Systemic dextromethorphan and dextrorphan are less toxic in rats than bupivacaine at equianesthetic doses

À doses équivalentes, le dextrométhorphan et le dextrorphan administrés par voie systémique sont moins toxiques pour les rats que la bupivacaine

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Abstract

Purpose Dextrorphan, a major metabolite of dextromethorphan, produces the duration of spinal and cutaneous anesthesia similar to bupivacaine. The purpose of this study was to test the central nervous system and cardiovascular toxicity of bupivacaine, dextromethorphan, and dextrorphan.

Methods First, dose-response curves for dextromethorphan, dextrorphan, and bupivacaine ($n = 8$ at each testing point) were determined for cutaneous analgesia on the rat back, and equipotent doses were calculated. Next, during continuous intravenous infusion of equipotent doses of bupivacaine, dextromethorphan, and dextrorphan ($n = 8$ in each group), we observed the time to seizure, apnea, and

complete cardiac arrest. A saline group ($n = 7$) was used for comparison. Mean arterial blood pressure (MAP), heart rate (HR), stroke volume (SV), and cardiac output (CO) were also monitored.

Results Bupivacaine, dextromethorphan, and dextrorphan produced dose-dependent cutaneous anesthesia. A longer duration of equipotent infusion doses was required to produce seizures in the dextromethorphan group (10.6 ± 1.3 min) than in the bupivacaine group (7.6 ± 2.1 min) ($P = 0.005$). Dextrorphan did not produce any seizures. Compared with bupivacaine, time to apnea and complete cardiac arrest was longer with dextrorphan ($P < 0.001$) and with dextromethorphan ($P = 0.001$). Cardiovascular collapse, defined as a decline in MAP, HR, CO, and SV, was slower in the dextromethorphan and dextrorphan groups than in the bupivacaine group ($P < 0.001$ for both comparisons).

Conclusion At equipotent doses for local anesthesia, dextromethorphan and dextrorphan were less likely than bupivacaine to induce central nervous system and cardiovascular toxicity.

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Résumé

Objectif Le dextrorphan, un métabolite majeur du dextrométhorphan, produit une anesthésie rachidienne et cutanée d'une durée similaire à la bupivacaine. L'objectif de cette étude consistait à évaluer la toxicité de la bupivacaine, du dextrométhorphan et du dextrorphan sur le système nerveux central et le système cardiovasculaire.

Méthode Tout d'abord, les courbes dose-réponse du dextrométhorphan, du dextrorphan et de la bupivacaine ($n = 8$ pour chaque essai) ont été déterminées pour l'analgésie cutanée sur le dos du rat, et des doses

équipotentes ont été calculées. Ensuite, pendant la perfusion intraveineuse continue des doses équipotentes de bupivacaïne, de dextrométhorphan et de dextrorphan ($n = 8$ dans chaque groupe), on a mesuré le délai de manifestation des convulsions, de l'apnée et de l'arrêt cardiaque complet. Un groupe sérum physiologique ($n = 7$) a été utilisé à titre comparatif. La tension artérielle moyenne (TAM), le rythme cardiaque (RC), le volume d'éjection (VE) et le débit cardiaque (DC) ont également été mesurés.

Résultats La bupivacaïne, le dextrométhorphan et le dextrorphan ont entraîné une anesthésie cutanée dépendante de la dose administrée. La durée d'administration par perfusion des doses équipotentes nécessaires à la manifestation des convulsions a été plus longue dans le groupe recevant du dextrométhorphan ($10,6 \pm 1,3$ min.) que dans le groupe recevant de la bupivacaïne ($7,6 \pm 2,1$ min.) ($P = 0,005$). Le dextrorphan n'a pas entraîné de convulsions. Le délai de manifestation de l'apnée et de l'arrêt cardiaque complet a été plus long avec le dextrorphan ($P < 0,001$) et le dextrométhorphan ($P = 0,001$) qu'avec la bupivacaïne. Le collapsus cardiovasculaire, caractérisé par une chute de la TAM, du RC, du VE et du DC, a nécessité davantage de temps dans les groupes recevant du dextrométhorphan et du dextrorphan que dans le groupe recevant de la bupivacaïne ($P < 0,001$ pour les deux comparaisons).

Conclusion À des doses équipotentes pour l'anesthésie locale, le dextrométhorphan et le dextrorphan étaient moins susceptibles que la bupivacaïne d'être toxiques pour le système nerveux central et le système cardiovasculaire.

Dextromethorphan, an antitussive drug, has been used clinically for more than 50 years. It is metabolized in humans primarily by O-demethylation to dextrorphan in the liver.¹ More recently, it has been demonstrated that both dextromethorphan and dextrorphan have the ability to block sodium channels² and produce dose-related local anesthetic effects on spinal and sciatic nerves, causing decreased motor function, proprioception, and nociception in rats.^{3,4} Moreover, dextromethorphan and dextrorphan are potent local anesthetics with a therapeutic index in animals (50% lethal dose/50% effective dose) 2.4- and 1.9-fold greater, respectively, than lidocaine when used for cutaneous anesthesia.^{5,6} Using either dextromethorphan or dextrorphan for cutaneous anesthesia^{5,6} and sciatic nerve blockade⁴ produces a longer effect than lidocaine, and spinal blockade using dextrorphan is similar in duration as bupivacaine,³ a long-acting local anesthetic. Thus, the suitability of these drugs as clinical local anesthetics is worth further evaluation.

Despite physical or chemical differences, all local anesthetics have central nervous system (CNS) toxicity and cardiovascular (CV) toxicity.⁷⁻¹² Although the toxicity of local anesthetics on one system compared with the other may vary, these differences are minor. This may be explained by their similar structures.⁸ Before considering the clinical use of dextromethorphan and dextrorphan as local anesthetics, the toxicity of these drugs should be tested. Bupivacaine carries significant CV toxicity.^{13,14}

The purpose of this study was to compare the CNS and CV toxicity of dextromethorphan, dextrorphan, and bupivacaine when given as intravenous infusions in equianalgesic doses. A model of infiltrative cutaneous anesthesia was used to determine the equivalent potencies of the drugs in non-anesthetized spontaneously breathing rats.

Materials and methods

Animals

Male Sprague-Dawley rats (260-310 g) were used to test cutaneous anesthesia and systemic toxicity. The rats were obtained from the Animal Center of National Cheng Kung University Medical College (Tainan, Taiwan) and housed in a climate-controlled room maintained at 21°C with 50% relative humidity. Lighting was on a 12-hr light/dark cycle (light on at 6:00 a.m.), with food and water available *ad libitum* up to the time of testing. The experimental protocols were approved by the Animal Investigation Committee of National Cheng Kung University Medical College, Tainan, Taiwan, and they conformed to the recommendations and policies of the International Association for the Study of Pain.

Drugs

Bupivacaine HCl, dextromethorphan hydrobromide monohydrate, dextrorphan tartrate, and sodium chloride were purchased from Sigma Chemical Co. (St. Louis, MO, USA). The drugs were dissolved in normal saline (0.9% NaCl).

Experimental protocol

The protocol was divided into two parts. In Part I, the effects of different doses of bupivacaine (8.0, 6.7, 2.0, 1.25 $\mu\text{mol}\cdot\text{kg}^{-1}$), dextromethorphan (20.0, 13.3, 5.3, 2.7 $\mu\text{mol}\cdot\text{kg}^{-1}$), dextrorphan (40.0, 26.7, 13.1, 6.7 $\mu\text{mol}\cdot\text{kg}^{-1}$), and saline on cutaneous anesthesia were evaluated ($n = 8$ rats for each dose of each drug) to determine the equivalent potencies of the drugs. In Part II, times to cause toxicity (seizures, apnea, and cardiac arrest),

mean arterial blood pressure (MAP), heart rate (HR), stroke volume (SV), and cardiac output (CO) were measured after equipotent doses of the drugs (bupivacaine, dextromethorphan, and dextrorphan) were infused into the rats ($n = 8$ rats for each dose of each drug). As a control, a group were infused with saline ($n = 7$ rats).

Part I - Infiltrative cutaneous anesthesia

Before subcutaneous injections, the hair on the dorsal surface of the rat's thoracolumbar region ($6 \times 10 \text{ cm}^2$) was mechanically shaved. Subcutaneous injections of drugs were administered as reported previously.^{5,6,15} Briefly, the drugs, which were dissolved in normal saline 0.6 mL, were injected subcutaneously in non-anesthetized rats using a 30-G needle on the dorsal surface of the thoracolumbar region. The back of each rat was divided into left and right parts, either of which received one drug injection with a washout period of one week. After the subcutaneous injection, a circular elevation of the skin, i.e., a wheal, approximately 2 cm in diameter occurred. The wheal was marked with ink within 30 sec after the injection. The cutaneous anesthetic effects of the drugs were evaluated using the cutaneous trunci muscle reflex, which is characterized by the reflex movement of the skin over the back produced by twitches of the lateral thoracispinal muscle in response to local dorsal cutaneous stimulation.^{5,6,15} A No.15 von Frey filament (Somedic Sales AB, Stockholm, Sweden) affixed with the cut end of an 18-G needle was used to produce the standardized nociceptive stimulus ($19 \pm 1 \text{ g}$). Six pinpricks (at six different points within each wheal) with a frequency of 0.5-1 Hz were used in each testing. With the investigator (Y.W.C.) blinded to the type of drug injected, the cutaneous analgesic effect of each drug was evaluated quantitatively as the number of times the pinprick failed to elicit a response. For example, complete nociceptive block was defined as the absence of response following each of the six stimuli (100% of possible effect or 100% PE). The drug duration of action was defined as the time from drug injection (i.e., time = 0) to full recovery (no analgesic effect or 0% PE recorded).^{5,6,15} After subcutaneously injecting the rats with four different doses of each drug ($n = 8$ for each dose of each drug), cutaneous anesthesia was plotted against time. The lower doses were tested first, and then larger doses were given until comparable doses of each drug were obtained.

Part II - Cardiovascular and neurological effects

On day 1, the animals were anesthetized with an intraperitoneal injection of pentobarbital sodium $50 \text{ mg} \cdot \text{kg}^{-1}$.

The right femoral artery and vein were cannulated with polyethylene catheters (PE-50) filled with heparinized ($30 \text{ U} \cdot \text{mL}^{-1}$ normal saline). The catheters with the 18-G needle were then tunnelled subcutaneously, and they exited the skin at the midline in the posterior cervical area below the level of the ears. The catheter was cut with 5 cm protruding from the skin, and it was then sealed by heating it with a match and compressing it with a hemostat.^{15,16} The animal's trachea was then intubated (PE 200), and its lungs were ventilated mechanically (Small Animal Ventilator Model 683, Harvard Apparatus, Holliston, MA, USA) at $50 \text{ breaths} \cdot \text{min}^{-1}$ with a tidal volume of $8 \text{ mL} \cdot \text{kg}^{-1}$ and a positive end expiratory pressure at $5 \text{ cmH}_2\text{O}$. After cutting into the rat's chest at the third intercostal space to expose the heart, a small section (1 cm long) of the ascending aorta was freed from connective tissue. A Transonic Flowprobe (Transonic Systems Inc, Ithaca, NY, USA) was implanted around the root of the ascending aorta, and the connecting wire was tunnelled subcutaneously and exited the skin at the midline in the posterior area of the head.^{15,17} Next, the chest was closed and the endotracheal tube was removed after implanting the Transonic Flowprobe. The rat's temperature was maintained via an electric blanket until the rat recovered from anesthesia.

On day 2, the awake animals were placed in a small cage with an open top to allow the tubes to reach the animals from the top and prevent the animals from chewing on the tubes. The tube in the femoral artery was connected to a transducer, and MAP and HR were recorded using a polygraph (MP36, BIOPAC Systems Inc, Goleta, CA, USA). The tube in the right femoral vein was connected to an infusion pump (Harvard Model 22 Infusion Pump, Harvard Apparatus Inc., Holliston, MA, USA) for delivery of the drugs. One investigator (Y.C.C.) administered the infusions, and another investigator (Y.W.C.) doing the parameter testing was not involved in the first experiment. The rats were used sequentially. A Transonic Flowprobe was connected to a Transonic transit-time blood flowmeter (T403, Transonic Systems Inc, Ithaca, NY, USA) to record the aortic blood flow. Cardiac output was calculated from the aortic blood flow, and SV was calculated by dividing CO by HR.¹⁵⁻¹⁷ After baseline measurements, the following infusions were begun at $400 \mu\text{L} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$: bupivacaine ($n = 8$ rats), dextromethorphan ($n = 8$ rats), dextrorphan ($n = 8$ rats), or normal saline ($n = 7$ rats). The drug concentration was adjusted so that equipotent doses of bupivacaine, dextromethorphan, and dextrorphan, equivalent to the dose producing 100% skin anesthesia as determined in Part I, were infused every minute in the same volume. The onset time of seizure, respiratory arrest, and complete cardiac arrest were evaluated, and MAP, HR, CO, and SV were measured continuously. The onset time of seizure was defined as the time when the first convulsion

occurred.^{15,16} Respiratory arrest was defined as apnea for 15 sec by observation of chest movement. Complete cardiac arrest was considered to occur when a HR of 0-min^{-1} was observed.

Statistical analysis

Values are presented as means $\pm$ standard deviation (SD). One-way analysis of variance and then the pairwise Tukey's honestly significant difference test were used to evaluate the differences in baseline data, the percent of maximum possible effect (%MPE), full recovery time, the area under the effect vs time curve (AUC), and the time to cause toxicity between medications. Analysis of variance with repeated measures followed by Duncan's multiple range test were used for *post hoc* multiple comparisons of means on MAP, HR, CO, and SV. The SPSS software for Windows (version 15.0, IBM Company, Chicago, IL, USA) was used for all statistical analyses. Statistical significance was set at $P < 0.05$.

Results

Infiltrative cutaneous anesthesia

After the rats were injected with four different doses of each drug ($n = 8$ for each dose of each drug) subcutaneously, the

local anesthetic effects of cutaneous anesthesia of these drugs (Fig. 1) were ascertained. The saline group demonstrated no cutaneous anesthesia. The 100% blockades (% MPE), full recovery time, and AUCs (Table 1) of cutaneous anesthesia were not significantly different between bupivacaine $8\text{ }\mu\text{mol}\cdot\text{kg}^{-1}$ dextromethorphan $20\text{ }\mu\text{mol}\cdot\text{kg}^{-1}$ and dextrorphan $40\text{ }\mu\text{mol}\cdot\text{kg}^{-1}$. These doses were considered equipotent for the systemic toxicity studies.

Systemic toxicity

There were no differences in baseline data for body weight, MAP, HR, CO, and SV between groups (Table 2). The time required to cause seizures was longer in the

Table 1 The %MPE, full recovery time, and AUCs of bupivacaine $8\text{ }\mu\text{mol}\cdot\text{kg}^{-1}$, dextromethorphan $20\text{ }\mu\text{mol}\cdot\text{kg}^{-1}$, and dextrorphan $40\text{ }\mu\text{mol}\cdot\text{kg}^{-1}$

	%MPE	Full Recovery Time (min)	AUCs (%·min)
Bupivacaine ($n = 8$ rats)	100 ± 0	101 ± 19	$6,970 \pm 1,555$
Dextromethorphan ($n = 8$ rats)	100 ± 0	123 ± 25	$6,559 \pm 1,462$
Dextrorphan ($n = 8$ rats)	100 ± 0	114 ± 32	$6,550 \pm 1,883$

Data are presented as means $\pm$ standard deviation (SD). %MPE = percent of maximum possible effect; AUC = area under curve. The %MPE, full recovery time, and AUCs between drugs were not significantly different

Fig. 1 Time courses of bupivacaine, dextromethorphan, and dextrorphan on cutaneous anesthesia in rats ($n = 8$ at each testing point). Saline produced no cutaneous anesthesia. Values are expressed as means $\pm$ standard deviation

Table 2 Baseline data of systemic toxicity measurement

Variable	Control (<i>n</i> = 7)	Bupivacaine (<i>n</i> = 8)	Dextromethorphan (<i>n</i> = 8)	Dextrorphan (<i>n</i> = 8)
Body weight (g)	266 ± 17	265 ± 10	269 ± 19	272 ± 21
MAP (mmHg)	107 ± 9	101 ± 15	101 ± 12	103 ± 16
HR (beats·min ⁻¹)	482 ± 39	468 ± 36	484 ± 27	456 ± 20
CO (mL·min ⁻¹)	64 ± 6	58 ± 8	58 ± 14	58 ± 13
SV (mL·beats ⁻¹)	0.14 ± 0.01	0.14 ± 0.02	0.13 ± 0.02	0.14 ± 0.02

Data are presented as means ± standard deviation. Baseline data were not significantly different among the groups. MAP = mean arterial blood pressure; HR = heart rate; CO = cardiac output; SV = stroke volume

Fig. 2 Time to cause toxicity of bupivacaine at $8 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, dextromethorphan at $20 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and dextrorphan at $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ at the onset of seizure, respiratory arrest, and time to cause complete cardiac arrest. In the saline group (*n* = 7), we did not detect (ND) toxicity symptoms. No seizures were noted in the dextrorphan group. Symbols (*a*, *b*) indicate $P = 0.005$ or $P = 0.001$ for dextromethorphan compared with bupivacaine, respectively. Symbols (*c*) indicate $P < 0.001$ for dextrorphan compared with bupivacaine. There was no significant difference between dextromethorphan and dextrorphan. Data are presented as means ± standard deviation

dextromethorphan group (10.6 ± 1.3 min) than in the bupivacaine group (7.6 ± 2.1 min) (Fig. 2) after the intravenous administration of equipotent analgesic doses ($P = 0.005$). There were no seizures in any of the animals in the saline and dextrorphan groups during the infusion period. After the intravenous infusion of equipotent analgesic doses, the times required to cause the respiratory arrest and complete cardiac arrest were longer in the dextromethorphan group (12.9 ± 2.6 min and 13.1 ± 2.6 min, respectively; $P = 0.001$ for both times) and the dextrorphan group (13.3 ± 1.0 min and 14.0 ± 1.0 min, respectively; $P < 0.001$ for both times) than in the bupivacaine group (8.8 ± 2.1 min and 9.0 ± 2.1 min, respectively) (Fig. 2).

The decline curve in MAP, HR, CO, and SV was slower in the dextromethorphan ($P < 0.001$) and dextrorphan ($P < 0.001$) groups compared with the bupivacaine group (Fig. 3). However, the decline in MAP, HR, CO, and SV did not differ between the dextromethorphan and the dextrorphan groups (Fig. 3).

Discussion

This study demonstrates that bupivacaine, dextromethorphan, and dextrorphan produce cutaneous anesthesia. At equipotent doses, intravenous dextromethorphan and dextrorphan do not elicit systemic toxicity as quickly as bupivacaine.

Dextromethorphan and the active metabolic compound, dextrorphan, are Na⁺ channel blockers.² They both produce spinal anesthesia,³ sciatic nerve blockade,⁴ and infiltrative cutaneous anesthesia^{5,6} in rats. We found that dextromethorphan and dextrorphan, as local anesthetics, were more potent than lidocaine,⁵ and the spinal blockade caused by dextrorphan was similar to that of bupivacaine.³ These findings suggest that there may be a great potential for the use of dextromethorphan and dextrorphan as local anesthetics in the clinical setting, provided that the CNS and CV toxicity is acceptable.

Though local anesthetics for cutaneous anesthesia are an acceptable option for management of surgical anesthesia or postoperative pain,¹⁴ accidental intravascular injection of local anesthetics carries the risk of CNS and CV toxicity.¹³ Using one animal model of local anesthesia, we performed the local anesthetic effects of infiltrative cutaneous analgesia of dextromethorphan, dextrorphan, and bupivacaine to determine the equipotent analgesic doses of these drugs. We began with the lowest doses, and then we tested larger doses until we thought we had the correct dose. Since dextromethorphan $20 \mu\text{mol}\cdot\text{kg}^{-1}$ dextrorphan $40 \mu\text{mol}\cdot\text{kg}^{-1}$ and bupivacaine $8 \mu\text{mol}\cdot\text{kg}^{-1}$ produced a similar blockade of cutaneous anesthesia (Table 2), we chose these doses as the equipotent analgesic dose of each drug. In this case, we were satisfied that the AUCs were essentially the same for the

Fig. 3 Mean arterial blood pressure (MAP), heart rate (HR), cardiac output (CO), and stroke volume (SV) change during infusion of either 1) bupivacaine ($n = 8$) at $8 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, dextromethorphan ($n = 8$) at $20 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, or dextrophan ($n = 8$) at $40 \mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ or 2) normal saline ($n = 7$) in a volume of $400 \mu\text{L}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (the same volume given to the animals in the

drug group) as infusion; 0 min is the start of infusion. Infusion was stopped when the test animals went into cardiac arrest. Symbols (a,b) indicate $P < 0.001$ for dextromethorphan or dextrophan compared with bupivacaine, respectively. There was no significant difference between dextromethorphan and dextrophan. Data are presented as means $\pm$ standard deviation

largest doses given. This technique is limited by the fact that these doses gave 100% maximal response, and errors can be generated if 100% responses are considered when trying to determine equipotent analgesic doses.

We showed that infusion of dextromethorphan or dextrophan at equipotent analgesic doses produced a delayed onset of CNS and CV toxicity when compared with bupivacaine. Of note, we observed that dextrophan produced no seizures. In both the dextromethorphan and bupivacaine groups, seizures were observed before respiratory and cardiac arrest. Although we did not determine the reason why dextrophan did not produce seizures, this finding is worth investigating in the future. These results may indicate that dextromethorphan and dextrophan may have a safer systemic toxicity profile than bupivacaine. However, the differences in CNS and CV toxicity between dextromethorphan, dextrophan, and bupivacaine are not significant. We found a difference of 25–30% between drugs in the time required to produce CNS or CV toxicity. Considering that there might be some error in the determination of equipotent analgesic doses and species differences might be present, the results should be interpreted with caution.

Many neural blockade techniques have been associated with CNS and CV toxicity caused by systemically absorbed local anesthetics.^{18,19} The incidence of systemic toxicity from local anesthetics appears to be decreasing with the use of safer local anesthetics^{20,21} and the widespread

introduction of procedural safety.²⁰ Since dextromethorphan and dextrophan are better tolerated systemically than bupivacaine in this animal model, these drugs should be investigated further as possible useful local anesthetics in the clinical setting. However, this study is a cumulative dose design, i.e., we administer an infusion and determine the time taken to observe the side effect in question. The underlying assumption here is that redistribution and metabolism of the drug are negligible during the infusion period. Nevertheless, when administered subcutaneously, local anesthetics are not meant to have the bioavailability that they have when administered intravenously, and the resorption from the subcutaneous tissues is not necessarily 100% as supposed by the methodology presented in this manuscript. It would have been more clinically relevant to apply a ratio between the subcutaneous dose and the intravenous dose given as an infusion, and this approach could be worthwhile studying in the future.

In the present study, we demonstrated that intravenous bupivacaine caused CV and CNS toxicity in rats, an outcome that has been demonstrated in the past.^{7,9,11,12,15} Ropivacaine, which has less CV toxicity than bupivacaine, was subsequently introduced into clinical practice.^{19,22} However, ropivacaine is at least 40% less potent than bupivacaine.²³ We did not compare the toxicity of dextromethorphan and dextrophan with that of ropivacaine, although this comparison could be worthwhile investigating in the future.

During the infusion period of our investigation, MAP, HR, and CO decreased; consequently, the values of SV decreased in the bupivacaine, dextromethorphan, and dextrorphan groups. Previous studies also demonstrated that bupivacaine administered as a rapid infusion was associated with a decrease in MAP and HR in rats.^{16,19} We also found that MAP increased in the bupivacaine group before death. This result could be due to hypercarbia and hypoxia caused by respiratory depression secondary to CNS toxicity.¹⁶ The decline curve in MAP, HR, CO, and SV of dextromethorphan or dextrorphan was slower than that of bupivacaine given at equipotent doses. This result indicates that dextromethorphan and dextrorphan are better tolerated than bupivacaine. We chose to use spontaneously breathing rats as an animal model, a clinical scenario when local anesthesia is performed on humans.

In this study, we did not evaluate whether dextromethorphan or dextrorphan had direct nerve toxicity; however, it is noteworthy that we detected no apparent side effects or behavioural abnormalities in our previous neurobehavioral studies after subcutaneous,^{5,6} sciatic notch,⁴ or intrathecal³ drug injection. Whether local tissue injury to nerves occurs after dextromethorphan or dextrorphan injection is an important issue that needs further investigation.

In conclusion, intravenous equipotent analgesic doses of dextromethorphan or dextrorphan are better tolerated to produce CNS and CV system toxicity than bupivacaine.

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Conflicts of interest None declared.

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