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Effect of Ceftriaxone on Isolated Gastrointestinal Muscles

M.G. Elsayed, A.A. Elkomy and M.H. Aboubakr
Department of Pharmacology, Faculty of Veterinary Medicine,
Benha University, 13736 Moshtohor, Toukh, Qalioubeya, Egypt

Abstract: The pharmacodynamic effect of ceftriaxone on smooth muscles was investigated in isolated organs. Maximum stimulation of isolated guinea pig's ileum and rabbit's duodenum and rat's fundic strip was achieved by addition of 1024 μg of ceftriaxone mL^{-1} bath. While in isolated rat's colon, it was achieved by 512 μg of ceftriaxone mL^{-1} bath. Trials were performed to locate the site of action of ceftriaxone on the guinea pig's ileum, rabbit's duodenum and rat's colon. After blocking the ganglia with large dose of nicotine and addition of atropine sulphate as muscarinic cholinergic receptor blocker, ceftriaxone was able to produce its stimulatory effect. Adrenaline was able to produce its inhibitory effect in presence of ceftriaxone. The above mentioned trials indicated that ceftriaxone might have a direct stimulatory effect on the ileal, duodenal and colon smooth muscles. Ceftriaxone in concentration of 1024 μg mL^{-1} bath has a serotonin like effect on rat's fundic strip.

Key words: Ceftriaxone, gastrointestinal, ileum, duodenum, colon, fundus

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 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 gastrointestinal 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: The isolated guinea pig's ileum, rabbit's duodenum and rat's colon was suspended in the organ bath containing warm oxygenated tyrod's solution at 37°C. While rat's fundic strip was suspended in the organ bath containing warm oxygenated Kreb's ringer solution at 37°C. The above mentioned physiological salt solutions were prepared as indicated by staff members of the University of Edinburgh, Department of Pharmacology (1970).

Chemicals

- Nicotine sulphate (Hopkin and Williams Company, England)
- Atropine sulphate (Memphis Company, Cairo, Egypt)
- Adrenaline (Cid, Giza, Egypt)

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 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.

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

Corresponding Author: M.H. Aboubakr, Department of Pharmacology, Faculty of Veterinary Medicine, Benha University, 13736 Moshtohor, Toukh, Qalioubeya, Egypt

isolated tissues. The method explained by Valeri *et al.* (1990) was used for studying the effect of ceftriaxone on the isolated ileum of guinea pigs. The method described by the staff members of Pharmacology Department, University of Edinburg UK, 1968 was used for studying the effect of ceftriaxone on isolated rabbit's duodenum and rat's colon. The effect of ceftriaxone on isolated rat's fundic strip was investigated according to the method described by Milenov and Kalfin (1996).

RESULTS AND DISCUSSION

The effect of ceftriaxone on isolated guinea pig's ileum, rabbit's duodenum, rat's colon and rat's fundic strip were shown in Table 1. The maximum stimulant effect of ceftriaxone on isolated guinea pig's ileum, rabbit's duodenum, rat's colon and rat's fundic strip were shown in Fig. 1a-d. The site of action of ceftriaxone on isolated guinea pig's ileum, rabbit's duodenum, rat's colon and rat's fundic strip were shown in Fig. 2a-d. The stimulant effect of ceftriaxone on the isolated intestinal smooth muscle preparations might be attributed to its direct effect. Ceftriaxone in concentration of 1024 μg mL^{-1} bath has a serotonin like effect on rat's fundic strip.

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 stimulates 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 Takai *et al.* (1980) who found that cefeperazone *in vivo* enhanced the ileal motility in guinea pigs at 62.5 and 125 mg kg^{-1}, respectively and *in vitro* enhanced slightly the motility of isolated rabbit's gastrointestinal tract at 0.001 g mL^{-1}. Also, these results were similar with those obtained by Yamaki *et al.* (1984) who stated that the spontaneous motility of smooth muscle was temporarily increased with 800 mg kg^{-1} cefminox when administered intravenously and in upper doses. In contrast, Hasegawa *et al.* (1979) stated that cefadroxil had no effects on the isolated smooth muscle organs in mice. In addition, Honda *et al.* (1980) stated that ceftizoxime sodium neither affected the spontaneous motility of isolated rabbits's and guinea pig's ileum at concentration equal to 10^{-2} g mL^{-1} nor interacted with acetylcholine or histamine on the isolated guinea-pig's preparation. Takai *et al.* (1982) found that the spontaneous movement

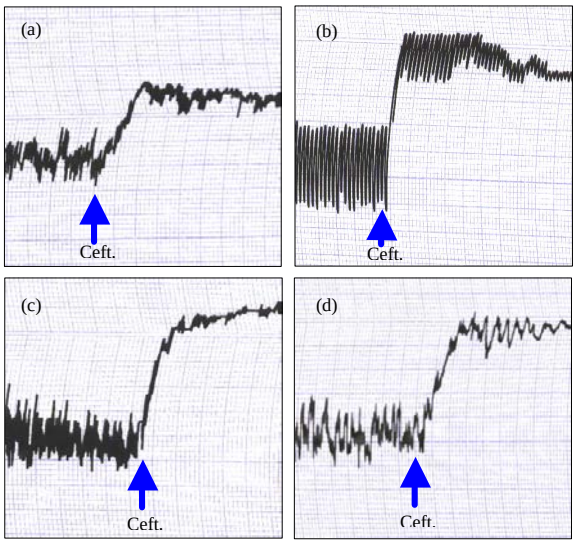

Fig. 1: Effect of Ceftriaxone (Ceft.) on isolated gastrointestinal muscles: a) 1024 μg mL^{-1} bath Ceftriaxone (Ceft.) on isolated guinea pig's ileum; b) 1024 μg mL^{-1} bath Ceftriaxone (Ceft.) on isolated rabbit's duodenum; c) 512 μg mL^{-1} bath Ceftriaxone (Ceft.) on isolated rat's colon and d) 1024 μg mL^{-1} bath Ceftriaxone (Ceft.) on isolated rat's fundic strip

Table 1: The effect of ceftriaxone on isolated guinea pig's ileum, rabbit's duodenum, rat's colon and rat's fundic strip

Concentrations	Responses of			
(μg mL^{-1} bath)	Guinea pig's ileum	Rabbit's duodenum	Rat's colon	Rat's fundic strip
8	No effect	No effect	No effect	No effect
16	No effect	Slight stimulation in the force	Slight stimulation in the force	No effect
32	Slight stimulation in the force	Slight stimulation in the force	Slight stimulation in the force	No effect
64	Slight stimulation in the force	Slight stimulation in the force	Slight stimulation in the force	Slight stimulation in the force
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
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 contraction	Marked inhibition in the force and rate of
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
1024	Maximum stimulation	Maximum stimulation	-	Maximum stimulation

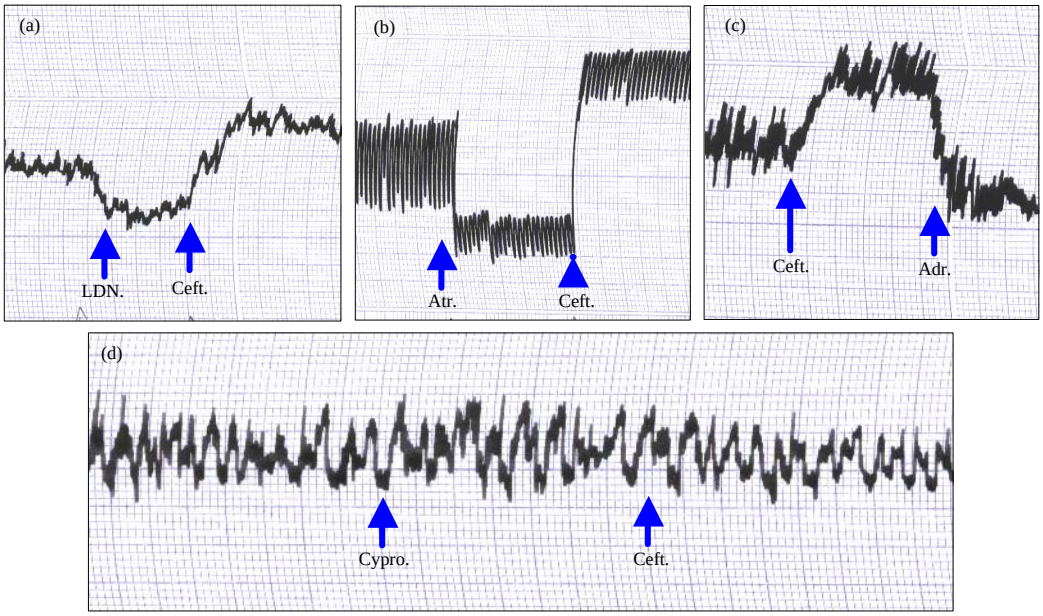

Fig. 2: Site of action of Ceftriaxone (Ceft.) on isolated gastrointestinal muscles: a) 5 μg mL^{-1} bath nicotine sulphate (LDN.) followed by 256 μg mL^{-1} bath Ceftriaxone (Ceft.) on isolated guinea pig's ileum; b) 1 μg mL^{-1} bath atropine sulphate (Atr.) followed by 256 μg mL^{-1} bath Ceftriaxone (Ceft.) on isolated rabbit's duodenum; c) 256 μg mL^{-1} bath Ceftriaxone (Ceft.) followed by 0.5 μg mL^{-1} bath Adrenaline (Adr.) on isolated rat's colon and d) Cyproheptadine 5×10^{-6} mmol (Cypro.) followed by 1024 μg mL^{-1} bath Ceftriaxone (Ceft.) on isolated rat's fundic strip

and tone of isolated ileum, colon and acetylcholine-, histamin-, nicotine- or barium chloride-induced contraction of ileum were not affected following cefbuperazone application. Further more, Goto *et al.* (1990) recorded that 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. Goto *et al.* (1992) stated also that cefetriaxone had no effect on the intestinal smooth muscle and did not show any antagonism against some smooth muscle contracting drugs. El-Sayed *et al.* (1997) proved that cefamandole at concentrations of 512 and 1024 micrograms mL^{-1} bath caused complete relaxation in isolated guinea pig's ileum and rabbit's duodenum, respectively. Ceran *et al.* (2006) found that maximum contractile responses to carbachol and histamine were significantly reduced in response to the ceftriaxone sodium. 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 sensetive preparation for detection of serotonin). These results might be attributed to the ability of ceftriaxone to release serotonin from its stores. The seotonin stimulating effect of ceftriaxone overcomed its direct effect on the smooth muscle of rat's fudnic strip. The obtained results came in harmony with those obtained by Jankovic *et al.* (1996) recorded that cefotaxime, ceftriaxone and ceftazidime cefamandole had stimulatory effect on the rat's fundic strips. On the other hand, Honda *et al.* (1980) who stated that ceftizoxime sodium after intravenous dose of 320-1000 mg kg^{-1} dose-dependently suppressed spontaneous contraction of the pyloric part in morphine-urethane-anesthetized dogs. Hasegawa *et al.* (1979) recorded that cefadroxil had no effects on the motility of the stomach in rabbits.

CONCLUSION

These findings indicated that ceftriaxone had stimulatory effect on isolated gastrointestinal smooth muscles.

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