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Effect of the Administration of Flumequine by Oral Route on the Resistance of *Escherichia coli* Against Quinolone During an Experimental Colibacillosis on Chiken of Flesh (Algeria)

[1]Nawel Lezzar, [1]Charaf Bensari, [2]Abdesselam Lezzar, [2]Farida Smati, [2]Kaddour Benlabed, [2]Chafia Bentchouala, [2]Houcine Laouar and [3]Dalila Satta

[1]Institut of Veterinary Science, Faculty of life sciences, Constantine1 University, Constantine, Algeria
[2]Service of Microbiology Laboratory of CHU of Constantine, Faculty of Médicine, Constantine3 University, Constantine, Algeria
[3]Department of Biology, Faculty of life sciences, Constantine1 University, Constantine, Algeria

Abstract: The aim of our study is to highlight the impact of an oral treatment with quinolones (flumequine for 3 days to 5 days and enrofloxacin for 3 days) on the emergence of resistant strains of *Escherichia coli* (O78:K80) in order to define the most adapted regimen in treatment of avian colibacillosis. The emergence of *Escherichia coli* resistant strains with high levels of resistance were found in subjects treated during 24 hours of drinking and particularly more pronounced in the strain ISA 15 treated with flumequine and enrofloxacin. The antibiotic molecule, the mode of administration and animal strain appear to be involved in this emerging antibiotic resistance to quinolones and their resistance levels. The supervision of antibiotic resistance based on the control of these three elements is required.

Key words: Oral Treatment · Fluméquine · Quinolones · *Escherichia coli* · Antibiotic Resistance · Broilers

INTRODUCTION

In veterinary medicine, improving the use of antibiotics and reduce the impact on antibiotic resistance requires work in two directions: - the first is to improve the process of establishing doses of antibiotics and their therapeutic indications, taking into account both their effectiveness and their therapeutic effects on the selection of resistance by integrating knowledge in pharmacology and epidemiology of resistance - the second is the development of studies and epidemiological surveys about the context of use of antibiotics to increase consideration of epidemiological information on animal diseases, including antibiotic resistance by veterinary practitioners. As part of good farming practices and good clinical practice, it will foster the development of monitoring networks implemented by practitioners and farmers, in partnership with the diagnostic laboratories to obtain a local management of antibiotic resistance.

In broilers, avian colibacillosis is frequently associated with *Escherichia coli* strains of serotypes *O1:K1*, *O2:K1* and *O78:K80* [1,5]. The major infectious diseases they cause are responsible for economic losses [3, 5,14].

The most effective antibiotic used in treatment of avian colibacillosis was quinolones and flumequine represents a standard treatment in this indication [3, 8, 11, 15,17].

Thus we tested two molecules: flumequine and enrofloxacin basing on the mode of administration and duration of treatment (03h/24h and 24h/24h of watering) on two strains of broiler strains (identified strain: ISA15 and unidentified strain: farm's chicken) in treatment of avian colibacillosis experimental.

Through this experience was undertaken to evaluate the emergence of resistant strains of *Escherichia coli*.

Corresponding Author: Nawel Lezzar, Institut of Veterinary Science, Faculty of Life Sciences, Constantine1 University, Constantine, Algeria.

MATERIALS AND METHODS

Animals and Housing: The experiment was conducted on identified broiler strain (ISA 15) and unidentified (farm's chicken), brought up on a litter of wooden shavings and subjected to natural lighting and static ventilation. Hoppers and siphon-like drinking troughs in appropriate number complete the equipment of breeding [3, 8, 11, 17].

Allotment: The allotment was made 4 days before the incubation (D-4). The subjects were divided in 6 experimental groups for every animal origin at the rate of 10 subjects / m^2.

- 1st and 2nd lot of 20 subjects for each inoculated and treated with the fluméquine on 03h/24h and 24h/24h watering respectively,
- 3rd and 4th lot of 20 subjects for each inoculated and treated with enrofloxacin on 03h/24h and 24h/24 h watering,
- 5th and 6th lot of 10 subjects as control (positive control =T+, inoculated and untreated and negative control=T-, uninoculated and untreated respectively) [3].

Inoculums and Inoculation: The experiment was carried out using a collection of highly pathogenic strain of *Escherichia coli* obtained from Veterinary Regional Laboratory of Constantine. The inoculums of serotype *O78:K80* was prepared in the same day of use by diluting the suspension in buffer media PBS (Phosphate Buffer Saline) at pH of 7.4 [3, 16, 18]. The inoculation was performed at D0, on subjects of 21 days old, by deep intramuscular injection into the breast muscle of a dose diluted in 1/5 (selected dose) in a volume of 0,1ml [3, 17, 19].

Treatment: Depending on whether the mode of treatment of drinking 03h/24h or 24h/24h watering, the dose of flumequine (Fluméquine10% in.) and enrofloxacin (Baytril ® 10% po) was calculated based on the weight of the bird and the amount of water consumed per day to allow the ingestion of a therapeutically effective dose. Treatments are introduced in drinking water 48 hours after inoculation (D+2) [17, 3]. The duration of treatment was 3 days for enrofloxacin (D+2 to D+4) and 3 to 5 days for flumequine (D+2 to D+4 or D+2 to D+6) according to changes in symptoms [3].

Samples of faeces by cloacal swabs: They are made before and after inoculation and treatment (D-4 to D+8) to define the sensitivity profile of *Escherichia coli* after their identification in this experimental study. A collection of droppings was taken on a subject chosen at random per lot per day [3]. Every day 12 samples were immediately transported to the bacteriology department of the CHU of Constantine. In total, 156 samples are intended for bacteriological analysis.

Identification of strains of *Escherichia coli*: The digital profile of *Escherichia coli* were defined by API20E gallery (BioMérieux, SA69280 Marcy-l'Etoile, France), which gives high reliability identification [20, 21, 3, 12, 5]. The serotype of *Escherichia coli* used in this experimental study were confirmed by the slide agglutination test with specific antiserum to strain *E. coli O78: K80* (Reagent *E. coli* / Poultry *O78: K80* / Lot: 100-02 / I-221-055-01) from the Veterinary Department of the Pasteur Institute of Algiers [3].

Susceptibility: It was performed on Mueller-Hinton (Pasteur institute in Algiers) using standardized according to the method of standardized disk diffusion antibiotic and interpreted according to the recommendations of the CASFM and the logicial WHONET [3]. To evaluate the sensitivity of the strain *E. coli O78:K80* before inoculation, thirty antibiotics were tested: nalidixic acid, amikacin, amoxicillin, amoxicillin + clavulanic acid, aztreonam, Cephalothin, cefepime, cefotaxime, cefoxitin, ceftazidime, chloramphenicol, ciprofloxacin, colistin, enrofloxacin, Flumequine, Gentamicin, Imipenem, kanamycin, minocycline, netilmicin, norfloxacin, pefloxacin, piperacillin, Streptomycin, Sulfonamides, Tetracycline, Ticarcillin, Tobramycin, trimethoprim, Sulfamethoxazole + trimethoprim + [16, 22, 29, 3, 12, 4, 26, 27, 14, 5]. These antibiotics were also tested on the reference strain *E. coli* ATCC 25922 Microbiology Laboratory of CHU of Constantine for proper interpretation of results. An antibiogram was performed before initiation of treatment (D-4 to D+1), to check the sensitivity of *Escherichia coli* used in this experimental study to six quinolones follows: nalidixic acid, ciprofloxacin, enrofloxacin, Flumequine, norfloxacin, pefloxacin [28, 29, 3]. These antibiotics are tested after initiation of treatment (D+2 to D+8) [3].

Table 1: Identification of strains of *Escherichia coli* (serotype profile digital) per lot and per animal strain

	ISA 15						PF					
Animal strain												
Allotment	T+	FL03+	FL24+	EN03+	EN24+	T-	T+	FL03+	FL24+	EN03+	EN24+	T-
D-4	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*
D-3	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*
D-2	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*
D-1	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*
D 0	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*
D+1	*O78:k80*	*E. coli1*	*O78:k80*	*O78:k80*	*O78:k80*	*E. coli1*	*O78:k80*	*O78:k80*	*O78:k80*	*O78:k80*	*E. coli1*	*E. coli1*
D+2	*O78:k80*	*O78:k80*	*O78:k80*	*E. coli1*	*E. coli1*	*E. coli1*	*O78:k80*	*O78:k80*	*E. coli1*	*O78:k80*	*O78:k80*	*E. coli1*
D+3	*E. coli1*	*E. coli1*	*O78:k80*	*O78:k80*	*E. coli1*	*E. coli1*	*O78:k80*	*O78:k80*	*E. coli1*	*E. coli1*	*E. coli1*	*E. coli1*
D+4	*O78:k80*	*E. coli1*	*E. coli1*	*O78:k80*	*O78:k80*	*E. coli1*	*E. coli1*	*E. coli1*	*O78:k80*	*O78:k80*	*O78:k80*	*E. coli1*
D+5	*O78:k80*	*O78:k80*	*O78:k80*	*O78:k80*	*O78:k80*	*E. coli1*	*O78:k80*	*O78:k80*	*O78:k80*	*E. coli1*	*O78:k80*	*E. coli1*
D+6	*E. coli1*	*O78:k80*	*O78:k80*	*E. coli1*	*E. coli1*	*E. coli1*	*O78:k80*	*E. coli1*	*O78:k80*	*O78:k80*	*O78:k80*	*E. coli1*
D+7	*E. coli1*	*E. coli1*	*O78:k80*	*E. coli1*	*O78:k80*	*E. coli1*	*O78:k80*	*O78:k80*	*O78:k80*	*O78:k80*	*E. coli1*	*E. coli1*
D+8	*O78:k80*	*O78:k80*	*O78:k80*	*O78:k80*	*O78:k80*	*E. coli1*	*E. coli1*	*O78:k80*	*E. coli1*	*O78:k80*	*O78:k80*	*E. coli1*

Animal strain : identified strain (ISA15) and unidentified strain (PF=farm's chiken) ; Allotment : T+ (positive control), T- (negative control), FL (flumequine), EN (enrofloxacin), 03 (watering on 3h), 24 (watering on24h), + (inoculated subjects), - (uninoculated subjects) ; D 0 (day of inoculation) ; Digital profil of *E.coli* (*E.coli1*) ; Serotype of *E.coli* (*O78:k80*).

Table 2: Susceptibility of *Escherichia coli* to quinolones per lot and per animal strain

	ISA 15						PF					
Animal strain												
Allotment	T+	FL03+	FL24+	EN03+	EN24+	T-	T+	FL03+	FL24+	EN03+	EN24+	T-
D-4	S	S	S	S	S	S	S	S	S	S	S	S
D-3	S	S	S	S	S	S	S	S	S	S	S	S
D-2	S	S	S	S	S	S	S	S	S	S	S	S
D-1	S	S	S	S	S	S	S	S	S	S	S	S
D 0	S	S	S	S	S	S	S	S	S	S	S	S
D+1	S	S	S	S	S	S	S	S	S	S	S	S
D+2	S	S	S	S	S	S	S	S	S	S	S	S
D+3	S	S	R++	S	R	S	S	S	R	S	R	S
D+4	S	S	R++	S	R++	S	S	S	R	S	R	S
D+5	S	S	R++	S	R	S	S	S	R	S	R	S
D+6	S	S	R++	S	R++	S	S	S	R	S	R	S
D+7	S	S	R	S	R++	S	S	S	R	S	R	S
D+8	S	S	R++	S	R	S	S	S	R	S	R	S

Animal strain : Identified strain (ISA15) and unidentified strain (PF=farm's chiken) ; Allotement : T+ (positive control), T- (négative control), FL (flumequine), EN (enrofloxacin), 03 (watering on 3h), 24 (watering on 24h), + (inoculated subjects), - (uninoculated subjects) ; D 0 (day of inoculation) ; Profil of susceptibility : S (sensible), R (resistant), R++ (highly resistant).

RESULTS

Bacteriological results: The 156 strains of *Escherichia coli* experimental study show the digital profile 5144572, which corresponds to *Escherichia coli*, according to the references of analytical catalog API 20 E (Biomerieux, SA69280 Marcy-l'Etoile, France) (Table 1). Only 54 of 156 strains of *Escherichia coli* of the experimental study were positive to the test slide agglutination with specific antiserum to the *E. coli* strain *O78: K80* from the inoculated lots (Table 1).

Evaluation of antibiotic resistance vs. sensitivity: Different susceptibility performed on the *E. coli O78: K80* before inoculation and the reference strain *E. coli* ATCC 25922 revealed their sensitivity to tested antibiotics. Strains of *Escherichia coli* (*E. coli 1* and *E. coli O78: K80*) were susceptible to quinolones before initiation of treatment (Table 2). After initiation of therapy, resistant strains of *Escherichia coli* (*E. coli 1* and *E. coli O78: K80*) to six quinolones appeared with two levels of resistance: resistance to more than two quinolones (nalidixic acid and flumequine) observed in resistant strains from groups receiving flumequine and enrofloxacin on 24h watering in both animal strains (ISA15 and farm's chicken) and resistance to six quinolones, observed in highly resistant strains from groups receiving flumequine and enrofloxacin on 24h watering only in the ISA15 (Table 2).

DISCUSSION

The results of our experiment performed on pathogenic and saprophytic strains of *Escherichia coli* before and after inoculation and treatment revealed the emergence of antibiotic resistance in a bacterial population initially sensitive, becoming resistant after contact with the antibiotic [3, 27, 14]. This bacterial population proved resistant to at least two quinolones (nalidixic acid and flumequine), with the appearance of multiresistant strains of commensal *Escherichia coli* (*E. coli 1*) and pathogens (*O78: K80*) [3, 27, 14]. We identified two resistance levels by the presence of bacterial strains resistant and highly resistant. The former are resistant to one or more than two quinolones and affect both animal strains (ISA15 and PF) and the second exhibit resistance to six quinolones and affect animal strain ISA15 only [3]. This antibiotic resistance was found only in treated groups at therapeutic doses over 24 hours of watering whatever the used quinolone [3].

On the basis of all these observations, the hypothesis of the presence of factors favoring the appearance of this antibiotic resistance is emitted. According to Brown [30] Mogenet and Fedida [31], this resistance depends on some parameters related to the administered antibiotic molecule (nature and concentration of the quinolone administered and the route of administration and duration of treatment) [3].

On the molecule, we believe that antibiotic resistance found in all subjects watering on 24 hours was directly related to the antibiotic [27] and the offending factor in addition to the mode of distribution of the molecule itself, since has been shown that anti-infectious such as flumequine may promote the selection of resistant mutants [17, 32, 3].

The results of an experimental study in chickens have shown the emergence and persistence of resistant strains to fluoroquinolones following treatment with enrofloxacin at therapeutic doses [33, 34, 3, 14]. Phenotype of resistance depends on the duration of treatment. This resistance seems to be also related to the animal strain. Indeed, the highly resistant strains appeared at ISA'S 15 only. The pathogenic agent transmitted resistance to saprophytic strains in subjects more receptive than others, hence the emergence of highly resistant strains in the ISA 15 [3]. This joins the results obtained by Mellata *et al*. [25].

CONCLUSION

This study has allowed establishing the impact of oral treatment with quinolones on the emergence of resistant strains of *Escherichia coli* in broiler and setting the most appropriate regimen in the treatment of avian colibacillosis. Flumequine remains a standard treatment in avian colibacillosis when it is distributed over three hours drinking.

The emergence of resistant strains of *Escherichia coli* with high levels of resistance were identified in patients treated for 24 hours drinking and more pronounced in the strain ISA 15 treated with flumequine and enrofloxacin.

Many factors such as the antibiotic molecule (flumequine or enrofloxacin), the mode of administration (03 h of watering) and animal strain (strain ISA 15) are likely to play a role in the development of resistant bacteria and act on their level of resistance. Therefore, monitoring of antibiotic resistance is needed at all levels of the poultry industry.

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