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Tissue Concentrations of Sulphaquinoxaline in Healthy and *E. tenella* Infected Chickens*

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Summary: The aim of this study is to investigate the tissue concentrations of sulphaquinoxaline after single administration of 100 mg/kg b.w. to healthy and *Eimeria tenella* (*E. tenella*) infected chickens. In this study, 200 one-day-old, male, *Avian* race, broiler chicks were used. The animals were divided into 5 equal groups (Group I, II, III, IV and V) and consisting of 40 chicks in each. The animals in Group IV and V were infected on 24th day with *E. tenella* inoculum that contains 10 000 *E. tenella* oocysts. The drug was applied to all chickens on the 30th day. The drug was given to Group I intravenously, intracrop to Group II and Group IV and, in drinking water to Group III and to Group V. Five animals from each group were sacrificed after the drug administration at 1, 4, 8, 12, 18, 24, 30 and 36th hours and samples were taken from the tissues of lung, liver, kidney, breast muscle and caecum of animals. The concentrations of drug in tissue samples were measured by spectrophotometry. The level of drug was determined much higher in the tissues of chickens (kidney, liver, lung, caecum and muscle) with coccidiosis than healthy ones. The highest level of drug accumulation was occurred in the kidney tissue and the concentration of drug determined much higher in the caecum tissues of coccidiosed chickens, compared to healthy counterparts. Additionally, it was found that the concentration of the drug in tissues was lower when the drug was given in drinking water than when it was given intracrop.

Key Words: Broiler chicken, *E. tenella*, sulphaquinoxaline, tissue concentration

Sağlıklı ve Koksidiyozlu Etlik Piliçlerde Sülfakinoksalin'in Doku Yoğunlukları

Özet: Bu çalışmanın amacı, sağlıklı ve *Eimeria tenella* (*E. tenella*) ile koksidiyoz oluşturulan etlik piliçlere tek seferde 100 mg/kg.c.a dozunda verilen sülfakinoksalinin doku yoğunluklarını araştırmaktır. Çalışmada günlük, 200 adet, erkek, Avian ırkı etçi civciv kullanıldı. Hayvanlar her bir grupta 40 hayvan olacak şekilde 5 eşit gruba (Grup I, II, III, IV ve V) ayrıldı. Grup IV ve V'deki hayvanlara çalışmanın 24. gününde 10 000 *E. tenella* oosisti içeren inokulum verildi. İlaç bütün hayvanlara 30. günde uygulandı. İlaç Grup I'deki hayvanlara damar içi, Grup II ve Grup IV'deki hayvanlara kursak içi, Grup III ve Grup V'deki hayvanlara ise içme suyuna katılarak verildi. İlacın verilmesini takiben 1., 4., 8., 12., 18., 24., 30. ve 36. saatlerde 5'er hayvan kesildi ve hayvanların akciğer, karaciğer, böbrek, göğüs kası ve kör bağırsak dokularından örnekler alındı. Doku ilaç yoğunlukları spektrofotometrik olarak belirlendi. İlaç koksidiyozlu hayvanların dokularında (böbrek, karaciğer, akciğer, kör bağırsak ve kas) sağlıklı hayvanlara göre daha yüksek yoğunluklarda tespit edildi. İlacın en fazla biriktiği dokunun böbrek dokusu olduğu ve koksidiyozlu hayvanların kör bağırsak dokusunda sağlıklı hayvanlara göre daha yüksek yoğunlukta bulunduğu tespit edildi. Ayrıca ilacın içme suyuyla verilmesi durumunda dokulardaki yoğunluklarının kursak içine göre daha düşük olduğu belirlendi.

Anahtar Kelimeler: Doku yoğunlukları, *E. tenella,* etlik piliç, sülfakinoksalin

Introduction

Several poultry diseases are caused by parasitic protozoa that produce severe morbidity and mortality. Parasitic diseases often differ from viral and bacterial diseases by the presence of a complicated life cycle, methods of transmission and absence of serological methods for diagnosis (17). Coccidiosis is one of the major problems in poultry husbandry with significant economic impact on broiler chicken production (11).

Coccidiosis is a disease that is caused by protozoan parasites of the genus *Eimeria*, developing within the intestine of most domestic and wild animals and birds (6). Nine species of *Eimeria* (*E. tenella, E. necatrix, E. acervulina, E. brunetti, E. maxima, E. mitis, E. mivati, E. praecox* and *E. hagani*) are recognized as infecting chickens (6,13). Coccidiosis caused by *E. tenella*

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is the best known of the avian types, partly because of the spectacular disease it causes nad partly because of its widespread importance in commercial broilers. This species inhabit the ceca and adjacent intestinal tissues causing a severe disease characterized by bleeding, high morbitidy and mortality, loss weight gain, emaciation and other signs attributed to coccidiosis (16).

Coccidiosis is one of the most expensive and common diseases in poultry in spite of advances in chemotherapy, management, nutrition, and genetics (16). The use of preventive medication for coccidiosis is now virtually in management of commercial broiler chickens. This is accomplished by mixing coccidiostatic drugs with feed or drinking water (7). Sulphonamides are relatively old antibacterial compounds, but still effective in the prevention and teratment of coccidiosis in poultry (10, 11). Their popularity is due to the wide spectrum of antibacterial activity and relatively low price compared with other chemotherapeutic agents (14). Sulphaquinoxaline, in sulphonamid derivatives, is used primarily for the control and prevention of coccidiosis and fowl cholera in chickens (8, 9, 18). Sulphaquinoxaline is more effective aganist cecal coccidiossis caused by *E. tenella* (12). Several studies reported that suphaquinoxaline had higher blood and tissue concentrations than other sulphonamides (7, 9, 15, 20). The objective of this present study was to determine the tissue concentrations of sulphaquinoxaline in healthy and *E. tenella* infected chickens.

Material and Methods

A total of 200 one-day-old, male, Avian broiler chicks were used and 5 groups (Group I, II, III, IV and V) were designed. Animals were fed on balanced ration free from therapeutic agents during the experimental period. Fresh clean drinking water was available *ad libitum*. Animals were performed daily fecal examination. The animals in Group IV and V were infected on 24th day with *E. tenella* inoculum that contains 10 000 *E. tenella* oocysts and animals were performed daily fecal examination. A strain of *E. tenella* was obtained from Institute for Animal Health Compton Laboratory-England. The drug was given to all animals on 30th day. A hundred mg/kg b.w. sulphaquinoxaline was given to Group I intravenously, to Group II and Group IV via intracrop administration, to Group III and to Group V in drinking water.

Animals were sacrificed after the drug administration at 1, 4, 8, 12, 18, 24, 30 and 36th hours and samples were taken from the tissues of lungs, liver, kidney, breast muscle and caecum of animals in order to determine drugs tissue level. The samples were taken in plastic bags and frozen at -20^{o}C until analyzed.

Concentrations of sulphaquinoxaline in tissue samples were determined by spectrophotometry procedures as described by Atef et al. (1), based on the Bratton-Marshall (5) coupling reaction. Recovery in tissue samples was determined as 76 % for sulphaquinoxaline. The limit of quantification of sulphaquinoxaline was 0.1 µg/g.

The SPSS 11.0 for Windows software package was used for statistical analyses. All data in this study were presented as arithmetic means±standart error of means (SEM). One-way ANOVA with Duncan's multiple range tests was used in order to determine the difference between the groups.

All experimental procedures were approved by Ethic Committee for Animal Experiments of Faculty of Veterinary Medicine, Ankara University (2001/14, 26.04.2001).

Results

Clinical signs were seen in animals at the 4th day of the administration of inoculum that contains sporulated *E. tenella* oocysts. Blood was seen in faeches at the 5th and 6th days of the infection. On the 6th day of the infection the caecum was enlarged as compared to healthy caecum; when the caecum was opened, it was found as full with blood. Necrotic areas were seen on the surface of the mucosa and thickening of the caecal wall was seen.

Concentrations of sulphaquinoxaline and C_{max} in liver, kidney, lung, muscle and ceacum samples were given in Tables 1-6.

Discussion and Conclusion

The tissue concentrations of the drug were higher in Group I (intravenous administration) compared to the other groups (intracrop and drinking water). In Group I, in the 1st hour, the highest drug concentration was detected in kidney, liver, caecum, lungs and muscle tissue respectively. After the 1st hour the tissue concentration was in decline gradually due to the excretion of the drug.

Table 1. Sulphaquinoxaline concentrations of the liver tissue in healthy and *E. tenella* infected chickens in different periods (µg/g) (Mean±SEM) (n:5).

Hours	Groups				
	Group I	**Group II**	**Group III**	**Group IV**	**Group V**
1	87.69±2.58^{a}	27.40±0.34^{bc}	23.95±0.36^{bcd}	30.85±0.36^{b}	22.24±1.40^{d}
2	82.57±4.05^{a}	33.50±1.44^{c}	27.15±1.15^{d}	39.76±1.80^{b}	26.39±1.23^{d}
8	73.61±2.41^{a}	52.91±2.42^{c}	30.88±1.98^{d}	72.51±4.45^{b}	31.81±1.84^{d}
12	66.27±3.39^{a}	44.32±1.54^{c}	32.19±1.54^{d}	61.81±1.94^{b}	43.42±2.63^{c}
18	59.25±3.20^{a}	37.65±1.53^{c}	37.62±1.66^{c}	48.10±2.02^{b}	35.38±1.82^{c}
24	49.28±2.12^{a}	20.53±1.30^{d}	20.65±1.08^{d}	34.40±1.42^{b}	29.49±1.70^{c}
30	39.42±2.18^{a}	15.58±0.51^{d}	13.25±0.76^{d}	28.40±1.40^{b}	23.62±0.72^{c}
36	31.17±1.61^{a}	10.94±0.38^{c}	8.45±0.30^{c}	23.89±1.21^{b}	11.70±1.24^{c}

$^{a, b, c, d.}$ Values followed by the different letters in the same lines are significantly different ($p<0,05$), according to one-way ANOVA.

Table 2. Sulphaquinoxaline concentrations of the kidney tissue in healthy and *E. tenella* infected chickens in different periods (µg/g) (Mean±SEM) (n:5).

Hours	Groups				
	Group I	**Group II**	**Group III**	**Group IV**	**Group V**
1	125.13±3.56^{a}	29.50±2.03^{d}	33.98±2.47^{cd}	46.78±1.96^{b}	40.10±2.09^{c}
4	99.13±3.30^{a}	39.96±1.53^{c}	36.37±2.12^{c}	51.72±1.85^{b}	46.82±2.15^{b}
8	86.20±2.92^{a}	45.49±1.57^{d}	43.62±1.94^{d}	61.07±2.97^{b}	52.96±1.96^{c}
12	72.92±2.18^{a}	53.56±2.60^{c}	55.47±2.08^{c}	73.35±2.49^{a}	62.01±2.59^{b}
18	62.58±2.17^{a}	50.09±2.80^{b}	49.13±1.91^{b}	62.56±2.84^{a}	53.53±2.08^{b}
24	55.78±1.72^{a}	39.72±2.35^{b}	40.51±2.15^{b}	58.93±1.89^{a}	44.39±1.75^{b}
30	50.36±2.10^{a}	32.65±1.50^{b}	33.28±1.94^{b}	51.79±1.83^{a}	36.82±1.63^{b}
36	45.23±1.50^{a}	30.15±1.41^{b}	30.33±1.63^{b}	45.93±2.05^{a}	32.12±1.36^{b}

$^{a, b, c, d.}$ Values followed by the different letters in the same lines are significantly different ($p<0,05$), according to one-way ANOVA.

Table 3. Sulphaquinoxaline concentrations of the caecum tissue in healthy and *E. tenella* infected chickens in different periods (µg/g) (Mean±SEM) (n:5).

Hours	Groups				
	Group I	**Group II**	**Group III**	**Group IV**	**Group V**
1	82.19±4.00^{a}	4.49±0.30^{e}	11.43±0.84^{d}	24.85±1.41^{c}	38.03±21.42^{b}
4	72.46±2.81^{a}	14.86±1.02^{c}	14.41±1.09^{c}	40.24±1.98^{b}	44.27±2.10^{b}
8	64.94±2.54^{a}	18.03±1.01^{c}	18.71±1.04^{c}	75.93±1.95^{a}	48.66±2.12^{b}
12	56.17±1.95^{ab}	35.00±2.16^{c}	22.18±0.93^{d}	62.77±2.22^{b}	68.91±2.29^{a}
18	48.91±1.95^{b}	26.49±1.72^{c}	29.35±0.86^{c}	51.30±2.31^{b}	58.44±2.10^{a}
24	34.04±1.77^{b}	20.24±1.15^{c}	14.39±1.36^{d}	35.74±2.01^{b}	45.26±2.24^{a}
30	20.96±1.26^{c}	14.33±0.79^{d}	12.16±0.88^{d}	25.62±1.70^{b}	30.07±1.56^{a}
36	15.43±0.99^{a}	9.08±0.71^{b}	8.11±1.33^{b}	15.77±1.53^{a}	15.13±0.71^{a}

$^{a, b, c, d.}$ Values followed by the different letters in the same lines are significantly different (p<0,05), according to one-way ANOVA.

Table 4. Sulphaquinoxaline concentrations of the lung tissue in healthy and *E. tenella* infected chickens in different periods (µg/g) (Mean±SEM) (n:5).

Hours	Groups				
	Group I	**Group II**	**Group III**	**Group IV**	**Group V**
1	81.74±3.49^{a}	18.80±1.78^{b}	21.29±1.36^{b}	24.54±1.04^{b}	24.48±1.34^{b}
2	74.03±3.47^{a}	22.64±1.28^{c}	21.53±1.18^{c}	34.64±1.30^{b}	29.45±1.77^{b}
8	68.78±2.07^{a}	25.77±1.43^{c}	26.03±1.42^{c}	51.24±1.30^{b}	32.31±1.02^{b}
12	64.06±2.14^{a}	45.17±1.90^{b}	26.60±1.25^{c}	47.57±1.42^{b}	45.60±1.36^{b}
18	58.69±1.95^{a}	40.12±1.62^{b}	40.28±1.45^{b}	43.09±1.46^{b}	42.19±1.89^{b}
24	47.49±2.13^{a}	34.33±1.45^{b}	25.18±1.31^{c}	38.83±1.74^{b}	27.89±1.92^{c}
30	40.25±1.88^{a}	28.45±1.32^{b}	16.39±1.38^{c}	32.31±2.02^{b}	20.65±1.60^{c}
36	35.00±1.75^{a}	21.20±1.41^{c}	9.14±0.77^{e}	25.26±2.08^{b}	14.28±1.07^{d}

$^{a, b, c, d.}$ Values followed by the different letters in the same lines are significantly different (p<0,05), according to one-way ANOVA.

Table 5. Sulphaquinoxaline concentrations of the muscle tissue in healthy and *E. tenella* infected chickens in different periods (µg/g) (Mean±SEM) (n:5)

Hours	Groups				
	Group I	**Group II**	**Group III**	**Group IV**	**Group V**
1	44.93±2.63[a]	8.20±0.30[c]	3.20±0.24[d]	18.11±0.93[b]	3.92±0.59[d]
4	42.47±2.26[a]	10.71±0.52[c]	6.52±0.55[d]	24.79±0.98[b]	6.75±0.30[d]
8	38.07±1.17[a]	19.87±0.60[b]	7.65±0.25[d]	35.59±1.84[a]	13.69±0.60[c]
12	32.27±1.62[a]	25.73±1.16[b]	10.10±0.51[d]	28.30±1.00[b]	17.66±0.93[c]
18	25.45±1.61[a]	20.95±1.66[b]	14.79±0.49[c]	22.23±1.00[b]	14.38±0.79[c]
24	21.61±1.79[a]	16.66±0.61[b]	9.01±0.08[c]	19.14±1.31[ab]	10.07±0.91[c]
30	17.18±0.76[a]	14.79±0.68[b]	7.89±0.62[c]	16.28±1.19[ab]	8.28±0.72[c]
36	14.79±0.64[a]	8.42±0.51[c]	6.67±0.38[d]	12.54±0.89[b]	6.10±0.60[d]

[a, b, c, d.] Values followed by the different letters in the same lines are significantly different (p<0,05), according to one-way ANOVA.

Table 6. C_{max} of sulphaquinoxaline in various tissues in healthy and *E. tenella* infected chickens (µg/g) (Mean±SEM) (n:40).

Tissues	Groups				
	Group I	**Group II**	**Group III**	**Group IV**	**Group V**
Liver	87.69±5.77[a]	52.91±5.41[c]	37.62±3.71[d]	72.51±9.94[b]	43.42±5.88[d]
Muscle	44.93±5.87[a]	25.73±2.59[c]	14.79±1.10[d]	35.59±4.11[b]	17.66±2.07[d]
Kidney	125.13±7.97[a]	53.56±5.81[d]	55.47±4.64[d]	73.35±5.56[b]	62.01±5.79[c]
Ceacum	82.19±8.95[a]	35.00±4.83[d]	29.35±1.92[d]	72.93±4.35[b]	68.91±5.13[c]
Lungs	81.74±7.80[a]	45.17±4.24[c]	40.28±3.24[c]	51.24±2.90[b]	45.60±3.05[c]

[a, b, c, d.] Values followed by the different letters in the same lines are significantly different (p<0,05), according to one-way ANOVA.

When the drug was administered by intracrop route, the tissue drug concentrations were higher in almost all of the periods compared to Group IV and Group II. These increases were statistically significant ($p<0.05$) in most of the periods. This can be atrributed to the increased absorbtion of the drug due to the decreased motility of the small intestine in *E. tenella* infections (3, 19). Another reason behind this increase could be the increase of the unbound drug concentration in plasma due to the significant decrease of the plasma protein levels in coccidiosed chickens (21). Williams et al. (22) showed that the concentration of sulphaquinoxaline were higher in various tissues (brain, lungs, liver, kidney, lipid and muscle) of the cocidiosed animals compared to the healthy animals. Also Atta et. al. (2) suggested that sulphadimidin, sulphadiazin and sulphaquinoxaline were maintained longer in tissue of the coccidiosed rabbits compared to the healthy animals. When the tissue drug concentration at certain periods were examined, it was detected that the drug showed the same concentration–time profile as plasma, the drug firstly reached a maximum concentration than showed a decrease. This decrease was rapid in all groups. Although similar changes were seen in both Group IV and II, there were significant ($p<0.05$) differences between the C_{max} values of the drug. The C_{max} of the drug in Group IV was high. These changes can be related to the physiological changes in poultry caused by the *Eimeria spp*. The difference between the C_{max} of the drug in Group II and Group IV was the highest in caecum. This showed that the drug rapidly passes through to the infected tissue. In fact, this transition revealed that the drug may be effective on the *Eimeria spp.* for an advanced degree for a long time. Evaluation of this aspect of the situation certainly seems to be an advantage. On the other hand it was understood that both in Group IV and Group II the drug highly accumulates in the kidney. This was followed by lungs, liver, caecum and muscle tissue respectively. Furthermore, Banerjee et al. (4), El-Sayed et al. (7) and Furusawa and Tsuzukida (9) and Righter et al. (18) detected that the drug was highly accumulated in the kidney. Other than the kidney tissue Banerjee et al. (5) showed that the accumulation was mostly seen in caecum, liver and lung, respectively. El-Sayed et al. (7), reported that the accumulation was mostly seen in lung, liver and muscle, respectively. Furusawa and Tsuzukida (9) showed that the accumulation was mostly seen in liver and muscle, respectively.

When the drug was given in drinking water; in all examined tissues, drug concentration in the tissue was higher in Group V compared to Group III in almost every time periods. The tissue C_{max} of the drug in Group V were significantly ($p<0.05$) increased in all tissues compared to Group III. Except for the caecum, in all tissues the drug concentration was significantly ($p<0.05$) decreased when administered in drinking water compared to the administration of the drug by intracrop route. This decline can also be seen in healthy animals in both way of the administration (drinking water and intracrop). The concentration of sulphaquinoxaline in caecum, as in intracrop route was increased in Group V compared to Group III. This increase can be explained by the influence of the drug, which is found in systemic circulation, to the infected tissues rather than the absorption of the drug in caecum. These results showed that administration of the drug in drinking water is more advantageous application in coccidiosed animals in terms of retention of the drug in the tissues. It was detected that the drug was mostly accumulated in the kidney when administered in drinking water. In Group III, the drug accumulation in kidney was followed by lung, liver, caecum and muscle, in Group V caecum, lung, liver and muscle, respectively. On the other hand, in caecum, a non-consumptive tissue where the *E. tenella* primarily located, the drug concentrations were increased more when administered in drinking water. This revealed that the administration of the drug in drinking water is very important in terms of treatment options.

As a result, the tissue drug concentration in coccidiosed animals were remained high compared to the healthy animals and the concentration of the drug was higher in caecum than other tissues when given by drinking water to the coccidiosed animals. Furthermore, findings of this study indicate that the withdrawal time in infected animals which has taken sulphaquinoxaline could be longer in comparison to the healthy chickens.

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