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Research Paper

Antimalarial primaquine for spinal sensory and motor blockade in rats

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Abstract

Objectives The purpose of the experiment was to estimate whether intrathecal antimalarial drugs could provoke spinal block, and their comparison with lidocaine.

Methods Rats were intrathecally administrated with antimalarial agents (primaquine, chloroquine, hydroxychloroquine and amodiaquine) and lidocaine, and neurobehavioural examinations (nociception, proprioception and motor function) were assessed; $n = 8$ per group. One-way and two-way analysis of variance were designed to analyse data.

Key findings At a concentration of 20 mM, primaquine (0.46 mg/rat) exhibited the longest duration and the most potent effect of nociceptive, proprioceptive and motor blockade ($P < 0.01$) among five drugs, whereas the other antimalarial drugs displayed a lesser or similar potency of spinal blockade compared with lidocaine (0.29 mg/rat). In dose-dependent studies, primaquine was more potent ($P < 0.01$) than lidocaine for spinal block. At ED25, ED50 and ED75 equipotent doses, primaquine produced a greater duration of spinal motor, proprioceptive and nociceptive blockade when compared with lidocaine ($P < 0.01$).

Conclusions Primaquine, chloroquine, hydroxychloroquine and amodiaquine produced spinal blockade. Primaquine was more potent and displayed a prolonged life of local anaesthetic effect compared with lidocaine, whereas the other antimalarial drugs displayed a lesser or similar potency compared with lidocaine.

Keywords: antimalarial medications; primaquine; lidocaine; spinal block; motor function; nociception

Introduction

Antimalarial drugs (i.e. primaquine, chloroquine, hydroxychloroquine and amodiaquine) are majorly used to treat malaria.[1] Antimalarial primaquine has been known to inhibit transmembrane action potentials.[2] Local anaesthetic agents reversibly blocked firing of action potentials by inhibiting sodium channels, and they processed sciatic nerve block, spinal/epidural anaesthesia and skin infiltration anaesthesia.[3] Since the 1940s local anaesthetic lidocaine with an intermediate duration of efficacy and rapid onset of action has been used safely. Intrathecal low-dose hyperbaric lidocaine in spinal anaesthesia for patients who receive ambulatory surgical procedures results in rapid recovery from motor and sensory blockade, while the incidence of transient neurologic symptoms appears to be small.[4] However, a higher risk of transient neurologic symptoms after lidocaine spinal anaesthesia has been reported.[5] Recently, isobaric lidocaine spinal anaesthesia seems to be an effective and safe option for knee and hip replacement surgery in a day-case setting, and all patients report no transient neurologic symptoms.[6]

Spinal block, by injecting a small amount of local anaesthetic with easy landmark, is a relatively easy technique that provides excellent operating conditions for surgeries.[7, 8] Because primaquine and chloroquine blocked voltage-gated sodium channels,[9, 10] chloroquine produced a dose-dependent effect on skin (peripheral) infiltration anaesthesia in rats.[11] To date, no study of spinal (central) anaesthesia with antimalarial drugs has been investigated. This study aimed to investigate whether intrathecal injection of antimalarial drugs (primaquine, chloroquine, hydroxychloroquine and amodiaquine) could produce a spinal anaesthetic effect and compared it with lidocaine as a reference drug. We demonstrated that antimalarial drugs (primaquine, chloroquine, hydroxychloroquine and amodiaquine) produced spinal motor and sensory blockade.

Method

Animals

The China Medical University (Taiwan) Institutional Animal Care and Use Committee approved the study (certification number: 2016–036; date of ethical approval: 4 December 2015). Male Sprague–Dawley (SD) rats, weighing 300–350 g, were acquired from BioLASCO Taiwan Co., Ltd (Taiwan), and they were housed in the Laboratory Animal Center (22°C; 50% relative humidity) under a standard 12 h light–dark cycle (6:00 am, on/6:00 pm, off).

Chemical agents

Chloroquine diphosphate salt, amodiaquine dihydrochlororide dihydate, hydroxychloroquine sulfate, primaquine bisphosphate and lidocaine hydrochloride monohydrate were acquired from Sigma Chemical Company of St. Louis and Aldrich Chemical Company of Milwaukee (MO, USA). Prior to injection, the agents were completely dissolved in 5% hydrous dextrose, and the pH was adjusted to the range ~5.5 to 6.5.

Experimental groups

In group 1, spinal nociceptive, proprioceptive and motor blockade by four antimalarial drugs and the local anaesthetic lidocaine at a concentration of 20 mM was examined (n = 8 per group). A 20 mM dose was chosen as according to our previous study the ED50 of lidocaine has been shown to be 20 mM.[12] In group 2, a study of the effect on spinal nociceptive, proprioceptive and motor blockade by primaquine (1.25, 1.00, 0.75, 0.50, 0.35 and 0.20 μmol) and lidocaine (2.40, 2.00, 1.00, 0.50 and 0.38 μmol) in a dose-dependent fashion was performed (n = 8 per group). In group 3, spinal nociceptive, proprioceptive and motor blockade effects by primaquine (25 mM; 0.57 mg/rat), lidocaine (48 μmol; 0.69 mg/rat) and 5% dextrose were compared (n = 8 per group). In group 4, the duration of full recovery caused via primaquine was compared with that caused via lidocaine for spinal blockade on an equianaesthetic (ED25, ED50, ED75) basis (n = 8 per group).

Intrathecal injection

Before injection, the rat was handled for 3–5 days to familiarize him with the laboratory room or researcher. Intrathecal injection (lumbar puncture) of the drug was performed in the conscious rat as described previously.[13, 14] One rat received only one injection of the agent. Before intrathecal injection, subcutaneous injection of 1% lidocaine (0.5 mL) was given at the lumbar L4–5 intervertebral space to each rat in the prone position. After 5 min, a 28-G needle with a Hamilton (Reno, Nevada) microlitre syringe was inserted into the L4–5 intervertebral space until tail flick. Then 50 μl of drug solution was administrated intrathecally into the lumbar 4–5 intervertebral space. A rat with a unilateral spinal block was not included in the study.

Neurobehavioural examination

Quantitative neurobehavioural testing (nociceptive, motor and proprioceptive function) was examined[15, 16] before, and 1, 3, 5, 7, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120 and 150 min after drug injection. A trained researcher, who was blinded to the treatment group or control group, was responsible for the evaluation of motor function, proprioception or nociception. Motor function was measured and presented as the force (g) that is produced by the thrust of the rat's hind feet touching the platform of the electronic balance (Mettler Toledo, PB 1502-S, Switzerland). The degree of motor deficit (motor block) is considered as a decrease in gram force, resulting from extensor muscle strength. The extent of nerve block was recorded as percent possible effect (%PE), which was defined as followed:

$$\%\ \mathrm{PE} = 100\%\mathrm{x}\,(\mathrm{Fb} - \mathrm{Fa}) \div (\mathrm{Fb} - 20)$$

where Fb and Fb refer to the maximum muscle strength measured on one foot of the rat before and after injection, respectively. The maximal %PE was reported as percent maximum possible effect (%MPE). A muscle strength measurement of <20 g means 100% block of motor function, and the control value before injection was interpreted as 0% block of motor function.[12, 17] Proprioceptive function was assessed through 'tactile placing' or 'hopping'. This evaluation was tested by lifting the upper body of the animal off the ground and standing on one foot only. We moved the animal in the direction of the weight-bearing leg, which generally caused the weight-bearing limb to swing rapidly in the same direction to prevent the rat from falling over. A block of proprioception caused a slower hopping, and then a larger lateral hopping occurred so the rat avoided falling over. In the case of complete block, there is no single-leg jump reaction. Proprioceptive evaluation was classified as 0 (100% MPE or completely impaired), 1 (67% MPE or severely impaired), 2 (33% MPE or slightly impaired) and 3 (0% MPE or normal). Nociceptive blockade was evaluated based on the vocalization (or withdrawal reflex) provoked via pinching the skinfold on the middle part of the tail, the dorsal skin of the rat adjacent to the base of the tail, or the lateral metatarsus of both right and left hindlimbs. A surgical locking forceps, the production of a standardized force (225 ± 10 g) without tissue damage, was performed to lock the

grasping surfaces in a closed position. The block of nociception was graded as 0% MPE (normal reaction), 25% MPE, 50% MPE, 75% MPE and 100% MPE (no reaction).

The parameters of spinal block

The duration (full recovery time) is the time from injection to complete recovery (0% MPE). The area under a curve (AUC) of spinal block was constructed by Kinetica version 2.0.1 software (InnaPhase Corporation, Philadelphia, PA) and was calculated as follows:

$$AUC = 1/2\ (C_1 + C_2)\,x\,(t_2 - t_1)$$

where t is the testing time point and C is the %PE. In addition, the dose-related curve was obtained after animals received 5–6 doses of each agent (n = 8 per group). Then, the SAS NLIN procedure (SAS Institute Inc., Carey, NC) was specially used for fitting the curve, and the ED50 was obtained.[11, 18] The ED75 or ED25 was derived via the SAS NLIN procedure that was employed to construct the median effective dose.[15, 19]

Statistical analysis

The data are presented as the mean±standard error (SE) from four independent experiments. Most of our experimental values conformed to the normal assumption after the Shapiro–Wilk test to examine whether our experimental values showed the normal distribution. For this reason, the parametric tests were used to analyse the differences among multiple groups. All types of data analysis were tested via SPSS for Windows (version 17.0). A P-value ≤5% was considered statistically significant. Experimental data among multiple groups were tested by one-way (Figures 1–3; Tables 1 and 2) and two-way (Figure 4) analysis of variance (ANOVA) with Tukey's honest significance difference (HSD).

Results

Spinal block following intrathecal injection of antimalarial drugs

Spinal block (%MPE) in proprioception, motor function or nociception by antimalarial primaquine (0.46 mg/rat), chloroquine (0.52 mg/rat), hydroxychloroquine (0.43 mg/rat) and amodiaquine (0.46 mg/rat) and the local anaesthetic lidocaine (0.29 mg/rat) at a concentration of 20 mM is shown in Figure 1. Among these drugs, primaquine had the higher potency in spinal nociceptive, proprioceptive and motor blockade when compared with lidocaine. Chloroquine or hydroxychloroquine provoked a similar potency of spinal blockade in comparison with lidocaine, while amodiaquine had the lower potency of spinal blockade when compared with lidocaine (Figure 1). Full recovery time of spinal blockade by antimalarial drugs (primaquine, chloroquine, hydroxychloroquine and amodiaquine) and lidocaine is shown in Figure 2. Using a 20 mM solution, full recovery time of spinal blockade by antimalarial drugs (primaquine, chloroquine, hydroxychloroquine and amodiaquine) was greater than that of lidocaine (Figure 2).

Dose-dependent studies of spinal block by primaquine and lidocaine

Lidocaine or primaquine produced spinal block of nociception, proprioception and motor function in a dose-dependent manner (Figure 3). Their ED75, ED50 and ED25 values are given in Table 1.

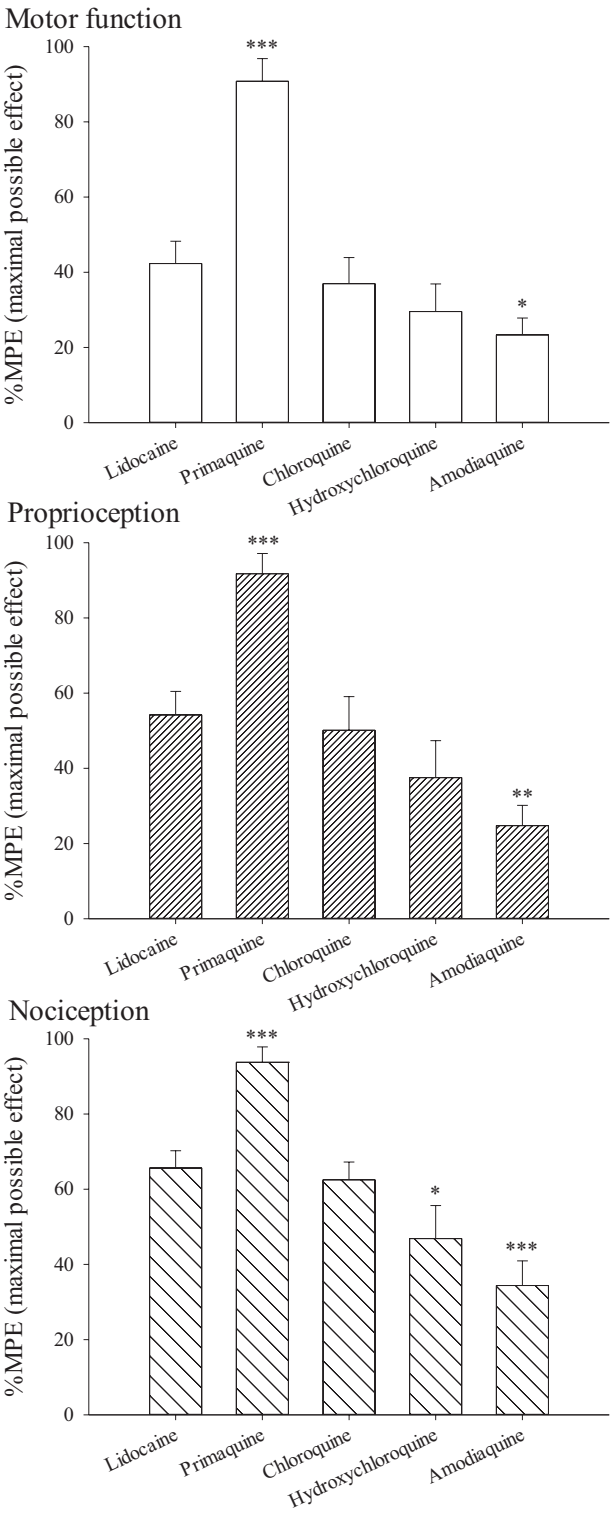

Figure 1 The percent of maximal possible effect (%MPE) of spinal blockade by antimalarial primaquine (0.46 mg/rat), chloroquine (0.52 mg/rat), hydroxychloroquine (0.43 mg/rat) and amodiaquine (0.46 mg/rat) and the local anaesthetic lidocaine (0.29 mg/rat) at 20 mM in rats (n = 8 in each group of different treatments). Data are reported as mean ± S.E.M. *P < 0.05, **P < 0.01, ***P < 0.001, when compared with lidocaine by using one-way analysis of variance followed by pairwise Tukey's honest significance difference test.

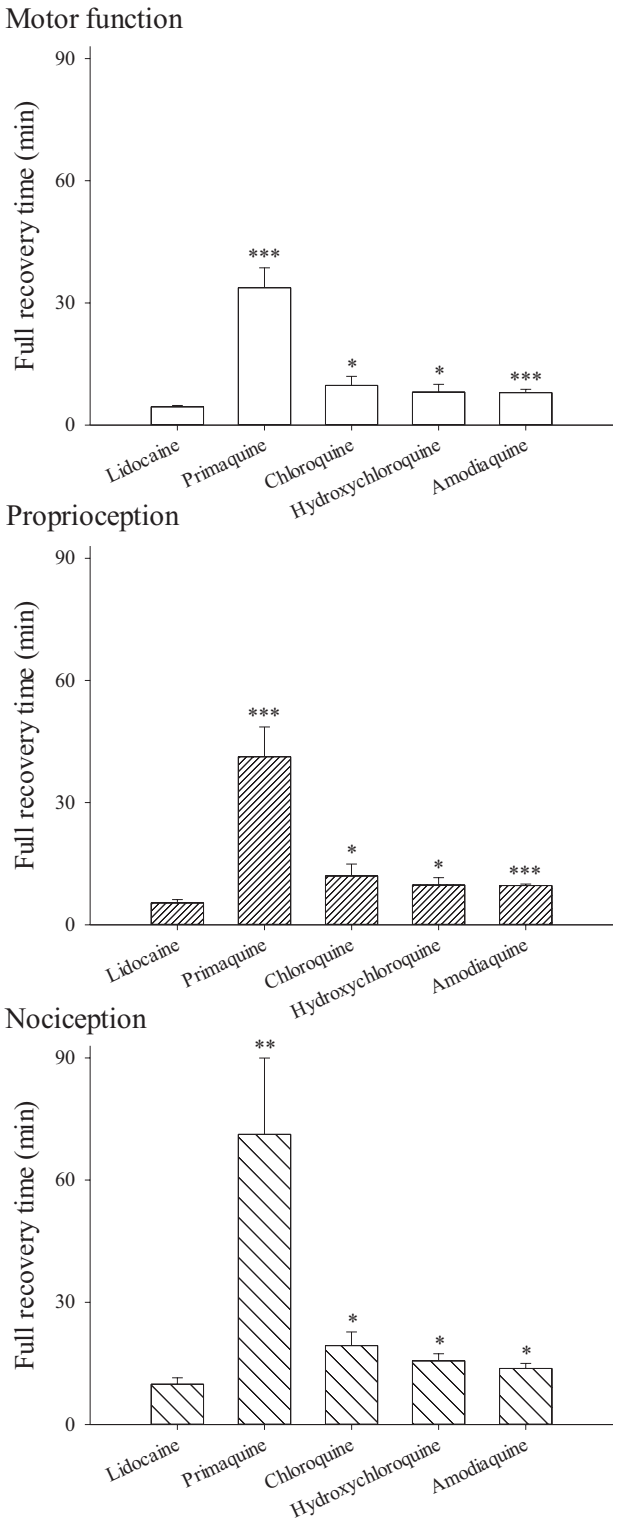

Figure 2 The duration of full recovery of spinal blockade by antimalarial primaquine (0.46 mg/rat), chloroquine (0.52 mg/rat), hydroxychloroquine (0.43 mg/rat) and amodiaquine (0.46 mg/rat) and the local anaesthetic lidocaine (0.29 mg/rat) at 20 mM in rats (n = 8 in each group of different treatments). Data are reported as mean ± S.E.M. *P < 0.05, **P < 0.01, ***P < 0.001, when compared with lidocaine by using one-way analysis of variance followed by pairwise Tukey's honest significance difference test.

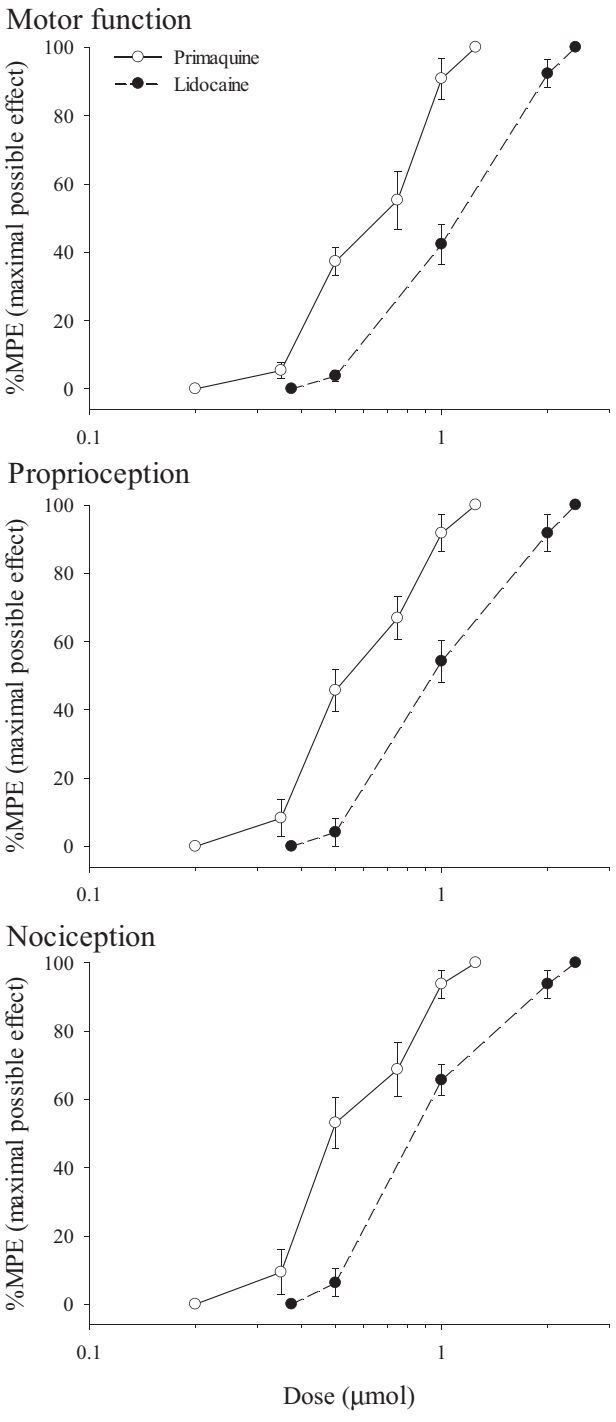

Figure 3 Dose–response curves of spinal blockade by antimalarial primaquine and the local anaesthetic lidocaine at 5–6 different doses in rats (n = 8 in each group of different treatments). Data are reported as mean ± S.E.M. The differences in potency of spinal blockade of primaquine versus lidocaine were evaluated by one-way analysis of variance followed by pairwise Tukey's honest significance difference test.

At an ED50 equipotent dose, the rank order of potency for spinal blockade of proprioception, nociception and motor function are primaquine > lidocaine (P < 0.01; Table 1). Intrathecal administration of 5% dextrose did not produce spinal blockade (Table 2). At a concentration of 25 mM, primaquine (0.57 mg/rat) produced complete blockade (100% MPE) in motor, proprioceptive and nociceptive functions with full recovery times of ~54.4, 67.5 and 106.9 min (Table 2), respectively. At a concentration of 48 mM, lidocaine (0.69 mg/rat) displayed complete blockade (100% MPE) in motor, proprioceptive and nociceptive functions

Table 1 ED50, ED25 and ED75 with 95% confidence interval (95% CI) of drugs for spinal blockade of motor function, proprioception and nociception in rats

Drug	Motor function	Proprioception	Nociception	Mean		
	ED50 (95% CI)	ED50 (95% CI)	ED50 (95% CI)	ED25	ED50	ED75
Primaquine	0.63 (0.58 –0.68)*	0.57 (0.52 –0.61)*	0.54 (0.49 –0.59)*	0.43	0.58	0.77
Lidocaine	1.07 (1.01 –1.14)	0.97 (0.90 –1.04)	0.88 (0.82 –0.93)	0.76	0.97	1.25

The EDs of drugs (μmol) were constructed from Figure 3. The potency ranking of drugs (ED50) was primaquine > lidocaine (*$P < 0.01$ for the differences) by using one-way ANOVA followed by pairwise Tukey HSD test.

Table 2 %MPE, duration of action and AUCs of primaquine (1.25 μmol; 0.57 mg/rat), lidocaine (2.40 μmol; 0.69 mg/rat) and 5% dextrose on spinal blockade of motor function, proprioception and nociception in rats

	%MPE	Duration (min)		AUC (%MPE x min)
		Complete blockade time	Full recovery time	
Motor function				
Primaquine	100 ± 0	9.1 ± 0.9**	54.4 ± 3.7***	2710 ± 224***
Lidocaine	100 ± 0	5.8 ± 0.9	26.3 ± 1.8	1205 ± 120
5% Dextrose	–	–	–	–
Proprioception				
Primaquine	100 ± 0	12.3 ± 0.8***	67.5 ± 4.0***	3737 ± 233***
Lidocaine	100 ± 0	6.1 ± 1.0	30.0 ± 1.9	1489 ± 129
5% Dextrose	–	–	–	–
Nociception				
Primaquine	100 ± 0	19.0 ± 1.3*	106.9 ± 8.2***	5891 ± 365***
Lidocaine	100 ± 0	11.6 ± 3.1	33.8 ± 1.8	1918 ± 213
5% Dextrose	–	–	–	–

Data are reported as mean±S.E.M.; $n = 8$ rats in each group. Of note, all of the animals displayed complete blockade (100% MPE) of any function tested in both primaquine and lidocaine groups. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, when compared with lidocaine by using one-way ANOVA followed by pairwise Tukey HSD test.

with full recovery times of ~26.3, 30.0 and 33.8 min (Table 2), respectively.

The AUCs, complete blockade time and duration of full recovery of spinal block by primaquine and lidocaine

At ED25, ED50 and ED75 equipotent doses, the duration of spinal motor, proprioceptive and nociceptive blockade by primaquine was longer than that of lidocaine ($P < 0.01$; Figure 4). AUCs and durations of action of primaquine were larger (all $P < 0.05$) than these of lidocaine for spinal motor, nociceptive and proprioceptive blockade (Table 2). All animals recovered fully following intrathecal injections.

Discussion

We are the first to show that antimalarial drugs (primaquine, chloroquine, hydroxychloroquine and amodiaquine) produced spinal motor and sensory (nociception and proprioception) block. Among four antimalarial drugs and the local anaesthetic lidocaine, primaquine had the best potency and produced the longest duration of spinal motor and sensory blockade. Intrathecal primaquine and lidocaine displayed dose-dependent spinal blockade.

Antimalarial drugs are commonly used to prevent or to treat malaria.[20] Antimalarial primaquine and chloroquine could inhibit the activity of Na^+ channels,[9, 10, 21] and chloroquine has been shown to produce the local anaesthetic effect of skin infiltration local anaesthesia in rats.[11] Local anaesthetics displayed the blockade of voltage-gated sodium channels, and they processed the generation of peripheral nerve block, skin infiltration anaesthesia and spinal/epidural anaesthesia.[3] Furthermore, antimalarial primaquine has been known to inhibit the generation of action potentials[2] and to produce use-dependent block of Na^+ channels.[10] In this study, we showed that antimalarial primaquine, chloroquine, hydroxychloroquine and amodiaquine at 1 μmol produced spinal blockade. Overall findings were in keeping with subcutaneous injection of chloroquine (12 μmol) producing skin infiltration anaesthesia in rats.[11] Although it is not a replacement for lidocaine, primaquine may have a value in local anaesthesia clinically.

Primaquine was the most potent among antimalarial drugs (primaquine, chloroquine, hydroxychloroquine ad amodiaquine) in spinal anaesthesia. Therefore, only primaquine and lidocaine were tested for dose-related studies. In addition, systemic lidocaine effectively reduced pain in patients with fibromyalgia.[22] This is similar to previous experiments showing that antimalarial drugs are effective in treating chronic pain and traumatic brain injury.[23, 24] Primaquine was almost 1.7-fold more potent than lidocaine for spinal blockade. Our resulting data resembled a previous study showing that bupivacaine was almost 11-fold more potent than chloroquine for skin infiltration anaesthesia.[11] At ED25, ED50 and ED75 equipotent doses, the duration of primaquine was greater than that of lidocaine for spinal blockade (Figure 4). In the future, it may be worth using the local anaesthetics (e.g. primaquine) for postoperative pain control and surgical procedures.

Based on their chemical structures, antimalarial drugs can be separated into secondary and tertiary amines. After intrathecal injection,

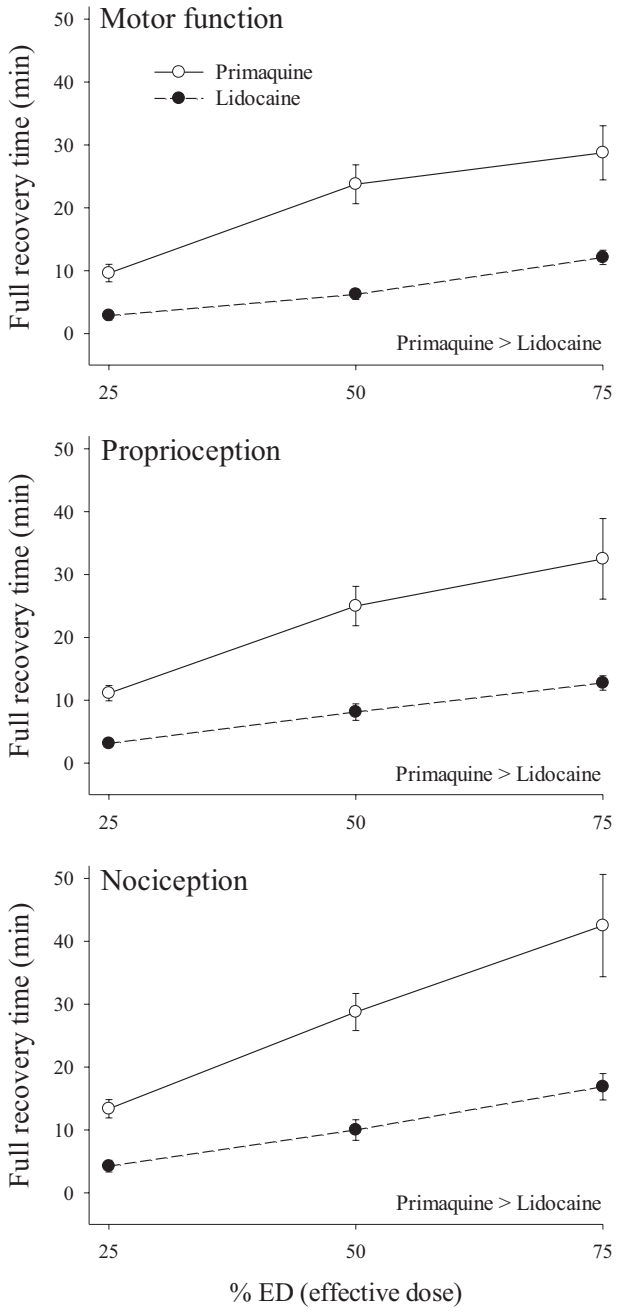

Figure 4 The duration of full recovery of spinal blockade by antimalarial primaquine and the local anaesthetic lidocaine at ED25, ED50 and ED75 in rats ($n = 8$ in each group of different treatments). Data are reported as mean ± S.E.M. The differences in duration of full recovery of spinal blockade by primaquine versus lidocaine were evaluated by a two-way analysis of variance followed by pairwise Tukey's honest significance difference test.

the tertiary amine agents (hydroxychloroquine, amodiaquine and chloroquine) demonstrated a similar or lower potency of spinal blockade when compared with lidocaine. The secondary amine agent (primaquine) exhibited a higher efficacy of spinal blockade than did lidocaine (Figure 1). We found that, in general, tertiary amine drugs are not as strong as secondary amine drugs for spinal sensory and motor blockade. In addition, primaquine (a secondary amine agent) induced a greater duration of spinal blockade than did lidocaine (Figure 2). Our resuls may be beneficial for patients who need more prolonged surgical procedures.

There are the limitations in this study. First, the evaluation of acute cardiovascular and central nervous system toxicity after antimalarials injection should be considered in the future. Second, we did not investigate if primaquine or other antimalarial drugs provoked local neurotoxicity. However, in our neurobehavioural study we did not observe apparent behavioural abnormalities after intrathecal injection. Third, it is worth conducting further experiments to confirm the possible mechanism (e.g. the block of sodium channels) by which antimalarial drugs provoke spinal sensory and motor blockade.

Conclusions

The main conclusion was that primaquine and the other antimalarials (chloroquine, hydroxychloroquine and amodiaquine) produced spinal sensory and motor blockade. Primaquine and lidocaine provoked dose-dependent spinal block. Primaquine exhibited greater potency and prolonged duration of action in comparison with lidocaine for spinal blockade, while the other antimalarials had similar or lesser potency when compared with lidocaine.

Author Contributions

Conception and design of research: An-Kuo Chou, Yu-Wen Chen, Ching-Hsia Hung. Conducted experiments: An-Kuo Chou, Chong-Chi Chiu, Jhi-Joung Wang, Yu-Wen Chen. Interpreted results of experiments: An-Kuo Chou, Chong-Chi Chiu, Yu-Wen Chen, Ching-Hsia Hung. Prepared figures: An-Kuo Chou, Chong-Chi Chiu, Jhi-Joung Wang. Drafted manuscript: An-Kuo Chou, Chong-Chi Chiu, Yu-Wen Chen, Ching-Hsia Hung, Jhi-Joung Wang. Approved final version of manuscript: An-Kuo Chou, Chong-Chi Chiu, Jhi-Joung Wang, Yu-Wen Chen, Ching-Hsia Hung. Edited and revised manuscript: Yu-Wen Chen, Ching-Hsia Hung.

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Conflict of Interest

None declared.

Data Availability Statement

Data available on request.

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