The Local Anesthetic Effect of Memantine on Infiltrative Cutaneous Analgesia in the Rat

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Short Title: Memantine produces cutaneous anesthesia.
Funding: The authors gratefully acknowledge the financial support provided for this study by the Cheng Hsin General Hospital (99-35) and the China Medical University (CMU96-099) of Taiwan.
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Submitted as a **Research Report**

Link to Title Page: http://www.aaauthor.org/pages/441-2010-Jun-04

IMPLICATIONS STATEMENT

Memantine is widely used in the therapy of Alzheimer's patients and has a wide safety margin with a low rate of untoward systemic side effects. In this study, we showed that memantine produced more potent and longer duration on cutaneous anesthesia, when compared with lidocaine. The clinical relevance of these effects warrants further investigation.

ABSTRACT

BACKGROUND: Memantine could block the Na^+ current, one principle mechanism of local anesthesia. Until now, no study mentioned that memantine has a local anesthetic effect, and therefore we investigated the local anesthetic effect of mamantine.

METHODS: The dose-dependent response of memantine on cutaneous anesthesia was compared with lidocaine in rats. The duration of drug action was evaluated and compared on an equipotent basis (ED_{20}, ED_{50} and ED_{80}). Lidocaine, a common used local anaesthetic, was used as control.

RESULTS: We demonstrated that memantine and lidocaine produced dose-dependent local anesthetic effects as infiltrative cutaneous analgesia. The relative potency was memantine > lidocaine ($P < 0.01$ for the difference). On an equipotent basis, memantine showed longer duration than lidocaine ($P < 0.05$ for the difference). Neither local injection of saline nor systemic administration of a large dose of memantine or lidocaine produced cutaneous anesthesia (data not shown).

CONCLUSIONS: This study indicated that memantine has a local anesthetic effect as infiltrative cutaneous analgesia in the rat. Memantine produced more potent and longer duration on cutaneous anesthesia, when compared with lidocaine.

KEY WORDS: Memantine; Cutaneous Anesthesia

INTRODUCTION

Memantine, an uncompetitive N-methyl-D-aspartate (NMDA) open channel blocker, is used clinically as an antispastic in the treatment of Parkinson's disease.[1] A recent study demonstrated that memantine provide an effective pharmacological prevention of periventricular leukomalacia (PVL) in the premature infant.[2] Memantine also shows clinical tolerance in the treatment of Alzheimer's disease in adults via its low affinity and relatively fast unblocking kinetics,[3-5] and reduces functional as well as morphological sequelae induced by ischemia.[6 7] Increasing evidence suggests that memantine with fast channel unblocking kinetics to prevent it from occupying the channel is a potent neuroprotectant without side effects.[7-9] Besides, memantine reversibly blocked tetrodotoxin-resistant Na^+ currents in small dorsal root ganglion neurons and displayed the use-dependent inhibition of the currents at 2-Hz stimulation.[1]

Although memantine is widely used in the therapy of Alzheimer's patients,[4] the pharmacologic effects of its channel bindings have not been well experimented, e.g., the Na^+ channel blockade. According to the effect of Na^+ channel blockade, local anesthetics produce infiltrative cutaneous anesthesia, spinal/epidural anesthesia, and peripheral neural blockades.[10 11] Because memantine blocks the Na^+ channels,[1] it may have a local anesthetic effect, e.g., cutaneous anesthesia. The aim of the present study

investigated the local anesthetic effect of memantine compared with lidocaine, a common used local anesthetic.

METHODS

Animals

Male Sprague-Dawley rats (200-250 g) 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 ℃ with approximately 50% relative humidity in Animal Center of China Medical University. 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.

Drugs

Memantine HCl and lidocaine HCl were purchased from Sigma Chemical Co. (St. Louis, MO, USA). All drugs were dissolved in 0.9% NaCl (saline).

Experimental protocols

Three aims were carried out. In aim 1, the potencies of memantine (53.3, 40.0, 26.7, 20.0, 13.3, 6.7, 2.7 μmol/kg) and lidocaine (53.3, 40.0, 26.7, 20.0, 13.3μmol/kg) on cutaneous analgesia were evaluated (n=8 rats for each drug). In aim 2, on an equipotent basis (ED_{20}, ED_{50} and ED_{80}), the duration of memantine was compared with that of lidocaine. In aim 3, two control groups were further added into the study

to rule out the possibility of vehicle or systemic effect of drugs on cutaneous analgesia. One group (n=8 rats) received subcutaneous injection of saline; another group (n=8 rats for each drug), subcutaneous injection of saline combined with intraperitoneal injection of testing drug (memantine or lidocaine) with a dose of $2ED_{80}$.

Injections of Drugs

On the day before subcutaneous injections, the hair on the rats' dorsal surface of the thoracolumbar region (10×10 cm^2) was mechanically removed. Subcutaneous injections of drugs were performed as reported previously.[12 13] In brief, the drugs were injected 0.6 mL subcutaneously using a 30-gauge needle in unanesthetized rats at the dorsal surface of the thoracolumbar region. In order to reduce the numbers of experimental animals used, the back of rat was further divided into left and right parts, either of which, after a washout period of 1 week, received one drug injection. After subcutaneous injection, a circular elevation of the skin, a wheal, approximately 2 cm in diameter occurred. The wheal was marked with ink within one minute after injection.[12 13] For consistency, one experienced investigator (Dr. Y.W. Chen) who was blinded to the drugs injected was responsible for evaluating the cutaneous analgesia effect.

Neurobehavioral Evaluation

The cutaneous anesthesia of drug was evaluated according to 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.[12 13] 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 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, with, for example, the complete absence of six responses was defined as complete nociceptive block (100% of possible effect; 100% PE). The test of six pinpricks was applied 10 min before drug injection, then every 5 min after injection for the first 30 min and every 10-15 min thereafter until the CTMR fully recovered from the block (no more than 3 h). During the test, the 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 100% MPE recorded).

Evaluation of 50% effective doses (ED_{50}), ED_{20} and ED_{80}

After rats were injected with different doses of each drug (n = 8 for each dose of each drug) subcutaneously, dose-response curves were constructed from the % MPE

of each dose of each drug. The curves were then fitted via a computer-derived SAS Nonlinear (NLIN) Procedures (version 9.1, SAS Institute, Cary, NC), and the value of ED_{50}, defined as the dose that caused 50% cutaneous anesthesia, were obtained.[14 15] Drug potencies were compared via ED_{50}s, constructed from dose-response curves. The ED_{20} and ED_{80} of drugs were obtained using the same computer-derived curve-fitting (SAS NLIN analysis) that was used to derive the ED_{50}.[14] The rats were subcutaneously injected with different doses of ED_{20}, ED_{50}, and ED_{80} drugs (n = 8 rats for each dose of each drug), and the duration of each spinal blockade, defined as the interval from injection to full recovery, were measured and compared.

Statistical Analysis

Data are presented as mean ± S.E.M. or ED_{50} values with 95% confidence interval (95% CI). The differences in potencies (ED_{50}s) between medications were evaluated using a one-way analysis of variance (ANOVA) and then the pairwise Tukey's honestly significant difference test. In the control groups, a one-way ANOVA followed by the Dunnett test was used to evaluate the effects of medications. The differences in durations among drugs were evaluated by a student-t test. SPSS for Windows (version 14.0) was used for all statistical analyses. Statistical significance was set at $P < 0.05$.

RESULTS

The memantine, as well as local anesthetic lidocaine produced a dose-dependent effect of cutaneous anesthesia in the rat (Fig. 1). The time courses of cutaneous anesthesia of memantine and lidocaine have been performed in Figure 1. At the dose of 53.3 μmol/kg, memantine demonstrated 100% of blockade (% MPE) with full recovery time of about 85 min. Lidocaine at 53.3 μmol/kg showed 100% of blockade with full recovery time of about 51 min. The AUC (area under curve) of memantine was larger than that of lidocaine ($p < 0.05$ for the difference between drugs) in Table 1.

The ED_{50}s of memantine and lidocaine were obtained from dose-response curves (Table 2). On the ED_{50} basis, the relative potency of these two drugs was found to be memantine > lidocaine (Fig.1 and Table 2). Full recovery time (duration) was measured as an interval from the time zero at the time of injection to the time of complete functional recovery. On an equipotent basis (ED_{20}, ED_{50}, and ED_{80}), the blockade duration caused by memantine was longer than that caused by lidocaine (Fig. 2). In this study, all rats recovered completely after subcutaneous injections of drugs.

DISCUSSION

In this report we indicated for the first time that memantine produced a dose-dependent local anesthetic effect on infiltrative cutaneous analgesia in rats. Another important finding in this work is that when compared to lidocaine, memantine produced a more potent and longer duration of action on cutaneous anesthesia.

Local anesthetics are drugs that produce neural blockade via inhibiting the Na^+ current in the nervous tissue through the voltage-gated Na^+ channel.[11] Because memantine has Na^+ channel blocking activity,[1] theoretically, it may have a local anesthetic effect. Our current study demonstrated that memantine produced a dose-dependent cutaneous anesthetic effect in rats. It was concluded that memantine has a local anesthetic effect as infiltrative cutaneous analgesia. Because it was already reported that memantine can block the Na^+ current,[1] the result of this study was expected.

Local anesthetics for cutaneous anesthesia is an acceptable option for management of postoperative pain and surgical anesthesia because of relatively free of side effects.[16] Memantine was found to have a local anesthetic effect on cutaneous analgesia that was more potent than that of lidocaine, a common used local anesthetic. Memantine produced almost 1.5-folds higher potency than lidocaine on cutaneous

anesthesia. In *in vitro* study, memantine also produced almost 1.6-folds higher potency than lidocaine, because half-maximal blocking concentrations (IC_{50}) in lidocaine (IC_{50} = 277 μM) and memantine (IC_{50} = 178 μM) were derived from concentration–inhibition curves for tonic block at the holding potential (-90 mV) on tetrodotoxin-resistant Na^+ channels in rat dorsal root ganglia.[1]

To rule out the possibility of vehicle or systemic analgesia of the drug, two control groups were used. We also found that neither local injection of saline nor systemic administration of a large dose of the drug produced cutaneous anesthesia (data not shown). The results support our finding that the cutaneous anesthesia of memantine and lidocaine were due to their local action on the skin. All rats recovered completely. Histologic studies should be performed in the future before further consideration of the agents for clinical trials.

Injection of long-acting local anesthetics for surgery and postoperative pain control is frequently performed.[17] The duration of drug action, defined as the interval from injection to full recovery, was evaluated for cutaneous anesthesia. In this study, we tested memantine for long-acting local anesthetics. At the dose of 53.3 μmol/kg, memantine produced longer duration of action than lidocaine (Table 1). Besides, the duration of drug action caused by memantine was longer than that caused by lidocaine on an equipotent basis (ED_{20}, ED_{50} and ED_{80}) (Fig. 2).

In summary, memantine had a local anesthetic effect on infiltrative cutaneous analgesia in the rat. Memantine was more potent than lidocaine on cutaneous anesthesia. The blockade duration on cutaneous anesthesia caused by memantine was longer than that caused by lidocaine.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support provided for this study by the Cheng Hsin General Hospital (99-35) and the China Medical University (CMU96-099) of Taiwan.

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Table 1. The %MPE, duration, and AUCs of memantine and lidocaine.

	%MPE	Duration (min)		AUCs (%min)
		Complete blockade	Full Recovery	
Memantine	100 ± 0	14 ± 3	90 ± 13*	4971 ± 622*
Lidocaine	100 ± 0	20 ± 2	51 ± 4	3461 ± 345

Percent of maximum possible effect (%MPE), duration of drug action, area under curves (AUCs) for memantine and lidocaine (mean±SEM) at the same dose of 53.3 μmol/kg (n = 8). Of note, all of the rats performed complete blockade (100%MPE) of any function tested. Symbols (*) indicate $P < 0.05$ when memantine compared with lidocaine.

Table 2. The 50% effective doses (ED_{50}s) of memantine and lidocaine.

Drug	ED_{20}	ED_{50} (95% CI)	ED_{80}
Memantine	7.7	17.6 (15.2 – 20.4)	28.3
Lidocaine	18.6	25.9 (23.8 – 28.1)	35.2

ED_{50}s of drugs (μmol/kg) were obtained from Figure 1. CI = confidence interval. The potency of drug (ED_{50}) was memantine > lidocaine (P<0.01, for each comparison) using a one-way ANOVA followed by pairwise Tukey's HSD test.

FIGURE LEGENDS

Fig. 1. Time courses (5-7 doses and saline in each drug) of infiltrative cutaneous analgesia in rats. Memantine and lidocaine were tested and results presented as dose-dependent curves, respectively. Values are expressed as mean±S.E.M. Each testing point of the dose-dependent curves and each group of the time course study contained eight rats.

Fig. 2. Full recovery time of drug effect on cutaneous anesthesia (% MPE) at doses of ED_{20}, ED_{50}, and ED_{80} (n = 8 at each testing point). Data are mean±S.E.M. The difference in duration was evaluated using a student-t test. Symbols (*) indicate $P < 0.05$ when memantine compared with lidocaine.