Polish Journal of Pharmacology
Pol. J. Pharmacol., 2003, 55, 51–56
ISSN 1230-6002

EFFECTS OF LOCAL ANESTHETICS ON PREGNANT UTERINE MUSCLES

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Effects of local anesthetics on pregnant uterine muscles. B. KARSLI, N. KAYACAN, Z. KUCUKYAVUZ, C. MIMAROGLU. Pol. J. Pharmacol., 2003, 55, 51–56.

Obstetric analgesia and anesthesia should provide optimal pain relief for the parturient with minimal risks. The local anesthetic agents are most commonly used for obstetric analgesia and anesthesia.

We investigated the effect of local anesthetic agents: prilocaine, bupivacaine, ultracaine on myometrium in pregnant rats. In our study, we evaluated the effects of three local anesthetics at cumulative concentrations on contractions of myometrium isolated from pregnant rats. The following characteristics of the contractions were analyzed after the addition of drugs: frequency, mean duration, amplitude of each contractions and integrated area under the contraction curve.

We observed that the exposure to prilocaine, bupivacaine and ultracaine decreased amplitude, duration and integrated area under the contraction curve.

In conclusion, the study drugs at higher concentrations decreased contractions of myometrium, but all drugs at higher concentrations elevated the frequency.

Key words: *prilocaine, bupivacaine, ultracaine, pregnant myometrium*

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INTRODUCTION

Regional anesthesia and analgesia have come into widespread use for women in gynecological procedures. The effects of local anesthetic agents on uterine contractions and umbilical blood flow are very important. The unexpected relaxation or contraction of myometrium can be harmful to fetus [7, 40].

The local anesthetic agents have been used in obstetric anesthesia and analgesia. Bupivacaine is the most commonly used local anesthetic agent. Prilocaine is less frequently used in obstetric patients than bupivacaine. The major advantage of bupivacaine appears to be in the area of epidural obstetric analgesia for labour [3, 7, 40]. Ultracaine is well-tolerated, safe and effective local anesthetic for use in clinical dentistry [10, 13, 14]. However, this agent is not used for obstetric analgesia yet.

In our study, the effects of three local anesthetics: prilocaine, bupivacaine, ultracaine on contractility of pregnant rat myometrium were studied and compared *in vitro*.

MATERIALS and METHODS

The albino rats pregnant for 18–21 days (n = 30) were taken care of in compliance with the guidelines of the Animal Care Center. Animals were killed by cervical subluxation. The uterine horns were rapidly excised and carefully cleaned of surrounding connective tissue and opened longitudinally along the mesenteric border. Fetuses of the late-stage pregnant rats were removed and non-uterine tissues were dissected away and discarded. We obtained a full-thickness myometrial muscle strip (measuring 4 × 10 mm) from each animal. Longitudinal strips were incubated and mounted vertically in 10 ml organ bath containing modified Krebs solution (composition in millimoles per liter: NaCl 125, KCl 2.4, $CaCl_2$ 1.8, $MgCl_2$ 0.5, $NaHCO_3$ 23.9 and glucose 11). The tissue baths were aerated continuously with 95% oxygen and 5% carbon dioxide at 37°C. The myometrial strips were allowed to equilibrate at 1 g tension for 30 min before the addition of experimental drugs. The myometrial isometric contractions were recorded with a Grass F TO3 force displacement transducer and registered on a Grass 79 E polygraph (Grass F TO3, 79 E, USA). The recorder paper speed was set at 5 mm/min.

When the contractions became regular, strips were exposed to increased concentrations of proilocaine (Citanest), bupivacaine (Marcaine) and ultracaine (Carticaine-Articaine) at cumulative concentrations to investigate their effect on spontaneous contractions of myometrium isolated from pregnant rats.

Prilocaine (10^{-4} – 10^{-3} M), bupivacaine (10^{-5} – 10^{-4} M) and ultracaine (10^{-4} – 10^{-3} M) were used in the study. Drug-containing solutions were prepared immediately before the experiment.

The characteristics of the contractions analyzed over 1000 s intervals immediately before and after the addition of drugs included frequency (number per 1000 s), mean duration and amplitude of each contraction and integrated area under the contraction curve (representing contractile force over 1000 s) measured with a digitized plotter. Data were presented as means ± SE and were analyzed by analysis of variance with $p < 0.05$ considered statistically significant.

RESULTS

The effects of prilocaine, bupivacaine and ultracaine on contractile activity of myometrial strips isolated from pregnant rats were evaluated. We investigated the effects of increasing concentrations of the drugs on spontaneous contractions of myometrium.

Prilocaine effects

A representative recording of a strip treated with prilocaine is shown Figure 1. The effects of all concentrations of prilocaine on contraction, frequency and duration are shown in Figure 2. The exposure to prilocaine at cumulative concentrations between 10^{-4} and 10^{-3} M decreased contractile activity of myometrial strips. The drug exerted the greatest effect on the amplitude and integrated area under the contraction curve and there was statistically significant difference between the control and

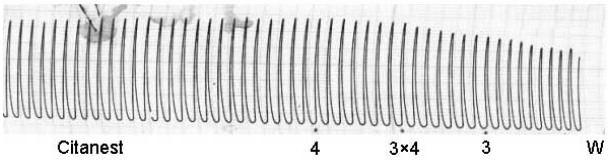

Fig. 1. The effects of different concentrations of prilocaine (Citanest) on contractions in myometrial strips

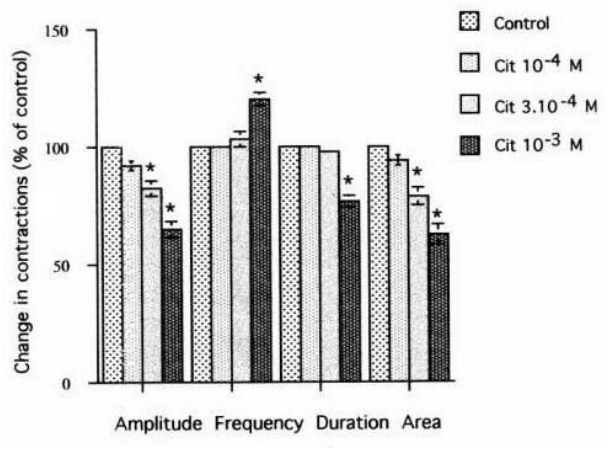

Fig. 2. The effects of three concentrations of prilocaine on contraction, amplitude, duration and integrated area under contraction curve

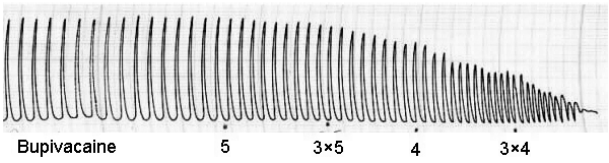

Fig. 3. The effects of different concentrations of bupivacaine on contractions in myometrial strips

the data obtained with three concentrations of prilocaine (10^{-4} – 10^{-3} M). The duration of contractions decreased only at 10^{-3} M concentration of prilocaine and the difference was statistically significant. Despite the lack of the effect of prilocaine at a concentration of 10^{-4} M on contraction frequency, it dramatically increased at 10^{-3} M (Fig. 2).

Bupivacaine effects

The exposure of myometrial strips isolated from pregnant rat to bupivacaine at cumulative concentrations of 10^{-5} – 10^{-4} M decreased the contractile activity (Fig. 3), with significant effect on the amplitude and integrated area under the contraction curve (Fig. 4). These changes were statistically significant. The duration of contractions decreased with increasing concentrations of bupivacaine, reaching statistical significance at a concentration of 10^{-4} M. Bupivacaine had no effect on frequency, but 3×10^{-4} M concentration of this drug produced an increase in the contraction frequency (Fig. 4).

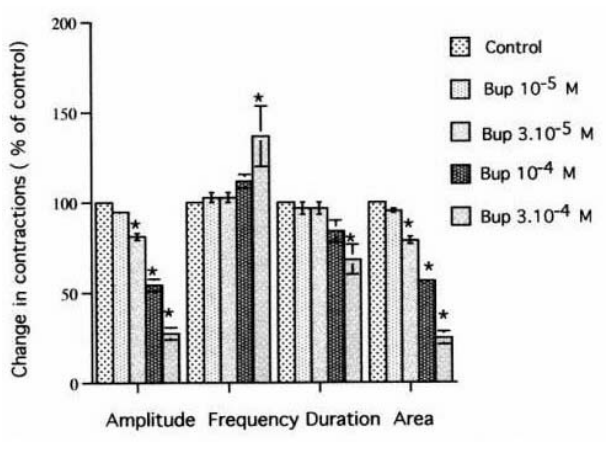

Fig. 4. The effects of three concentrations of bupivacaine on contraction, amplitude, duration and integrated area under contraction curve

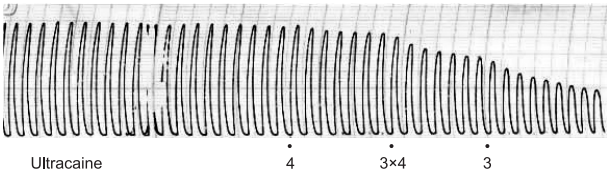

Fig. 5. The effects of different concentrations of ultracaine on contractions in myometrial strips

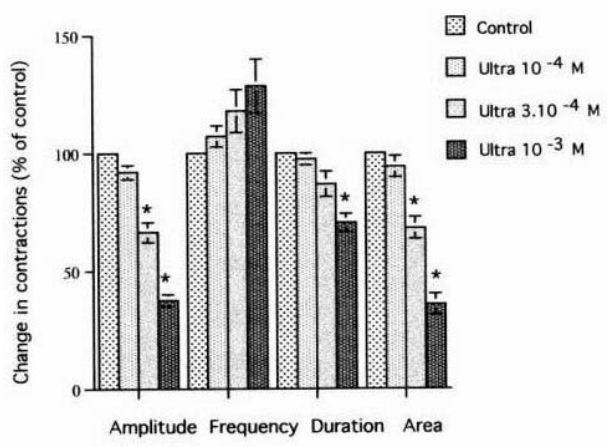

Fig. 6. The effects of three concentrations of ultracaine on contraction, amplitude, duration and integrated area under contraction curve

Ultracaine effects

Ultracaine at cumulative concentrations of 10^{-4} – 10^{-3} M decreased contractile activity of myometrial strips isolated from pregnant rat (Fig. 5) with significant effects on their amplitude, duration and

integrated area under the contraction curve (Fig. 6). Higher concentration of ultracaine (10^{-3} M) produced significant reduction in these parameters. Ultracaine produced an increase in the frequency of contractions at its three concentrations (Fig. 6).

DISCUSSION

Pain control is a major component of patient's comfort and safety. The goal of obstetric analgesia is to provide optimal pain relief for the parturient with minimal risks to herself and fetus. Local anesthetics are the most effective agents for reducing pain during labor and postoperative period. This study measured the effects of three local anesthetics on contractility of the isolated pregnant rat myometrial strips.

Ultracaine, a relatively new agent, is being used increasingly for dental procedures and peripheral-central nerve blocks [9, 22, 29–31, 35]. However, this local anesthetic agent is most commonly used for dental procedures, but it is not applied in obstetric patients. Some authors report on the toxicity of articaine (ultracaine) that was examined in *in vitro* and *in vivo* experiments. These mutagenicity studies have shown no mutagenic potential [10]. The cardiodepressant effects of articaine were compared with those of lidocaine and bupivacaine. Articaine and lidocaine were less potent than bupivacaine [18]. We have investigated the effect of ultracaine on the contraction of myometrial strips isolated from pregnant rats. Ultracaine contractions of 10^{-4} – 10^{-3} M decreased contractile activity in myometrial strips. Recent studies suggested that this agent was well-tolerated, safe and effective local anesthetic and had no mutagenic potential [10, 13, 14]. However, its effects on uterine blood flow and contractions were not reported. Ultracaine has been introduced into clinical practice recently and is undergoing clinical trials.

Prilocaine is the least toxic of the amino-amide local anesthetics. It is useful for infiltration, peripheral nerve blockade and epidural anesthesia. Methemoglobinemia may occur after the use of large doses of prilocaine. This unusual side effect has essentially eliminated the use of this drug in obstetrics although prilocaine has not been reported to cause any significant adverse effects in mother, fetus or newborn [3]. In this study, we examinated the effect of prilocaine on contractions of the isolated pregnant rat myometrium. Prilocaine at cumulative concentrations from 3×10^{-4} to 10^{-3} M decreased contractile activity of myometrial strips. The duration of contractions was decreased by 10^{-3} M concentration of prilocaine, reaching statistical significance at a concentration of 10^{-3} M. Despite the lack of effect of prilocaine at 10^{-4} M on contraction frequency, it increased at 10^{-3} M.

Willdeck-Lund and Nilsson attempted to evaluate the effects of prilocaine, bupivacaine, lidocaine and etidocaine on nonpregnant human uterus activity *in vitro*. Similarly to our results, the authors demonstrated that lidocaine and etidocaine had a significantly greater inhibitory effect on myometrial contractions than prilocaine and bupivacaine [39]. In our study, frequency of myometrial contractions was increased by prilocaine at 10^{-3} M concentration. Similarly, Lograno et al. reported that prilocaine caused an increase of frequency of the contractions in rat urinary bladder [12]. Studies of other authors gave similar results demonstrating that prilocaine had concentration-dependent inhibitory effects on vascular and other smooth muscle [12, 34, 36, 37].

Bupivacaine is used for various regional anesthetic and analgesic procedures [1, 2, 5, 8, 16]. This agent is local anesthetic the most commonly used in obstetric practice for anesthesia and analgesia. Bupivacaine was shown to be effective in reducing pain during labor [3, 4, 7, 11, 40]. *In vivo* clinical studies suggested that bupivacaine had no effect on uterus contractility [4, 15, 20, 25]. However, *in vitro* effects of bupivacaine on uterine contractions are not well documented. In this study, we investigated the effects of bupivacaine on contractions of uterine smooth muscle strips from pregnant myometrium. Bupivacaine at cumulative concentrations (10^{-5} – 10^{-4} M) decreased spontaneous contractile activity of myometrial strips. Frequency and duration of contractions were changed by 3×10^{-4} M concentration of bupivacaine reaching statistical significance at a concentration of 10^{-4} M. Silva de Sa et al. assessed the direct effects of bupivacaine on the umbilical artery. In that study, bupivacaine increased the frequency of phasic contractions [28]. There were some studies which examined the direct vascular effects of local anesthetics. Various local anesthetic agents (such as bupivacaine, ropivacaine and lidocaine) have been shown to cause relaxation of the isolated arterial smooth muscle [19, 32].

Bupivacaine is frequently used for epidural anesthesia in women undergoing labor. Some clinical

studies investigated the influence of epidural block with bupivacaine on uterine activity and the frequency and intensity of contractions [4, 6, 11, 15, 20, 23–25, 33, 38]. Uterine activity was found to decrease following epidural block [11, 23, 24, 38]. Similarly to those results, our study demonstrated that exposure to bupivacaine decreased contractile activity in myometrial strips. However, bupivacaine had no effect on frequency of contractions. Contrary to the findings of the abovementioned authors, the frequency of uterine contractions before and after epidural block was similar [20, 25]. Guidozzi et al. showed that continuous low-dose epidural analgesia had no significant effect on uterine work during the labor [4]. Thorn et al. showed that epidural bupivacaine significantly changed the gastroduodenal motility [33].

Many studies demonstrated that bupivacaine decreased contractile activity of muscles [17, 21, 26, 27]. The effects of bupivacaine on myocardial contraction were examined in isolated dog papillary muscle. The authors reported that bupivacaine produced dose-dependent depression of contraction [26, 27]. The effect of bupivacaine on bladder smooth muscle has also been studied. Those results showed that bupivacaine had inhibitory effects on contraction of bladder smooth muscle [17, 21]. Wali suggested that local anesthetic drugs might have an anti-spasmic effect on tracheal smooth muscle and inhibited the contractions [37].

In conclusion, three local anesthetic agents, ultracaine, prilocaine and bupivacaine were tested with regard to their influence on the contraction amplitude and frequency of contractions of pregnant rat myometrium *in vitro*. All drugs had an inhibitory effect on contractions. Local anesthetics may help to reduce myometrial contractile activity clinically but further studies are required to verify this possibility both in experimental animals and in pregnant women.

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Received: April 24, 2002; in revised form: July 30, 2002.