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ORIGINAL ARTICLE

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5-HT3 receptor antagonists do not alter spontaneous contraction of pregnant myometrium in vitro

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ABSTRACT
Background: 5-HT3 receptor antagonists are effective antiemetics for perioperative use. However, their effects on myometrial contractility remain unknown. We examined whether three different 5-HT3 receptor antagonists could affect the contraction of human myometrium.
Methods: Samples of human myometrium were taken from parturients undergoing elective cesarean delivery. Effects of ondansetron, granisetron and tropisetron (over a range of $1–10^4$ ng/mL) on spontaneous contraction (ratios of amplitude, interval, and duration of the contraction) were examined and compared to saline controls (n=6 for each agent).
Results: None of the three 5-HT3 receptor antagonists significantly affected myometrial contraction.
Conclusion: 5-HT3 receptor antagonists do not affect the contraction of myometrial strips isolated from term pregnant women.

Keywords: 5-HT3 receptor antagonists; Myometrium; Term pregnancy

Introduction

Nausea and vomiting occur in 60–80% of parturients receiving neuraxial anesthesia for cesarean delivery.[1] Selective 5-HT3 receptor antagonists, such as ondansetron, granisetron and tropisetron, act on both peripheral and central 5-HT3 receptors,[2–4] and are effective perioperative antiemetic agents in parturients.[5] 5-HT3 receptors are primarily located in vagal afferents in the gut and regions of the central nervous system (CNS) that are involved in emesis, including the chemoreceptor trigger zone and the nucleus tractus solitarii.[6] Inhibition of 5-HT3 receptors reduces acetylcholine (ACh) release from parasympathetic nerve terminals, and subsequently decreases motility of gastrointestinal (GI) smooth muscle.[7] In addition, 5-HT3 receptor antagonists have been used for intrathecal fentanyl-induced pruritus.[5,8,9] Whether 5-HT3 receptor antagonists affect contraction of isolated human pregnancy myometrium remains unknown.

The uterus is mainly innervated by sympathetic and parasympathetic nerves (the vagus, pelvic, and sacral nerves);[10] these autonomic nerves mediate uterine contraction via α,β-adrenergic and cholinergic receptors. Cholinergic receptor antagonists completely inhibit stimulated uterine contraction, while α-noradrenergic antagonists do so only partially in non-pregnant rats,[11] indicating that post-ganglionic cholinergic nerves play a more prominent role in uterine contraction than the adrenergic component.

It appears that the 5-HT system has synergistic function with the cholinergic system. 5-HT potentiates the vagal negative chronotropic effect on cardiac function,[12] and can excite striatal cholinergic interneurons.[13] A series of rodent and human studies have established that the 5-HT system is an endogenous regulator of myometrial contractility. Activation of some other 5-HT receptor subfamilies, such as 5-HT2A, 5-HT2B, 5-HT1A and 5-HT7, can stimulate the contraction of uterine strips.[14–17] However, currently, there is a lack

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of direct evidence for the presence of 5-HT3 receptors in the uterus. The only evidence being that ICS205930, a potent 5-HT3 receptor antagonist, produces rightward shifts of the concentration–response curves of 5-HT-induced uterine contractions in rats.[18] We hypothesized that 5-HT3 receptor antagonists inhibit uterine contraction by indirect suppression of the uterine cholinergic system and/or direct inhibitory action on myometrium. The present study was designed to examine the potential effects of the 5-HT3 receptor antagonists, ondansetron, granisetron and tropisetron, on contraction of isolated myometrial strips of parturients at term.

Methods

All parturients provided written informed consent for participating in the study. Acquisition and use of tissue specimens were approved by the local Ethics Committee at the authors' affiliated institution (2012001) and were carried out in accordance with established institutional and national ethical guidelines regarding the use of human tissue for research. The study was registered with the Chinese Clinical Trial Registry (ChiCTR-ORC-12002210).

Myometrial tissue specimens were obtained from 24 ASA I and II term parturients who underwent elective cesarean delivery. Exclusion criteria were: lack of consent; prior exposure to oxytocin and 5-HT3 receptor antagonists; history of drug allergies or adverse reaction to 5-HT3 receptor antagonists; labor induction or augmentation medications; and obstetric and/or medical comorbidities including preeclampsia, cardiac, renal, neurological or other systemic diseases (e.g. a history of GI tract obstruction).

Tissue preparation was based on previous studies.[19–21] Parturients underwent spinal anesthesia for cesarean delivery. After delivery of the fetus and placenta, and before oxytocin administration, a small piece of the myometrium was removed from the upper midline portion of the uterine incision in the lower uterine segment. The tissue specimen was immediately placed in pre-chilled Krebs buffer (composition in mM/L: NaCl 119, KCl 4.7, $NaHCO_3$ 25, KH_2PO_4 1.2, $CaCl_2$ 2.5, $MgSO_4$ 1.5, glucose 11) and transferred to the laboratory within 30 min. Longitudinal myometrial strips (approximately $10 \times 3 \times 3$ mm) were suspended using a 40-μm Tungsten wire in a myograph organ bath chamber (model HV-4; Chengdu Tme Technology Co, Ltd, China) containing Krebs buffer at 37°C and saturated with 95% O_2 and 5% CO_2. The myometrial strip was suspended on the adjustable arm with the Tungsten wire at one end and to a force transducer at the other. Myometrial strips were equilibrated for 30 min with a resting tension of 2 g, which has been found to be optimal.[20–22] Stable contraction of the myometrium was defined as the appearance of three stable consecutive contractile waveforms. The experiments with 5-HT3 receptor antagonists started after a stable pattern of contraction (at least three identical consecutive contractile waveforms) was established. Six myometrial strips were used to test each of the following agents: ondansetron, granisetron, and tropisetron, at increasing concentrations of 1, 10, 10^2, 10^3 and 10^4 ng/mL. Saline control was carried out using the remaining six myometrial strips. Each new dose was added after achieving at least three stable consecutive contractile waveforms.

The contraction (tension increase) was recorded using a computer-based data acquisition system (BL-420F Biological Data Acquisition & Analysis System, Chengdu Tme Technology Co, Ltd, China)[23,24] that enabled data capture every second. As described in our previous study, uterine contraction activity, including amplitude, duration and interval, was recorded.[19] After spontaneous contractions were stable, the contractile amplitude was measured from baseline to the top of the contraction waveform peak, the contractile interval was calculated from the end of the previous contraction waveform to the start of the next contraction waveform, and the duration was defined from the start to the end of a contraction waveform (Fig. 1). All results (including contractile amplitude, interval and duration) are presented as the percentage of baseline measurement. The first stable spontaneous contraction was defined as the baseline. The mean ratios of the three consecutive contractile waveforms were calculated and are presented as mean ± standard deviation (SD).

Statistical analysis

Statistical analyses were performed using SPSS statistical software 13.0 (IBM, SPSS Inc., Chicago, IL, USA). Results for each agent were analyzed independently using one-way analysis of variance (ANOVA), followed by Student–Newman–Keuls (SNK) test for pairwise comparison if necessary. $P < 0.05$ was considered to be statistically significant.

Results

Our pilot experiments using saline control showed that the spontaneous contraction of the myometrial

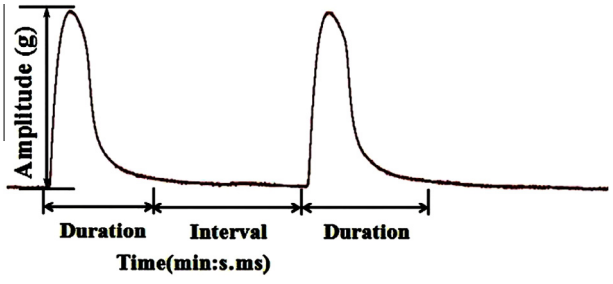

Fig. 1 Definition of myometrial contractile amplitude, interval and duration