Effects of Tulathromycin (Draxxin) on Contractility of Isolated Myometrium in Rats

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Abstract: Tulathromycin that used as trade name of Draxxin in market is an active part of drug and belonged to new macrolide classes named triamilides, this drug has been using in veterinary broadly. In this study (interventional & descriptive)about 84 female Wistar rats (250-300 g) were selected and divided to 14 groups (n=6). In first group; oxytocin plus Tulathromycin and in second group KCl plus Tulathromycin were used. Probably Tulathromycin blocks the entrance of calcium and calcium dependent contraction pathway in the uterus. The effects of Tulathromycin are reversible and dose dependent. In the existence of Tulathromycin the dose responsive curve of calcium contraction reduced significantly (p<0.05). The result of this study showed that Tulathromycin can used for treatment of preterm labour and inhibition of parturition.Indeed the approving of abovementioned hypothesis in clinical trials needs to more investigation because the actual dosage of drug and pregnancy induced side effects must be recognized.

Key words: Tulathromycin • Uterus • Rat

INTRODUCTION

Macrolids have a significant importance in controlling of infectious and inflammatory diseases especially pneumonia which is resistant to treatment as well as other clinical cases such as increasing digestive tract in diabetic patients who have gastropathy, treatment and controlling the Idiopathic Preterm Labor as a tocolytic drug, treatment of asthma due to anti-inflammatory and anti-bacterial nature [1, 2]. Recently, they have been used as controlling compounds of tissue metalloproteinase level in preventing of heart graft failure in rats [1, 2]. It has been clear in clinical studies that macrolidic antibiotics, especially erythromycin, have twin effects on arrector pili muscles' contractibility. It has stimulus effect on arrector pili muscles of stomach and duodenum and it seems that this process is done by mutilin receivers [3-5]. Erythromycin has direct controlling effects on human's and pig's gall bladder and arrector pili muscles of rat's urinary system [6-9]. Also; in pigs' linear intestinal muscle [9] and bronchial arrector pili muscles [10] has controlling and loosening effect on animal. Besides, claritromycin has relaxing effect on rat's arrector pili muscles of uterus [11]. Tulathromycin is a semi-synthetic macrolide of tri amilid subgroup which is important as a primary treatment in pneumonia controlling. With regard to twin effects of macrolids in occurrence of different behaviors in arrector pili muscles' kinetic, especially uterus muscles, it seems necessary to clear Tulathromycin effects on uterus as a new macrolide; so that clinical decisions were made by internal professionals.

MATERIALS AND METHODS

In this experimental study 84 Wistar male rat weighing between 250-300 g were collected and then these rats divided into 14 groups (N=6):  

- Oxytocin + Tulathromycin  
- KCL + Tulathromycin  
- Oxytocin + Tulathromycin + Propranolol  
- Oxytocin + Tulathromycin + Tetraethylammonium  
- Oxytocin + Tulathromycin + Glibenclamide  
- Oxytocin + Tulathromycin + Nifedipine

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Preparation of Uterus Smooth Muscles: A female Wistar rat of 250-300 g was injected subcutaneously with Estradiol valerat (0.1 mg/kg) was killed using ether. A scission was created in abdomen region and two parts of tissue were separated. The fats of tissue were separated and a longitudinal fissure was introduced in tissue. Endometrium was left out in some tissue but was removed in others by mechanical method. After preparing the tissue a thread was tied to upper end and another thread to lower end of the tissue and transferred to the bath. The lower thread was connected to a fixed place in the bath and the upper one was connected to Grass FT03C transducer; so a 1g base tone will be created in tissue. The tissue contractions were recorded using Grass 7D.

Statistical Analysis: The results were expressed in mean ± S.E.M. The obtained results from contractions of isolated uterus tissue in physiologic serum were assigned as control curve. The difference between control and test curves was distinguished using ANOVA statistical test, Post test, Tukay's, Unpaired t-test and P<0.051 has been assigned meaningful for each point.

RESULTS AND DISCUSSION

In general, the results of the present study demonstrated that Tulathromycin in the form of dose-dependent suppress or inhibiting contracting reaction arising from potassium chloride induction on rat's isolated uterus which in this case the effective dosage is 50% drug equal to 6.417±0.477. By linear regression analysis the 50% effective dosage of the drug was identified and the dependence and relationship between dosage and reaction (R=0.954) is 6.417±0.477. In the rest of the study 50% effective dosage of the drug was selected for examining the drug effective mechanism; then its elaxing effect was evaluated at the at the presence of effective dosage of Tulathromycin the dose-response calcium-free media in uterus isolated tissue was depicted and compared with control group. The results show that Tulathromycin shifts the dose-response curve to the right which is significant in some of calcium chloride dosages (P<0.05 and P<0.01). For studying the role of potassium channels the influence of Glibenclamide and tetraethyl ammonium in loosening effect of 50% effective dosage of Tulathromycin was evaluated. Glibenclamide blocks most
of potassium channels in high dosage randomly by potassium channels dependent on ATP and TEA. With regard to the fact that these drugs didn't decrease the rate of reaction to Tulathromycin so it can be concluded that relaxing effect of Tulathromycin is independent of potassium channels. For studying the role of prostaglandins in loosening effect of Tulathromycin, the effect of Tulathromycin was evaluated in the presence of indomethacin; therefore indomethacin did not decrease meaningfully the rate of relaxing effect reaction arising from Tulathromycin on created contraction by potassium chloride (80 mMol). Then, prostaglandins don't have a role in loosening effects of Tulathromycin. Regarding beta receivers effective in Tulathromycin's loosening mechanism it can be claimed that there are β₂ receivers in uterine tissue that their stimulation leads to relaxation of uterine tissues. In order to evaluate the role of these receivers, the loosening effect of Tulathromycin on contraction arising from potassium chloride in the presence of propranolol, which is a non-selective beta blocker, was evaluated and it was observed that inedral can’t decrease contractive reaction of Tulathromycin, meaningfully. Probably, Tulathromycin decreases the rate of calcium entrance and contractive reaction to calcium in uterine tissue. It seems that Tulathromycin has dose-dependent effects and the effects are returnable. The dose-response curve in the presence of Tulathromycin decreases meaningfully in the case of administrating some drugs. Furthermore, the results of the present study demonstrate that Tulathromycin removes contractive response arising from oxytoxin induction in rat's uterine muscle as a dose-dependent factor. The most important result of the present study was that Tulathromycin can decrease the contraction frequencies besides decreasing of contractions amplitude. In general, uterus is an automatic active organ i.e. doesn't require the hormonal and neural stimulations for movements and a section of pregnant or non-pregnant animal can ever produce some automatic and sudden contractions [13].

The results of the present study demonstrated that Tulathromycin can decrease contractions of isolated uterus of rat in the form of dose-response and consequently leads to fatigue of the uterine muscle contraction to weakness the uterus function. There are most previous studies about the controlling effect of antibiotics on myometrium contractions, for instance, in a study conducted by Grisaru-Granovsky et al., it was cleared that erythromycin can induce the controlling effects in rat's uterus, too [11]. In the present study Tulathromycin has identical effect such as erythromycin i.e. causes uterus loosening that conforms to the results of other researchers. In similar studies, also, there are some reports about controlling effects of antibiotics, e.g. in the studies conducted by Phillipe in 1994 and Kadanali in 1996 it was reported that neomycin, gentamycin, clindamycin control the uterus contractions induced by oxytoxin, potassium chloride or fluoride aluminum [14, 15]. It seems that may be the controlling effect of Tulathromycin on uterus contractions arising from adenil syclasia but other effects such as opening the potassium channels and decrease of intracellular calcium are effective in relaxing process of arrector pili muscles of uterus following administration of Tulathromycin [13].

According to the statements of Kaya, 1999 and Sanborn, 2001, there are indirect evidences that very likely Tulathromycin prevents calcium entrance to cytoplasm of uterus arrector pili muscles via controlling the L calcium channels which results in decreasing the amplitude of uterine contractions [15, 16]. Another strong theory that can be mentioned accounting for controlling effects of Tulathromycin, is that Tulathromycin or draxxin can block
CONCLUSION

In conclusion it can be said that controlling effects obtained by administration of Tulathromycin on uterus tissue are helpful in treatment of preterm labour. In any case the claim of such a clinical finding may have some limitations due to various reasons; the last considered dosage, for example, for this purpose must be designed. Also probable side-effects of the drug during pregnancy must be studied. In any case in the present study, for the first time, it was cleared that Tulathromycin or draxxin contains controlling effects on contractions of rat's isolated muscle and causes to rat's uterus myometrium relaxation.

REFERENCES