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The lack of pharmacokinetic interaction of diclofenac and amoxicillin given intravenously in ewes

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ABSTRACT

The aim of this study was to evaluate the effect of diclofenac on the disposition and renal clearance of amoxicillin. In this cross over study with a 1 week washout period, 10 ewes received amoxicillin intravenously (10 mg/kg body mass) alone or plus diclofenac sodium (2.5 mg/kg b.m.), given intramuscularly 30 minutes prior to amoxicillin administration. Concentrations of amoxicillin in plasma and urine were measured using high performance liquid chromatography (HPLC) with fluorescence detection. Concomitant administration of diclofenac with amoxicillin resulted in no significant alterations in the pharmacokinetic parameters or renal elimination for amoxicillin following intravenous administration. Intravenous administration of amoxicillin alone or concomitant with diclofenac resulted in mean ± SD elimination half-life ($t_{1/2\beta}$), of 0.79 ± 0.11 h versus 0.8 ± 0.09 h, mean residence time (MRT) of 0.8 ± 0.15 h versus 0.9 ± 0.17 h, total body clearance (CL_B) of 0.25 ± 0.02 L/h/kg vs 0.24 ± 0.04 L/h/kg and area under the curves (AUC) of 35.2 ± 6.2 μg/h/mL vs 39.5 ± 5.7 μg/h/mL, respectively. Amoxicillin was eliminated unchanged via the urine, with renal clearance (Cl_R) of 0.24 ± 0.05 L/h/kg and 0.27 ± 0.07 L/h/kg in the animal given amoxicillin alone or concomitant with diclofenac, respectively. Concurrent administration of diclofenac had no significant effect on the single-dose pharmacokinetics or renal elimination of amoxicillin given intravenously in ewes.

Key words: amoxicillin, diclofenac, elimination, ewes, pharmacokinetics, renal clearance

Introduction

Amoxicillin (AMX), a broad spectrum a-amino-p hydroxybenzylpenicillin, is a commonly used antibiotic in veterinary medicine, which has improved bioavailability after oral administration (SUTHERLAND et al., 1972; VERBIST, 1974). AMX is used successfully alone or in combination with clavulanic acid for the treatment of severe

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respiratory, gastrointestinal, urinary, dermal and dental infections (PALMER et al., 1976; PRESCOT, 2000).

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) with excellent analgesic and anti-pyretic activities. It acts via inhibition of cyclooxygenase (COX), which catalyzes the rate-limiting step in the formation of prostanoids, prostaglandins and thromboxane A2 (FITZGERALD and PATRONO, 2001). Antibiotic and non-steroidal anti-inflammatory agents are frequently used concomitantly in human and animals by oral or injectable routes. Drug interactions were verified when diclofenac was given concomitantly with amoxicillin orally. Diclofenac reduced the serum and tissue concentration of amoxicillin, as well as its antibacterial activity and increased its total body clearance by 18% according to other studies by GROPPO et al. (2004) and BERGAMASCHI et al. (2006). It has been postulated that the later effect of diclofenac on amoxicillin is due to its effect on the absorption as well as the renal excretion of amoxicillin. However, these previous studies could not provide any information about the effect of diclofenac on the renal clearance of amoxicillin. The purpose of this study was to assess the effect of concomitantly administered diclofenac on the pharmacokinetics and urinary excretion of amoxicillin given intravenously in ewes.

Materials and methods

Drugs. A commercially available amoxicillin preparation (E-Mox, 1 g sterile powder, Eippico, Cairo, Egypt) was used as an aqueous solution of 200 mg/mL. Diclofenac sodium (Voltaren, Novartis Co., Switzerland) was purchased as a 2.5 mg/mL injectable solution.

Animals. Ten ewes, ranging in age from 1-1.5 years and weighing 42.4-55.6 kg, were used. All ewes were considered healthy by clinical examination, complete blood picture, biochemical blood analysis and urinalysis. Each ewe was housed in a separate well-ventilated hygienic pen. Feed consisted of alfalfa hay, concentrate and green fodder, and drinking water was provided *ad libitum*.

Experimental design. A two-period cross-over design study, with a 1 week washout period, was conducted. Each animal received amoxicillin sodium by intravenous route (10 mg/kg body mass) alone or plus diclofenac sodium (2.5 mg/kg body mass) given intramuscularly 30 minutes prior to the amoxicillin. Blood samples were collected from the left jugular vein into heparinized syringes before and 5, 10, 15, 30 minutes and 1, 2, 4, 6, 8, 10, 12, 24 and 48 hrs after amoxicillin injection. Plasma was separated by centrifugation at 2000 g for 10 min and stored at -20 ^{o}C until assayed. The ewes were catheterized with an indwelling balloon catheter (Foley urinary catheter, No. 12, Timedco, Atlanta, Ga.). Catheters were connected to a 2 L container. Urine samples were collected just before and at 30 minutes and 1, 2, 4, 6, 8, 10, 12, 24, 36 and 48 hours

after administration of the drug. The volume of urine voided at each sampling time was measured and 10 mL aliquots were kept at -70 °C until assayed.

Amoxicillin assay

Instrumentation. Drug concentration in plasma was determined using reverse phase high performance liquid chromatography (HPLC), according to the method previously explained by DELIS et al. (2009a). The HPLC system consisted of an autosampler, equipped with a temperature - controlled rack (Waters), controller, solvent delivery pump (Waters, Milford, MA, USA), , and variable wave length fluorescence detector.

Chromatographic conditions. The mobile phase (35:65, v/v) of acetonitrile and a phosphate buffer (potassium dihydrogen phosphate 50 mM) containing 5 mM 1-octanesulfonic acid sodium salt monohydrate. pH of the mobile was adjusted to 3.5 with 1 M ortho-phosphoric acid. Separation was accomplished using a reverse phase C18 column (Discovery, Supelco, 5 µm, 4.6×150 mm). The emission wavelengths were 355 and 435 nm, and the flow rate was 1 mL/min.

Calibration curve. For preparation of the calibration curve, antibiotic naïve ewes plasma and urine were spiked with 0.01, 0.05, 0.1, 0.5, 1.0 and 5.0 µg/mL amoxicillin, and ampicillin was used as the internal standard. The standard curves of amoxicillin in the plasma and urine were linear between 0.01 and 5 µg/mL. The correlation coefficients (r) of standard curves were >0.97 for plasma and urine with lower quantitation limit (LOQ) of 0.01 µg/mL.

Sample extraction. The plasma and urine samples or calibration standards to be assayed (300 µL) were placed in centrifuge tube and spiked with 75 µL of internal standard (ampicillin 5 µg/mL in 0.05 M phosphate buffer) and vortexed. Plasma and urine samples (1 mL) were extracted by addition of 150 µL perchloric acid (20%) and samples were then vortexed, the supernatant was taken by aspiration and 150 µL aliquot were transferred to autosampler and the injection volume was adjusted to 20 µL.

Validation of the assay method. The precision and accuracy of the method were evaluated by repetitive analysis of the plasma and urine samples (n = 10) spiked with 0.01, 0.5, 1 and 5 µg/mL amoxicillin. The recovery was calculated by comparison of the extracted plasma and urine samples with those of the similar standard concentrations in the mobile phase (n = 10).

The values of intra-assay and interassay precision were <3.7% for plasma and urine samples. The intra-assay and interassay accuracies were >94% for plasma and urine. Recovery of amoxicillin from plasma and urine was >89%.

Pharmacokinetics analysis. The plasma concentration versus time data of the drug were fitted to a two compartment open model system (BAGGOT, 1978) according to the following biexponential equation: $C_t = Ae^{-\alpha t} + Be^{-\beta t}$ where C_t is the plasma concentration

of amoxicillin; t is time after intravenous administration; A and α are the intercept and slope, respectively in the distribution phase; B and β are the intercept and slope of the elimination phase. Pharmacokinetic variables were calculated by the WinNonlin program (Pharsight Corporation, Mountain View, CA, USA). The distribution and elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$), the volume of distribution at steady state (V_{dss}) and the total body clearance (Cl_B) were calculated according to standard equations (GIBALDI and PERRIER, 1982). The area under the plasma concentration time curve ($AUC_{0-\infty}$) and the area under the first moment curve ($AUMC_{0-\infty}$) were calculated by the trapezoidal rule for all measured data, with extrapolation to infinity using Clast/β, where Clast is the plasma concentration at 8 hours in ewes treated with amoxicillin alone or plus diclofenac. The mean residence time (MRT) was calculated as $MRT = AUMC_{0-\infty}/AUC_{0-\infty}$.

The renal clearance (CL_R) of amoxicillin was determined using plasma and urine concentrations of the drug and urine volume for samples collected over the sampling interval from 0 to 12 h. post i.v. administration of the drug. The following equation was used for calculation (ISMAIL, 2005):

$$CL_R = \frac{(A \times V)_{0-12}}{AUC_{0-\infty} \times b.m.}$$

In this equation, $(A \times V)_{0-12}$ is the cumulative amount of the drug excreted during the sampling period from 0 to 12 h, where A is the concentration of amoxicillin excreted in each urine sample; V is the volume of urine sample; $AUC_{0-\infty}$ is the area under the concentration time curve over the same sampling period and b.m. is the mass of each ewe in kilograms.

Estimation of endogenous creatinine clearance. The levels of creatinine in plasma and urine samples were estimated according to SIEST et al. (1985) using a commercial creatinine diagnostic kit (Bio Merieux, Paris, France). Endogenous creatinine clearance (CL_{cr}) was calculated by standard clearance equation. Fractional clearance (CL_R/CL_{cr}) of the drug was calculated as the ratio between its renal clearance and endogenous creatinine clearance (OSBALDISTON, 1971).

Statistical analysis. All the data are presented as mean ± S.D. One-way analysis of variance (ANOVA) was performed by SPSS® 6.1.3 software package (SAS, Cary, NC, USA) and significant differences between the means assessed using the student t test . Statistical significance was set at $P<0.05$.

Results

Following intravenous administration of amoxicillin (10 mg/kg) alone or plus diclofenac in all ewes, the plasma concentration versus time data complied with the

two compartment open model and exhibited a biphasic decline. Table 1 shows the pharmacokinetic parameters of amoxicillin following i.v. administration alone or plus diclofenac in ewes. There was no significant difference in any of the tested pharmacokinetic variables reported in this study.

Table 1. Pharmacokinetic variables (Mean ± SD) of amoxicillin given intravenously at a dose of 10 mg/kg b.m. alone or concomitantly with diclofenac in ewes (n = 10)

Parameters	Units	Mean ± SD	
		Amoxicillin	Amoxicillin+ Diclofenac
$T_{1/2a}$	h	0.09 ± 0.01	0.083 ± 0.02
b	/h	0.87 ± 0.12	0.86 ± 0.1
$T_{1/2b}$	h	0.79 ± 0.11	0.8 ± 0.09
V_c	L/kg	0.06 ± 0.009	0.067 ± 0.007
V_{dss}	L/kg	0.176 ± 0.04	0.18 ± 0.06
Cl_B	L/h/kg	0.25 ± 0.02	0.24 ± 0.04
$AUC_{0-\infty}$	µg/h/ml	35.2 ± 6.2	39.48 ± 5.7
MRT	h	0.8 ± 0.15	0.9 ± 0.17

Table 2. Renal disposition parameters (Mean ± SD) of amoxicillin given intravenously at a dose of 10 mg kg^{-1} b. wt. alone or concomitantly with diclofenac in ewes (n=10)

Parameters	Units	Mean ± SD	
		Amoxicillin	Amoxicillin+ Diclofenac
Cl_R	L/h/kg	0.24 ± 0.05	0.26 ± 0.07
FC	N	1.26± 0.3	1.4± 0.2
DF	%	93.8 ± 9.6	95.3 ± 7.8

$Cl_{R,}$ renal clearance, FC; fractional clearance, DF; cumulative dose fraction recovered up to 12 hours.

The mean values of endogenous creatinine clearance (CL_{cr}) were 0.19 ± 0.06 L/h/kg, the mean values of fractional clearance (FC) were 1.26 ± 0.3 and 1.4 ± 0.2 and the cumulative dose fraction (DF) recovered in the urine within 12 hours post administration were 93.8% and 95.3% (Table 2) in ewes treated with amoxicillin alone and amoxicillin plus diclofenac, respectively. Amoxicillin was detected in the plasma and urine for 8 hours for 12 hours post intravenous administration, , in animals treated with amoxicillin alone or plus diclofenac respectively.

Discussion

The clear impact of diclofenac on the plasma levels of amoxicillin as well as certain pharmacokinetic variables when both drugs were given concomitantly has been shown in rats and humans in previous studies (GROPPO et al., 2004; BERGAMASCHI et al., 2006). However, the particular mechanism involved in the interaction of these drugs has not been identified. Thus, this study assessed the impact of diclofenac on renal clearance of amoxicillin, following simultaneous administration by intravenous route rather than oral route.

In the present study, following the intravenous (i.v.) administration of amoxicillin alone or simultaneously with diclofenac, the plasma concentration time curve of amoxicillin followed the two compartment open model. This finding is in agreement with the previous report by CRAIGMILL et al. (1992) and FERNANDEZ et al. (2007). In contrast, other studies employed compartmental pharmacokinetic analysis in sheep (DELIS et al., 2010) and concluded with a three compartment disposition.

No significant differences were reported in pharmacokinetic parameters following i.v. administration of amoxicillin alone or simultaneous administration with diclofenac. The elimination half-life of amoxicillin reported in this work is close to the value reported by CRAIGMILL et al. (1992) and shorter than the values (1.62 h) reported by DELIS et al. (2009b) and (1.43 h) by CARCELES et al. (1995) whereas, it was longer than that (0.38 h) reported by FERNANDEZ et al. (2007).

The terminal elimination half-life and MRT for amoxicillin when administered alone or plus diclofenac were similar, as confirmed by the insignificant difference in the total body clearance after both treatments. Total body clearance (Cl_B) values reported in this study for amoxicillin are close to the values reported previously and are located within the range of those reported in sheep (0.09-0.61 L/h/kg) by other authors (CRAIGMILL et al., 1992; CARCELES et al., 1995; FERNANDEZ et al., 2007).

The low values of Vd_{ss} reported for amoxicillin administered alone or plus diclofenac in this study are consistent with its polar nature. Based on the p*K*a values of amoxicillin (2.8, 7.2) , a large fraction of the drugs carry a net negative charge at physiological pH and consequently its inability to attain substantial intracellular concentration (AGERSO and FRIIS, 1998; BAGGOT, 2001). This finding is in agreement with that reported by CRAIGMILL et al. (1992) and DELIS et al. (2009b).

Diclofenac did not affect the fraction of the dose of amoxicillin recovered unchanged in urine and most of the administered dose was recovered unchanged in the urine within 12 hours of administration of the drug in ewes. Our findings are consistent with previous reports showing that amoxicillin was excreted unchanged by both glomerular filtration and active tubular secretion (REYNOLDS, 1996; RIVIERE, 1999; BAGGOT, 2001). The

value of renal clearance of amoxicillin administered alone and with diclofenac was close to the relevant values for total body clearance and this is consistent with its excretion unchanged in urine. The values (1.27 v. 1.4) of fractional clearance (clr/clcr) emphasized that renal elimination of amoxicillin in ewes follows the same pattern previously mentioned. Additionally, our findings showed that diclofenac did not significantly alter the renal clearance of amoxicillin. Tubular secretion of beta lactam antibiotics occurs mostly via the organic anion transporters (OAT) and the proton-coupled oligopeptide transporter (PepT) (HAN et al., 1999; HOSOYAMADA et al., 1999; TERADA et al., 2000). It was reported by KHAMDANG et al. (2002) that diclofenac inhibited organic anion uptake.

Additionally, LI et al. (2006), has reported that the proton-coupled oligopeptide transporter (PepT) is the main tubular transporter for amoxicillin, whereas organic anion transporters (OAT) are not involved in the renal uptake of this antibiotic. These findings are consistent with our results regarding the lack of a modulating effect of diclofenac on the renal clearance of amoxicillin following concomitant i.v. administration.

In contrast, an earlier study by BERGAMASCHI et al. (2006) showed a significant reduction in amoxicillin total body clearance of 18%, following concomitant oral administration with diclofenac. This difference may be attributed to the significant alteration of diclofenac regarding other oral pharmacokinetic parameters of amoxicillin in this study.

The findings of the present study show that the hypothesis of the impaired renal clearance of amoxicillin by concomitant administration of diclofenac is impractical and indicate the lack of pharmacokinetic interaction between amoxicillin given intravenously.

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SAŽETAK

Cilj rada bio je procijeniti učinak diklofenaka na raspodjelu i bubrežni klirens amoksicilina. Nakon jednotjednog razdoblja ispiranja, u 10 ovaca intravenski je bio primijenjen samo amoksicilin (10 mg/kg tjelesne mase) ili/i natrijev diklofenak intramuskularno (2,5 mg/kg tjelesne mase) 30 minuta prije primjene amoksicilina. Koncentracija amoksicilina u plazmi i mokraći izmjerena je visokotlačnom tekućinskom kromatografijom na osnovi fluorescencije. Primjena diklofenaka s amoksicilinom nije značajno utjecala na promjene farmakokinetičkih pokazatelja za amoksicilin ili na njegovo izlučivanje putem bubrega nakon intravenske primjene. Srednja vrijednost ± SD poluživota izlučivanja amoksicilina ($t_{1/2\beta}$) iznosila je kod njegove intravenske primjene 0,79 ± 0,11 sati, a kod primjene s diklofenakom 0,8 ± 0,09 sati. Srednje vrijeme zadržavanja amoksicilina bilo je 0,8 ± 0,15 sati, a s diklofenakom 0,9 ± 0,17 sati. Ukupni tjelesni klirens za sam amoksicilin iznosio je 0,25 ± 0,02 L/h/kg, a u kombinaciji s diklofenakom 0,24 ± 0,04 L/h/kg, dok je srednja vrijednost površine ispod krivulje eliminacije samo za amoksicilin bila 35,2 ± 6,2 μg/h/mL, a u kombinaciji s diklofenakom 9,5 ± 5,7 μg/h/mL. Amoksicilin se izlučio nepromijenjen mokraćom s bubrežnim klirensom (Cl_R) od 0,24 ± 0,05 L/h/kg, a primijenjen s diklofenakom od 0,27 ± 0,07 L/h/kg. Može se zaključiti da primjena diklofenaka nije imala značajan utjecaj na farmakokinetiku ili izlučivanje amoksicilina primijenjenog intravenski u ovaca.

Ključne riječi: amoksicilin, diklofenak izlučivanje, ovce, farmakokinetika, bubrežni klirens