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Ifenprodil for prolonged spinal blockades of motor function and nociception in rats

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ABSTRACT

Background: The aim of the study was to compare the proposed spinal anesthetic effect of ifenprodil, an a1 adrenergic receptor antagonist, with that of the long-acting local anesthetic bupivacaine.
Methods: After intrathecally injecting the rats with five different doses of each drug, the dose–response curves of ifenprodil and bupivacaine were constructed to obtain the 50% effective dose (ED_{50}). The spinal blockades of motor function and nociception of ifenprodil were compared with that of bupivacaine.
Results: We showed that either ifenprodil or bupivacaine produced spinal blockades of motor function and nociception dose-dependently. On the ED_{50} basis, the potency of ifenprodil (0.42(0.38–0.46) μmol; 0.40(0.36–0.44) μmol) was equal ($p > 0.05$) to that of bupivacaine (0.38(0.36–0.40) μmol; 0.35(0.32–0.38) μmol) in motor function and nociception, respectively. At the equianesthetic doses (ED_{25}, ED_{50}, and ED_{75}), duration produced by ifenprodil was greater than that produced by bupivacaine in motor function and nociception ($p < 0.05$ for the differences). Furthermore, both ifenprodil and bupivacaine showed longer duration of sensory blockade than that of motor blockade ($p < 0.05$ for the differences).
Conclusions: The resulting data demonstrated that ifenprodil produces a dose-dependent local anesthetic effect in spinal anesthesia. Ifenprodil shows a more sensory-selective duration of action over motor block, whereas the duration of anesthesia is significantly longer with ifenprodil than with bupivacaine.

Introduction

Ifenprodil (2-(4-benzyl-piperidino)-1-(4-hydroxyphenyl)-1-propanol), an α1 adrenergic receptor antagonist, is initially developed as a vasodilating and anti-ischemic agent [1,2] and then has been clinically used in the treatment of peripheral arterial obliterative disease and cerebrovascular diseases [3–5]. Subsequently, ifenprodil is also the first agent found to be a noncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors highly selective for the NMDA receptor 2B (NR2B) subunit [6,7] as a widely used therapeutic drug [8]. In *in vivo* studies, potential therapeutic targets of NR2B selective NMDA receptor antagonists (*i.e.*, ifenprodil) are epileptic seizures [9], anti-nociceptive effects [10], and alcoholism [11]. In *in vitro* studies, ifenprodil interacts with serotonin (5-hydroxytryptamine; 5-HT) receptors [2] and sigma-1 or sigma-2 receptor [12–14].

As well as binding to those receptors, ifenprodil also blocks G protein-activated inwardly rectifying K^+ channels [15], tetrodotoxin-resistant Na^+ channels [16], voltage-gated Ca^{2+} channels [17–19], and Na^+/Ca^{2+} exchanger in neurons [20]. Through blockade of voltage-gated Na^+ channels, local anesthetics reversibly inhibit the conduction of electrical impulses in nerves [21,22]. Because ifenprodil shows a Na^+ channel blocking activity, it produces a local/peripheral anesthetic effect in the guinea pig cornea and skin theoretically [23].

Intrathecal injections of local anesthetics are often performed for the procedures and surgeries [24,25]. Spinal/central anesthesia

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is a relatively simple technique, which processes satisfactory surgical conditions through administrating a small amount of local anesthetic solution with easy landmarks [25,26]. Additionally, intrathecal administration of ifenprodil exhibited a marked reduction of neuropathic pain caused by chronic dorsal root ganglia compression in rats [27]. However, to the best of our knowledge, no study of spinal anesthesia with ifenprodil has been reported to date. The purpose of the study was to estimate the blocking properties of intrathecal administration of ifenprodil on sensory and motor function in rats. Bupivacaine, a long-lasting local anesthetic, was used as a control agent.

Materials and methods

Animals

Male Sprague–Dawley rats (300–350 g) were purchased from National Cheng Kung University (Tainan, Taiwan) and were kept in the animal housing facilities at National Cheng Kung University, with controlled room temperature (22 °C), humidity (approximately 50% relative humidity), and a 12-h light/dark cycle (light on at 6:00 a.m.). The investigative procedures were approved *via* the Institutional Animal Care and Use Committee of National Cheng Kung University.

Experimental designs

Three specific experiments were carried out ($n = 8$ in each group). In experiment 1, spinal anesthesia with ifenprodil (0.25, 0.36, 0.68, 0.90, and 1.13 μmol) and bupivacaine (0.23, 0.32, 0.45, 0.68, and 0.90 μmol) were performed randomly in a dosage-dependent fashion. In experiment 2, the percent of maximal possible effect (%MPE), full recovery time, complete blockade time, and area under the curves (AUCs) of spinal anesthesia with ifenprodil (1.13 μmol), bupivacaine (0.90 μmol), and vehicle (5% dextrose) was estimated. In experiment 3, the duration of spinal anesthesia with ifenprodil was compared with that of bupivacaine on the equipotent basis (25% effective dose ED_{25}, ED_{50} and ED_{75}).

Drugs

Ifenprodil (+)-tartrate salt (molecular weight = 800.98), lidocaine HCl monohydrate (molecular weight = 288.81), and bupivacaine HCl (molecular weight = 324.89) were purchased from Sigma–Aldrich Chemical Co. (St. Louis, MO, USA). Before intrathecal injection, drugs in stock were freshly dissolved in 5% dextrose as solution.

Spinal anesthesia

Lumbar puncture was given on conscious rats while each rat was intrathecally injected once in the study. Before intrathecal injection, each 50-μl of 0.5% lidocaine was injected into the right- and left-side of paraspinal space (0.5 cm in depth) that was 0.5 cm away from the mid-point of the longitudinal line of the lumbar 4–5 (L4–L5) intervertebral space. Following an optimal flexion of rat lumbar spine under prone position, 90-μl of drug was injected into the spinal (L4–L5) space by a 27-gauge needle attached to a 100-μl syringe (Hamilton, Reno, Nevada). Moreover, intrathecal injection of high volumes (100-μl) of amitriptyline results in long-acting spinal anesthesia in rats [28]. Rats were observed for the development of spinal anesthesia, indicated by paralysis of both hind limbs [28,29]. Rats, that showed unilateral block, were excluded from the experiment and were sacrificed using an overdose of isoflurane.

After intrathecal injection, two neurobehavioral examinations, which consisted of motor and sensory blockades, were constructed [30,31]. An experienced investigator, who was blinded to the treatment groups, was responsible for all neurobehavioral evaluations to keep experimental consistency. The magnitude of spinal blockade was expressed as the percent of possible effect (%PE) while the maximal block in a time course of spinal anesthesia was described as the %MPE. Nociception was examined through the vocalization or withdrawal reflex evoked by pinching a skin fold over each rat's back at 1 cm from the proximal part of the tail, the dorsal part of the mid-tail, and the lateral metatarsus of bilateral hind limbs. Only a pinch was given to each of four testing areas, and the time interval between two pinches at different areas was around 3 s. 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). Motor function was tested by measuring 'the extensor postural thrust' of the rat hind-limb. The extensor thrust was recorded as the gram force, which resisted contacting the platform when the rat heel applied to a digital platform balance (Mettler Toledo, PB 1502-S, Greifensee, Switzerland). A reduction of the force, representing decreased extensor muscle tone, was considered as a deficit of motor function and expressed as a percent of the control force. A force < 20 g (also referred to a weight of the 'flaccid limb') was interpreted the absence of extensor postural thrust or 100% motor block (100% MPE).

AUCs, effective doses (EDs), ED_{50} and full recovery time

The AUCs of spinal anesthesia with drugs were calculated through using Kinetica v 2.0.1 (MicroPharm International, USA). After intrathecally injecting the rats with five different doses of each drug, two dose–response curves were constructed by the %MPE. The curves were then fitted using the SAS Nonlinear (NLIN) Procedures (SAS Institute Inc., Carey, NC, USA), and the value of ED_{50}, defined as a dose that elicited 50% spinal anesthesia, was obtained [32,33]. The ED_{25} and ED_{75} of drugs were calculated using the same curve-fitting (SAS NLIN Procedures) that was used to derive the ED_{50}. The full recovery time was defined as the interval from drug injection to full recovery of block (0% MPE).

Statistical analysis

Data are expressed as means ± SEM or ED_{50} values with 95% confidence interval (95% CI). The values were analyzed by either one-way (studies 1 and 2) or two-way (study 3) analysis of variance (ANOVA) followed by pairwise Tukey's honest significance difference (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 to be statistically significant.

Results

Intrathecal ifenprodil caused significant motor or nociceptive blockade

Intrathecal ifenprodil, as well as the long-lasting local anesthetic bupivacaine produced a dose-dependent local anesthetic effect in spinal anesthesia in rats (Fig. 1). The ED_{25}s, ED_{50}s, and ED_{75}s of ifenprodil and bupivacaine are presented in Table 1. On the ED_{50} basis, the potency of ifenprodil in motor function and nociception was comparable to that of bupivacaine (Table 1, $p > 0.05$).

The spinal block effect of equipotent ifenprodil and bupivacaine

Ifenprodil (1.13 μmol) exhibited 100% and 100% of block (%MPE) in motor function and nociception with duration of action of about 41 and 96 min, respectively (Fig. 2 and Table 2). At a given dose of 0.9 μmol, bupivacaine displayed 100% and 100% of block

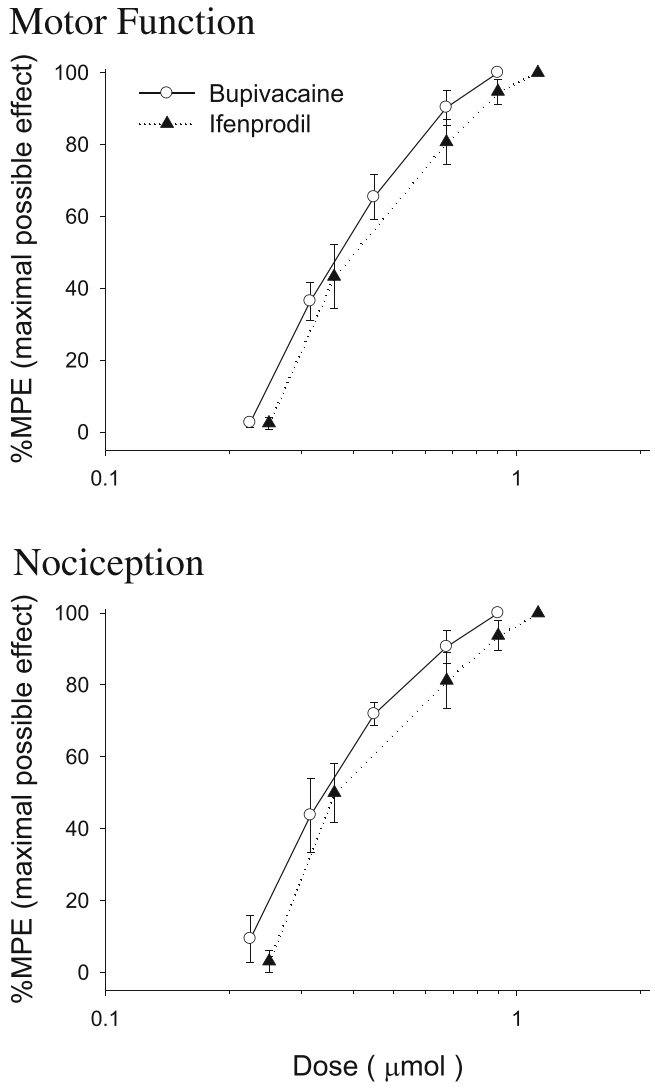

Fig. 1. Spinal blockades (%MPE) of motor function and nociception of ifenprodil and bupivacaine in a dosage-dependent fashion ($n = 8$ at each testing point). Data are expressed as means ± SEM; %MPE = percent of maximal possible effect.

(%MPE) in motor function and nociception with duration of action of about 35 and 61 min, respectively (Fig. 2 and Table 2). Intrathecal 5% dextrose (vehicle) did not elicit any spinal blocks of motor function and nociception (Table 2).

Duration and AUCs of ifenprodil and bupivacaine in spinal anesthesia

Full recovery time and AUCs of ifenprodil spinal block in motor function and nociception are significantly greater ($p < 0.05$) than those of bupivacaine, whereas complete blockade time of ifenprodil spinal block in nociception, but not motor function, is significantly greater ($p < 0.05$) than that of bupivacaine in Table 2. Furthermore,

Table 1
The 25% effective dose ED_{25}, ED_{50}, and ED_{75}.

	ED_{50} (95% CI)		Mean		
	Motor Function	Nociception	ED_{25}	ED_{50}	ED_{75}
Bupivacaine	0.38 (0.36–0.40)	0.35 (0.32–0.38)	0.28	0.37	0.47
Ifenprodil	0.42 (0.38–0.46)	0.40 (0.36–0.44)	0.31	0.41	0.54

The EDs of ifenprodil and bupivacaine (μmol) were obtained from Fig. 1. CI, confidence interval. There is no significant difference between drugs (ED_{50}) in nociception and motor function.

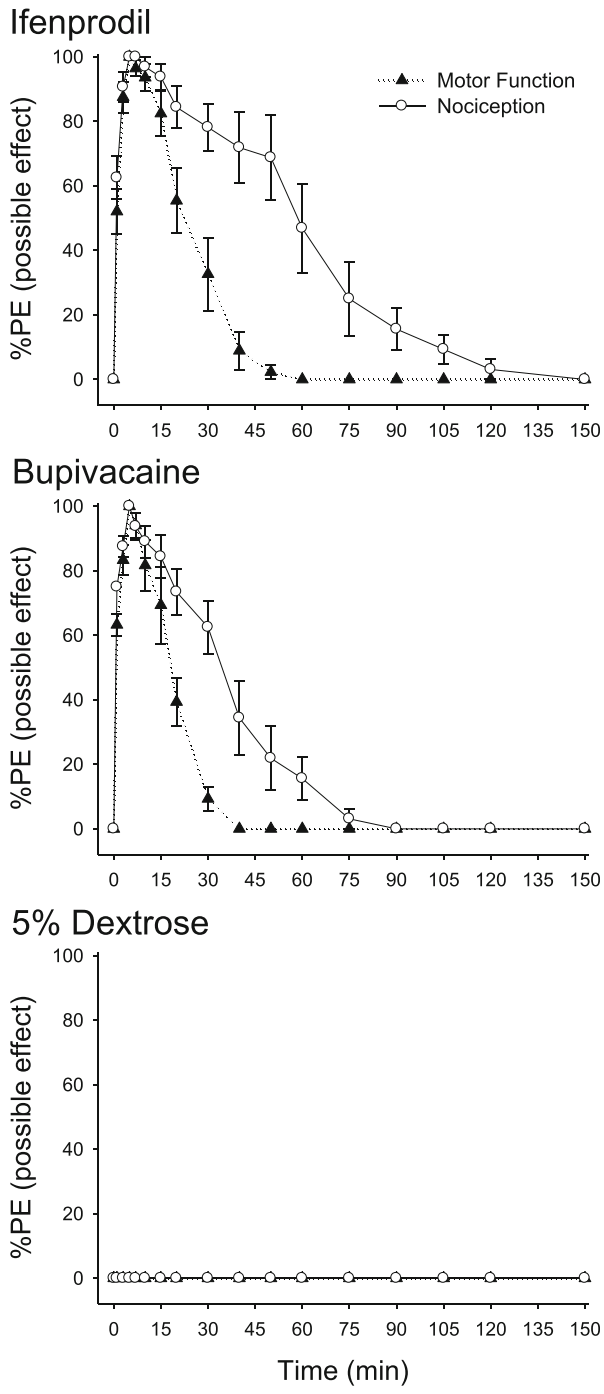

Fig. 2. Time courses of spinal anesthesia with ifenprodil at 1.13 μmol and bupivacaine at 0.9 μmol. Intrathecal 5% dextrose (vehicle) produced no spinal anesthesia. Values are presented as means ± SEM. Each testing point of the time course study contained eight rats.

both ifenprodil and bupivacaine displayed longer duration (AUC) of nociceptive/sensory block than that of motor block (Table 2). On the equianesthetic basis (ED_{25}, ED_{50}, and ED_{75}), the spinal blockades of motor function and nociception caused by ifenprodil were greater ($p < 0.05$) than those produced by bupivacaine (Fig. 3). All animals recovered completely after intrathecal injections.

Discussion

The results of the present study indicated for the first time that intrathecal ifenprodil elicited spinal block of motor function and

Table 2
The percent of maximal possible effect (%MPE), duration, area under the curves (AUCs).

	%MPE	Duration (min)		AUCs (%MPE × min)
		Complete blockade time	Full recovery time	
Motor function				
Ifenprodil	100 ± 0	10.1 ± 2.8	41.3 ± 4.4[a]	2172 ± 287[a]
Bupivacaine	100 ± 0	6.0 ± 1.7	35.0 ± 1.9	1623 ± 182
5% dextrose	–	–	–	–
Nociception				
Ifenprodil	100 ± 0	27.5 ± 7.1[a,b]	96.3 ± 12.0[a,d]	5559 ± 834[a,c]
Bupivacaine	100 ± 0	8.9 ± 3.2	60.6 ± 7.2[c]	3240 ± 450[c]
5% dextrose	–	–	–	–

Spinal anesthesia (means ± SEM) with ifenprodil at 1.13 μmol and bupivacaine at 0.9 μmol ($n = 8$ in each group). Of *note*, all of the animals receiving ifenprodil and bupivacaine showed complete block (100%MPE) of any function tested. The symbol (a) indicates $p < 0.05$ when ifenprodil compared with bupivacaine, whereas symbols (b, c, d) indicate $p < 0.05$, $p < 0.01$, $p < 0.001$ when nociception compared with motor function.

nociception. The spinal anesthetic effect of ifenprodil was comparable to that of the long-acting local anesthetic bupivacaine. Ifenprodil as well as bupivacaine showed greater duration of nociceptive/sensory block than motor block. At the equianesthetic doses (ED_{25}, ED_{50}, and ED_{75}), the duration of spinal anesthesia with ifenprodil was greater than that of bupivacaine.

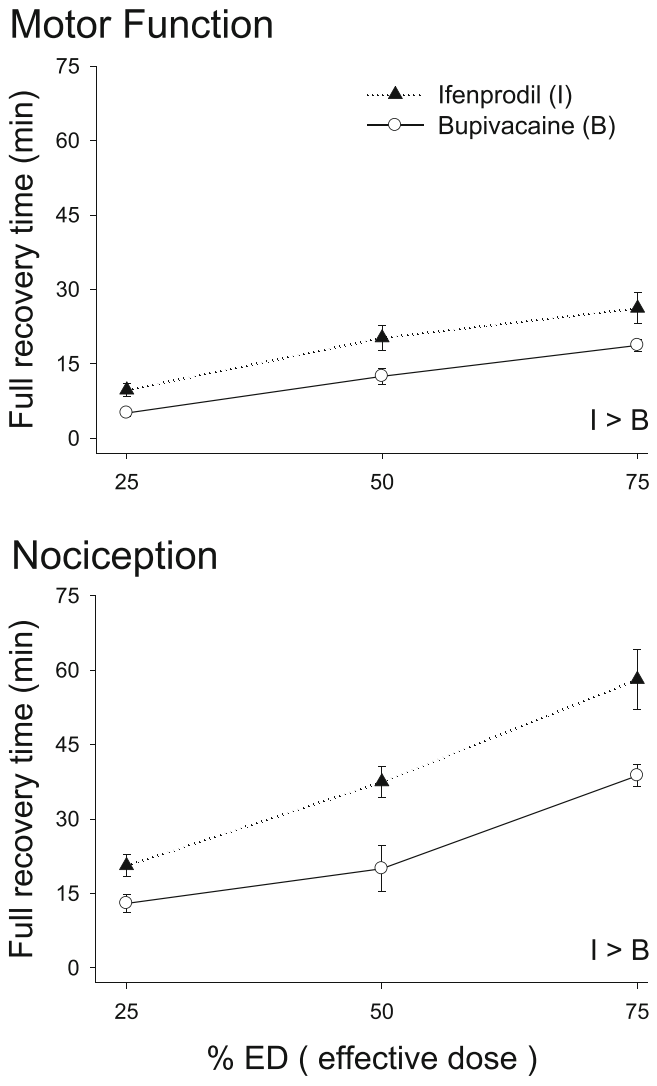

Fig. 3. Duration (full recovery time) of spinal anesthesia with ifenprodil and bupivacaine at the equipotent doses (25% effective dose ED_{25}, ED_{50}, and ED_{75}) ($n = 8$ at each testing point). Data are expressed as means ± SEM.

Ifenprodil, a synthetic phenylethanolamine, originally developed as a vasodilator because of its antagonistic activity at α1 receptors [1] and subsequently was found to have a highly selective antagonist at the NMDA receptor 2B (NR2B) subunit [6]. Recently, ifenprodil was used in the treatment of opiate addiction [34], cerebral stroke [35], and alcoholism [11]. Furthermore, ifenprodil had several effects on receptors and channels, including sigma receptors [36], serotonin (5-HT) receptors [2,37], sigma-1 and sigma-2 receptors [12–14], G protein-activated inwardly rectifying K^+ channels [15], tetrodotoxin-resistant Na^+ channels [16], voltage-gated Ca^{2+} channels [17–19], and Na^+/Ca^{2+} exchanger in neurons [20]. In the present study, we demonstrated that ifenprodil produced a local anesthetic effect in spinal anesthesia. Our findings are in agreement with the report by Tanahashi et al. [16] who suggest that ifenprodil reaches the same binding site as the local anesthetic lidocaine because it has similar electrophysiological characteristic to lidocaine.

It has been accepted that local anesthetics produce neural block through suppressing the Na^+ currents in the nervous tissues [38]. Because ifenprodil produced the use-dependent block of tetrodotoxin-resistant Na^+ currents [16], ifenprodil (1.13 μmol) elicited complete spinal blockades of motor and sensory functions, suggesting that ifenprodil has the characteristics of the local anesthetics. In agreement with the previous animal study, ifenprodil showed a local/peripheral anesthetic action in the guinea pig cornea and skin [23]. Additionally, we demonstrated that ifenprodil and bupivacaine displayed dose-dependent spinal/central anesthesia, while ifenprodil was equal-potent to bupivacaine in spinal anesthesia. Interestingly, the half-maximal inhibitory concentration of tetrodotoxin-resistant Na^+ currents by ifenprodil was 2.7 μmol [16], whereas bupivacaine blocked the tetrodotoxin-resistant Na^+ current in a reversible and concentration-dependent manner (50% inhibitory concentration value: 32 μmol/l) [39].

In the present study, we revealed that intrathecal ifenprodil produced a longer duration of nociceptive/sensory block than that of motor block (Table 2). In addition to use-dependent block of voltage-gated Na^+ channels by ifenprodil [16], the results were supported by a host of previous experiments which demonstrated that antagonizing the NMDA receptors attenuated neuropathic pain behaviors caused by peripheral nerve injury [27,40–42]. Awakening of NMDA receptors is intended to activate intracellular cascades by Ca^{2+} influx and protein kinases activation, which in turn intensify nociceptive transmission and regulate cell membrane excitability [27]. Moreover, it has been shown that intrathecal administration of the NR2B-selective antagonist ifenprodil (0.5 μg/μl) completely reversed a marked reduction of mechanical allodynia and thermal hyperalgesia in chronic compression of the dorsal root ganglia (CCD) rats [27]. Ifenprodil is also used to control moderate to severe pain, and its analgesic effect has been reported in some models of inflammation and

neuropathic pain [10,35,43]. In addition, pre-administration of ifenprodil (0.6 μg) shows the improvement of the anti-hyperalgesic effect produced by ketamine in rat's hind paw following prostaglandin E2-induced hyperalgesia [44].

Surgery and postoperative pain control *via* intrathecal administration of long-acting local anesthetics is commonly performed [24,25]. However, the technique is limited due to the short duration of analgesia or anesthesia [45]. For this reason, bupivacaine is chosen because of its longer duration of effective analgesia [46]. Unfortunately, bupivacaine carries significant cardiovascular toxicity [47,48]. At an equipotent dose, spinal block duration of ifenprodil was greater than that of bupivacaine (Table 2). Clinically, there are few cases where spinal anesthesia for ultra-short surgical procedures is needed [49]. For the reason, they use 2-chloroprocaine or lidocaine [50,51]. Here we evaluated intrathecal ifenprodil and bupivacaine at the equianesthetic basis. In the present study, the duration of spinal anesthesia produced by ifenprodil was greater than that produced by bupivacaine on an equipotent basis (ED_{25}, ED_{50}, and ED_{75}) (Fig. 3). Administration of local anesthetics (*e.g.*, ifenprodil) for postsurgical pain control or surgery requires further exploration.

The NMDA receptors play an important role in neuronal development, memory formation, pituitary activity, excitatory neurotransmission, synaptic plasticity, and central sensitization during persistent pain [52–55]. NMDA receptor antagonists (*e.g.*, ifenprodil) selectively addressing NR2B subunit containing NMDA receptors can display an improved side effect profile because of the limited expression of the NR2B subunit in the CNS. Lately, ifenprodil was reported to have prominent neuroprotection with lesser side effects when compared with conventional NMDA receptor blockers [56]. We did not estimate whether local injection of ifenprodil induced neurotoxicity, however, it is noteworthy that in the neurobehavioral studies we did not see any side effects after intrathecal injection. Serious histologic experiment must be performed in the future before the possible application of ifenprodil as spinal analgesic in humans.

Conclusions

Our preclinical data showed that intrathecal ifenprodil produced a dose-dependent local anesthetic effect in spinal anesthesia. The potency of ifenprodil in spinal anesthesia was similar to that of bupivacaine, whereas duration of spinal anesthesia with ifenprodil was greater than that of bupivacaine. Furthermore, ifenprodil as well as bupivacaine exhibited significantly sensory-specific over motor block. The neural block of ifenprodil is worth testing in further.

Conflict of interest

The authors declare that there are no conflicts of interest.

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