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Ceftriaxone Reduces Contractility of Isolated Uterine Smooth Muscles of Pregnant and Non-Pregnant Rat

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Abstract: The effects of ceftriaxone on isolated non-pregnant and pregnant rat uterus have been investigated. The isolated uterine horns were mounted into organ bath containing De Jalon's solution connected to an oscillograph with an isotonic transducer to measure the contractions. Ceftriaxone was injected into the organ bath to study the pharmacological effects on the uterine smooth muscles. Trials were performed to locate the site of action of ceftriaxone on rat's uterus and the obtained results revealed that ceftriaxone had a depressant effect on rats at various stages of sex cycle. It had a direct myometrial depressant effect since, presence of acetylcholine in a small concentration (0.25 μg mL^{-1} bath) produced its stimulatory effect in the presence of ceftriaxone 256 μg mL^{-1} bath and 256 μg mL^{-1} bath of ceftriaxone relaxed the uterus after its stimulation with propranolol 1 μg mL^{-1} bath.

Key words: Ceftriaxone, isolated, uterus, pregnancy, rat, oscillograph, Egypt

INTRODUCTION

Ceftriaxone is a broad spectrum cephalosporin resistant to various types of β-lactamases with potent activity against gram-positive and negative bacteria including Enterobacteriaceae, *Haemophilus influenzae*, *Streptococcus pneumoniae* and other *Nonenterococcal streptococci*, *Methicillin-resistant staphylococci*, Enterococci, *Pseudomonas aeruginosa* and *Bacteroides fragilis* were typically resistant (Neu *et al*., 1981). The drug acts through inhibition of transpeptidase enzymes responsible for the final step in bacterial cell wall synthesis (Waxam and Strominger, 1982) and has broad stability against beta-hydrolysis (Neu, 1985). In human medicine, ceftriaxone is widely used because of its prolonged terminal half-life (5.4-8.2 h) that allows its prescription on a single administration per day basis (Patel *et al*., 1982; Meyers *et al*., 1983; Ti *et al*., 1984; Zhou *et al*., 1985; Bourget *et al*., 1993). So, expanded informations concerning the pharmacodynamic effects of ceftriaxone will be of benefits to physicians and their patients. The present study was aimed to study pharmacodynamic aspects of ceftriaxone on isolated uterine smooth muscles.

MATERIALS AND METHODS

Drug: Ceftriaxone is a sterile, semisynthetic, broad-spectrum 3rd generation cephalosporin antibiotic for intravenous or intramuscular administration. Ceftriaxone is a white to yellowish-orange crystalline powder which is readily soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol. The pH of a 1% aqueous solution is approximately 6.7. It was produced by Smithkline Beecham for Novartis Pharma Company (Egypt) and has the commercial name Ceftriaxone®.

Perfusion fluids for pharmacological experiments De Jalon's solution:	
Sodium chloride	9.00 g
Potassium chloride	0.42 g
Calcium chloride	0.24 g
Glucose	0.50 g
Sodium bicarbonate	0.50 g
Distilled water	1000 mL

The above mentioned physiological salt solutions were prepared as indicated by Staff members (University of Edinburgh, Department of Pharmacology, 1970).

Chemicals: Acetylcholine chloride (Hoffman-La Roche Company, France). Propranol hydrochrolide (Inderal®, I.C.I, Macclesfield, England).

Devices

Glass jar bath: A glass water bath of about 750 mL capacity fitted into a metal stand in which a movableelectric heater was located to maintain the temperature as requied. An inner glass tube (organ bath) of 40 mL capacity passed through the bottom of the stand and was connected by a T-shaped glass tube.

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Harvard universal oscillographe and transducers: Two channels curvilinear oscillograph (Harvard U.K) with an isotonic transducer (Harvard App. Ltd.) which was employed for recording the effect of ceftriaxone on isolated tissues.

Preparation of rat's uterine smooth muscle: The method described by staff members (University of Edinburgh, Department of Pharmacology, 1970) was used for studying the effect of ceftriaxone on uterine muscle of rats at various stages of sex cycle. In this respect, mature female rats at various stages of sex cycle (estrus, non-estrus, early pregnant and late pregnant) were used where vaginal smear was performed for determination of the stage of sex cycle of the animals (Sharaf, 1954). Animals after being examined were killed, their uteri were dissected out and one uterine horn was suspended in the organ bath containing warm oxygenated De Jalon's solution at 32°C from the bottom end by tying to a glass hook and the top end was tied by a thread to an isotonic transducer using cotton thread. The transducer was coupled to an amplifier driving a direct writing Harvard universal oscillograph. The speed was adjusted to be 0.25 mm sec^{-1}.

The tissues were subjected to a resting tension of 1.0 g, the strips were allowed to equilibrate for approximately 30 min by the change of bath solution every 15 min after that the normal uterine motility was recorded and the effects of graded increased concentrations of ceftriaxone was demonstrated. The site of action of ceftriaxone was also investigated.

RESULTS AND DISCUSSION

The effect of ceftriaxone on isolated rat's uterus were shown in Table 1. The effect of ceftriaxone on isolated rat's uterus at various stages of sex cycle were shown in Fig. 1a-d. Trials were performed to locate the site of action

Table 1: Effect of ceftriaxone on uterine motility of rats at various stages of sex cycle

	Response of uterine motility			
Concentrations (μg mL^{-1} bath)	Non-estrus	Estrus	Early pregnant	Late pregnant
32	No effect	No effect	No effect	No effect
64	Slight inhibition in the force and frequency	Slight inhibition in the force and frequency	Slight inhibition in the force and frequency	No effect
128	Slight inhibition in the force and frequency	Marked inhibition in the force and frequency	Marked inhibition in the force and frequency	Moderate inhibition in the force and frequency
256	Complete relaxation	Complete relaxation	Complete relaxation	Complete relaxation

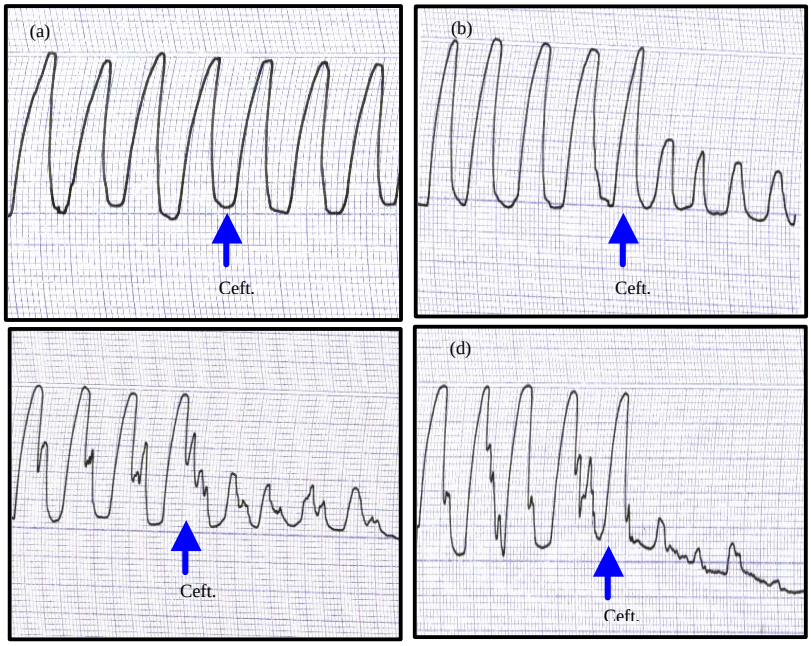

Fig. 1: Effect of ceftriaxone (Ceft.) on isolated rat's uterus: a) 32 μg mL^{-1} bath ceftriaxone (Ceft.) in non-estrus stage; b) 64 μg mL^{-1} bath ceftriaxone (Ceft.) in estrus stage; c) 128 μg mL^{-1} bath ceftriaxone (Ceft.) in early pregnancy stage and d) 256 μg mL^{-1} bath ceftriaxone (Ceft.) in late pregnany stage

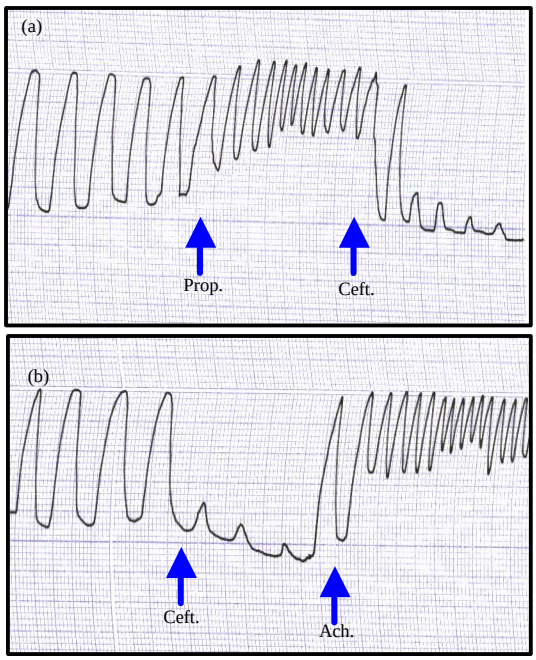

Fig. 2: Site of action of ceftriaxone (Ceft.) on isolated rat's uterus during estrus stage: a) 1 μg mL^{-1} bath propranolol (Prop.) followed by 256 μg mL^{-1} bath ceftriaxone (Ceft.) and b) 256 μg mL^{-1} bath ceftriaxone (Ceft.) followed by 0.25 μg mL^{-1} bath acetylcholine (Ach.)

of ceftriaxone on rat's uterus and the obtained results revealed that ceftriaxone had a depressant effect on rats at various stages of sex cycle. It had a direct myometrial depressant effect since presence of acetylcholine in a small concentration (0.25 μg mL^{-1} bath) produced its stimulatory effect in the presence of ceftriaxone 256 μg mL^{-1} bath and 256 μg mL^{-1} bath of ceftriaxone relaxed the uterus after its stimulation with propranolol 1 μg mL^{-1} bath.

The site of action of ceftriaxone on isolated rat's uterus during estrus stage was shown in Fig. 2a, b. The present investigation showed that ceftriaxone *in vitro* inhibited the contractility of rat's uterus during non-pregnant stages (estrus and non-estrus) and during pregnant stages (early and late pregnancy). The effect was dose dependant.

These effects might be attributed to the direct action of the ceftriaxone on the isolated uterus. During the non- pregnant and pregnant stages, the addition of acetylcholine in a small concentration (0.25 μg mL^{-1} bath) produced its stimulatory effect in the presence of ceftriaxone (256 μg mL^{-1} bath) and the ceftriaxone in the same concentration, relaxed the uterus after its stimulation with 1 μg propranolol mL^{-1} bath. The obtained results were consistent with those recorded by Takai *et al.* (1980) who found that cefeperazone depressed the uterine motility in two of six experiments while during pregnancy they found that cefoperazone might not affected or depressed and/or stimulated the uterine motility. In other observation, Kai *et al.* (1992) recorded that cefepime had no effect on the delivery status of the offspring rats and Takai *et al.* (1982) who found that the spontaneous movement and tone of isolated uterus were not affected following cefbuperazone application. The obtained results during estrus and non-estrus stages were not consistent with those obtained by El-Sayed *et al.* (1997) who recorded that concentrations of 2048 and 4096 μg cefamandole mL^{-1} bath caused marked stimulation in force and frequency of rat uterine muscle in all stages of sex cycle. These differences were explained by Jankovic *et al.* (1996) who proved that effects of β-lactam antibiotics on smooth muscle isolated preparations were tissue and species dependent indicating selectivity of their action.

CONCLUSION

These findings indicated that ceftriaxone had a direct depressant effect on isolated uterine smooth muscles.

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