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

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Short heading (40 characters or less); Dextromethorphan or dextrorphan is less toxic.

Summary: Dextromethorphan and dextrorphan produce cutaneous anesthesia. Dextromethorphan and dextrorphan were less likely to induce systemic toxicity when compared to bupivacaine. There is a trend in slower decrease of such parameters (mean arterial blood pressure, heart rate, cardiac output, and stroke volume) in the dextromethorphan and dextrorphan groups.

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Abstract

Purpose Dextrorphan, a major metabolite of dextromethorphan, produces the duration of spinal and cutaneous anesthesia similar to bupivacaine, and the suitability of dextrorphan for clinical use is worth further investigation. The purpose of this study was to test the central nervous system and cardiovascular toxicity of bupivacaine, dextromethorphan, and dextrorphan.

Methods First, equipotent doses were determined for cutaneous analgesia on the rat back by determination of dose–response curves for dextromethorphan, dextrorphan and bupivacaine (n = 8 rats at each testing point). Then, during continuous intravenous infusion of equipotent doses of bupivacaine, dextromethorphan, dextrorphan and saline (n = 8 rats in each group except saline group, n =7 rats), we observed the time to seizure, apnea and complete cardiac arrest. 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 infusion of equipotent infusion doses was required to produce seizures in the dextrometorphan 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. Time to apnea and complete cardiac arrest was shorter in the bupivacaine

group than in the dextrorphan ($P < 0.001$ between bupivacaine and dextrorphan) and dextrometorphan groups ($P = 0.001$ between bupivacaine and dextrometorphan). The decline curve in MAP, HR, CO, and SV was slower in the dextromethorphan and dextrorphan groups compared with the bupivacaine group ($P < 0.001$ between bupivacaine and dextromethorphan or dextrorphan).

Conclusions Dextromethrophan and dextrorphan were similar to bupivacaine at producing durations of cutaneous anesthesia but were less likely than bupivacaine to induce central nervous system and cardiovascular toxicity.

Key Words: cutaneous anesthesia, systemic toxicity, dextromethorphan, dextrorphan, bupivacaine

Introduction

Dextromethorphan, an antitussive drug, has been used for more than 50 yr clinically, and is primarily metabolized by O-demethylation to dextrorphan in human liver.[1] Recently, an experiment demonstrated that dextromethorphan and dextrorphan are sodium channel blockers[2] that 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 2.4- and 1.9-folds higher systemic safety indices (50% lethal doses/50% effective doses) than lidocaine on infiltrative cutaneous anesthesia.[5, 6] The local anesthetic durations of dextromethorphan and dextrorphan on cutaneous anesthesia[5, 6] and sciatic nerve blockade[4] are longer than that of lidocaine, but the spinal blockade caused by dextrorphan was similar in duration to 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, local anesthetics all have central nervous system (CNS) toxicity and cardiovascular (CV) toxicity.[7-12] Although some may have less toxicity to the CNS or CV system, however, the differences are minor. This may be explained by their similar structures.[8] Before dextromethorphan and dextrorphan, two potentially novel local anesthetics, are used in clinical practice, the

toxicity of these drugs should be tested. There are no studies evaluating the systemic toxicity of dextromethorphan and dextrorphan; it is known that bupivacaine carries significant CV toxicity.[13, 14]

The purpose of the study is to compare the CNS and CV toxicity of dextromethorphan, dextrorphan and bupivacaine given as intravenous infusions, when given 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. They 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 degree C with 50% relative humidity. Lighting was on a 12-hr 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 National Cheng Kung University Medical College, Tainan, Taiwan and 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). Drugs were dissolved in normal saline (0.9% NaCl).

Experimental protocol

The protocol was divided into two parts. In Part I, the effect of different doses of bupivacaine (8.0, 6.7, 2.0, 1.25 $\mu mol \cdot kg^{-1}$), dextromethorphan (20.0, 13.3, 5.3, 2.7 $\mu mol \cdot kg^{-1}$), dextrorphan (40.0, 26.7, 13.1, 6.7 $\mu mol \cdot kg^{-1}$), and saline on cutaneous

anesthesia was evaluated ((n = 8 rats for each dose of each drug) to determine the equivalent potencies of the drugs. In Part II, time to cause toxicity (seizures, apnea and cardiac arrest), mean arterial blood pressure (MAP), heart rate (HR), stroke volume (SV), and cardiac output (CO) were evaluated after equipotent doses of the drugs (bupivacaine, dextromethorphan, and dextrorphan) were infused into the rat ((n = 8 rats for each dose of each drug). Saline group (n = 7 rats) was used as a control.

Part I - Infiltrative cutaneous anesthesia

Before subcutaneous injections, the hair on the rats' dorsal surface of the thoracolumbar region (6×10 cm^2) was mechanically shaved. Subcutaneous injections of drugs were performed as reported previously.[5, 6, 15] In brief, the drugs, dissolved in 0.6 mL normal saline, were injected subcutaneously using a 30-gauge needle in unanesthetized rats on the dorsal surface of the thoracolumbar region. The back of the rat was further divided into left and right parts, either of which received one drug injection with a washout period of 1 wk. After subcutaneous injection, a circular elevation of the skin, a wheal, approximately 2 cm in diameter occurred. The wheal was marked with ink within 30 seconds after injection. The cutaneous anesthetic effects of drugs was evaluated using the cutaneous trunci muscle reflex (CTMR), 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 Von Frey filament (No.15; Somedic Sales AB, Stockholm, Sweden), to which the cut end of an 18-gauge needle was affixed, was used to produce the standardized nociceptive stimulus (19±1 g). Six pin-pricks (at six different points within each wheal) with a frequency of 0.5-1 Hz were used in each testing. Each drug's cutaneous analgesic effect was evaluated quantitatively as the number of times the pinprick failed to elicit a response by the operator (Dr. Y.W. Chen). The operator did not know what was injected. For example, the complete absence of six responses was defined as complete nociceptive block (100% of possible effect; 100% PE). During the test, the maximum value of %PE was presented as percent of maximum possible effect (% MPE). Each drug's duration of action was defined as the time from drug injection (i.e., time=0) to full recovery of CTMR (no analgesic effect was found or 0% MPE recorded).[5, 6, 15] After subcutaneously injecting the rats with four different doses of each drug (n = 8 for each dose of each drug), time courses of cutaneous anesthesia were constructed. We have started with the lowest doses, and then we tested larger doses until we thought we have just the right dose. Durations of drug effect defined as the intervals from injection to complete recovery were measured.

Part II - Cardiovascular and neurological effects

On day 1, animals were anesthetized with an intraperitoneal injection of pentobarbital sodium (50 $mg.kg^{-1}$) and cannulated in the right femoral artery and vein

with polyethylene catheters (PE-50), which were filled with heparinized (30 $U.mL^{-1}$) normal saline. The catheters with 18-gauge needle were then tunneled subcutaneously and 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 sealed by heating it with a match and compressing it with a hemostat.[15, 16] Then the animal's trachea was intubated (PE 200) for artificial ventilation (Small Animal Ventilator Model 683, Harvard Apparatus, USA) at 50 $breaths.min^{-1}$ with tidal volume of 8 $mL.kg^{-1}$ and a positive end expiratory pressure at 5 cmH_2O. 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 tunneled subcutaneously and exited the skin at the midline in the posterior area of the head.[15, 17] Then, the chest was closed and the endotracheal tube was extubated after implanting the Transonic Flowprobe. The temperature of rat was maintained via an electric blanket until the rat was recovery.

On day 2, the animals were placed in a small cage with an open top to allow the lines to reach the animal from the top and prevent the animal from chewing on the lines. They were awake. 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) for delivery of the drugs. Another investigator (Y.C. Chen) administered the infusions, and that the one (Dr. Y.W. Chen) doing the parameter testing was not involved in the first experiment. 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. The cardiac output (CO) was calculated from the aortic blood flow, and stroke volume (SV) was expressed as CO divided by HR.[15-17] After infusions were begun of either 1) bupivacaine (n = 8 rats), dextromethorphan (n = 8 rats), dextrorphan (n = 8 rats) or 2) normal saline (n = 7 rats) in the volume of 400 $\mu L \cdot kg^{-1} \cdot min^{-1}$ (the same volume given to the animals in the drug group), the onset time of seizure, respiratory arrest, time to cause complete cardiac arrest, MAP, HR, CO, and SV were evaluated. The onset time of seizure was defined as the time when the first convulsion occurred.[15, 16] Respiratory arrest time was defined as the time point when there was apnea for 15 s by observation of chest movement. The time to cause complete cardiac arrest was marked by observing a decrease in HR to 0 bpm.

Statistical analysis

Values are presented as means ± SD. The differences in baseline data, %MPE,

full recovery time, AUCs, and the time to cause toxicity between medications were evaluated using one-way analysis of variance (ANOVA) and then the pairwise Tukey's honestly significant difference test. Analysis of variance with repeated measures followed by Duncan’s multiple-range test was used for post hoc multiple comparisons of means on MAP, HR, CO, and SV. SPSS for Windows (version 15.0) was used for all statistical analyses. Statistical significance was set at $P < 0.05$.

Results

Infiltrative Cutaneous Anesthesia

The baseline data of body weight, MAP, HR, CO, and SV showed no significant differences among groups (Table 1). After 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 constructed. The saline group demonstrated no cutaneous anesthesia. The 100% blockades (% MPE), full recovery time, and AUCs (Table 2) of cutaneous anesthesia between bupivacaine at 8 μmol · kg^{-1}, dextromethorphan at 20 μmol · kg^{-1}, and dextrorphan at 40 μmol · kg^{-1} were not significantly different.

Systemic Toxicity

The time required to cause seizures was longer in the dextromethorphan group (10.6±1.3 min) than in the bupivacaine (7.6±2.1 min) group (Fig. 2) after the intravenous administration of equipotent analgesic doses (P = 0.005 for the difference). All animals in the saline and dextrorphan groups had no seizure response during the infusion period. After the intravenous infusion of equipotent analgesic doses, the time required to cause the respiratory arrest and complete cardiac arrest were longer in the dextromethorphan (12.9±2.6, P = 0.001; 13.1±2.6 min, P = 0.001) and dextrorphan (13.3±1.0, P < 0.001; 14.0±1.0 min, P < 0.001) groups than in the

bupivacaine (8.8±2.1 and 9.0±2.1 min) group (Fig. 2).

There were no differences in baseline data for body weight, MAP, HR, CO, and SV between groups (Table 1). There is a trend in slower decrease of such parameters (MAP, HR, CO, and SV) before CV collapse in the dextromethorphan and dextrorphan groups (Fig. 3). In this group, the MAP showed a tendency to increase before CV collapse (Fig. 3). The decline curve in MAP, HR, CO, and SV was slower in the dextromethorphan ($P < 0.001$) or dextrorphan ($P < 0.001$) group compared with the bupivacaine group (Fig. 3). However, the decline in MAP, HR, CO, and SV was not different between dextromethorphan and dextrorphan groups (Fig. 3).

Discussion

This study demonstrates that bupivacaine, dextromethorphan, and dextrorphan produce cutaneous anesthesia. At equipotent doses, 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 are more potent than lidocaine,[5] and the spinal blockades caused by dextrorphan were similar to 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 investigated.

Though local anesthetics for cutaneous anesthesia is 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 have started with the lowest doses, and then we tested larger doses until we thought we have just the right

dose. Because dextromethorphan at 20 μmol · kg^{-1}, dextrorphan at 40 μmol · kg^{-1}, and bupivacaine at 8 μmol · kg^{-1} produced 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 for the largest doses given, the areas under the curve (AUC) were essentially the same. The limitations of such a technique are that these doses gave 100% maximal response, and errors can be generated if 100% responses are considered when trying to determine equipotent analgesic doses.

At equipotent analgesic doses, we showed that infusion of dextromethorphan or dextrorphan produced a delayed onset of CNS and CV toxicity when compared with bupivacaine. Of note, we observed that dextrorphan produced no seizures. In both the dextromethorphan and bupivacaine groups, seizures were observed before respiratory and cardiac arrest. Although we did not know why dextrorphan produced no seizures, this was worth investigating in the future. These results may indicate that dextromethorphan and dextrorphan may feature a safer systemic toxicity profile than bupivacaine. However, the differences in CNS and CV toxicity between dextrometrophan, dextrorphan and bupivacaine are not very large. Differences of 25-30% in the time required to produce CNS or CV toxicity were found between drugs, and this depends entirely on the exact determination of equipotent analgesic doses, which might be off considering the way we did it. In addition, there might be

species differences.

Many neural blockade techniques have been associated with CNS and CV toxicity caused by systemically absorbed local anesthetic.[18, 19] The incidence of systemic toxicity from local anesthetics appears to be decreasing with the use of safer local anesthetics[20, 21] and widespread introduction of procedural safety.[20] Since dextromethorphan and dextrorphan are better tolerated systemically than bupivacaine in this animal model, they may have an opportunity to be used as local anesthetics clinically. However, this study is a cumulative dose design. That is, 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 may be negligible during the infusion period. Nevertheless, local anesthetics are not supposed to have the bioavailability when given subcutaneous as compared to intravenous. And the resorption from the subcutaneous tissues is not supposed to be 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 it was worth studying in the future.

In the recent study, we demonstrated that intravenous bupivacaine caused CV and CNS toxicity in rats, and the toxicity of bupivacaine has been demonstrated a long time ago [7, 9, 11, 12, 15]. Ropivacaine, which has less CV toxicity than bupivacaine,

was later 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 dextrorphan with that of ropivacaine, and these proposals certainly await future investigation.

This is the first investigation to determine the toxic profile of dextromethorphan and dextrorphan, using selected surrogate parameters. During the infusion period, MAP, HR, and CO decreased, and therefore the values of SV decreased in bupivacaine, dextromethorphan, and dextrorphan groups. Previous studies also demonstrated that bupivacaine administered as rapid infusions declined the value of MAP and HR in rats.[16, 19] We also found that MAP increased in bupivacaine group before death. This could be because of 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 on equipotent doses. This demonstrated that dextromethorphan and dextrorphan were better tolerated than bupivacaine. We chose the animal model with the spontaneously breathing rats, a clinical scenario when local anesthesia is performed on humans.

In this study, we did not evaluate whether dextormethorphan or dextrorphan had direct nerve toxicity; however, it is noteworthy that in our previous neurobehavioral studies we detected no apparent side effects or behavioral abnormalities after

subcutaneous,[5, 6] sciatic notch,[4] or intrathecal[3] 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 central nervous system and cardiovascular system toxicity than bupivacaine.

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Table 1. Baseline data of systemic toxicity measurement

Parameters\Drug	Control (n=7)	Bupivacaine (n=8)	Dextromethorphan (n=8)	Dextrorphan (n=8)
Body weight (g)	266±17	265±10	269±19	272±21
MAP (mmHg)	107±9	101±15	101±12	103±16
HR (bpm)	482±39	468±36	484±27	456±20
CO (mL•min-1)	64±6	58±8	58±14	58±13
SV (mL•beat-1)	0.14±0.01	0.14±0.02	0.13±0.02	0.14±0.02

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

Table 2. The %MPE, full recovery time, and AUCs of bupivacaine at 8 μmol · kg^{-1}, dextromethorphan at 20 μmol · kg^{-1}, and dextrorphan at 40 μmol · kg^{-1}

	%MPE	Full Recovery Time (min)	AUCs (%min)
Bupivacaine	100 ± 0	101 ± 19	6970 ± 1555
Dextromethorphan	100 ± 0	123 ± 25	6559 ± 1462
Dextrorphan	100 ± 0	114 ± 32	6550 ± 1883

Percent of maximum possible effect (%MPE), duration of drug action, area under curves (AUCs) (means ± SD) for bupivacaine (n = 8 rats), dextromethorphan (n = 8 rats), and dextrorphan (n = 8 rats). The %MPE, full recovery time, and AUCs between drugs were not significantly different.

Legends to figures

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

Fig. 2. Time to cause toxicity of bupivacaine at 8 μmol · kg^{-1}, dextromethorphan at 20 μmol · kg^{-1}, and dextrorphan at 40 μmol · kg^{-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, and 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 not significantly different between dextromethorphan and dextrorphan. Data are presented as means ± SD.

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 μmol · kg^{-1} · min^{-1}, dextromethorphan (n = 8) at 20 μmol · kg^{-1} · min^{-1} or dextrorphan (n = 8) at 40 μmol · kg^{-1} · min^{-1} or 2) normal saline (n = 7) in the volume of 400 μL · kg^{-1} · 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 dextrorphan

compared with bupivacaine, respectively. There was no significantly different between dextromethorphan and dextrorphan. Data are presented as means ± SD.