Clarithromycin Inhibits Myometrial Contractions in Isolated Human Myometrium Independent of Stimulus

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Summary

Erythromycin has a well-known dual effect on the contractility of the gastrointestinal system and recently has also been shown to inhibit contractions of the rat myometrium. The aim of the present study was to investigate the effects of clarithromycin on oxytocin, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and KCl-induced contractions of human myometrium *in vitro*. Myometrial strips were obtained from pregnant women undergoing elective Cesarean section and the strips were suspended in a jacketed organ bath filled with Krebs solution at 37 $^{\circ}$C (pH 7.4) and continuously aired with 95 % oxygen and 5 % carbon dioxide. Isometric contractions were measured using a force displacement transducer. Oxytocin, $PGF_{2\alpha}$, KCl and clarithromycin were applied to the tissue bath and the amplitude and frequency of contractions were evaluated at 20-min intervals. Freidmann analysis of variance, Kruskal Wallis and Wilcoxon Rank tests were used for statistical analysis of the data. Clarithromycin dose dependently inhibited the amplitude of contractions independent of the stimulus. Pre-treatment with apamin prevented clarithromycin-induced effects on amplitude and frequency of contractions. We conclude that the macrolide antibiotic clarithromycin may have a direct inhibitory effect on contractions of human myometrium.

Introduction

It is well established that the macrolide antibiotic erythromycin has a dual effect on the contractility of smooth muscle. In smooth muscles of the stomach and duodenum, it has a stimulatory effect that was suggested to be mediated by motilin receptors (Peeters *et al.* 1989, Collard *et al.* 1999). It also has a direct inhibitory effect in guinea-pig and human gallbladder, the rat urinary bladder smooth muscle (Nissan *et al.* 1999), in the longitudinal smooth muscle of the guinea-pig small intestine (Minocha *et al.* 1991) and in bronchial smooth muscle (Tamaoki *et al.* 1995). However, the exact mechanism of inhibition induced by erythromycin is not known. Furthermore, a recent study has reported that erythromycin inhibits myometrial contractions of rat independent of stimulant (Granovsky-Grisaru *et al.* 1998). Since structural analogs of erythromycin are not antibiotic but are prokinetic, the modulatory effect of erythromycin on smooth muscles contractions is not

related to its antimicrobial activity (Omura *et al.* 1987). Clarithromycin is the new member of the macrolide family of antibiotics with a broad spectrum of activity *in vitro* against clinically important gram-positive and gram-negative aerobes and anaerobes. The modulatory effect of clarithromycin on contractility of smooth muscle has been poorly studied compared to erythromycin, with the exception of one study evaluating its effect on myometrial contraction.

The aim of the present study was to investigate whether clarithromycin has any similar effect as its progenitor, erythromycin, on myometrial contractility. To our knowledge, our study shows for the first time the inhibitory effects of clarithromycin using human isolated myometrium.

Methods

The protocol of this study was approved by the Firat University Local Ethics Committee for Research on Human Subjects and a written informed consent was obtained from each subject donating a tissue sample. Patients undergoing elective Caesarean section, gestation period of 37-42 weeks, in the Department of Obstetrics and Gynecology at The Firat University Medical Center were included in this study. Patients with medical problems, including diabetes, hyperthyroidism, hypertension, pre-eclampsia or connective tissue diseases were excluded from this study. None of the subjects were under any regular medication. Socio-demographic characteristics of sample donating patients are given in Table 1. Two myometrial strips were used from each patient.

A single full-thickness myometrial strip was removed from the upper margin of the lower uterine segment incision at the time of the Caesarean section after the infant had been delivered. The strip was than immediately placed in a Krebs' solution. Small strips (10 x 2 x 2 mm) of myometrial tissue were cut from uterine samples. Each strip was placed in a 20 ml jacketed tissue bath containing Krebs' solution at 37 ^{0}C and pH 7.4. The composition of the Krebs' solution was (in mmol/l): sodium chloride 121, potassium chloride 4.5, sodium bicarbonate 15.5, sodium phosphate 1.2, calcium chloride 2.5, magnesium chloride 1.2, and glucose 11.5. The Krebs' solution was constantly gassed with 95 % O_2– 5 % CO_2. A silk thread was used to attach the myometrial strips to a fixed hook and an isometric force displacement transducer (Harvard Apparatus Limited, Kent, England).

Table 1. Socio-demographic characteristics of sample donating patients (n=150).

	Mean ±S.D.	**Max - Min**
Age (years)	28.7±6.6	39-19
Number of pregnancies	2.6±1.3	5-1
Number of births	2.1±0.7	3-1
Number of aborts	1.9±0.4	3-0
Gestational age (days)	271.1±7	280-260

The contractile activities were recorded using a Harvard Universal Oscillograph (Harvard Apparatus Limited, Kent, England). The myometrial strips were initially placed under 2.0 g tension and a 90-min equilibration period was allowed before the start of each experiment. Most of the strips developed spontaneous contractions within 30 to 90 min and strips with no spontaneous activity in this period were discarded. After development of spontaneous contractions 800 mU/l oxytocin, $PGF_{2\alpha}$ (1 μM) or KCl (30 mM) was applied to amplify these contractions.

The amplitude of contractions was evaluated at 20 min periods before (control) and after application of clarithromycin. The first minute of the control period was taken as the starting point for this comparison. The mean amplitude of the contractions under control conditions and after application of clarithromycin were determined and compared. The frequencies of contractions were also evaluated at 20 min intervals before and after application of clarithromycin. In some experiments, after amplification of spontaneous contractions with agonists (oxytocin, $PGF_{2\alpha}$ or KCl), apamin was applied for 5 min before clarithromycin application.

The agents used in the present study included clarithromycin lactobionate (Abbot Laboratories, intravenous injection, Wiesbaden, Germany), oxytocin (Synpitan iv, 5IU/ml, Deva, Istanbul, Turkey), $PGF_{2\alpha}$, KCl (Sigma) and apamin (Alomone Labs, Israel).

Statistical analysis: The results are expressed as means ± S.D. All statistical analysis was performed using the statistical program SPSS for Windows (version 6.0.1, SPSS Inc. Chicago, Illinois).

Statistical analysis was performed using Wilcoxon Rank test. Figures were made using Origin version 5.0 (Microcal Software Inc. Northampton, USA).
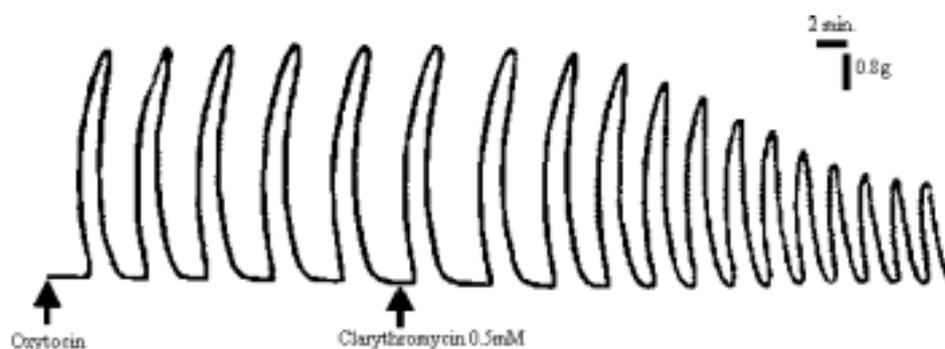
Fig. 1. *Representative tracing showing the effect of 0.5 mM clarithromycin on oxytocin-induced myometrial contractile activity reported in grams of tension generated. Spontaneous contractions were noted during period preceding 20-min time point; subsequently oxytocin and clarithromycin was applied at points indicated by the arrow.*

Results

A total of 300 myometrial strips from 150 patients were used in this study. 284 out of these strips developed spontaneous contractions (in 95 % cases).

Each dose of clarithromycin was tested on 30, 20, and 10 myometrial strips contracted by oxytocin, $PGF_{2\alpha}$, or KCl, respectively.

Myometrial strips were contracted by application of oxytocin (800 mU/l), $PGF_{2\alpha}$ (1 μM) and KCl (30 mM). The mean peak amplitude and frequency values after each agonist and the dose-dependent effects of clarithromycin on these parameters are given in Table 2.

The effect of clarithromycin was dose dependent. 0.1 mM clarithromycin had no significant effect on either parameter of agonist-induced contractions (Tabs. 2, 3, p>0.05). The inhibition of the amplitude and increased frequency of contractions were significant after application of 0.2 mM clarithromycin (Tabs. 2, 3, p<0.05).

The inhibitions of the amplitude of oxytocin-induced contractions were 5 %, 15 %, and 44 % after applications of 0.2 mM, 05 mM (Fig. 1) and 1 mM clarithromycin, respectively (Tab. 2). The effects of 0.2

Table 2. Dose-dependent effects of clarithromycin on peak amplitude of agonist-induced (oxytocin, $PGF_{2\alpha}$ or KCl) myometrial contractions.

Drug	Oxytocin			$PGF_{2\alpha}$			KCl		
	Control	Cla	P	Control	Cla	P	Control	Cla	P
0.1 mM Cla	4.4 ± 0.5	4.2 ±0.2	>0.05	4.4±0.5	4.1±0.3	>0.05	4.4±0.3	4.3± 0.2	>0.05
0.2 mM Cla	4.1 ± 0.3	3.5 ± 0.3	<0.05	4.2 ± 0.2	3.7 ± 0.2	<0.05	4.2 ± 0.2	3.6 ± 0.2	<0.05
0.5 mM Cla	4.4 ± 0.3	2.5 ± 0.7	<0.05	4 ± 0.4	2.6 ± 0.5	<0.05	4.1 ± 0.6	2.7 ± 0.7	<0.05
1 mM Cla	4.3 ± 0.2	2.1 ± 0.4	<0.05	4.1 ± 0.6	2 ± 0.7	<0.05	4.2 ± 0.7	1.5 ± 0.5	<0.05
Lactobionat	4.3 ± 0.1	4.0 ± 0.6	>0.05	4.4 ± 0.3	4.2 ± 0.4	>0.05	4.3 ± 0.6	4.2 ± 0.4	>0.05
Apamin + 1 mM Cla	4.4 ± 0.3	4.2 ± 0.6	>0.05	4.2 ± 0.3	4.1 ± 0.5	>0.05	4.3 ± 0.4	4.1 ± 0.3	>0.05

Cla: clarithromycin, $PGF_{2\alpha}$: prostaglandin $F_{2\alpha}$, KCl: potassium chloride. Data are presented as mean ± SD (each dose of clarithromycin was tested on n= 30 strips for oxytocin-induced, n= 30 strips for $PGF_{2\alpha}$-induced and n= 10 strips for KCl-induced contractions, lactobionat was tested on n=7 strips for each agonist, apamin+ 1 mM clarithromycin was tested on n=8 strips for each agonist), p<0.05 statistically significant.

mM, 0.5 mM, and 1 mM clarithromycin enhanced the frequency of oxytocin-induced contractions by 24 %, 66 % and 79 %, respectively (Tab. 3).

The effects of clarithromycin on the $PGF_{2\alpha}$-induced contractions led to a 7 %, 12 % and 55 % decrease in amplitude (Tab. 2), while an increase of

29 %, 59 % or 83 % of frequency was found for 0.2, 0.5 and 1 mM, respectively (Tab. 3).

When 0.2 mM, 0.5 mM and 1 mM clarithromycin was applied to myometrium contracted with KCl there was an inhibition in amplitude of 18 %, 36 % and 65 % (Tab. 2), and an increase of 12 %, 47 % and 59 % in frequency of contractions (Tab. 3).

When lactobionat, the vehicle of clarithromycin, was applied in comparable concentrations (1 mM), it had no significant effect on either amplitude or frequency of agonist-induced contractions of myometrium (n= 7 for each agonist, Tabs. 2, 3).

Additional experiments were performed to investigate the possible role of Ca^{2+}-activated K^+ channels on the inhibitory action of clarithromycin on the amplitude of agonist-induced contractions using apamin. For these experiments, 1 mM dose of clarithromycin were applied on oxytocin, $PGF_{2\alpha}$ or KCl-induced contractions. After pre-treatment with apamin (1 µM) for 5 min, application of clarithromycin had no significant effect on amplitude and frequency of contractions independent of stimulant (n=8 for each agonist, Tabs. 2, 3).

Table 3. Dose-dependent effects of clarithromycin on frequency of agonist-induced (oxytocin, $PGF_{2\alpha}$ or KCl) myometrial contractions.

Drug	Oxytocin			$PGF_{2\alpha}$			KCl		
	Control	Cla	*P*	Control	Cla	*P*	Control	Cla	*P*
0.1 mM Cla	5.5 ± 0.5	6.1 ± 0.4	>0.05	5.5 ± 0.4	6.0 ± 0.4	>0.05	5.6 ± 0.5	5.7 ± 0.5	>0.05
0.2 mM Cla	5.3 ± 0.3	6.6 ± 0.3	<0.05	5.2 ± 0.3	6.7 ± 0.3	<0.05	5.6 ± 0.3	6.6 ± 0.3	<0.05
0.5 mM Cla	5.1 ± 0.4	8.5 ± 0.5	<0.05	5.4 ± 0.5	8.6 ± 0.4	<0.05	5.7 ± 0.2	8.4 ± 0.4	<0.05
1 mM Cla	5.8 ± 0.6	10.4 ±0.7	<0.05	5.5 ± 0.3	9.9 ± 0.7	<0.05	5.5 ± 0.9	10.4 ± 0.7	<0.05
Lactobionat	5.4 ± 0.4	5.3 ± 0.4	>0.05	5.7 ± 0.4	5.5 ± 0.4	>0.05	5.6 ± 0.4	5.7 ± 0.2	>0.05
Apamin + 1 mM Cla	5.6 ± 0.5	5.2 ± 0.3	>0.05	5.8 ± 0.3	5.3 ± 0.4	>0.05	5.4 ± 0.3	5.5 ± 0.3	>0.05

Cla: clarithromycin, $PGF_{2\alpha}$: prostaglandin $F_{2\alpha}$, KCl: potassium chloride. Data are presented as mean ± SD (each dose of clarithromycin was tested on n= 30 strips for oxytocin-induced, n= 30 strips for $PGF_{2\alpha}$-induced and n= 10 strips for KCl-induced contractions, lactobionat was tested on n=7 strips for each agonist, apamin+1 mM clarithromycin was tested on n=8 strips for each agonist). Frequency reflects number of contractions in 20 minute-periods. p<0.05 statistically significant.

Discussion

The data presented in this study demonstrate the ability of clarithromycin to inhibit oxytocin, $PGF_{2\alpha}$, and KCl-induced contractile activity of uterine tissues from pregnant women at term. However, clarithromycin also caused an increase in frequency of contractions independently of stimulant. The inhibitory effect of clarithromycin was dose dependent, significant inhibition on peak amplitude started after 0.2 mM whereas 0.1 mM had no significant effect either on amplitude or frequency.

Previous studies have shown inhibitory effects of antibiotics on myometrial contractions. The finding of the inhibitory effect of erythromycin on rat myometrial contractions by Granovsky-Grisaru *et al.* (1998) was the starting point of the present study. Similarly, there are

reports about inhibitory effects of neomycin, gentamycin and clindamycin on myometrial contractions induced by oxytocin, KCl or aluminium fluoride (Phillipe 1994, Kadanalı *et al.* 1996).

The finding of inhibition at peak amplitude of myometrial contractions by clarithromycin is consistent with a result of the previous study where other macrolide erythromycin was used (Granovsky-Grisaru *et al.* 1991). However, contrary to erythromycin, clarithromycin increased the frequency of contractions. This may be due to species differences but there may also be a mechanistic difference involved. Similar to clarithromycin, erythromycin inhibited the amplitude but increased the frequency of oxytocin-induced contractions in isolated pregnant human myometrium (Celik *et al.* 2001). Another possible explanation of the different effects of these two macrolides could be due to the different uterus

parts being studied. We obtained myometrial samples from the lower uterine segment whereas Granovsky-Grisaru *et al.* (1991) used the uterine horns. However, the explanation by anatomical difference is not very convincing because there were no significant differences in the contractile rate and force production produced by myometrium from the upper and lower segments when biopsies were obtained from women undergoing classical Caesarean section (Luckas *et al.* 2000).

The inhibitory activity of clarithromycin in the uterine tissue may be the result of activation of adenylate cyclase, but also from other effects such as the opening of potassium channels and a decrease of intracellular free Ca^{2+} levels (Wray 1993). Although no direct evidence is available, it is also possible that clarithromycin may inhibit Ca^{2+} entry through the L-type calcium channels and thereby cause inhibition of amplitude of agonist-induced myometrial contractions (Kaya *et al.* 1999, Sanborn 2001). Inhibition of KCl-induced contractions by clarithromycin provides evidence for the latter hypothesis.

Clarithromycin inhibited myometrial contractions induced by oxytocin, $PGF_{2\alpha}$, and KCl suggesting that the effect of clarithromycin is independent of the stimulant. High concentrations of KCl induce contractions by membrane depolarization and a subsequent increase in free intracellular Ca^{2+} concentration resulting from influx *via* membrane Ca^{2+} channels (Wray 1993, Trujillo *et al.* 2000). Oxytocin causes increase in intracellular free Ca^{2+} mediated by inositol 1,4,5-triphosphate (IP_3) formation while prostaglandins increase intracellular free Ca^{2+} via voltage or receptor-operated Ca^{2+} channels (Wray 1993). The only evidence relating the mechanism underlying the inhibitory effect of clarithromycin was that the specific Ca^{2+}-activated K^+ channel blocker apamin prevented the inhibitory effect of clarithromycin on oxytocin-induced contractions suggesting involvement of Ca^{2+}-activated K^+ channels. These channels are reported to play important role in modulation of uterine contractility (Anwer *et al.* 1993).

We have no explanation for the increase in frequency of contractions after clarithromycin application. This could be the result of increased pacemaker activity that is considered to be related with T-type Ca^{2+} channels (Wray 1993). But the amplitude of contractions gradually decreased (Fig. 1). Since apamin prevented the inhibitory effect of clarithromycin, it seems likely that this is related to the increase in frequency and inhibition *via* activation of Ca^{2+}-activated K^+ channels. Clarithromycin may be activating the T-type calcium channels and the resultant increase in free intracellular Ca^{2+} may in turn activate the Ca^{2+}-activated K^+ channels.

The inhibitory effects of clarithromycin on the contractility found in this study made us to consider the possibility that this could be used in the treatment of preterm labour. There are some limitations regarding this point. Firstly, the dose of clarithromycin used in this study is higher than the levels achieved after its therapeutic administration (its peak plasma concentration is 2.4 µg/ml after a 500-mg oral dose) (Cheng *et al.* 1998). Secondly, the use of clarithromycin in pregnancy has not been studied thoroughly and available data on clarithromycin are too limited for recommendation its use during pregnancy. It was found in a study performed on a restricted population of patients that clarithromycin increased spontaneous miscarriage in the first trimester without any evidence of teratogenic actions (Einarson *et al.* 1998). Further studies need to be performed in order to determine the effects of clarithromycin in this respect and relation to the gestational age should be addressed. There is no report in the literature about the effects of clarithromycin on the contractility of smooth muscles.

In conclusion, we have shown for the first time the inhibitory effects of clarithromycin on agonist-induced contractions of the isolated myometrium from pregnant women.

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