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EFFECT OF CEFTRIAXONE ON ISOLATED GASTROINTESTINAL, TRACHEAL AND UTERINE SMOOTH MUSCLES

M. G. Elsayed, A. A. Elkomy and M. H. Aboubakr*

Department of Pharmacology, Faculty of Veterinary Medicine, Benha University, Egypt

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Correspondence to Author:

Mohamed Hafez Aboubakr

Assistant lecturer, Department of pharmacology, Faculty of Veterinary Medicine, Benha University, Egypt

ABSTRACT

The pharmacodynamic effect of ceftriaxone on smooth muscles was investigated in isolated organs. Maximum stimulation of isolated guinea pig's ileum, rabbit's duodenum and rat's fundic strip was achieved by addition of 1024 µg of ceftriaxone/ml bath. While in isolated rat's colon, it was achieved by 512 µg of ceftriaxone/ml bath. The effect of graded increased concentrations of ceftriaxone on isolated tracheal muscles and rat's uterine muscles was examined during estrus, non estrus, early pregnant and late pregnant stages. Trials were performed to locate the site of action of ceftriaxone on isolated smooth muscles. It was concluded that, ceftriaxone directly stimulates the smooth muscles of intestines; ceftriaxone in concentration of 1024 µg/ml bath has a serotonin like effect on rat's fundic strip and had a direct myometrial depressant effect. Ceftriaxone in all tested concentrations did not induce any effects on the resting tonus of isolated guinea pig's tracheal chain.

INTRODUCTION: Ceftriaxone is a broad spectrum cephalosporin resistant to various types of beta-lactamases, with potent activity against gram-positive and gram-negative bacteria, including *Enterobacteriaceae*, *Haemophilus influenzae*, *Streptococcus pneumoniae* and other non enterococcal *streptococci*, Methicillin-resistant *staphylococci*, *Enterococci*, *Pseudomonas aeruginosa* and *Bacteroides fragilis* were typically resistant [1]. The drug acts through inhibition of transpeptidase enzymes responsible for the final step in bacterial cell wall synthesis and has broad stability against beta-hydrolysis [2]. 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 [3, 4]. 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 gastrointestinal, tracheal and uterine smooth muscles.

MATERIALS AND METHODS:

Materials:

Drug: Ceftriaxone is a sterile, semisynthetic, broad-spectrum third 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. It was produced by Smithkline Beecham for Novartis Pharma Company (Egypt) and has the commercial name Ceftriaxone®.

Perfusion fluids for pharmacological experiments: The isolated guinea pig's ileum, rabbit's duodenum, rat's colon and tracheal chain were suspended in the organ bath containing warm oxygenated Tyrod‹s solution at 37°C. While rat's fundic strip was suspended in Kreb´s Ringer solution at 37°C and uterine muscles were suspended in De Jalon's solution at 32°C.

The above mentioned physiological salt solutions were prepared as indicated by [5].

Devices:

Glass jar bath: A glass water bath of about 750 ml capacity fitted into a metal stand in which a movable electric heater was located to maintain the temperature as required. 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.

Harvard Universal Oscillograph 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.

Methods: The method explained by [6], was used for studying the effect of ceftriaxone on the isolated ileum of guinea pigs. The method described by [5], was used for studying the effect of ceftriaxone on isolated rabbit's duodenum, rat's colon and uterine muscles of rats at various stages of sex cycle. The effect of ceftriaxone on isolated rat's fundic strip was investigated according to the method described by [7]. The method described by [8], was used for studying the effect of ceftriaxone on isolated guinea pig tracheal smooth muscle using the glass jar bath apparatus.

RESULTS: The effect of ceftriaxone on isolated guinea pig's ileum, rabbit's duodenum, rat's colon and rat's fundic strip and guinea pig's tracheal chain were recorded in **table 1.** The effect of ceftriaxone on uterine motility of female rats at various stages of sex cycle were recorded in **table 2.** Trials were performed to locate the site of action of ceftriaxone on the gasrtointestinal motility and the results showed that, ceftriaxone had a direct intestinal smooth muscles stimulant effect and has a serotonin like effect on rat's fundic strip **(Figure 1).** Ceftriaxone depressed the uterine motility at various stages of sex cycle and these effects might be attributed to the direct effect of ceftriaxone also it had no effect on the resting tonus of the isolated guinea pig's tracheal chain but histamine (60 µg/ml bath) was not able to produce its contractile effect in the presence of ceftriaxone (1024 µg/ml bath) as shown in **figure 2.** This indicated that, cefepime might have an antihistaminic like effect on trachea smooth muscles.

TABLE 1: THE EFFECT OF CEFTRIAXONE ON ISOLATED GUINEA PIG'S ILEUM, RABBIT'S DUODENUM, RAT'S COLON, RAT'S FUNDIC STRIP AND GUINEA PIG'S TRACHEAL CHAIN

Conc. (µg/ml bath)	Responses of				
	Guinea pig's ileum	Rabbit's duodenum	Rat's colon	Rat's fundic strip	G. pig's Tracheal chain
8	No effect	No effect	No effect	No effect	No effect
16	No effect	Slight stimulation in the force	Slight stimulation in the force	No effect	No effect
32	Slight stimulation in the force	Slight stimulation in the force	Slight stimulation in the force	No effect	No effect
64	Slight stimulation in the force	Slight stimulation in the force	Slight stimulation in the force	Slight stimulation in the force	No effect
128	Slight stimulation in the force	Slight stimulation in the force	Marked inhibition in the force and rate of contraction	Slight stimulation in the force	No effect
256	Marked inhibition in the force and rate of contraction	Marked inhibition in the force and rate of contraction	Marked inhibition in the force and rate of contraction	Marked inhibition in the force and rate of contraction	No effect
512	Marked inhibition in the force and rate of contraction	Marked inhibition in the force and rate of contraction	Maximum stimulation	Marked inhibition in the force and rate of contraction	No effect
1024	Maximum stimulation	Maximum stimulation	----------	Maximum stimulation	No effect

(------) Not done

TABLE 2: EFFECT OF CEFTRIAXONE *ON* UTERINE MOTILITY OF RATS AT VARIOUS STAGES OF SEX CYCLE

Concentrations (µg/ml bath)	Response of uterine motility			
	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	Marked 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

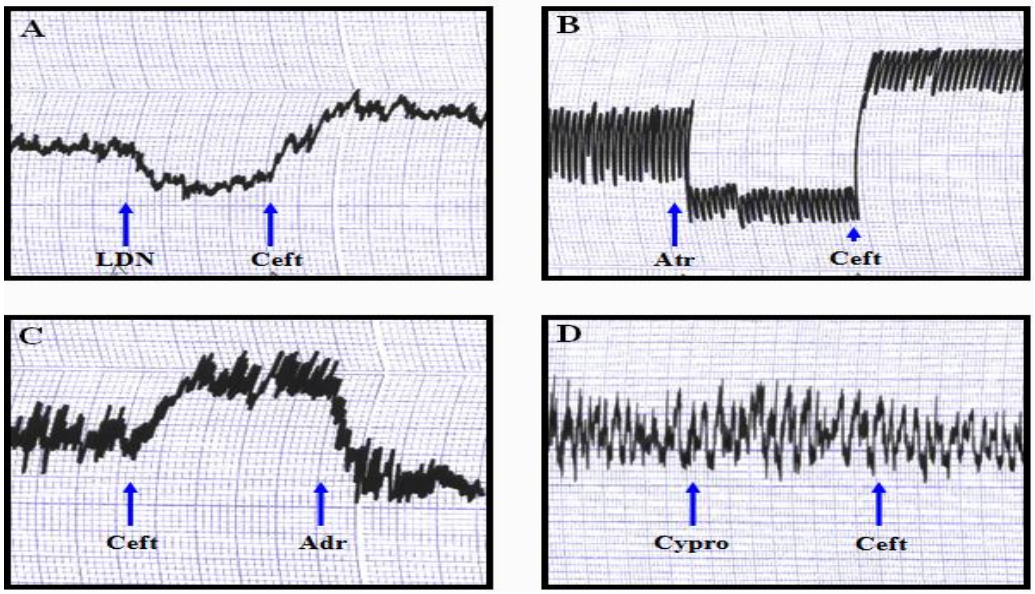

FIG. 1: SITE OF ACTION OF CEFTRIAXONE (CEFT) ON ISOLATED GASTROINTESTINAL MUSCLES

(A) 5 µg/ml bath nicotine sulphate (LDN) followed by 256 µg/ml bath ceftriaxone (Ceft) on isolated guinea pig's ileum. (B) 1µg/ml bath atropine sulphate (Atr) followed by 256 µg/ml bath ceftriaxone (Ceft) on isolated rabbit's duodenum. (C) 256 µg/ml bath ceftriaxone (Ceft) followed by 0.5 µg/ml bath adrenaline (Adr) on isolated rat's colon. (D) Cyproheptadine 5×10^{-6} mmol (Cypro) followed by 1024 µg/ml bath ceftriaxone (Ceft) on isolated rat's fundic strip.

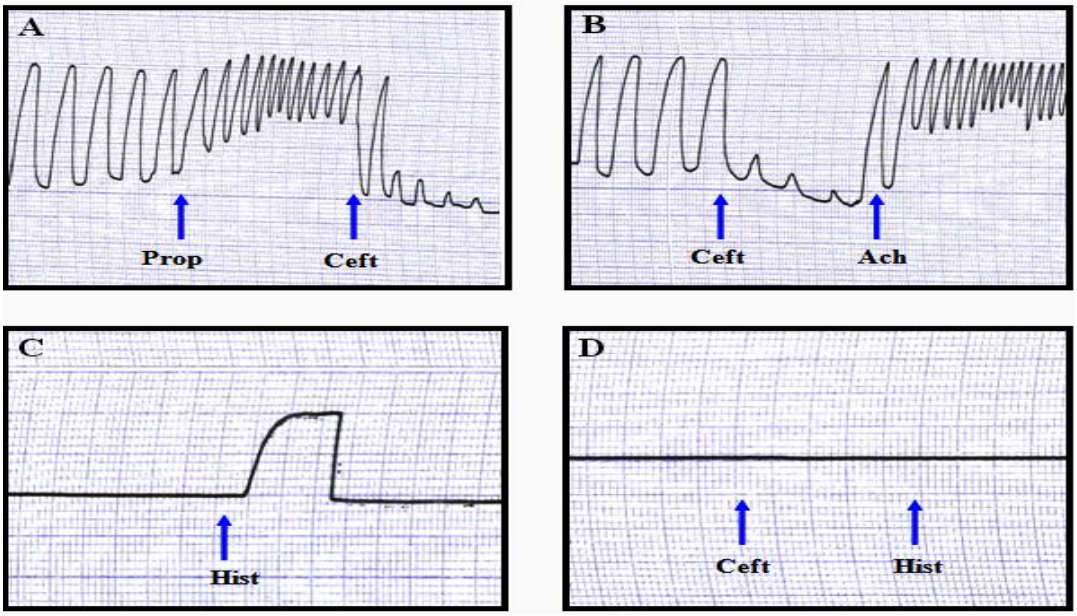

FIG. 2: SITE OF ACTION OF CEFTRIAXONE (CEFT.) ON ISOLATED RAT'S UTERUS DURING ESTRUS STAGE AND GUINEA PIG'S TRACHEAL CHAIN

(A) 1 µg/ml bath propranolol (Prop) followed by 256 µg/ml bath ceftriaxone (Ceft) on isolated rat's uterus during estrus stage. (B) 256 µg/ml bath ceftriaxone (Ceft) followed by 0.25 µg/ml bath acetylcholine (Ach) on isolated rat's uterus during estrus stage. (C) 60 µg/ml bath histamine (Hist) on isolated guinea pig's tracheal chain. (D) 1024 µg/ml bath ceftriaxone (Ceft) followed by 60 µg/ml bath histamine (Hist) on isolated guinea pig's tracheal chain.

DISCUSSION: The present investigation showed that, ceftriaxone *in vitro* stimulated the contractility of guinea pig's ileum, rat's colon and rabbit's duodenum. The stimulatory effect of ceftriaxone was proportional to the graded tested concentrations. Presence of atropine sulphate as muscarinic cholinergic receptor blocker and large dose of nicotine sulphate as ganglionic (Nicotinic receptor) blocker did not inhibit the stimulatory effect of ceftriaxone. In addition, the adrenaline as adrenoceptor agonist produced its inhibitory effect in presence of ceftriaxone.

These results proved that, ceftriaxone might directly stimulate the intestinal smooth muscles of rabbit's duodenum, guinea pig's ileum and rat's colon. These obtained results were similar to those obtained by [9] who found that, cefeperazone *in vitro* enhanced slightly the motility of isolated rabbit's gastrointestinal tract at 0.001 g/ml. Also spontaneous motility of smooth muscle was temporarily increased with 800 mg/kg cefminox when administered intravenously and in upper doses [10].

In contrast, cefprozil did not affect the isolated smooth muscles of rat's uterus, guinea pig's ileum or rabbit's duodenum and did not influence ganglionic transmission in cats [11]. Cefamandole at concentrations of 512 and 1024 micrograms/ml bath caused complete relaxation in isolated guinea pig's ileum and rabbit's duodenum, respectively [12]. Maximum contractile responses to carbachol and histamine were significantly reduced in response to the ceftriaxone sodium [13].

Ceftriaxone stimulated contractility of the rat's fudnic strip. This stimulatory effect was dose dependant. Ceftriaxone in a high concentration produce a serotonin like effect on rat's fundic strip (a sensitive preparation for detection of serotonin). These results might be attributed to the ability of ceftriaxone to release serotonin from its stores. The serotonin stimulating effect of ceftriaxone over come its direct effect on the smooth muscle of rat's fundic strip. The obtained results came in harmony with those obtained by [14] which recorded that, cefotaxime, ceftriaxone and ceftazidime produced concentration-dependent tonic contractions of rat's fundus and [8] found that, cefamandole had stimulatory effect on the rat's fundic strips. On the other hand, ceftizoxime sodium after intravenous dose of 320 to 1000 mg/kg dose-dependently suppressed spontaneous contraction of the pyloric part in morphine-urethane-anesthetized dogs [15].

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 (0.25µg/ml bath) produced its stimulatory effect in the presence of ceftriaxone (256µg/ml bath) and the ceftriaxone in the same concentration, relaxed the uterus after its stimulation with 1µg propranolo/ml bath.

The obtained results were consistent with those recorded by [9] 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, cefepime had no effect on the delivery status of the offspring rats [16], and **[17]** 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 [12] which recorded that, concentrations of 2048 and 4096 micrograms cefamandole/ml bath caused marked stimulation in force and frequency of rat uterine muscle in all stages of sex cycle. These differences were explained by [14] who proved that, effects of beta-lactam antibiotics on smooth muscle isolated preparations were tissue and species dependent, indicating selectivity of their action. The guinea pig's tracheal smooth muscles seemed to be insensitive to the tested concentraions of ceftriaxone. In presence of ceftriaxone, histamine was not able to produce its stimulatory effect.

The obtained results in this study was similar with those obtained by [11, 12] which recorded that, cefprozil and cefamandole respectively in different graded concentrations had no effect on the tracheal smoothe muscles. On the other hand, ceftizoxime and cefminox

relaxed the resting tonus of the isolated guinea pig's tracheal chain preparation [15, 10]. Cefoperazone and cefteram pivoxil respectively caused slight stimulation of the isolated guinea pig's tracheal smooth muscles [9, 18].

CONCLUSION : From the present study it could be concluded that, ceftriaxone had a stimulant effect on gastrointestinal muscles, not affected tracheal smooth muscles at graded concentrations and had a depressant effect on uterine muscles during estrus, non estrus, early pregnant and late pregnant stages.

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