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RESEARCH ARTICLE

Comparative Pharmacokinetics of Gentamicin in Laying Hens [1]

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Summary

The aim of this study was to compare pharmacokinetics of gentamicin sulphate (5 mg/kg body weight) after single intravenous, intramuscular and subcutaneous administration in laying hens. Blood samples were collected at time 0 (pretreatment), and at 0.083, 0.166, 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 24, 36 and 48 h after drug administration in 24 laying hens. Gentamicin concentrations were determined using the HPLC method recommended by the European Union by some modifications. The total concentration of the gentamicin (C1, C2 and C1a) was calculated. The lowest detection limit was 0.01 µg/ml. Noncompartmental pharmacokinetic analyses were performed using Excel add-in program, PK solver. Following IV administration the area under the plasma time-concentration curve from time zero to infinity (AUC0-∞), first-order elimination rate constant (λz), terminal half-life (t1/2λz) and mean residence time (MRT) were 224.46 µg/mL h, 0.06 h-1, 11.52 h and 9.50 h, respectively. After i.m. and s.c. dosing, the mean maximum plasma concentrations (C_{max}) were 26.64 and 36.92 µg/mL, achieved at a same post-injection times (T_{max}) of 0.75 h, respectively. The t1/2λz was 8.35 and 8.24 h, the MRT was 11.05 and 9.79 h, respectively, after IM and SC administration. There are no significant between IM and SC administration excluding the Cmax values and between i.v. and other administration excluding the t1/2λz values.

Keywords: *Gentamicin, Pharmacokinetics, Laying hens*

Yumurta Tavuklarında Gentamisinin Karşılaştırmalı Farmakokinetiği

Özet

Çalışmada, yumurtlayan tavuklara damar içi, kas içi ve deri altı yolla verilen gentamisin sülfatın (5 mg/kg canlı ağırlık) karşılaştırmalı farmakokinetiğinin belirlenmesi amaçlandı. 24 tavuğa ilaç uygulandıktan sonra kan örnekleri 0 (uygulama öncesi), 0.083, 0.166, 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 24, 36 ve 48. saatlerde toplandı. Gentamisin konsantrasyonları Avrupa Birliği tarafından önerilen yöntemde modifikasyon yapılarak belirlendi. Gentamisinin toplam konsantrasyonu (C1, C2 ve C1a) ölçüldü. En düşük belirlenme limiti 0.01 µg/ml olarak hesaplandı. Non-kompartmental farmakokinetik analizleri Excel ile çalışan program olan PK solver ile belirlendi. Damar içi uygulamayı takiben plazma konsantrasyonu zaman eğrisinin altında kalan alan (AUC0-∞), ilk hız atılma sabitesi (λz), yarı-ömür (t1/2λz) ve ortalama tutulma zamanı (MRT) sırasıyla 224.46 µg/mL saat, 0.06 saat-1, 11.52 saat ve 9.50 saat olarak ölçüldü. Kas içi ve deri altı uygulamadan sonra ortalama maksimum plazma konsantrasyonu (C_{max}) sırasıyla26.64 ve 36.92 µg/mL, maksimum konsantrasyona ulaşmak için geçen zaman (T_{max}) ise aynı (0.75 saat) olarak belirlendi. Yine kas içi ve deri altı uygulamadan sonra sırasıyla t1/2λz 8.35 ve 8.24 saat, MRT ise 11.05 ve 9.79 saat olarak ölçüldü. Kas içi ve deri altı uygulama arasında Cmax değerleri hariç ve damar içi ile diğer uygulamalar arasında t1/2λz değerleri hariç tutulursa önemli farklılıklar olmadığı sonucuna varılmıştır.

Anahtar sözcükler: *Gentamisin, Farmakokinetik, Yumurta tavuğu*

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INTRODUCTION

Gentamicin is an aminoglycoside antibiotic for treating a variety of bacterial infections in pigs, cattle, poultry and horses. In veterinary medicine it is normally used as the sulphate salt [1]. It is effective against gram-negative and some gram-positive bacteria, but not anaerobic bacteria [2,3]. In view of their polar nature and high aqueous solubility, aminoglycosides are poorly absorbed after oral administration. However, the absorption after intramuscular (IM) or subcutaneous (SC) administration in most species is good with peak blood concentrations occurring within 30 to 90 min. Aminoglycosides are not metabolized and are eliminated unchanged in the urine by glomerular filtration. Within 24 h 80 to 90% of the administered dose is eliminated [4]. In mammals and birds, systemic administration of aminoglycosides is complicated by their nephrotoxicity [5,6]. There are no avian-specific data on the pharmacokinetics of systemic aminoglycosides, but as avian and mammals both exhibit aminoglycoside-induced nephrotoxicity, it is likely that elimination occurs via the renal pathway in avian as it does in mammals [2,7].

Therapeutic use of antibiotics in laying hens poses a particular problem because it may result in drug residues in the eggs that are laid during and after treatment. The elimination of gentamicin residues in eggs was reported by Filazi et al.[8]. When administered to laying hens via IM or SC routes, gentamicin was deposited in egg yolk and albumen, with residues persisting for longer periods in the yolk [8,9].

Although the aminoglycosides have been extensively reviewed, few studies on the pharmacokinetics of gentamicin are available in chickens, but none in laying hens. Therefore, the aim of this study was to compare pharmacokinetics of gentamicin sulphate (5 mg/kg body weight) after single intravenous (IV), IM and SC administration.

MATERIAL and METHODS

Chickens

Twenty-four ISA Brown laying hens, 30 weeks of age, were kept individually in fibre cages (30 cm x 35 cm x 45 cm), within a ventilated, heated room (20°C) and given 14 h of light a day. The animals were monitored for 3 weeks for any apparent clinical signs and to ensure that they were free from antibiotics before drug administration. They received a standard commercial layer mash (120 g/d) and water *ad libitum*. The study was authorized by the official ethical committee of Faculty of Veterinary Medicine in Ankara University (2004/17-45)

Drug

A veterinary drug containing 50 mg gentamicin in 1 mL was used (Gentavet, Vetaş Company, Istanbul, Turkey).

Experimental Design

Chickens were individually weighed before drug administration (1.6-2.0 kg body weight) and doses were calculated accordingly. They were divided into three equal groups (8 birds/group). Chickens of groups 1, 2 and 3 were given a single dose of gentamicin (5 mg/kg bw) by IV, IM and SC administration, respectively. Gentamicin was given in the left brachial vein, pectorals muscle and neck for IV, IM and SC administration, respectively. Blood samples (1-1.5 ml) were collected from brachial and cutaneous ulnar veins into heparinized tubes at time 0 (pretreatment) and at 0.083, 0.166, 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 24, 36 and 48 h after drug administration in 24 laying hens. They were directly centrifuged at 3000 rpm for 5 min to obtain clear plasma and were stored at -21°C until assayed. Gentamicin concentrations were determined using the HPLC method recommended by the European Union by some modifications. The total concentration of the gentamicin (C1, C2 and C1a) was calculated [8,10]. The lowest detection limit was 0.01 µg/ml.

Statistics and Data Analysis

Variance analysis was applied to all data and a multiple range test was used to determine whether or not there were differences among the groups (SPSS Release 17). Non-compartmental pharmacokinetic analyses were performed using Excel add-in program, PK solver [11].

RESULTS

All chickens were clinically healthy throughout the experimental period. The mean plasma concentration-time profiles of gentamicin (5 mg/kg bw) after IV, IM and SC administration are shown in *Fig. 1*.

The pharmacokinetics parameters of gentamicin after single IV, IM and SC administration are shown *Table 1*.

DISCUSSION

Parenterally administered gentamicin is much more bioavailable than when given orally; therefore, it is generally administered by IV, IM and SC routes [12]. Thus, all of the AUC values were high.

After all routes of administration of gentamicin, the terminal half-life was higher than values reported in turkeys [12,13], eagles [14], roosters [15] and broiler chicks [16]. This may due to differences in drug formulation and the gentamicin assay.

As shown *Table 1*, gentamicin is rapidly absorbed after IM and SC administration with C_{max} of 26.64 and 36.92 µg/mL at 0.75 h. These results are higher than values reported in turkeys [12], roosters [13] and broiler chicks [14]. This may due to individual differences that interfere with the drug

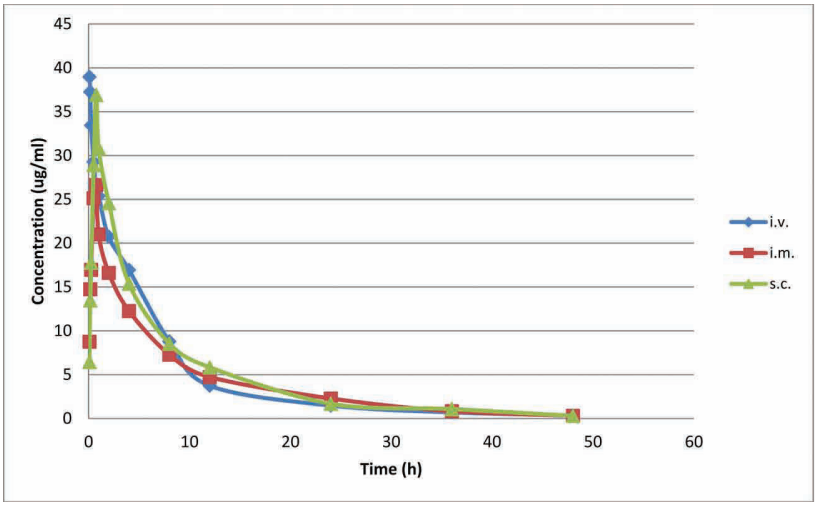

Fig 1. Plasma concentration-time profile of gentamicin after IV, IM and SC administration of 5 mg/kg bw as determined by HPLC, Values are mean ±SE (n=8)

Şekil 1. Damar içi, kas içi ve deri altı yolla 5 mg/kg canlı ağırlık dozunda uygulanan gentamisinin HPLC ile ölçülen plazma konsantrasyonu-zaman grafiği, Değerler ortalama±SE olarak verilmiştir (n=8)

Table 1. *Pharmacokinetic parameters of gentamicin (5 mg/kg bw) in laying hens after a single parenteral administration*
Tablo 1. *Tek bir parenteral uygulamayla yumurta tavuklarına 5 mg/kg dozunda verilen gentamisinin farmakokinetik parametreleri*

Parameter	Units	Administration Route		
		Intravenous	Intramuscular	Subcutaneous
λz	h^{-1}	0.06	0.08	0.08
$t_{1/2\lambda z}$	h	11.52*	8.35	8.24
MRT	h	9.50	11.05	9.79
C_{max}	µg/mL	-	26.64	36.92**
T_{max}	h	-	0.75	0.75
$AUC_{0-\infty}$	µg/mL.h	224.46	202.56	242.86

λz: *First-order elimination rate constant,* $t_{1/2\lambda z}$***:*** *Terminal half-life, MRT: Mean residence time,* C_{max}***:*** *Mean maximum plasma concentration,* T_{max}***:*** *time of peak plasma concentration,* $AUC_{0-\infty}$***:*** *The area under the plasma time-concentration curve from time zero to infinity, * Values differ significantly compared with IM and SC (P<0.05), ** Values differ significantly compared with IM (P<0.05)*

distribution, which will result in delay or acceleration of the drug elimination.

Since the effect of gentamicin is concentration dependent, such that the antimicrobial drug kills bacteria to a greater extent at increasing exposure concentration, the efficacy of gentamicin is achieved when C_{max} reaches 8-10 times above the MIC of it against the susceptible microorganisms [15]. The reported MICs of gentamicin against susceptible microorganisms isolated from different species of animals were 2, 1.2, 8, 4 and 0.8 µg/ml for *Escherichia coli*, *Proteus* spp., *Pseudomonas aeruginosa*, *Klebsiella pneumonia* and *Staphylococcus aureus*, respectively [18] and 1 µg/ml for both *E. coli* and *Salmonella* species isolated from diseased chickens [12]. The results of this study showed that (C_{max}/MIC>10) for most susceptible bacteria after parenteral administration. Therefore, a dose of 5 mg/kg bw seems to be suitable therapeutic dose of gentamicin in laying hens.

It should be noted that therapeutic use of gentamicin in laying hens poses a particular problem because it may result in drug residues in the eggs that are laid during and after treatment [7]. In contravention of the regulations in European Union, Turkey and some other countries, there is a tendency for withdrawal times for drugs used for laying hens to be ignored, because of the producer's financial loss in large poultry flocks. In cases where it is necessary to use gentamicin, an appropriate period must be taken into consideration by producers and the eggs containing gentamicin residues should not enter the human food chain during this withdrawal period. Obeying the legislation regarding drug residue withdrawal periods is essential to protect consumer health.

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