lidocaine | 100 ± 0 | 13.6 ± 1.5** | 38.8 ± 3.0** | 2339 ± 191*** |
| Lidocaine | 98 ± 2 | 6.3 ± 1.6 | 23.1 ± 2.8 | 1173 ± 153 |
| Proprioception | | | | |
| Propranolol+Lidocaine | 100 ± 0 | 16.5 ± 1.6** | 42.5 ± 2.5* | 2640 ± 179** |
| Lidocaine | 96 ± 4 | 8.1 ± 1.6 | 30.6 ± 3.3 | 1648 ± 215 |
| Nociception | | | | |
| Propranolol+Lidocaine | 100 ± 0 | 25.3 ± 2.0* | 48.8 ± 3.0** | 3364 ± 221** |
| Lidocaine | 97 ± 3 | 14.6 ± 3.3 | 31.9 ± 3.5 | 2031 ± 276 |

Percent of maximal possible effect (%MPE), duration of drug action, and area under curves (AUCs) of motor, proprioceptive, and nociceptive blockades (mean ± SEM) for lidocaine alone or co-administration of lidocaine and propranolol (n = 8 in each group). Of note, all of the rats in the co-administration of propranolol and lidocaine group show complete blockade (100% MPE) of any function tested. Symbols (*,**,***) indicate $P < 0.05$, $P < 0.01$, $P < 0.001$, respectively, when co-administration of propranolol and lidocaine compared to lidocaine alone.

## Legends to figures

**Fig. 1.** Time courses of spinal blockades of motor, proprioception, and nociception (% PE) by lidocaine and propranolol in rats (n=8 at each testing point). The 5% dextrose (vehicle) group is as the control. Data are mean ± SEM.

**Fig. 2.** The time course of lidocaine at 2.92 μmol/kg ($ED_{50}$) or coadministration of lidocaine at 2.92 μmol/kg and propranolol at 0.82 μmol/kg on spinal anesthesia in rats. Values are expressed as mean ± SEM. For each group of the time course study, n=8 rats.

**Fig. 3.** The time course of lidocaine at 7.46 μmol/kg ($ED_{95}$) or coadministration of lidocaine at 7.46 μmol/kg and propranolol at 0.82 μmol/kg on spinal anesthesia in rats. Data are mean ± SEM. Each testing point of the time course study contained eight rats.

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**Figure 1**

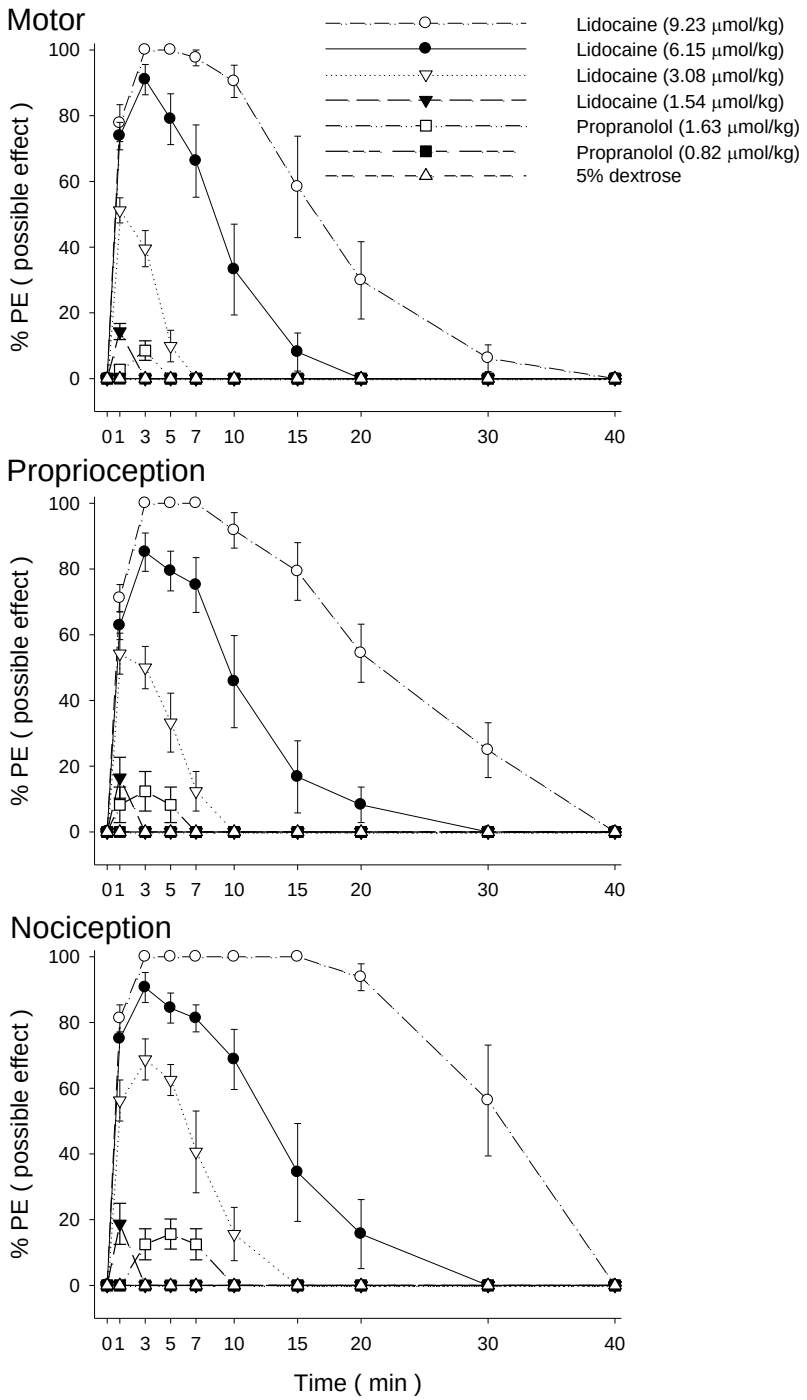


Fig. 1.

**Figure 2**

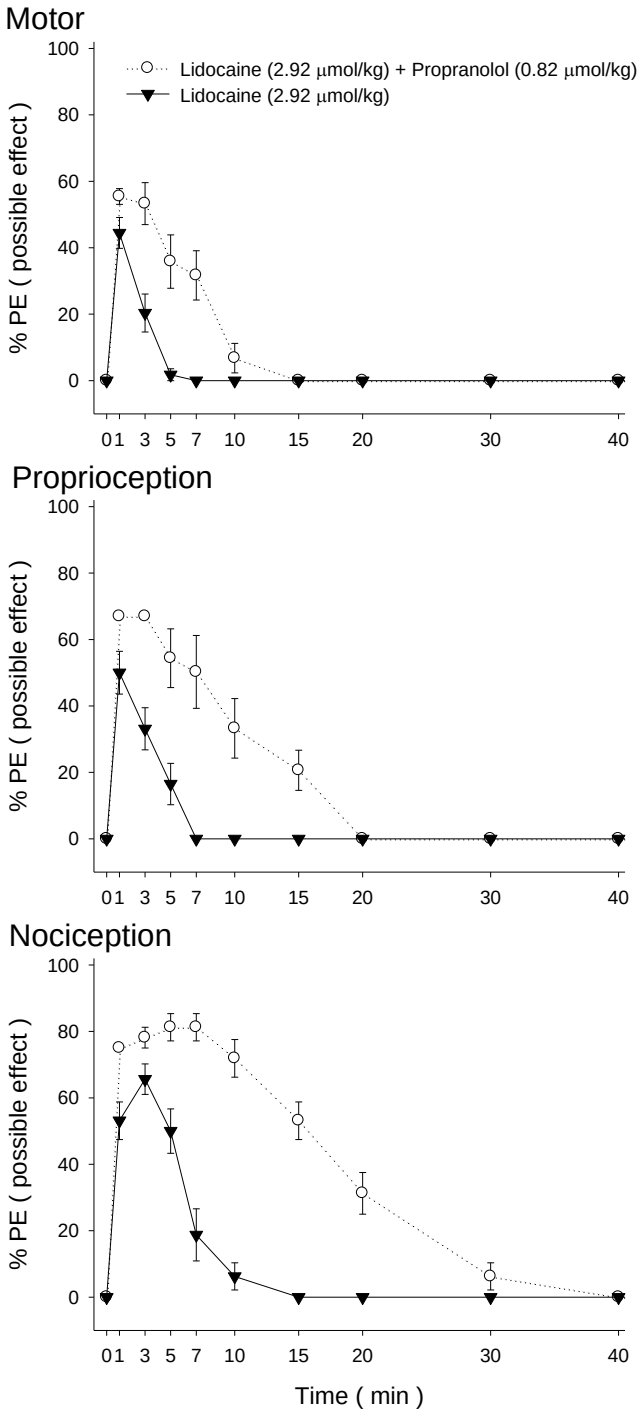


Fig. 2.

**Figure 3**

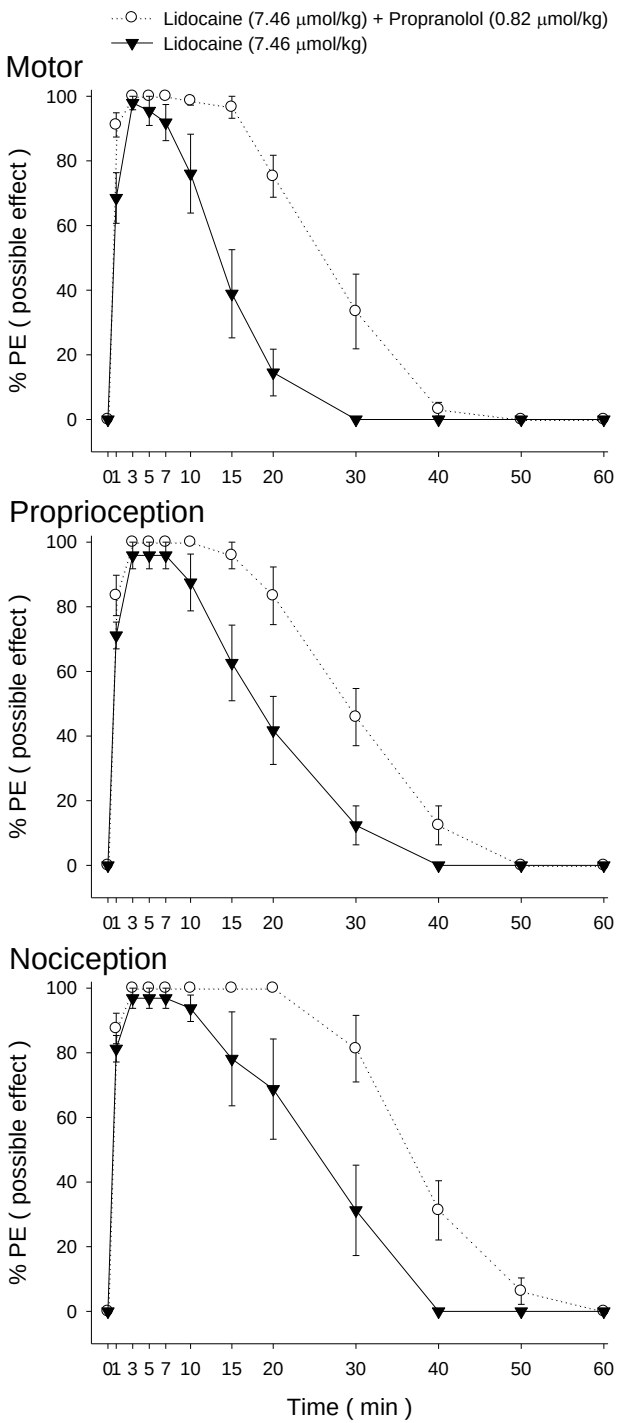


Fig. 3.