



RESEARCH ARTICLE

**Effect of ceftriaxone on blood pressure, respiration and its analgesic and antipyretic activities**

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**Özet**

**Aboubakr M, Elsayed M, Elkomy A.** Sefriaksonun kan basıncı ile solunuma etkisi ve anajezik ile antipretik aktiviteleri. *Eurasian J Vet Sci*, 2012, 28, 1, 41-46

**Amaç:** Araştırmanın amacı seftriaksonun köpeklerde kan basıncı ve solunuma etkisini aratırmaktır. Ayrıca seftriaksonun fare ve ratlarda anajezik ve antipretik etkiliği de araştırıldı.

**Gereç ve Yöntem:** Farklı dozlarda seftriaksonun (26.66, 53.33, 106.66 mg/kg, IV) anestezi altındaki köpeklerde kan basıncı ve solunuma etkisi belirlendi. İki farklı dozda seftriaksonun ise fare ve ratlarda anajezik ve antipretik etkinliği belirlendi.

**Bulgular:** Seftriaksonun anestezi altındaki köpeklerin kan basıncı ve solunuma etkisinin olmadığı belirlendi. Ancak seftriaksonun (260 ve 520 mg/kg) dört saat süresince analjezik ve 180 ile 360 mg/kg dozlarında sırasıyla 2.5 ve 1.5 saat süresince antipretik etkinlik gösterdiği belirlendi.

**Öneri:** Seftriakson bakterial ve ateşli enfeksiyonlarda antibakteriyel, analjezik ve antipretik etkinliğinden dolayı tercih edilebilir.

**Abstract**

**Aboubakr M, Elsayed M, Elkomy A.** Effect of ceftriaxone on blood pressure, respiration and its analgesic and antipyretic activities. *Eurasian J Vet Sci*, 2012, 28, 1, 41-46

**Aim:** The aim of this study was to determine the effect of ceftriaxone on blood pressure and respiration in dog. In addition, analgesic and antipyretic activities of ceftriaxone were investigated in mice and rats.

**Materials and Methods:** Effect of different doses of ceftriaxone (26.66, 53.33, 106.66 mg/kg, IV) on blood pressure and respiration rate were determined in anesthetized dogs. Analgesic and antipyretic activities of two different doses of ceftriaxone were investigated in mice and rats, respectively.

**Results:** Ceftriaxone had no effect on blood pressure and rate of respiration in anesthetized dogs. However, ceftriaxone (260 and 520 mg/kg) had a significant analgesic effect for four hours and had a significant antipyretic effect at 2.5 and 1.5 hours at doses of 180 and 360 mg/kg, respectively.

**Conclusion:** Ceftriaxone is preferable in bacterial infections or feverish conditions owing to its antibacterial, antipyretic and analgesic activities.

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## ► Introduction

Ceftriaxone is a broad spectrum cephalosporin resistant to various types of betalactamases, with potent activity against gram-positive and gram-negative bacteria (Neu et al 1981). 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 (Harold 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 (Zhou et al 1985, Bouget et al 1993).

Although the effects of cephalosporins on the blood pressure and respiration were reported (Hasegawa 1979, Takai et al 1980, Takai et al 1982, Kurebe et al 1984, Hirai et al 1986, Goto et al 1992, Shetler et al 1993, El-Sayed et al 1997), there are no information available on the effect of ceftriaxone on blood pressure and respiration. In addition, the analgesic and antipyretic activities of ceftriaxone have not been studied. Recently, Rawls et al (2010) observed that ceftriaxone preserved analgesic efficacy during chronic morphine exposure and also, Rawls et al (2007) described that ceftriaxone attenuates morphine-evoked hyperthermia in rats.

It has been hypothesized that ceftiaxone may change blood pressure, and it has analgesic and antipyretic activities, like some other cephalosporins. Hence it become preferable in bacterial infections associated with pain and feverish conditions.

The purpose of this study was to investigate the effect of ceftriaxone on blood pressure and rate of respiration in anaesthetized dog. Also, to determine its analgesic and antipyretic activities and these informations will be of benefits to physicians and their patients.

## ► Materials and Methods

Three beagle dogs (15-20 kg) were used for studying the effect of ceftriaxone (Ceftriaxone inj., Smithkline Beecham for Novartis Pharma Company, Egypt) on blood pressure and respiration. Twenty Swiss mice (20-25 g) and twenty Wistar rats (150-180 g) were used to determine analgesic and antipyretic activities of ceftriaxone, respectively. Animals were kept in standard environmental conditions and maintained on standard diet and water ad libitum. All animals were obtained from animal house, Faculty of Veterinary Medicine, Benha Univerisity and this investigation was approved by the Animal Research Ethic Committee, Benha University.

Effects of different doses of ceftriaxone (26.66, 53.33 and 106.66 mg/kg) on blood pressure and rate of respiration in anaesthetized dog were determined by previously mentioned method (Jackson 1939). Dogs were anaesthetized using thiopental sodium intravenously in a dose of 20 mg/kg. Each anaesthetized dog

was laid on its back on the operating table and its head and limbs were fixed to the attachment of the table. Femoral artery and vein were exposed. The latter was cannulated with a venous cannula, which connected by a rubber tube with a bottle containing saline solution and used for injection of ceftriaxone. Heparin was injected at a dose of 500 IU/kg to prevent blood coagulation. The femoral artery was exposed and cannulated with arterial cannula, which was attached to blood pressure transducer via a tube containing 4% sodium citrate solution to prevent blood coagulation and connected with two channels Harvard universal oscillograph. The effect of ceftriaxone on the rate of respiration of anaesthetized dog was recorded with arterial blood pressure using stethograph, which was composed of a rubber blent fixed around the thorax of the dog at the tip of xyphoid cartilage and connected with a tambour by rubber tube. The metal plate of the tambour was attached to an isotonic transducer, which connected with two channels Harvard universal oscillograph. Chart speed, was 2 millimeters/second. The traces of systemic blood pressure and rate of respiration were recorded immediately before and at different time intervals following intravenous injections of ceftriaxone.

The analgesic effect of ceftriaxone was investigated using the hot plate method (Jenien and Jageneau 1957, Eddy 1982). Twenty mice divided into four groups, each of five mice. The first group was left as control and was given normal saline intramuscularly. The second group was given ketoprofen at dose of 13 mg/kg intramuscularly as a standard analgesic. The third and fourth groups were given ceftriaxone at doses of 260 and 520 mg/kg, respectively. Each mouse was placed singly in a beaker, 2-litre capacity, put on a hot plate kept constant at 55 °C for determining the analgesic activity of ceftriaxone. The time elapsed until the mouse jumps or licks its paws was recorded and considered as the reaction time.

Antipyretic activity of ceftriaxone was determined by previously mentioned method (Alperman 1972). Twenty rats were divided into four groups, each of five rats. All rats were made hyperthermic by subcutaneous injection of 20% suspension of Brewer's yeast in physiological saline in a dose of 0.1 mL/100 g body weight. After 17 hours, the initial body temperature of each rat was measured rectally using medical thermometer. The first group was kept as control and given normal saline intramuscularly. The second group was given metamizole sodium in a dose of 150 mg/kg intramuscularly as a standard antipyretic. The third and fourth groups were given ceftriaxone at doses of 180 and 360 mg/kg intramuscularly, respectively. The temperature of each rat was then recorded before and after 30, 60, 90, 120, 150, 180, 210, 240 minutes in treated and control groups. The difference in temperature between the treated and control groups was taken as a measure of the antipyretic activity.

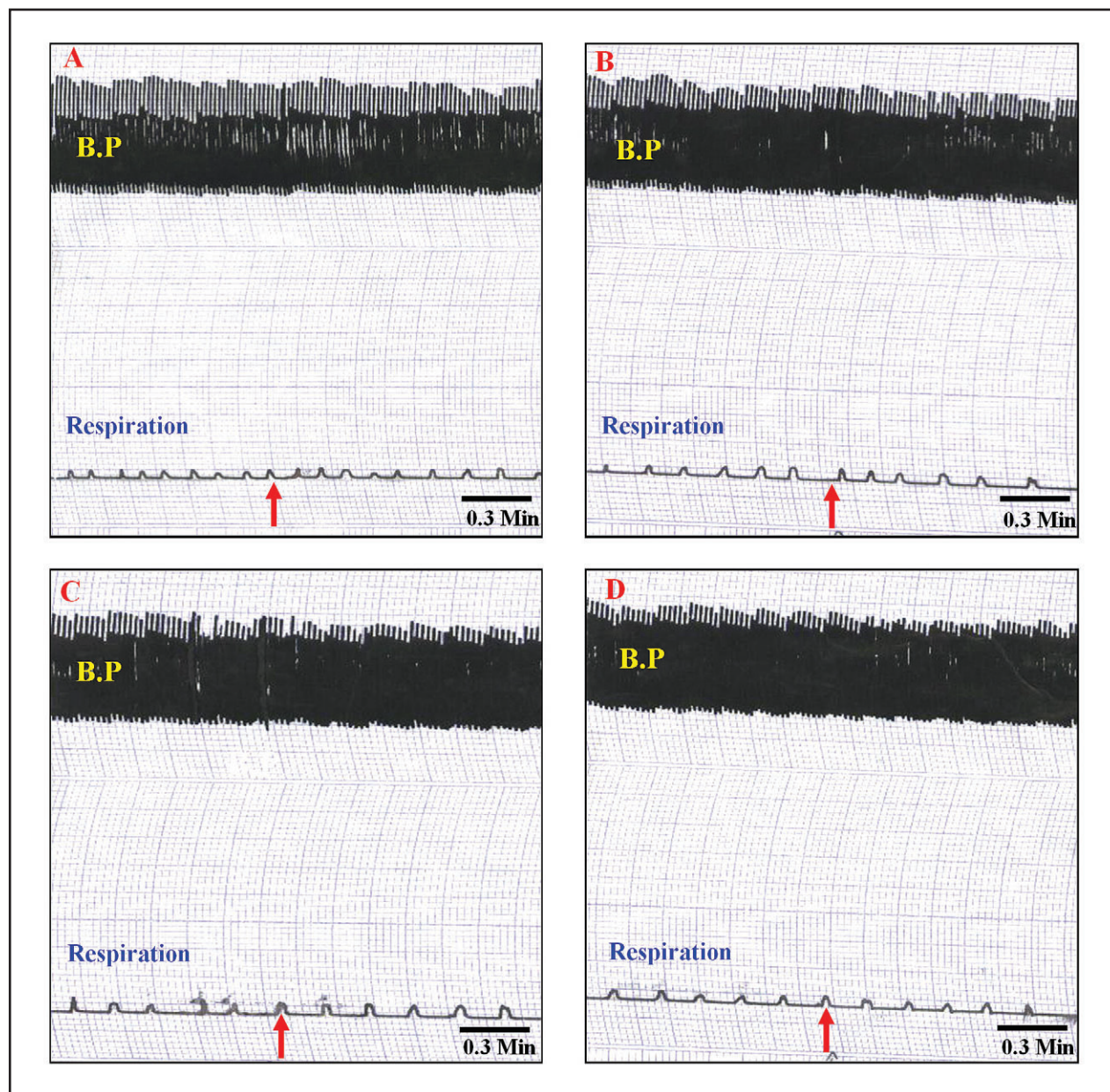


Figure 1. Effect of ceftriaxone on blood pressure and rate of respiration in anesthetized dogs (A; before injection, B; 26.66 mg/kg ceftriaxone, C; 53.33 mg/kg ceftriaxone, D; 106.66 mg/kg ceftriaxone).

Data were expressed as mean  $\pm$  SE and statistically analyzed using Student t-test to express the differences between groups.  $p < 0.05$  was accepted statistically significance.

### ► Results

Intravenous injection of ceftriaxone at doses of 26.66, 53.33 and 106.66 mg/kg had no effect on blood pressure and rate of respiration in anesthetized dogs as shown in Figure (1). The analgesic effect of ceftriaxone in mice was shown in Table 1. Ceftriaxone at doses of 260 and 520 mg/kg induced a highly significant analgesic effect for four hours of the experiment which was indicated by the longer reaction time in treated than control group. The antipyretic effect of ceftriaxone in rats was shown in Table 2. Ceftriaxone

in a dose of 180 mg/kg had an antipyretic effect after 2.5 hours of administration while ceftriaxone in dose of 360 mg/kg had a significant antipyretic effect after 1.5 hours of administration.

### ► Discussion

Ceftriaxone had no effect on blood pressure and rate of respiration in anaesthetized dogs (Figure 1). Similar result has been reported in the dogs (Hasegawa et al 1979). However, effects of beta-lactams on the blood pressure and respiration were not same and very different results have reported (Takai et al 1980, Takai et al 1982, Kurebe et al 1984, Hirai et al 1986, Goto et al 1992, Shetler et al 1993, El-Sayed et al 1997). These differences mainly depend on molecular distinction. Depressant effects of ceftriaxone on iso-

Table 1. Analgesic activity of ceftriaxone in mice (n=5).

Groups	Time after injection (hours)								
	Before experiment	0.5	1	1.5	2	2.5	3	3.5	4
Control group	7.0±0.18	6.8±0.15	6.7±0.17	6.8±0.30	6.3±0.18	6.2±0.31	6.1±0.29	6.5±0.29	6.3±0.27
Ketoprofen (13 mg/kg)	6.6±0.21	17.8±0.45 <sup>a</sup>	16.1±0.94 <sup>a</sup>	15.5±0.45 <sup>a</sup>	14.5±0.74 <sup>a</sup>	12.5±0.70 <sup>a</sup>	12.4±0.80 <sup>a</sup>	12.9±0.59 <sup>a</sup>	12.0±0.52 <sup>a</sup>
Ceftriaxone (260 mg/kg)	6.7±0.21	9.4±0.25 <sup>a</sup>	10.3±0.49 <sup>a</sup>	10.2±0.30 <sup>a</sup>	11.8±0.57 <sup>a</sup>	11.2±0.66 <sup>a</sup>	12.4±0.45 <sup>a</sup>	11.7±0.67 <sup>b</sup>	11.4±0.71 <sup>a</sup>
Ceftriaxone (520 mg/kg)	6.2±0.27	9.0±0.54 <sup>b</sup>	8.9±0.36 <sup>a</sup>	10.9±0.61 <sup>a</sup>	13.2±0.42 <sup>a</sup>	11.8±0.40 <sup>a</sup>	11.0±0.46 <sup>a</sup>	10.6±0.68 <sup>a</sup>	11.8±0.49 <sup>a</sup>

<sup>a</sup>, different from control value  $p<0.001$ , <sup>b</sup>, different from control value  $p<0.01$  (student t-test).

Table 2. Antipyretic activity of ceftriaxone in rats (n=5).

Groups	Before Experiment	Time after injection (hours)								
		0.5	1	1.5	2	2.5	3	3.5	4	
Control group	36.5±0.07	37.2±0.05	37.5±0.07	37.4±0.07	37.4±0.12	37.4±0.12	37.6±0.13	37.4±0.12	37.4±0.11	37.4±0.10
Metamizole (150 mg/kg)	36.5±0.18	37.7±0.10	37.1±0.16	36.9±0.12 <sup>c</sup>	36.8±0.11 <sup>c</sup>	36.7±0.11 <sup>b</sup>	36.5±0.07 <sup>a</sup>	36.4±0.07 <sup>a</sup>	36.4±0.05 <sup>a</sup>	36.3±0.06 <sup>a</sup>
Ceftriaxone (180 mg/kg)	36.5±0.16	37.6±0.17	37.5±0.09	37.5±0.10	37.4±0.10	37.2±0.07	36.9±0.09 <sup>b</sup>	37.0±0.09 <sup>c</sup>	36.8±0.09 <sup>b</sup>	36.8±0.10 <sup>b</sup>
Ceftriaxone (360 mg/kg)	36.6±0.14	37.7±0.15	37.6±0.10	37.4±0.10	37.0±0.05 <sup>c</sup>	37.0±0.04 <sup>b</sup>	36.8±0.05 <sup>a</sup>	36.8±0.05 <sup>a</sup>	36.6±0.05 <sup>a</sup>	36.5±0.05 <sup>a</sup>

<sup>a</sup>( $p<0.001$ ), <sup>b</sup>( $p<0.01$ ), <sup>c</sup>( $p<0.05$ ) different from control value (student t-test).

lated heart and auricles, and the alpha adrenoceptor blocking effects of ceftriaxone on the isolated aortic strip were reported (El-Sayed et al 2011). This difference might be attributed to the higher doses of ceftriaxone in the organ bath.

Ceftriaxone at doses of 260 and 520 mg/kg induced significant analgesic effect against thermal stimuli. This was evidenced by longer reaction time in hot plate test. The obtained result was consistent with that reported by Goto et al (1992) who observed that significant analgesia was observed at the highest dose of cefepime in mice. Also, beta-lactam antibiotic (ceftriaxone) preserved analgesic efficacy during chronic morphine exposure and reduces morphine analgesic tolerance in rats through Glutamate transporter subtype 1 transporter activation (Rawls et al 2010). The obtained result was inconsistent with that reported by Takai et al (1982) who stated that cefbuperazone did not show analgesic activity in mice after intravenous doses of 250-1000 mg/kg.

Ceftriaxone at doses of 180 and 360 mg/kg had a significant antipyretic effect. This was evidenced by decrease of rat's feverish body temperature. This effect seemed to be mediated centrally through an action on heat regulating center in such manner to increase heat loss by peripheral vasodilatation of skin blood vessels, as well as the direct vascular relaxant effect of ceftriaxone. The obtained result was similar with that recorded by Goto et al (1992) who observed that significant hypothermia was observed at the highest dose of cefepime in mice. Also, beta-lactam antibiotic, ceftriaxone attenuates morphine-evoked hyperthermia in rats. Beta-lactam antibiotics were the first practical pharmaceuticals capable of increasing activity of the glutamate transporter in the CNS. One such drug was morphine, which caused hyperthermia in rats by an increase in glutamatergic transmission. Since drugs (e.g. antibiotics) that enhance glutamate uptake also decrease glutamatergic transmission. This supported the hypothesis that ceftriaxone, a beta-lactam antibiotic, would block the glutamate-dependent portion of morphine-evoked hyperthermia (Rawls et al 2007). The obtained result was dissimilar with that of Honda et al (1980) and Takai et al (1982) who found that ceftizoxime and cefbuperazone did not affect body temperature in mice and rabbits respectively. Also, cefoperazone caused pyrexia in rabbits at 1.000 mg/kg dose (Takai et al 1980). The body temperature was raised slightly by an injection of more than 400 mg/kg of cefminox and cefteteram respectively (Kurebe et al 1984, Hirai et al 1986).

### ► Conclusions

Ceftriaxone had no effect on blood pressure and rate of respiration in anesthetized dogs. Ceftriaxone possessed potent analgesic and antipyretic activities.

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