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The effect of fosbac on liver and kidney function parameters in broilers

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ABSTRACT

Objective: To investigate the effect of fosbac on some blood biochemical variables in broilers.
Methods: Fosbac with the dose of 160 and 320 mg/kg was added to drinking water of poultry for 5 days. For each dose, a separate control group was considered. Blood samples were collected 1 day post treatment (four groups of eight 20-day-old broilers) in the first experiment, and after 7 days post treatment (another four groups of eight 20-day-old broilers) in the second experiment. The serum aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase activity, uric acid, creatinine and urea concentrations were measured using routine laboratory methods.
Results: The results of this study showed that oral fosbac caused no significant effect on important liver and kidney function parameters.
Conclusions: It can be concluded that this antibiotic can be used safely in broilers.

1. Introduction

Growing and improving poultry industry is attributed to continuous application of antibiotics against infectious agents worldwide. Antibiotic fosfomycin is generally recognized for its wide-ranging properties against infectious diseases of broiler chickens[1-3]. Oral fosfomycin, not only has good safety profile with a low incidence of adverse events, but also possesses protective effect against nephrotoxicity in animals[4,5]. In addition, it exerts beneficial effects on lymphocyte and neutrophil functions[6]. Fosbac is an amazing bactericidal antibiotic which is created by attaching fructose 1, 6 diphosphate to double phosphate epoxy radical group on fosfomycin. This part is able to hide the portion of the molecule and help its transport into the cell. Once the bacteria uptake this drug as a nutrient by mistake, it inhibits phosphoenolpyruvate synthetase and prevents the formation of *N*-acetylmuramic acid and consequently, interferes with cell wall synthesis in both Gram-positive and Gram-negative bacteria. Its exclusive action provides synergistic effects to other antibiotics such as beta-lactams, aminoglycosides, and fluoroquinolones[7-12]. Despite significant difference in structure between fosfomycin and fosbac, and widely using of it in veterinary farms, the possible adverse effects of this drug have not been analyzed in birds. Clinical chemical analysis is a fundamental tool applied in human and veterinary medicine for diagnostic and therapeutic purposes. Hence, by conducting a pharmacological study in broilers, we evaluated the safety and effect of this drug on some liver function profiles such as serum lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alkaline phosphatase activity (ALP) as well as kidney variables such as serum creatinine, uric acid and urea.

2. Materials and methods

2.1. Birds

One-day-old chicks were purchased from a local hatchery

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All experiment procedures involving animals were conducted in accordance to the guidelines for use of animals in research and approved by the State Committee on Animal Ethics, School of Veterinary Medicine, Shahid Bahonar University of Kerman, Kerman, Iran.

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(Mahan Chicken Meat Production Complex, Kerman, Iran). This study was carried out at the hen house of Faculty of Veterinary Medicine, Shahid Bahonar University of Kerman, Kerman, Iran. The temperature of the place was (29 ± 1) ˚C and humidity 40%–50%. The light was given for 15 h per day from 6:00 am to 9:00 pm. They were maintained as flock for 20 days and then were assigned randomly into eight groups (each group contained eight chicks). They were fed on a regular starter diet for 7 days and then feed with grower diet, which were both formulated by Javaneh Khorasan Co., Iran. Food and fresh water were *ad libitum*. Fosbac® was purchased from Bedson Co., Argentina.

2.2. Ethical statement

All experiment procedures involving animals were conducted in accordance to the guidelines for use of animals in research and approved by the State Committee on Animal Ethics, School of Veterinary Medicine, Shahid Bahonar University of Kerman, Kerman, Iran.

2.3. Test procedure

We designed two experiments, including 32 chicks in each one. In the first experiment, we had four groups in which two were considered as controls and the other two groups as tests (each group contains eight chicks). The test groups for five consecutive days, received fosbac in their water at 160 mg/kg and 320 mg/kg, respectively. The first dose (160 mg/kg) is the therapeutic dose in broilers according to the instruction of the drug manufacturing company Bedson (www.bedson.co.za). We chose the second dose (320 mg/kg) two fold higher for assessing the safety of the drug. The required amount of fosbac® (g) per day was calculated according to Bedson company catalogue (www.bedson.co.za) as follows:

The required amount = Weight of animal (kg) × Number of animals × Dosage of fosbac (0.16)

In the first experiment, the blood samples were gathered one-day post treatment, *i.e*. on Day 6. Second experiment was just like the first one, but the blood samples were taken 7 days post treatment on Day 12. Each treatment group had its own control group in which their water contained no antibiotic. Fosbac was medicated orally through drinking water for consumption in the first 6–8 h of each day followed by fresh water for the rest of the day. Blood samples were collected in sterile test tubes and allowed to clot for 30 min. The sera were separated by following centrifugation at 4 000 r/min for 10 min and stored at –20 ˚C until assay.

2.4. Biochemical analysis

The serum was analyzed for AST, ALP, urea, uric acid and creatinine by using a commercial kit (Pars Azmoon Co., Tehran, Iran), LDH by (pyruvate-lactate) method.

2.5. Statistical analysis

Data were statistically analyzed by the software SPSS 22 (Statistical Package for the Social Sciences, version 22, SPSS; Chicago, USA). Independent samples *t*-test was used for the comparison of AST, LDH, ALP, uric acid, creatinine and urea means between control and test groups. Results are expressed as mean ± SEM. $P < 0.05$ was considered as statistically significant.

3. Results

Figures 1–3 represent the activity of enzymes AST, LDH and ALP in control and test groups, respectively. Concentrations of uric acid, creatinine and urea in control and test groups were shown in Figures 4–6, respectively. Oral consumption of fosbac had no effect on AST and ALP activities ($P > 0.05$). Non-significant difference was observed in LDH activity between control and test groups. There were no significant differences in creatinine and uric acid concentrations between control and test groups. On Day 6, there was a significant increase in urea concentration in the test group, which received 160 mg/kg of fosbac in comparison with control group ($P < 0.01$). On Day 12, urea concentration was also higher in test group of broilers, which received 320 mg/kg of this antibiotic in comparison with control group ($P < 0.01$).

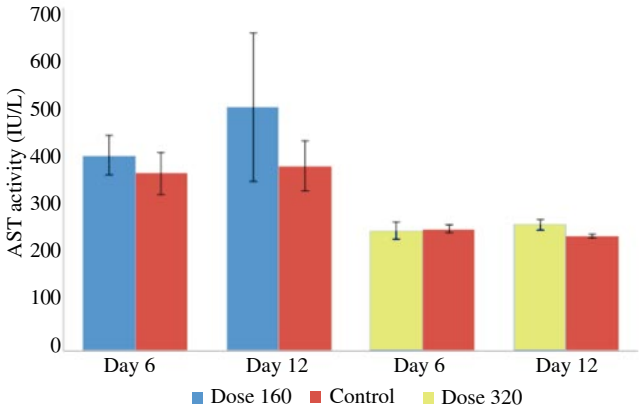

Figure 1. Fosbac effect on AST activity on broiler chickens in Days 6 and 12. Data presented as mean ± SEM.

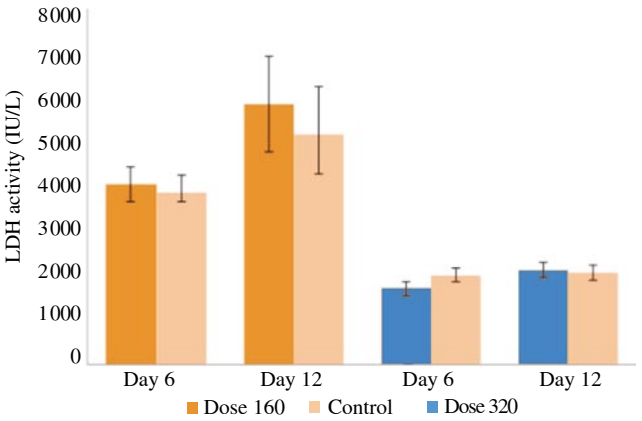

Figure 2. Fosbac effect on LDH activity on broiler chickens in Days 6 and 12. Data presented as mean ± SEM.

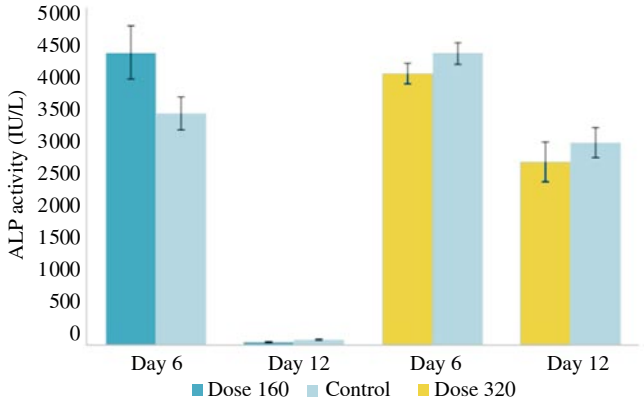

Figure 3. Fosbac effect on ALP activity in broiler chickens in Days 6 and 12.
Data presented as mean ± SEM.

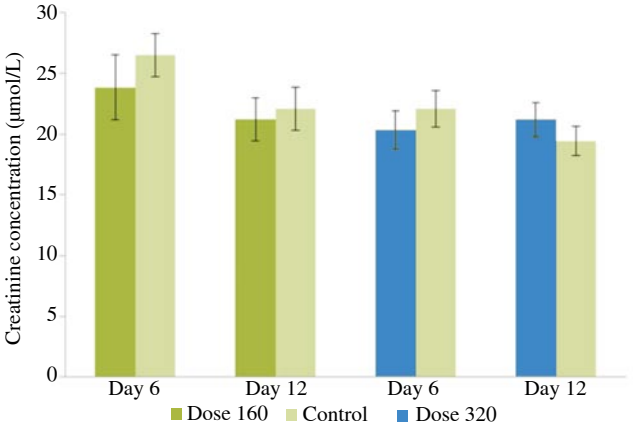

Figure 5. Fosbac effect on creatinine concentration in broiler chickens in Days 6 and 12.
Data presented as mean ± SEM.

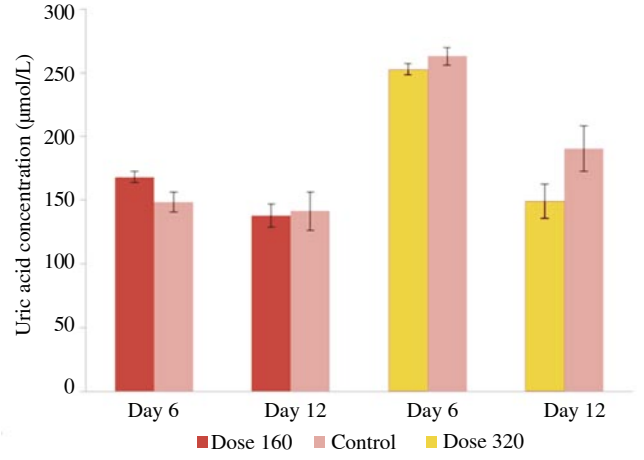

Figure 4. Fosbac effect on uric acid concentration in broiler chickens in Days 6 and 12.
Data presented as mean ± SEM.

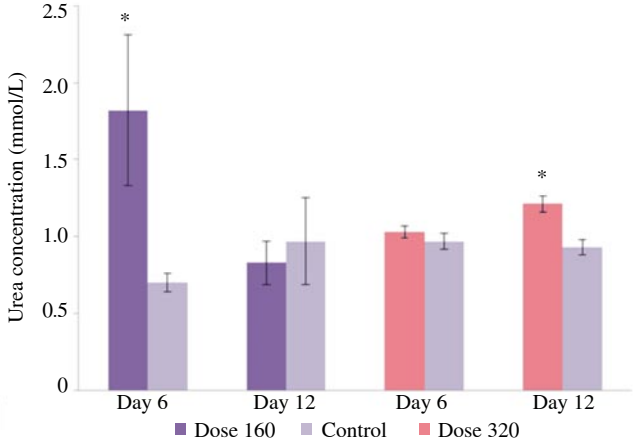

Figure 6. Fosbac effect on urea concentration in broiler chickens in Days 6 and 12.
Data presented as mean ± SEM. $P < 0.05$ was considered significantly different compared with control group. *: Significant difference ($P < 0.01$) compared with its own control group.

4. Discussion

In the present study, fosbac administration (160 and 320 mg/kg for 5 days) did not alter the important biochemical profile of liver and kidney in broiler chickens. Fosbac is a broad-spectrum antibiotic composed of fosfomycin and fructose 1, 6 diphosphate. The latter makes fosbac an antibiotic drug with low microbial resistance, due to gaining access into the cell as nutritional agent. In addition, its high permeability even to abscesses and areas with a poor vascularization makes it a popular drug for treatment of infectious poultry diseases. Fosfomycin pharmacokinetics have been well studied in veterinary field[13-15]. For example, Soraci *et al.*[13] showed that after intramuscular administration (15 mg/kg body weight) of disodium FOS, the drug reaches concentrations above the MIC90 of pathogens such as *Streptococcus*, for more than 8 h in bronchial epithelial lining fluid. These results demonstrate that FOS is useful for treating diseases caused by extracellular microorganisms that are involved in swine respiratory disease[13]. Despite all these advantages of fosbac, to the authors' knowledge, possible adverse effects of fosbac remain unclear in birds. To evaluate these effects on liver (as the principal site of drug detoxification), we assayed the activity of enzymes like AST, LDH and ALP. In our study, as shown in Figure 1, fosbac administration for 5 days at two different doses had no effect on AST activity between groups ($P > 0.05$). High AST activity has been reported in the liver such as ALT and in skeletal and heart muscles, brain, and kidney of birds[16,17]. Routinely, increase in plasma AST activity in birds is suggested when such activity is greater than 275 IU/L and it results from either hepatic or muscle injury, which allow the leakage of intracellular AST into the blood. Although this is not a specific test for providing information about hepatic function, but when AST activity is greater than 800 IU/L, it is indicative of a severe hepatic disorder[18]. In most species including birds, plasma ALT activity, also increases in such situations but has not get convenient advantage over AST as a test for hepatocellular disease[16,17]. As shown in Figure 2, there was no significant difference in LDH activity, between control and test groups. LDH is found in nearly all avian tissues and its plasma activity is less than 1 000 IU/L in normal birds, LDH increased activity above this value has been associated with hepatocellular disease[16,17]. Compared with AST and ALT, increase and then decline in plasma LDH activity is more rapid after liver or muscle damage[17,18]. No change in AST and LDH activity, after receiving

fosbac, suggests that fosbac is a safe drug for the liver. ALP activity occurs in multiple tissues including bone and liver. Outflow of this enzyme from injured cells and osteoblasts in birds resulted in plasma ALP elevation[19]. Based on Figure 3, non-significant difference in ALP activity was observed followed by fosbac treatment in test groups. Kidney injury, which is evidenced by significant elevation in the serum uric acid and creatinine levels, was not seen in our test groups. Uric acid, produced by the liver and kidneys, is the principal product of nitrogen metabolism in birds[19]. The kidneys clear most of the blood uric acid; therefore, a blood uric acid concentration greater than 13 mg/dL (750 μmol/L) has been extensively used in the detection of kidney disease in birds caused by multiple disorders such as urinary obstruction, nephritis, nephrocalcinosis, nephropathy and aminoglycoside antibiotics[20]. Creatinine is commonly considered to have diagnostic value just for severe renal disease[19]. As observed in Figures 4 and 5, fosbac administration had no effect on uric acid and creatinine concentrations between groups ($P > 0.05$); hence, it confirmed that fosbac is a safe drug for kidneys at these two doses. Significant increase in concentration of urea ($P < 0.01$) is the only parameter found after fosbac administration at 160 mg/kg on Day 6 and 320 mg/kg on Day 12 (Figure 6); whilst, urea concentration in former group was decreased non-significantly on Day 12 compared to Day 6. Additionally, birds are uricotelic and they have only very small quantities of urea in their plasma. Consequently, compared with uric acid, in most cases, urea has little diagnostic value in the detection of renal impairments in birds[19,21]. Our experiment indicated that fosbac administration for 5 days did not alter important liver and kidney biochemical parameters and this antibiotic is safe enough for using in poultry industry.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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References

[1] Gutierrez L, Ocampo L, Rosario C, Sumano H. Pharmacokinetics of disodium fosfomycin in broilers and dose strategies to comply with its pharmacodynamics versus *Escherichia coli*. *Poult Sci* 2010; **89**(10): 2106-15.

[2] Perez DS, Tapia MO, Soraci AL. Fosfomycin: uses and potentialities in veterinary medicine. *Open Vet J* 2014; **4**(1): 26-43.

[3] Perez DS, Soraci A, Tapia MO. Tissue disposition and withdrawal time of fosfomycin in swines after oral and intramuscular administration. *J Anim Prod Adv* 2013; **3**(4): 107-19.

[4] Pullukcu H, Tasbakan M, Sipahi OR. Fosfomycin in the treatment of extended spectrum beta-lactamase-producing *Escherichia coli*-related lower urinary tract infections. *Int J Antimicrob Agents* 2007; **29**(1): 62-5.

[5] Sweetman SC. *Martindale: the complete drug reference.* 35th ed. London: Pharmaceutical Press; 2007.

[6] Roussos N, Karageorgopoulos DE, Samonis G, Falagas ME. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections. *J Antimicrob Agents* 2009; **34**(6): 506-15.

[7] Gómez-Garcés JL, Gil-Romero Y, Sanz-Rodríguez N, Muñoz-Paraíso C, Regodón-Domínguez M. *In vitro* activity of fosfomycin, alone or in combination, against clinical isolates of carbapenem resistant *Pseudomonas aeruginosa*. *Enferm Infecc Microbiol Clin* 2016; **34**(4): 228-31.

[8] Hauser C, Hirzberger L, Unemo M, Furrer H, Endimiani A. *In vitro* activity of fosfomycin alone and in combination with ceftriaxone or azithromycin against clinical *Neisseria gonorrhoeae* isolates. *Antimicrob Agents Chemother* 2015; **59**: 1605-11.

[9] Kunakonvichaya B, Thirapanmethee K, Khuntayaporn P, Montakantikul P, Chomnawang MT. Synergistic effects of fosfomycin and carbapenems against carbapenem-resistant *Pseudomonas aeruginosa* clinical isolates. *Int J Antimicrob Agents* 2015; **45**(5): 556-7.

[10] Cunha BA, Gran A, Raza M. Persistent extended-spectrum beta lactamase-positive *Escherichia coli* chronic prostatitis successfully treated with a combination of fosfomycin and doxycycline. *Int J Antimicrob Agents* 2015; **45**(4): 427-9.

[11] Di X, Wang R, Liu B, Zhang X, Ni W, Wang J, et al. *In vitro* activity of fosfomycin in combination with colistin against clinical isolates of carbapenem-resistant *Pseudomas aeruginosa*. *J Antibiot* 2015; **68**(9): 551-5.

[12] Wind CM, de Vries HJ, van Dam AP. Determination of in vitro synergy for dual antimicrobial therapy against resistant *Neisseria gonorrhoeae* using Etest and agar dilution. *Int J Antimicrob Agents* 2015; **45**(3): 305-8.

[13] Soraci AL, Perez DS, Martinez G, Dieguez SN, Tapia MO, Amanto F, et al. Disodium-fosfomycin pharmacokinetics and bioavailability in post weaning piglets. *Res Vet Sci* 2011; **90**(3): 498-502.

[14] Gutierrez OL, Ocampo CL, Aguilera JR, Luna J, Sumano LH. Pharmacokinetics of disodium - fosfomycin in mongrel dogs. *Res Vet Sci* 2008; **85**(1): 156-61.

[15] Soraci AL, Perez DS, Tapia MO, Martínez G, Dieguez SN, Buronfosse-Roque F, et al. [Pharmacokinetics and bioavailability of fosfomycin in broiler chicken]. *Rev Med Vet* 2011; **162**(7): 358-63. French.

[16] Orlewick MS, Vovchuk E. Alanine aminotransferase. New York: Medscape; 2013. [Online] Available from: http://emedicine.medscape.com/article/2087247-overview [Accessed on November 14th, 2013]

[17] Senanayake SSHMML, Ranasinghe JGS, Waduge R, Nizanantha K, Alexander PABD. Changes in the serum enzyme levels and liver lesions of broiler birds reared under different management conditions. *Trop Agric Res* 2015; **26**(4): 584 -95.

[18] Hochleithner M, Hochleithner C, Harrison LD. *Clinical avian medicine.* Florida: Spix Publishing; 2005, p. 441-50.

[19] Terry W. Clinical chemistry of birds. In: Thrall MA, Weiser G, Allison RW, Campbell TW, editors. *Veterinary hematology and clinical chemistry.* Hoboken: John Wiley & Sons, Inc; 2012, p. 582-90.

[20] Goldstein DL, Skadhauge E. Renal and extrarenal regulation of body fluid composition. In: Whittow GC, editor. *Sturkie's avian physiology.* San Diego: Academic Press; 2000.

[21] Harr KE. Clinical chemistry of companion avian species: a review. *Vet Clin Pathol* 2002; **31**(3): 140-51.