EURASIAN
JOURNAL OF VETERINARY SCIENCES
www.ejvs.selcuk.edu.tr

RESEARCH ARTICLE

Effects of drugs on kinetic values of cytokines, adenosine deaminase and 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$ in endotoxemia: A different approach

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Özet

Altan F, Elmas M, Er A, Üney K, Çetin G, Traş B, Yazar E. Endotoksemide ilaçların sitokinler, adenozin deaminaz ve 13,14-dihidro-15-keto-prostaglandin $F_{2\alpha}$'nın kinetik değerlerine etkisi: Farklı bir yaklaşım. ***Eurasian J Vet Sci, 2010, 26, 1, 15-19***

Amaç: Lipopolisakkaritle (LPS) oluşturulan deneysel endotoksemide sitokinler, adenozin deaminaz (ADA) ve 13,14-dihidro-15-keto-prostaglandin $F_{2\alpha}$ (PGM)'nın kinetik değerlerine tek başlarına ve/veya kombine uygulanan enrofloksasin (ENR), fluniksin meglumin (FM) ve deksametazonun (DEX) etkilerini belirlemektir.

Gereç ve Yöntem: Araştırmada kullanılan ratlar 7 gruba ayrıldı. Deneysel endotoksemi oluşturmak için pozitif kontrol grubu dahil bütün gruplara LPS uygulandı. Diğer altı gruba ENR, FM, düşük doz DEX, yüksek doz DEX, ENR+FM+düşük doz DEX ve ENR+FM+yüksek doz DEX uygulandı. Uygulama sonrası 0, 1, 2, 4, 6, 8, 12, 24 ve 48. saatlerde kan örnekleri toplandı. Tümör nekroz faktör alfa (TNF_{α}), interlökin-6 (IL-6), interlökin-10 (IL-10), ADA ve PGM düzeyleri ELISA ile belirlendi. Eğri altında kalan alan (EAA_{0-48}) farmakokinetik programla, plazma veya serum maksimum konsantrasyon (C_{max}) ile maksimum konsantrasyona ulaşma zamanı (t_{max}) direk bakı yöntemiyle belirlendi.

Bulgular: Pozitif kontrol (LPS) grubuyla kıyaslandığında EAA_{0-48} değerlerinin; ENR grubunda PGM için artarken ($p<0.05$), IL-6, IL-10 ve ADA için azaldığı ($p<0.05$); FM grubunda IL-6 ve ADA'ya özgü olarak küçüldüğü ($p<0.05$); DEX tek başına veya kombine uygulandığı gruplarda da azaldığı ($p<0.05$) belirlendi.

Öneri: Farklı örnekleme zamanlarında çok sayıda ölçülen aynı endotoksemi belirteçlerinin toplu değerlendirilmesinde kinetik parametrelerden özellikle EAA'nin farklı ve akılcı bir yaklaşım olarak dikkate alınabileceği kanaatine varıldı.

Abstract

Altan F, Elmas M, Er A, Uney K, Cetin G, Tras B, Yazar E. Effects of drugs on kinetic values of cytokines, adenosine deaminase and 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$ in endotoxemia: A different approach. ***Eurasian J Vet Sci, 2010, 26, 1, 15-19***

Aim: The objective of this study was to determine the effects of enrofloxacin (ENR), flunixin meglumine (FM) and dexamethasone (DEX) on kinetic values of cytokines, adenosine deaminase (ADA) and 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$ (PGM) in lipopolysaccharide-induced endotoxemia.

Materials and Methods: Rats were divided into seven groups. To induce endotoxemia, lipopolysaccharide (LPS) was injected into all groups, including the positive control. The six other groups received the following drugs: ENR, FM, low-dose DEX, high-dose DEX, ENR + FM + low-dose DEX and ENR + FM + high-dose DEX. After the treatments, blood samples were collected at 0, 1, 2, 4, 6, 8, 12, 24, and 48 hours. Serum tumor necrosis factor alpha (TNF_{α}), interleukin-6 (IL-6), interleukin-10 (IL-10), ADA and plasma PGM levels were determined by ELISA. Area under the concentration time curve (AUC_{0-48}), maximal concentration in plasma or serum (C_{max}) and time to reach (t_{max}) values were determined by pharmacokinetic computer program.

Results: ENR increased ($p<0.05$) AUC_{0-48} of PGM and decreased ($p<0.05$) AUC_{0-48} of IL-6, IL-10 and ADA, while FM decreased ($p<0.05$) AUC_{0-48} of IL-6 and ADA compared to LPS group. DEX alone and combined administrations caused the lower AUC_{0-48} of all values ($p<0.05$).

Conclusion: Kinetic values, especially AUC, may be used for total evaluation of endotoxemia markers determined at different sampling times in same groups as a different and logical approach.

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Received: 15.04.2010, Accepted: 29.04.2010
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Anahtar kelimeler: Enrofloksasin, fluniksin, deksametazon, kinetik, endotoksemi belirteçleri

Keywords: Enrofloxacin, flunixin, dexamethasone, kinetic, endotoxemia markers

► Introduction

Lipopolysaccharide (LPS), exists on the outer membrane of Gram (-) bacteria, causes endotoxic shock. Endotoxic shock may cause the high mortality rate dose dependent manner (Andreasen et al 2008, Er et al 2009). The presence of LPS in the bloodstream causes disseminated intravascular coagulation, oxidative stress, cytokine production, prostaglandin production, multiple organ damage and, in severe cases, death (Keskin et al 2005, Elmas et al 2009, Yazar et al 2010a, Yazar et al 2010b).

Cytokines, produced mainly by the immune system cells, may be stimulated by microorganisms and/or their products such as LPS. They can be expressed two different subtypes as proinflammatory [tumor necrosis factor alpha (TNFα), interleukin-1beta (IL-1β), interleukin-6 (IL-6)] and anti-inflammatory [interleukin-10 (IL-10)]. Great produced proinflammatory cytokines can cause vasodilatation, hypotension, multiple organ failure, shock and ultimately, death. IL-10 inhibits the activation of the proinflammatory cytokines (Aldridge 2002, Netea et al 2003, Jean-Baptiste 2007). Adenosine deaminase (ADA), produced against to infection by the immune system cells, inhibits the cytokine release during the early phase of endotoxemia (Tofovic et al 2001, Conlon and Law 2004). 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$ (PGM), a main metabolite of prostaglandin $F_{2\alpha}$, is augmented during the inflammation. It can be also accepted as a marker of lipid peroxidation of the cyclooxygenase (COX) pathways (Basu and Eriksson 2000, Basu et al 2000).

Antibiotics, glucocorticoids (GCs) and non-steroid anti-inflammatory drugs (NSAIDs) are generally applied the treatment of endotoxemia in veterinary medicine (Elmas et al 2009, Er et al 2009). Enrofloxacin (ENR), a fluoroquinolone antibiotic, and flunixin meglumine (FM), a NSAID, are suggested to the management of endotoxemia or gram (-) bacterial infections (Elmas et al 2002, Elmas et al 2005, Elmas et al 2006a, Elmas et al 2007, Elmas et al 2008). GCs are also administered the treatment of endotoxemia (Yazar et al 2004a, Yazar et al 2004b, Er et al 2009). However, dosage, timing and duration of administration of GCs are unclear and still discussed. High-dose GC was recommended in the 1960s, while there was no determined the valuable effect of high doses in the 1990s (Meduri 1999, Minneci et al 2004). Currently, low-dose GC has been chosen in the human medicine (Sevransky and Natanson 2000). Although FM and/or GCs are recommended in the treatment of septic shock or endotoxemia (Smith 2005, Elmas et al 2006b, Yazar et al 2007), there are few studies that have evaluated the two classes (NSAID and GC) of drugs in the veterinary medicine (Smith 2005).

Endotoxemia markers (cytokines, ADA, DIC, oxidative stress, organ damage etc) have been generally evaluated and/or demonstrated as tables or graphics (Elmas et al 2006b, Elmas et al 2009, Yazar et al 2010a, Yazar et al 2010b). However, we hypothesized that presentation of kinetic values [area under the concentration time curve (AUC_{0-48}), maximal concentration in plasma or serum (C_{max}), time to reach C_{max} (t_{max})] of same markers measured in many different times might be favorable than table or graphic. Especially AUC value may be accepted the total amount of measured parameter during all sampling times. For this reason, some results of our project were reevaluated in this paper.

The aim of this study was to determine effects of ENR, FM, low-dose DEX, high-dose DEX, low-dose DEX combined with ENR + FM, and high-dose DEX combined with ENR + FM on AUC_{0-48}, C_{max} and t_{max} values of TNFα, IL-6, IL-10, ADA and PGM in endotoxemia.

► Materials and methods

A total of 342 Sprague–Dawley rats (6-8 months, female, n: 171; 213±20.4 g, male, n:171; 348±39.2 g, Laboratory Animal Unit, Akdeniz University, Antalya, Turkey) were used, and the study protocol was approved by The Ethics Committee of the Veterinary Faculty. Animals were fed standard pellet diet and tap water ad libitum.

The rats were divided into 7 groups (n=48, 24 females, 24 males). For LPS-induced endotoxemia, LPS was injected (4 mg, intraperitoneally, *Escherichia coli* 0111:B4, Sigma-Aldrich Chemie, Deisenhofen, Germany) in all groups (Yazar et al 2010a). The positive control group received LPS only. The other 6 groups received the following drug doses (simultaneously with LPS); ENR (10 mg/kg, subcutaneously, Baytril® %10 enj, Bayer Turk Kimya San. Ltd. Sti, Istanbul, Turkey), FM (2.5 mg/kg, subcutaneously, Finadyne® enj. Sol., Dogu Ilac Veteriner Urunleri, Istanbul, Turkey), low-dose DEX (0.6 mg/kg, intramuscularly, Dekort® amp, Deva Ilac, Istanbul, Turkey), high-dose DEX (10 mg/kg, intramuscularly), ENR + FM + low-dose DEX, and ENR + FM + high-dose DEX. 6 rats (3 females, 3 males) were used for a 0^{th} sampling point for all groups. After the treatments, serum and plasma samples (n = 6, 3 females, 3 males) were collected under thiopental sodium anesthesia by cardiac puncture at 0, 1, 2, 4, 6, 8, 12, 24 and 48^{th} hours. Serum TNFα (Biosource, Nivelles, Belgium), IL-6 (Biosource, Nivelles, Belgium) and IL-10 (Biosource, Nivelles, Belgium), and plasma PGM (13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$ EIA kit, Cayman Chemical, Michigan, USA) levels were determined by an ELISA reader (MWGt Lambda Scan 200, Bio-Tek Instruments, USA). Serum ADA level was determined by a previously reported method using the ELISA reader (Guisti 1974).

The plasma concentration versus time curves obtained after each treatment in individual animals, were fitted with the WinNonlin (4.1) software program (Pharsight Corporation, North Carolina, USA). Pharmacokinetic parameters for each animal were

analysed using non-compartmental model analysis. C_{max} and t_{max} were obtained from the plotted concentration–time curve of each drug in each animal. The linear trapezoidal rule was used to calculate the area under the plasma concentration time curve (AUC).

The pharmacokinetic parameters are reported as mean ± SE except for t_{max}. Mean pharmacokinetic parameters were statistically compared by one-way analysis of variance (ANOVA) and Duncan test. t_{max} was compared with non-parametric (Mann Whitney U test) method, and data were expressed as median. Mean/median values were considered significantly different at $P < 0.05$.

► Results

AUC_{0-48}, C_{max} and t_{max} of TNFα, IL-6, IL-10, ADA and PGM are shown in Table 1. ENR increased ($p<0.05$) AUC_{0-48} of PGM and decreased ($p<0.05$) AUC_{0-48} of IL-6, IL-10 and ADA compared to LPS group. FM decreased ($p<0.05$) AUC_{0-48} of IL-6 and ADA compared to LPS group. Lower AUC_{0-48} of all parameters were determined ($p<0.05$) in DEX alone and combined treatments.

► Discussion

Endotoxemia may cause high mortality. Immune cell mediated products and prostaglandin metabolite are accepted as diagnostic parameters in endotoxic shock. In this study, effects of ENR, FM and DEX on kinetic values of some endotoxemia markers, especially AUC_{0-48}, were evaluated (Table 1). Higher AUC_{0-48} of all measured values was determined ($p<0.05$) in the LPS group. It is well known that LPS increases the production of cytokines, ADA and PGM (Yazar et al 2007, Elmas et al 2009, Yazar et al 2010a, Yazar et al 2010b).

ENR increased ($p<0.05$) AUC_{0-48} of PGM and decreased ($p<0.05$) AUC_{0-48} of immune cell mediated markers except for TNFα (Table 1). However, this effect of ENR was not observed in our previous study (Yazar et al 2010a, Yazar et al 2010b). This difference may be mainly due to distinction of evaluation method. Although time points were evaluated in the other studies, total amount was evaluated in this research. It has been reported that effects of fluoroquinolones on cytokine synthesis may be depend on cell type and cytokine researched (Dalhoff and Shalit 2003). ENR may be used the treatment of endotoxemia, despite its stimulator effect on AUC_{0-48} of PGM. In the current study, FM decreased AUC_{0-48} of IL-6 and ADA. Interestingly, FM did no decrease the AUC_{0-48} of PGM compared to AUC_{0-48} of LPS. But it generally decreased PGM level in our previous study (Er et al 2010). DEX alone and combined treatments decreased ($p<0.05$) the AUC_{0-48} of all measured values. Similar results were also reported (Yazar et al 2010a, Yazar et al 2010b, Er et al 2010). Depressor effect of GCs on immune system and prostaglandin synthesis is reported (Lee et al 2006,

Table 1. Effect of drugs on kinetic values of some endotoxemia markers.

Values		LPS	ENR	FM	LD	HD	C-LD	C-HD
TNFα	AUC pg.h/mL	6133±798^{a}	7656±2262^{a} (↑%25)	5966±593^{a} (↓%3)	2092±547^{b} (↓%66)	909±241^{b} (↓%85)	1294±96.7^{b} (↓%79)	1905±525^{b} (↓%69)
	C_{max} ng/mL	1601±79.4^{a}	1302±53.2^{a}	1418±9.48^{a}	891±53.3^{b}	722±210^{b}	927±124^{b}	1278±60.2^{a}
	t_{max} h	1^{a}	1^{a}	1^{a}	1^{a}	1^{a}	1^{a}	1^{a}
IL-6	AUC pg.h/mL	81862±3364^{a}	51165±6755^{b} (↓%37)	41124±2800^{c} (↓%50)	6013±491^{d} (↓%93)	7441±1064^{d} (↓%91)	6449±545^{d} (↓%92)	12273±2337^{d} (↓%85)
	C_{max} pg/mL	5272±255^{a}	5031±240^{a}	5105±156^{a}	1668±201^{cd}	2367±404^{c}	1547±174^{d}	4252±243^{b}
	t_{max} h	5^{a}	5^{a}	6^{a}	3^{a}	4^{a}	4^{a}	2^{a}
IL-10	AUC pg.h/mL	14848±666^{a}	10463±1250^{b} (↓%30)	12686±1537^{ab} (↓%15)	3514±431^{d} (↓%76)	3067±737^{d} (↓%79)	6445±526^{c} (↓%56)	3768±220^{d} (↓%75)
	C_{max} pg/mL	1089±86.6^{a}	896±70.6^{ab}	748±71.7^{bc}	606±79.5^{cd}	358±36.6^{e}	652±72.7^{cd}	505±33.1^{de}
	t_{max} h	1.5^{a}	1.5^{a}	10^{a}	1^{a}	6^{a}	6^{a}	1^{a}
ADA	AUC IU.h/mL	6314±514^{a}	4409±302^{b} (↓%30)	5173±245^{b} (↓%18)	2372±85.4^{c} (↓%62)	2877±222^{c} (↓%54)	2697±114^{c} (↓%57)	2317±145^{c} (↓%63)
	C_{max} IU/mL	412±55.5^{a}	320±39.3^{a}	323±12.9^{a}	224±32.7^{b}	203±27.6^{b}	180±10.6^{bc}	101±12.9^{c}
	t_{max} h	5^{a}	5^{a}	5^{a}	4^{a}	4^{a}	5^{a}	5^{a}
PGM	AUC pg.h/mL	6618±935^{b}	8809±511^{a} (↑%33)	5516±472^{bc} (↓%16)	4357±244^{c} (↓%34)	5364±352^{bc} (↓%19)	3968±194^{c} (↓%40)	4154±300^{c} (↓%37)
	C_{max} pg/mL	542±98.7^{a}	623±112^{a}	195±28.9^{b}	153±15.5^{b}	196±42.2^{b}	134±16.5^{b}	177±20.4^{b}
	t_{max} h	1^{a}	1^{a}	5^{a}	1.5^{a}	10^{a}	0.5^{a}	2^{a}

LPS; lipopolysaccharide (4 mg, intraperitoneally), ENR; lipopolysaccharide + enrofloxacin (10 mg/kg, subcutaneously), FM; lipopolysaccharide + flunixin meglumine (2.5 mg/kg, subcutaneously), LD; lipopolysaccharide + low-dose dexamethasone (0.6 mg/kg, intramuscularly), HD; lipopolysaccharide + high-dose dexamethasone (10 mg/kg, intramuscularly), C-LD; lipopolysaccharide + enrofloxacin + flunixin meglumine + low-dose dexamethasone, C-HD; lipopolysaccharide + enrofloxacin + flunixin meglumine + high-dose dexamethasone. TNFα; tumor necrosis factor-α, IL-6; interleukin-6, IL-10; interleukin-10, ADA; adenosine deaminase, PGM; 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$, a, b, c, d, e; different letters in the same line are statistically significant ($p<0.05$).

Chatterjee et al 2007, Yazar et al 2010b). Nowadays, the inhibition of proinflammatory mediator production is mostly accepted clinical approaches to the treatment of inflammation. Activated nuclear factor kappaB stimulates by any agent including bacterial components (including LPS) stimulates the regulation of genes encoding proinflammatory cytokines, chemokines, and inducible enzymes. Hence, activated NF-KB may be playing a central role in the inflammation (Hanada and Yoshimura 2002, Macdonald et al 2003). Inhibitory effects of GCs on NF-KB (Wang et al 2006) may decrease the synthesis of cytokines and PGM.

► Conclusion

In the endotoxemia or septic shock studies in which markers are evaluated, very different results may be reported. However, blood markers of endotoxemia may alter within hours and/or alive or death. Especially AUC, due to allow monitoring of all fluctuations during trough experimental period, may be evaluated particularly in the experimentally endotoxemia studies.

► Acknowledgements

This study was a part of research supported by The Scientific and Technological Research Council of Turkey (TUBITAK, 107O042) and SUBAPK (08401001). Abstract was presented to 3rd National Congress of Veterinary Pharmacology and Toxicology Kusadası, Aydın. Abstract will be pressed in the proceeding book.

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