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Mechanical and electrophysiological effects of mepivacaine on direct myocardial depression *in vitro*

W. KON PARK AND C. KOOK SUH

Summary

The effects of various concentrations (20, 50, and 100 μmol litre^{-1}) of mepivacaine were studied in isolated guinea pig and rat right ventricular papillary muscles by measuring the effects on myocardial contractility and electrophysiological parameters. Mepivacaine produced dose-dependent depression of peak force during 0.5 to 3 Hz stimulation rates in guinea pig papillary muscles. Conduction block was frequently noted, especially at higher stimulation rates (2 and 3 Hz) with mepivacaine 50 and 100 μmol litre^{-1}. In rat papillary muscle experiments, about 20% depression of peak force was shown at rested state contraction. Shortening of action potential (AP) duration (APD_{50}: about 10%, APD_{90}: about 10%) and rate-dependent depression of d*V*/d*t* max was observed with mepivacaine 100 μmol litre^{-1}. In 26 mmol litre^{-1} K^+ Tyrode's solution, mepivacaine 50 and 100 μmol litre^{-1} produced a dose-dependent depression of early (50 μmol litre^{-1}: about 20%, 100 μmol litre^{-1}: about 30%) and late (50 μmol litre^{-1}: about 30%, 100 μmol litre^{-1}: about 50%) force development. In slow APs, neither shortening of AP duration nor changes of d*V*/d*t* max were shown by mepivacaine 100 μmol litre^{-1}. An approximate 30% depression of contracture induced by rapid cooling after 2 Hz stimulation rates was observed with mepivacaine 100 μmol litre^{-1}. It may be concluded that the direct myocardial depressant effect of mepivacaine is likely to be caused by inhibition of Ca^{2+} release from the sarcoplasmic reticulum. The Na^+ channel blocking action may contribute indirectly to the depression of contractility. (*Br. J. Anaesth.* 1998; **81**: 244–246)

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In vivo[1] and *in vitro*[2] animal studies have shown that local anaesthetics produce dose-related depression of cardiac output or negative inotropic action with minimal changes in peripheral vascular resistance. Although the electrophysiological basis of local anaesthetic action is block of sodium channels, the mechanisms of myocardial depression may involve additional actions indirectly related to the regulation of intracellular calcium such as Ca^{2+} entry into the cell or Ca^{2+} release from the sarcoplasmic reticulum.

Mepivacaine, an amide local anaesthetic agent with potency similar to lidocaine, has been reported to show clinical effects similar to lidocaine, although it is closely related in chemical structure to bupivacaine. Although the negative inotropic effect of mepivacaine has been reported in an *in vivo* study,[1] direct myocardial depression has not yet been defined. Therefore, the purpose of this study was to determine the degree and mechanisms of direct myocardial depression produced by mepivacaine.

Methods and results

EXPERIMENT WITH NORMAL K^+ TYRODE'S SOLUTION

According to a procedure approved by the Yonsei University College of Medicine Animal Research Committee, the right ventricular papillary muscle was removed from female guinea pigs (300–400 g) or Sprague–Dawley rats (300–400 g) after intraperitoneal pentobarbital sodium injection (50 mg kg^{-1}). The tendinous end of the muscle was attached by a strut to a GRASS FT03 force transducer. The bath was superfused at 37°C at a rate of 8 ml min^{-1} with normal Tyrode's solution (mmol litre^{-1}: Na 143, K 5, Ca 2, Cl 127, $MgSO_4$ 1.2, HCO_3^- 25, glucose 11, Ethylenediaminetetraacetic acid (EDTA) 0.1) bubbled with 95% oxygen/5% carbon dioxide maintaining mean pH (SD) at 7.4 (0.5). The muscles were field-stimulated by a GRASS S44 stimulator (GRASS Instruments, Quincy, MA, U.S.A.).

Membrane potential and its rate of rise during the action potential (dV/dt max) was monitored by a conventional 3 M KCl-filled glass microelectrode (10–20 MΩ) attached to a WPIVF-1 preamplifier. In rat experiments, the contractile response to 100 μmol litre^{-1} mepivacaine in normal Tyrode's solution only was observed. As rat papillary muscle showed progressive deterioration of contractility over time, time control experiments were performed separately to those of mepivacaine administration.

Whereas mepivacaine 20 μmol litre^{-1} caused contractile depression at 1–3 Hz stimulation rates, mepivacaine 50 and 100 μmol litre^{-1} showed depression at all stimulation rates. Effects of 50 μmol litre^{-1} were greater than those of 20 μmol litre^{-1}, and effects of 100 μmol litre^{-1} were greater than those of mepivacaine

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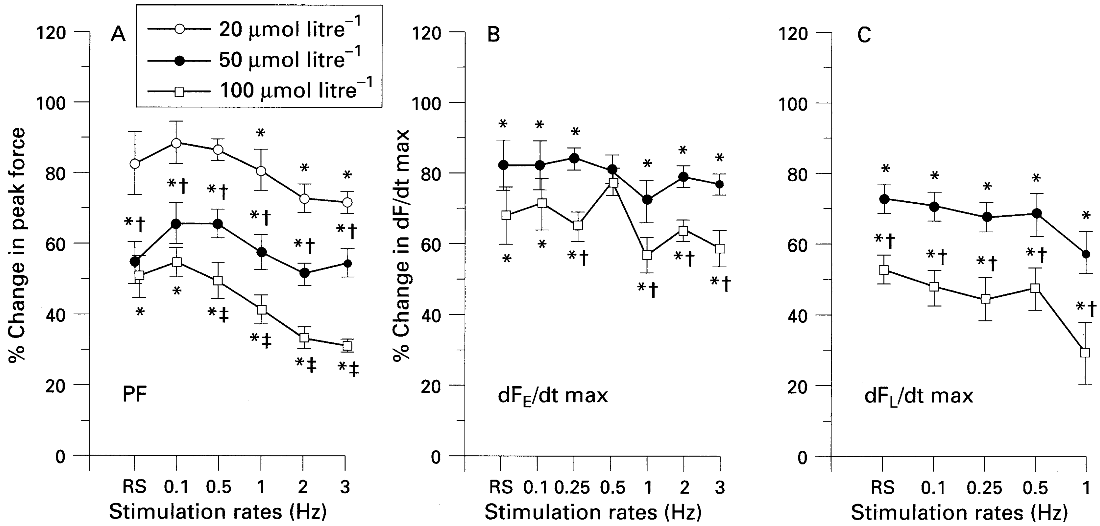

Figure 1 (A) Effects of increasing concentrations of mepivacaine on peak force (PF) in normal K^+ Tyrode's solution at various stimulation rates in guinea pig papillary muscles. Results are plotted as mean (SEM) percentage of control ($n=7$). *, †, and ‡ indicate differences ($P<0.05$) from control, mepivacaine 20 μmol litre^{-1}, and 50 μmol litre^{-1}, respectively (ANOVA). (B) Effects of mepivacaine 50 and 100 μmol litre^{-1} on the maximum rate of early force development (dF_E/dt max) ($n=5$) in 26 mmol litre^{-1} K^+ Tyrode's solution with isoprenaline 0.1 μmol litre^{-1} at various stimulation rates in guinea pig papillary muscles, (C) Effects of mepivacaine 50 and 100 μmol litre^{-1} on the maximum rate of late-force development (dF_L/dt max) ($n=5$) in 26 μmol litre^{-1} K^+ Tyrode's solution with isoprenaline 0.1 μmol litre^{-1} at RS–1 Hz stimulation rates in guinea pig papillary muscle. Results are plotted as mean (SEM) percentage of control. *, † Indicate differences ($P<0.05$) from control and mepivacaine 50 μmol litre^{-1}, respectively (ANOVA).

50 μmol litre^{-1} from 0.5 to 3 Hz stimulation rates. Contractile depression at 2–3 Hz was greater than that at rested state (RS)–0.1 Hz with mepivacaine 100 μmol litre^{-1} (fig. 1A).

With mepivacaine 20 μmol litre^{-1}, the contraction of guinea pig papillary muscles responded normally to field stimulation at all stimulation rates. While mepivacaine 50 μmol litre^{-1} showed a normal contractile response at low stimulation rates (RS–1 Hz), stimulation block was frequently observed at higher stimulation rates (2, 3 Hz). Block of stimulation was frequently observed at all stimulation ranges except RS with mepivacaine 100 μmol litre^{-1}. Drug washout for 15 min resulted in satisfactory stimulation resulting from the control voltages at all stimulation rates.

In rat papillary muscles, mepivacaine 100 μmol litre^{-1} produced contractile depression (about 20%) at RS.

In normal action potential (AP) experiments, mepivacaine 100 μmol litre^{-1} produced shortening of APD_{50} and APD_{90} (0.5 Hz: about 18%, 1 Hz: about 12%, 2 Hz: about 7%) from 0.5 to 2 Hz stimulation rates. Mepivacaine 100 μmol litre^{-1} significantly depressed d*V*/d*t* max from 0.5 to 3 Hz, and rate-dependent depression of d*V*/d*t* max was shown at 2 and 3 Hz stimulation rates. There was no tendency for the muscles to depolarize.

EXPERIMENTS WITH 26 MMOL LITRE^{-1} K^+ TYRODE'S SOLUTION

Muscle force and APs were also studied in 26 mmol litre^{-1} K^+ Tyrode's solution (mmol litre^{-1}: Na 122, K 26, Cl 121, Ca 2, $MgSO_4$ 1.2, HCO_3^- 25, glucose 11, EDTA 0.1) with isoprenaline 0.1 μmol litre^{-1}. A sequential increase in stimulation rates from rest to 1 Hz was performed. Increasing concentrations of mepivacaine (50 and 100 μmol litre^{-1}) were applied sequentially in contraction studies, and mepivacaine 100 μmol litre^{-1} was only used to assess the drug effect in slow APs.

Early force development was depressed by about 30% and 45% with mepivacaine 50 and 100 μmol litre^{-1}, respectively (fig. 1B). In the late developing force, mepivacaine 50 and 100 μmol litre^{-1} caused an approximate 25% and 50% depression, respectively (fig. 1C). Stimulation block was not observed. Mepivacaine 100 μmol litre^{-1} caused neither change in resting membrane potential, slow AP amplitude, and d*V*/d*t* max, nor shortening in AP duration at 0.1, 0.25, 0.5, and 1 Hz stimulation rates.

RAPID COOLING CONTRACTURE EXPERIMENTS

After the 15-min rest at 37°C, rapid cooling was induced by perfusion at a flow rate of about 50 ml min^{-1} with 0°C normal Tyrode's solution (<5°C achieved within 1.5 s) in which 95% oxygen/5% carbon dioxide was bubbled. Following the measurement of RS rapid cooling contracture, the chamber was changed to normal Tyrode's solution at 37°C. After full rewarming to 37 °C, stimulation at 0.1 Hz, followed by 1 and 2 Hz stimulation rates, was sequentially applied until maximal and stable contractions were elicited after 2 Hz. Rapid cooling was induced again. Following control measurements, muscles were exposed to mepivacaine 100 μmol litre^{-1} for 15 min at 37 °C before eliciting the rapid cooling contracture.

After 15-min rest, there was no change in RS rapid cooling contracture with mepivacaine 100 μmol litre^{-1}. Peak force at 2 Hz contraction was diminished to about 58% of control by mepivacaine 100 μmol litre^{-1}, while contracture was depressed from 5.11 to 3.86 mN mm^{-2} (about 70% of control). Time to peak contracture remained unchanged (control: 13.6 s, 100 μmol litre^{-1} 14.5 s).

In force studies, mean cross-sectional areas were 0.81 (0.29) (mean (SD), $n=40$) and 0.88 (0.45) mm^2 (mean (SD), $n=13$) in guinea pigs and rats, respectively.

Repeated measures of analysis of variance (ANOVA) followed by Fisher PLSD multiple range test was applied to test for significant differences in the stimulation rates and among the mepivacaine concentrations. A P value <0.05 was considered significant.

Comment

Moderate depression by mepivacaine of cardiac output and stroke volume (about 15%) with little change in systemic vascular resistance has been reported in an *in vivo* animal study. Although etidocaine and bupivacaine caused more marked depression of cardiac output (about 50% and 100%, respectively), lidocaine showed modest depression at the same dose.[1] In the present study, mepivacaine 50 μmol litre^{-1} caused an approximate 40% depression of peak force, which was comparable to that of lidocaine 40 μmol litre^{-1} in a previous guinea pig papillary muscle study.[2]

Our results in normal Tyrode's solution demonstrated that depression of myocardial contractility and frequency-dependent block of dV/dt max are more pronounced at higher (2, 3 Hz) stimulation rates with mepivacaine 100 μmol litre^{-1}. The block of Na^+ currents at higher frequencies may account in part for the more decreased contractile depression observed in guinea pig ventricular muscle at 2 and 3 Hz.

The present results of force development in 26 mmol litre^{-1} K^+ Tyrode's solution suggest the inhibition of the two different Ca^{2+} release sites on the sarcoplasmic reticulum membrane activated by depolarization which results from the inhibition of Ca^{2+} efflux from the sarcoplasmic reticulum and/or depression of Ca^{2+} entry.[3] Depression of Ca^{2+} entry may contribute to decreased Ca^{2+} content in the sarcoplasmic reticulum and may have subsequently caused the depression of late developing force. Based on the modest depression of Ca^{2+} influx by mepivacaine, the present biphasic contractile depression may be caused mainly by inhibition of Ca^{2+} release from the sarcoplasmic reticulum. In rat papillary muscles, an approximate 20% depression of RS contraction by mepivacaine 100 μmol litre^{-1} when compared with control also provides further supporting evidence for inhibition of Ca^{2+} release from the sarcoplasmic reticulum.

Cerebral symptoms suggesting systemic intoxication during caudal analgesia have been reported to be associated with a mean mepivacaine concentration in blood of 6.27 μg ml^{-1} (25.48 μmol litre^{-1}).[4] If we assume that the protein binding of mepivacaine at this concentration is approximately 40%,[5] the free plasma concentration will be estimated as 3.76 μg ml^{-1} (15.28 μmol litre^{-1}). As the therapeutic concentrations of mepivacaine observed after a lumbar extradural administration range from 4 to 6 μg ml^{-1} (5.69–8.54 μmol litre^{-1} if we assume 65% protein binding at this range of concentration),[6] this free drug concentration is unlikely to cause myocardial depression. However, in the case of inadvertent administration of mepivacaine, the transient increase in blood concentration may produce cardiac contractile depression if we consider peak blood concentration of lidocaine to be about 30 μg ml^{-1} (128 μmol litre^{-1}) when 3 mg kg^{-1} was injected i.v.[7]

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