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DETERMINATION OF THIAMPHENICOL LEVEL IN BREEDER CHICKENS BLOOD AND ITS RESIDUES IN FERTILE EGGS

By

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ABSTRACT

Thiamphenicol is a chloramphenicol homologue. Thiamphenicol (TAP) serum and egg concentrations in breeder hens were investigated in this study. with special reference to the fertility percent. One hundred-Twenty breeder hens and fifteen cockerels were used for the purpose of the experiment The hens were divided into three equal groups of 40 hens at random each and 5 cockerel the 1st and 2nd experimental groups received Thiamphenicol (30 mg/kg, 60 mg/kg orally for 5 days) was given to the first two groups, while the third was held as a control. TAP concentrations in serum and eggs were measured at 1, 3and 6 days post administration by using HPLC. Ten eggs were randomly collected for fertility detection at 1, 3and 6 days post administration. Thiamphenicol was distributed to serum and egg on the first day after the last dose, reaching (0.12± 0.06 mg/dL and 0.65±0.02 mg/gm) in the 30 mg/kg BW treated group and (0.63±0.03) mg/dL and 1.80±0.17 mg/gm) in the 60 mg/kg BW treated group. According to the previous findings, the maximum concentration was found in egg in the 60 mg/kg BW group. On the3rd day after last dosage, the measured level was not detected in serum in 30mg/kg comparison with groups Thiamphenicol detected only in serum of group 60 by 0.22±0.09 mg/dL but on egg it was detected as 1.4±0.19 mg/gm and 4.0±0.29 mg/gm in group 30 and group 60 respectively.

On the 6 day, the level of Thiamphenicol was still detectable only in the eggs of 60 mg/kg bw treated group (0.48±0.02) mg/gm.

It is clear from the study that, the concentration of Thiamphenicol in eggs was higher than the concentration in serum. In the 60 mg/kg groups, there was evidence of decreased fertility; on the third day, the fertility percentage was 0%. The control group, on the other hand, had a fertility rate of 70%. Fertility was poor until the sixth day following treatment. In this

treatment group, no chicks were hatched. There were no problems in hatching chicks once hatchability was returned to normal. While no abnormalities were discovered at necropsy on any of the hens, egg breakouts revealed that fetal deaths happened around day 5 of development.

Keywords:

Thiamphenicol,serum, egg, fertility and laying hens.

INTRODUCTION

Thiamphenicol (TAP), a broad-spectrum antibiotic belonging to the amphenicol family, is commonly used in veterinary and aquacultural medicine **(Campa-Córdova *et al.*, 2005; Dowling, 2013).** Antibiotics of this type attach to the ribosomal subunit in an irreversible manner, inhibiting protein synthesis **(Dowling, 2013).** Thiamphenicol is a chloramphenicol (CAP) derivative in which the p-nitro group is replaced by a sulfomethyl group, whereas florfenicol (FFC) replaces the hydroxyl group at the C-3 location with a fluorine atom. **(Sams, 1995)**.

Because of the deadly consequence of aplastic anemia, chloramphenicol, a strong bacteriostatic agent, is only used for serious infections when other medications are ineffective or more toxic **(Turton et al., 2000).** To reduce toxicity, Thiamphenicol (TAP) [d] (+) - Threo - 2 - di- chloroacetamido-1- (4-methylsulphonylphenyl) propane-1, 3-diol] is synthesized by substituting the aromatic nitro group with a methyl sulphonyl group. **(Kitamura *et al.*, 1997and Drago *et al.*, 2000).**

To detect the presence of drug residues, it is also required to use sensitive and precise procedure**. (Shankar *et al* 2010).** Drug residues are formed in animal end-products due to a lack of information about correct drug withdrawal times and the overuse or misuse of specific veterinary treatments. **(Seri, 2013).** To avoid the accumulation of residues in animal flesh, drug withdrawal times should be set.

(Kozarova *et al.*, 2004). To detect the presence of drug residues, it is also vital to use sensitive and precise procedures. Thiamphenicol was primarily used to treat bacterial infections in aquaculture, swine, and cattle, such as respiratory disorders and/or foot rot. However, it was only recently introduced to the poultry sector in order to improve flock health and production. **(Park *et al.*, 2008 and Koc *et al.*, 2009).** Only a few studies looked at

the dose, pharmacokinetics, and long-term effects of FFC in chickens. **(Shen *et al.*, 2003 and El-Banna and El-Zorba 2011).** However, before it is overused in the clinical application of breeder chickens, adequate toxicological and residue investigations should be undertaken. Veterinarian medications and feed additives can pass through the laying hen's digestive system and then into the egg. These chemicals' pharmacokinetic behavior and distribution to and within the egg are determined by their physicochemical properties. Drugs and additives that are lipid soluble are often expected to leave residues only in the fat-rich yolk. Conversely, the lipid-soluble medication doxycycline, and many other treatments,left larger concentrations in egg white than those in yolk after lengthy dosing. **(Cornelis and Michael, 2000).**

Despite the fact that florfenicol is currently permitted for use in veterinary medicine, its use in chickens is still restricted due to concerns about acquired antimicrobial resistance in avian species due to preexisting genes (FloR, CFC, or fexA). **(Kehrenberg and Schwarz, 2006)**. However, because to Thiamphenicol's advantages over other amphenicols and its availability as a feed addition, more residual data is required to protect against improper usage of the drug. Florfenicol is a known reproductive toxin, with most of the data coming from traditional mammalian laboratory toxicity testing. According to a summary material safety data sheet released by the **Schering-Plough (2012).**

Florfenicol, a widely known veterinarian compound, has been noted to also have prompted a major drop through egg production it has been used off-label on a laying hens brood stock farm in South Africa. Egg production fallen by 80 percent for close to a week after a 5 course of 10 mg/kg (both genders treated) to cure an Escherichia coli infestation. While research on mammalian toxicity suggest the possibility of early embryonic death in utero or testicular death, damage **AL-ShahraniandNaidoo2015).**On the avian toxicity of Thiamphenicol, there is just a little body of knowledge.

Therefore, the goal of this study is to determine Thiamphenicol residual levels in blood and eggs after breeder hens were given oral treatments of 30 mg/kg BW and 60 mg/kg BW for 5 days. HPLC was used to determine TAP concentrations in serum and eggs at 1, 3, and 6 days after withdrawal, with specific attention paid to the harmful effects of Thiamphenicol on egg fertility percent in breeder hens.

MATERIAL AND METHODS

Drug:

Thiamphenicol was given orally to breeder hens in therapeutic doses of 30 mg/kg BW and 60 mg/kg BW **(Shen *et al.*,2003)** as well as a twice-as-strong therapeutic dose To guarantee proper exposure, thiamphenicol was given directly into the crop once a day for five days.

Breeder hens:

One hundred - Twenty breeder hens and fifteen cockerels of 36 weeks old obtained from private company for poultry were used for the experiment. The chickens were divided into three groups of 40 hens each and five cockerels at random. Within breeder flocks, the hen to cockerel ratio was at the required 8:1 for maximum fertility. **(Al-Rawi.,1980)**.

Breeder hens were kept under hygienic condition and maintained on commercial balanced ration and water. Day light was the only source of light. Breeder chickens were observed for 20 days prior to the start of the experiment.

Design of an experiment:

One hundred - Twenty laying hens and fifteen cockerels were divided into three groups, each with 40 hens and five cockerels. Group 1 chickens received 5 oral doses of Thiamphenicol at 30 mg/kg BW over 5 days as a therapeutic dose **(Shen *et al.*, 2003).** Group 2 hens were administered the medicine at a twice therapeutic dose of 60 mg/kgBW. In the same way the third group, which was kept as a control group, did not get the medicine.

Sampling:

Blood and egg samples were taken from breeder hens (5 samples from each group) at 1, 3 and 6 days after the last dose. At the start, all blood samples were centrifuged. We took blood samples. From each bird's wing vein. In a clean centrifuge tube, for estimation of Thiamphenicol residue in serum and eggs of breeder hens by HPLC.

Forty-five Eggs were randomly collected fifteen eggs from each group on days 1, 3 and 6 post treatments for monitoring of fertility %.

Methods:

The levels of Thiamphenicol residue in serum and eggs of laying hens and egg were measured by HPLC All samples (Blood serum and eggs) were prepared and analyzed in Biochemistry Department, Animal Health Research Institute. On days 1, 3, and 6 after withdrawal, eggs from each group were randomly collected for Thiamphenicol content quantification using a

modified method of **Varma (1994).**The yolks and albumin were homogenized after cracking the eggs and discarding the shells. Two grams of egg homogenate in natural proportions were mixed with 100 µl of 10 µg/ml Thiamphenicol (internal standard) and 9 ml ethyl acetate, vortexed and subsequently centrifuged at 2000 Rpm for 15 min.

The supernatant was decanted into a fresh tube and dried for 30 minutes at 60°C under a stream of nitrogen before being combined with 2 ml Milli Q and 2 ml hexane and centrifuged at 2000 g for 15 minutes. The supernatant was treated to solid phase extraction (Varian BondElut C18) on cartridges primed with 4 ml methanol and 4 ml Milli Q50 water for final extraction. Following the sample loading, the cartridge was washed again with 2 mL Milli Q50 water before being vacuum dried for 5 minutes. 3 mL methanol was used for the final elution, which was done under vacuum for 5 minutes. The eluent was dried under a stream of nitrogen for 30 min at 60 °C, prior to being reconstituted in 500 ul of 30 % acetonitrile in reverse osmosis water (mobile phase) of which 100 µl was injected onto the column [Phenomenex guard cartridges (AJO - 4287) and LG reverse phase, Luna 5µaC18 (2); 100A; 150 × 4.6 mm] under isocratic flow of 1 ml/min. At 223 nm, a diode array on a Beckman HPLC was used for detection. Serum from each group was collected at random on days 1, 3, and 6 after withdrawal for determination of Thiamphenicol concentrations using a modified method of **Lewbart *et al.* (2005).** Ethyl acetate was used to extract the serum samples (1 mL) twice and then evaporated to dryness. The centrifuge tube was filled with 10 mL ethyl acetate. For 10 minutes, the mixture was violently shaking. The supernatant was transferred into another tube after centrifugation for 5 minutes at 5500 rpm.The preceding extraction phase was carried out a second time.

In a water bath at 45-50°C, the extracts were evaporated to dryness under nitrogen stream. After adding 2 millilitres of methanol, the tube was vortexed for roughly 30 seconds.

The tube was then filled with ten millilitres of 4 percent sodium chloride and twenty millilitres of hexane.

After that, the mixture was shaking violently for around 30 seconds. After allowing the layers to separate for a while, the hexane layer was aspirated out. The extract was defatted again, and a mild stream of nitrogen was used to evaporate it to dryness in a water bath. At 45-50 °C.

Clean-up:

Before analysis,the residues were reconstituted in 2 mL of mobile phase, vortexed, and put into an auto-sampler vial via a 0.45 m nylon centrifuge. After that, the extract was ready to be analyzed.

Calibration curve:

The peak regions and working solution concentrations were used to create the calibration curve. A series of working standard Thiamphenicol solutions at concentrations of 10.0, 5.0, 2.5, 1.0, 0.5, 0.25, 0.10, 0.05, 0.01 µg/mL which were made by diluting the stock solutions with acetonitrile-water (25:75) and then injecting them into HPLC and analyzing them.

Method validation:

Selectivity and Sensitivity.

At the retention time of the examined samples, no interference was found.

Thiamphenicol had a retention time of 3.4 minutes.

Accuracy and Precision:

The recovery was calculated by evaluating blank chicken serum spiked with a known concentration of Thiamphenicol on a regular basis.

For serum samples, the method's accuracy percent recovery varied from 89 to 97 percent, with relative standard deviations reflecting precision. (% RSD) of 0.37%.

Linearity:

The calibration curve was determined as Y= 4E - 06X -0.03 (r2 = 0.999) using the linear regression equation approach. The X symbol denoted the region under the peak, whereas the Y symbol denoted the Thiamphenicol concentration.The correlation coefficient was 0.999, indicating high linearity in the 0.039 to 2.5. µg/m range.

Fertility monitoring of birds:

Every day, hens and cockerels were examined for clinical symptoms. On certain days, eggs were collected for incubation (Buckeye egg incubator at 37 to 37.5 °C, 50% relative humidity, automatically flipped hourly) in order to determine fertility through candling, egg break-outs, or hatchings. Per time point, a total of 30 eggs were incubated.

On day 18, the eggs were candled for the final time. Break-outs were performed on eggs that were judged infertile after candling to identify the timing of embryonic death using conventional charts. **(Hyline, Technical Library 2012**), Fertile eggs, on the other hand, were

taken to hatch. The percentage of eggs containing viable fetuses from the break-outs is used to calculate fertility (percent fertility). Chicks were examined for general quality, such as their capacity to stand, feather cover, and shape of their beaks, movement abilities, and the presence or absence of open navels, for eggs taken to hatch.

Statistical analysis:

The data were presented in the form of a mean, standard error, and a Student (t) test. **(Snedicor and Cochran, 1987)**.

RESULTS AND DISSCUSION

During this time, no one died. Fertility is measured through candling, egg break-outs, and hatchings (Relative humidity is automatically switched hourly). A total of 30 eggs were incubated at each time point.

The eggs were candled for the final time on day 18. During research time, break-outs were conducted on eggs that were deemed infertile after candling to determine the timing of embryonic demise using traditional charts. In addition, hens treated with Thiamphenicol showed no symptoms of toxicity. Thiamphenicol toxicity appears to be limited to the developing embryo as a result of Thiamphenicol accumulation within the egg before to laying, given the lack of overt toxicity in hens **(Tavakkoli *et al.*, 2014).**

Serum and egg detection of Thiamphenicol is represented in (Table 1), Fig. (1.2, 3 and 4). All control samples were free from any residues. Thiamphenicol was dispersed to serum and egg on the first day after the previous treatment. (0.12±0.06 mg/dL and 0.65±0.02 mg/gm) respectively in 30 mg/kg bw treated group and (0.63±0.03 mg/dL and 1.8±0.17 mg/gm) in 60 mg/kg bw. According to the previous findings, the maximum level was found in egg in the 60 mg/kg bw group. On the3rd day after last dosage, the measured level was not detected in serum in 30mg/kg comparison with groups Thiamphenicol detected only in serum of group 60 by 0.22 ± 0.09 mg/dL but on egg it was detected as 1.4 ± 0.19 mg/gm and 4.0 ± 0.29 mg/gm in group 30 and group 60 respectively.

Thiamphenicol levels were still detectable on day 6 only in the eggs of the 60 mg/kg bw treatment group (0.48±0.02) mg/gm. **Samah *et al*. (2012).** Found a virtually same effect with low plasma Thiamphenicol levels. Thiamphenicol has a low affinity for blood proteins, resulting in extensive distribution of the medication in strongly perfused organs and tissue

(Chang *et al.,* 2009). It's also possible to conclude that in therapeutic doses, it's safe. **Lohani *et al.,* (2010**) determined a withdrawal time of 72 hours based on a depletion research for Florfenicol in poultry plasma and established Florfenicol pharmacokinetics in poultry plasma. Florfenicol was given to hens as a daily orally administered dose of 30 mg/kg bw for 5 days. Our investigation found a greater concentration of Thiamphenicol in eggs when compared to concomitant serum concentrations, which is consistent with previous findings. **Filazi *et al.,* (2014)** on the first day of both oral and parenteral dosage, 57 percent of Florfenicol was eliminated from the egg yolk, according to the researchers. In groups that received a single oral, intramuscular, or subcutaneous dose, FF was eliminated in 8 days, 9 days in groups that got multiple oral doses for 3 days, and 10 days in groups that received multiple oral doses for 5 days. **Giorgim *et al.,* (2000)** Average yolk and albumin Thiamphenicol concentrations vs. time data revealed that Thiamphenicol concentration was not identified in the yolk on the first day and was present in low concentration on the second day after a single oral treatment of 40 mg: kg of the drug to laying hens. On the sixth day, the drug concentration peaked, and then progressively declined until it was undetectable on the eleventh day.

Table (1): Concentration of Thiamphenicol (mg/dL) in the serum and eggs (mg/gm) (n = 5) after the withdrawal of treatment.

Dose / Time	30		60		Control	
	Serum	**Egg**	**Serum**	**Egg**	**Serum**	**Egg**
Day 1 after withdrawal	**0.12±0.06**	**0.65 ±0.02***	**0.63 ±0.03***	**1.8 ±0.17***	**ND**	**ND**
Day 3 after withdrawal	**ND**	**1.4± 0.19**	**0.22±0.09**	**4.0 ±0.29***	**ND**	**ND**
Day 6 after withdrawal	**ND**	**ND**	**ND**	**0.48±0.02**	**ND**	**ND**

The mean difference is significant at the 0.05 level ND non-detected.

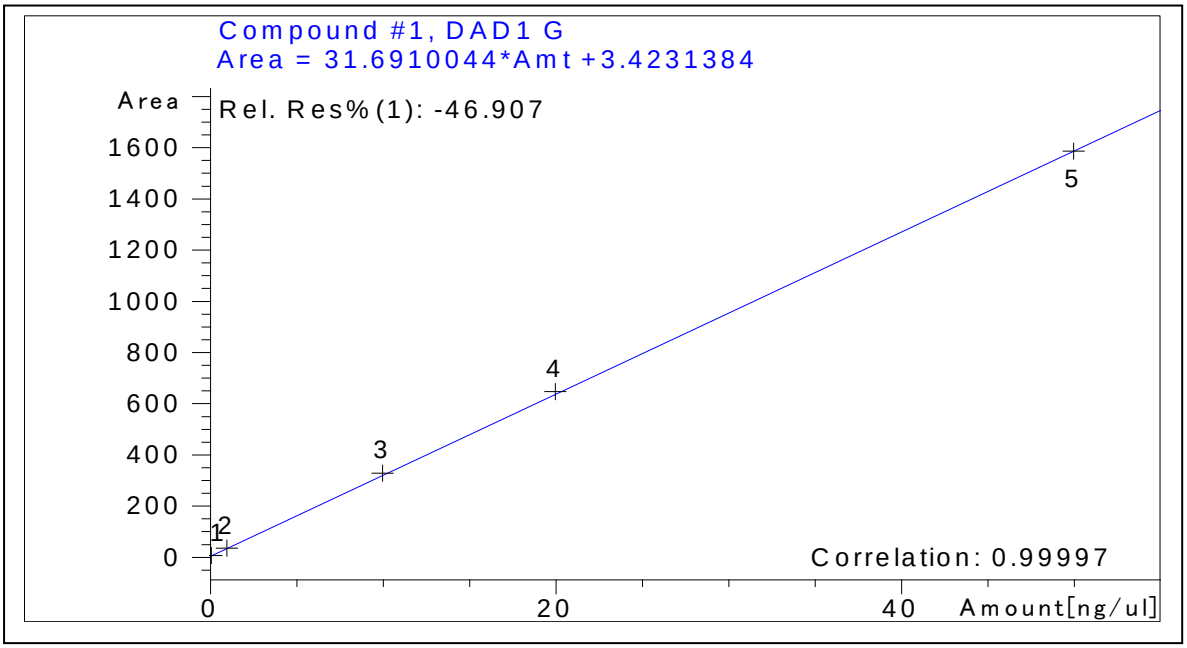

Fig. (1): The standard curve of the concentrations of Thiamphenicol prepared using peak areas obtained in HPLC.

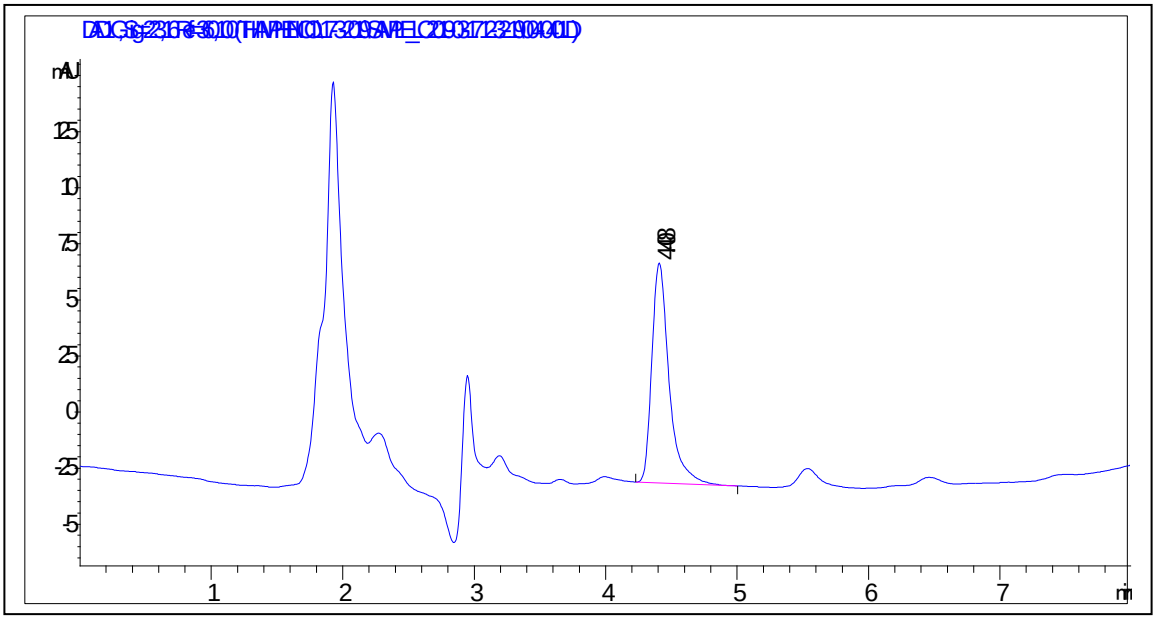

Fig. (2): Egg concentration (mg/gm) of Thiamphenicol following multiple dose (30 and 60 mg/ kg b.wt) oral administration in breeder hens.

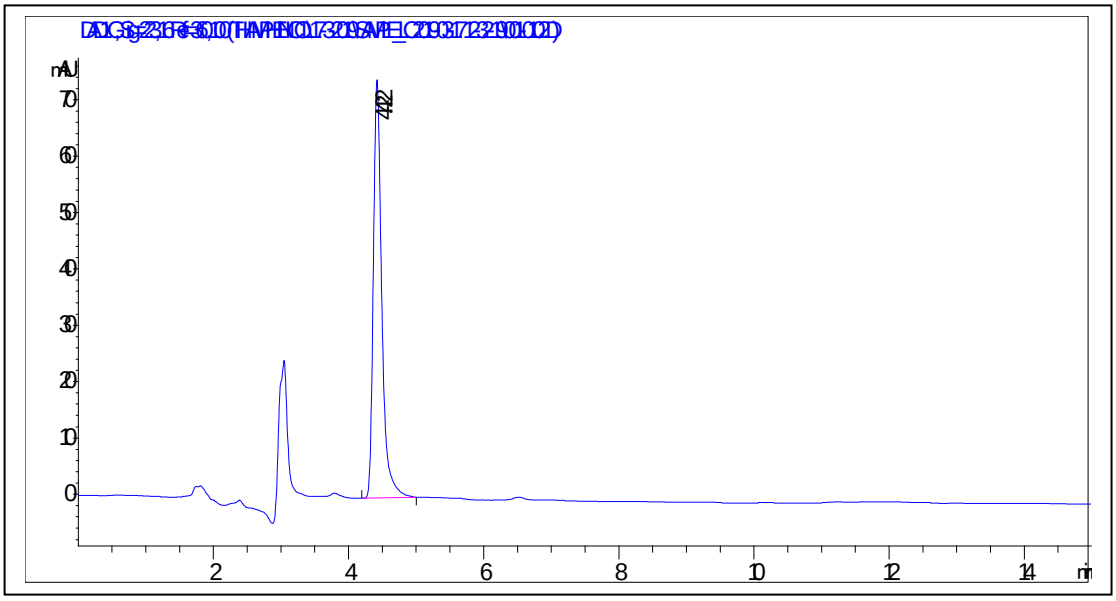

Fig. (3): Serum concentration (mg/ml) of Thiamphenicol following multiple dose (30 and 60 mg/kgBW) oral administration in breeder hens.

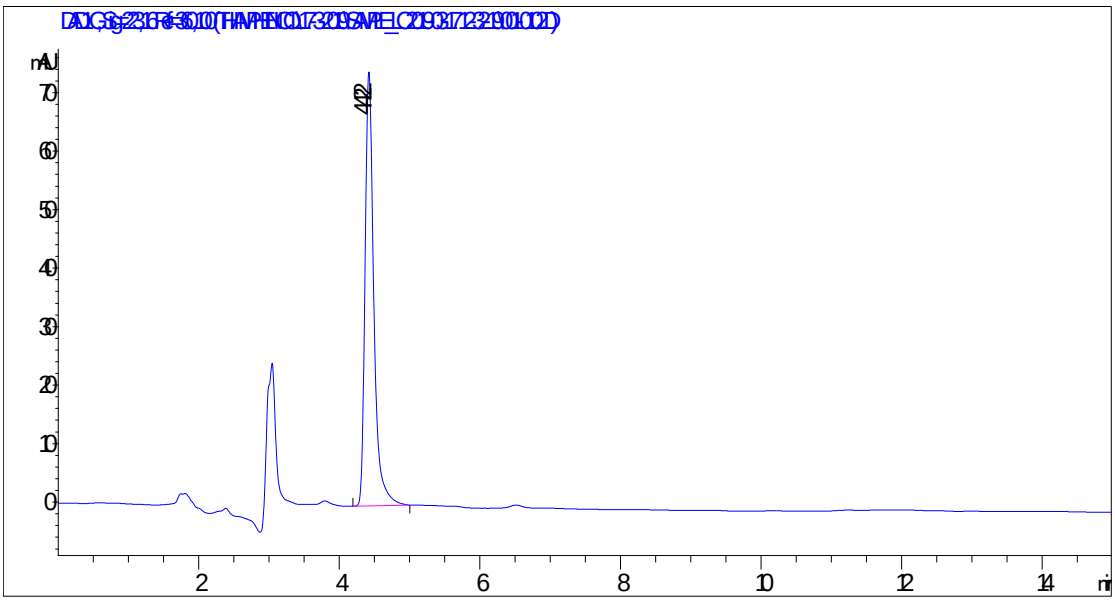

Fig. (4): Serum concentration (mg/ml) of Thiamphenicol following multiple dose (30 and 60 mg/kg BW) oral administration in breeder hens.

Table (2) the flock's fertility was typically outstanding, with break-outs indicating that it was above 70% at the start of each phase, and was comparable to the industry standard **(Anonymous 2007)**, with hatchability declining as expected as the flock became older. On certain days, fertility as assessed by hatchings was not as good as it had been for the break-outs. Because the oscillations are a natural occurrence, the treatment groups' findings were constantly compared to the control group to rule out any environmental influences on hatchability. In the 60 mg/kg groups, there was evidence of decreased fertility (Table 2), with day 3 percentage fertility being 0%. In comparison, the control group had a percentage fertility of 70 %. Fertility remained low until day 6 after treatment cessation, with no chicks hatching from treated group. Here after that, the percentage fertility of the control group was 70%. The treated group's fertility remained low until day 6 after treatment ended, with no chicks hatching. After hatchability had restored to normal, there were no signs of abnormalities in hatching chicks. While necropsy revealed no abnormalities in any of the hens, egg breakouts revealed that fetal fatalities occurred around day 5 of development.

Hatchability restored to control levels once there were no signs of anomalies in hatching chicks. While no abnormalities were discovered at necropsy on any of the hens, egg breakouts revealed that fetal deaths happened around day 5 of development. Finally, it was discovered that chloramphenicol interfered directly with mitochondrial protein synthesis by reducing the generation of mitochondrial cytochrome oxidase enzyme in a rat model of teratogenicity (Cytochrome C oxidase is the terminal enzyme in the electron transport chain located on the inner mitochondrial membrane) **(Bass*et al* .,1999).**

Because florfenicol and chloramphenicol both impede protein synthesis in the same way, it's likely that florfenicol is hazardous to the early stages of embryonic development by inhibiting fetal protein synthesis. Florfenicol works by blocking the peptidyl transferase enzyme and ribosomal translocation, both of which reduce protein synthesis, **(Sams, 1994) and Cannon, 1990).**

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Table (2): Fertility percentage recorded in treated hens and cockerels at 30, 60 mg/kg (n =15).

Time	Fertility percentage Dose administered (mg/kg)		
	(control)	30 (mg/kg)	60 (mg/kg)
Day 1 after withdrawal	70 %	64 %	12 %
Day 3 after withdrawal	74 %	71 %	0 %
Day 6 after withdrawal	80 %	80%	60 %

The time of egg collecting in relation to treatment is indicated by the word "time Fertility is expressed as a proportion of the total number of eggs incubated.

CONCLUSION

Thiamphenicol elevate residues in blood and consequently in fertile egg in which has an adverse effect on fertility % when administered at dose concentration of 60 mg/kg, its fetal Deaths occurred around the fifth day of development.

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قياس مستوى الثيامفنكول فى دم امهات الدجاج ومتبقياته فى البيض المخصب

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الملخص العربى

الثيامفينيكول هو نظير للكلورامفينيكول حيث تم قياس متبقيات الثيامفينيكول فى مصل الدم والبيض في امهات الدجاج مع الإشارة بشكل خاص إلى نسبة الخصوبة. تم استخدام مائة - عشرون دجاجة و 15 دبك (ديك لكل 8 دجاجات). تم تقسيم الطيور عشوائياً إلى ثلاث مجموعات من 40 دجاجة و 5 دبوك اعطيت الثيامفينيكول (30 مجم / كجم ، 60 مجم / كجم عن طريق الفم لمدة 5 أيام متتالية) .تم تحديد تركيزات الثيامفينيكول فى المصل والبيض في 1 و 3 و 6 أيام بعد االتوقف عن اعطاء الدواء. تم جمع البيض عشوائيا للكشف عن الخصوبة في 1 و 3 و 6 أيام. بعد االتوقف عن اعطاء الدواء وأظهرت النتائج انه في اليوم الأول بعد آخر جرعة ، تم توزيع متبقيات الثيامفينيكول على المصل والبيض وقد لوحظ ان أعلى مستوى في مجموعة البيض 60 ملغم / كغم من وزن الجسم. في الثالث بعد الجرعة الأخيرة ، لم يستدل غلى الثيامفينيكول في المصل في الدجاج الذى تناول 30 ملغم / كغم من وزن الجسم مقارنة مع في مصل المجموعة التى حصلت على 60 مجم / كجم . ، في حين تم زيادة المستوى المقاس بشكل كبير في البيض بالمقارنة مع اليوم الاول في كلا المجموعتين التجريبية. بينما في اليوم السادس، كان مستوى الثيامفينيكول لا يزال قابلاً للاكتشاف فقط في بيض المجموعة المعالجة 60 ملغم / كغم من وزن الجسم. في هذه الدراسة ، من الواضح أن تركيز الثيامفينيكول في البيض كان أعلى مقارنةً بتركيز المصل المتزامن. وأظهرت النتائج انخفاض الخصوبة في المجموعات 60 ملغ / كلغ). ظلت الخصوبة منخفضة حتى اليوم لثالث بعد توقف العلاج ثم عاودت الارتفاع حتى 60 % فى اليوم السادس ، ، فقد أظهرت النتائج ان الثيامفنيكول يسبب نقص الخصوبه وموت مبكر للاحنه عند استخدامه بجرعة60 مليحرام لكل كيلو حرام.