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*Full Length Research Paper*

# Pharmacokinetics of albendazole and albendazole sulfoxide after oral administration to farm chicken

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The present study was conducted to determine the pharmacokinetic parameters of two anti-parasite drugs: albendazole and albendazole sulfoxide, following oral administration to farm chicken at a single dose of 10 mg/kg body weight. The experiment was done on eight male adult chickens. The HPLC technique was used to determine drug concentrations in plasma. Various pharmacokinetic parameters, including the area under curve (AUC), the maximum plasma concentration (C<sub>max</sub>), the maximum concentration (T<sub>max</sub>), and the mean residence time (MRT), were determined for both anthelmintics and their metabolites albendazole sulfoxide (ABZSO) and albendazole sulfone (ABZSO<sub>2</sub>). The ABZ was detectable up to 32 hours with a maximum plasma concentration C<sub>max</sub> of (0.393-0.557ug/ml) and its metabolites ABZSO and ABZSO<sub>2</sub> were detected with a C<sub>max</sub> of (0.393-0.557 ug / ml) and (0.393-0.557ug /ml) with a T<sub>max</sub> of (6.75 , 3.49h) and (16.125-6.59h, respectively. The metabolites of ABZ remain detectable up to 48 hours. The administration of ABZSO to farm chicken showed better bioavailability compared to ABZ. In conclusion, both anthelmintics showed more favorable pharmacokinetic results on farm chicken compared to data collected on broiler chicken.

**Keywords:** Farm chickens, Albendazole, Single dose, Oral administration, Pharmacokinetics

## I-INTRODUCTION

Rural poultry that live at large and find their own food help to fight against insects and pests such as cattle ticks. They produce manure that is used to fertilize crops and vegetables. Extensive poultry production does not produce huge amounts of waste and does not use industrial feeds containing monoculture cereals.

In Morocco village poultry sells at a higher price than commercial poultry because they have not been treated with antibiotics or hormones.

Traditional or farmed poultry breeding plays a primordial socio-economic role in the rural regions of Morocco, where it contributes to the improvement of the nutritional status and household income.

Furthermore, such type of breeding makes it possible to attenuate the gender effect since it is a female activity. This

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sector could thus be a lever for sustainable rural development. In fact, several egg hatching units have been established in various parts of the country to supply the chicken market. However, the development of the farm chicken sector faces numerous technical and health constraint (Arfaoui 2000; Kichou et al., 2002).

In terms of health, the absence of pharmacological data specific to farm chicken prevents the use of medicines with a maximum of efficiency and safety in this poultry. In fact, the drugs are currently used according to the established procedures for industrial chicken. This approach may entail risks to both the animal (therapeutic failure / toxicity) and the consumer (residues).

## II- MEDIUM, MATERIAL AND METHOD

### II-1-Medium of study

The rural commune of Ichou is part of the circle of Oulmas, province of Khemisset. It is located on the plateau of Oulmes has an altitude of 830m and occupies an area of 98,23km<sup>2</sup>.

Geographically, the rural commune of Ichou is limited :

- To the north, by the rural commune of Ikkou;
- To the south, by the rural commune d Oulmes;
- In the east, by the rural district of Boukachmir;
- To the west, by the rural community of Tiddas.

### II-2- MATERIAL AND METHOD

Eight healthy male local chickens body weight an average of 1.5 kg at the beginning of the tests. Water soluble powder of albendazole (2,5%) and albendazole sulfoxide (1,9%) was obtained from Intervet-Morocco and diluted 1/5 of sterile water to prepare oral solution at the final concentration of 200mg/ml. The solution for two drugs were administered by oral gavage with an appropriate length plastic catheter at a dose of 10mg/kg BW, a 10-day rest period separates the two experiments. Blood samples were collected at time 0 (before administration), and 1h, 3h, 6h, 9h, 12h, 24h, 32 h and 48 h. The blood samples (about 1ml) were collected from the wing vein and collected into the heparin zed tubes using the syringe coated by heparin. Then plasma was collected by centrifugation at 3000 rpm for 10 min and stored at -18°C until further analysis. In this study, another 6 farm chickens served as control group, and they were not treated with ABZ and ABZSO. Plasma samples were collected from them simultaneously with the treatment group and then used for drug quantization and method validation.

## III-RESULTS AND DISCUSSIONS

Concentration of albendazole and its metabolites albendazole sulfoxide and albendazole sulfone were determined by high-performance liquid chromatography (HPLC) technique inspired by that described in the literature (Bogan and Marriner 1980) for ABZ and (El gadari 2001), for ABZSO. Calibration standard were made spiking blank plasma with albendazole and its metabolites, to concentration of 0.01, 0.05, 0.1 and 0.5µg / ml and 0.01, 0.05, 0.5, 1.2 and 5 µg / ml of mobile phase for ABZSO and its metabolite ABZSO<sub>2</sub>. The extraction of ABZ and ABZSO consists of: 100 µl of plasma is deproteinized with 300 µl of ethyl acetate, the solution was shaken in vortex for 20 s and centrifuged at 5400 rpm for 10 min, The organic phase is collected in conical tubes and evaporated to dryness at 60 °C under a stream of air. The dry extract is taken up in 200 µl of methanol. Elution and separation of the analytes was performed using a mobile phase composed of acetonitrile: ammonium carbonate (0.025M) (30:70; v: v). 20 µl of each extract is injected into the chromatograph equipped with of a Nucleosil RP C18 column, 150 x 4.6 mm, 7 µm. The mobile phase was filtered (0.45 µm of porosity), degassed under vacuum and used at a flow rate of 0.7 ml/ min. The detection was performed at a wave length of 282 nm for ABZ and 296 nm for ABZSO.

The HPLC technique used was validated to assess linearity and reliability and to determine the rate of extraction. The HPLC assay method presented was found to be linear and reproducible across the range from 0.1 to 10µg/ml. The technique makes it possible to obtain extraction rates of 70%, 85.7%, and 74.4% for the ABZ, the ABZSO and the ABZSO<sub>2</sub>, respectively and all interday and intraday coefficients of variation were below respectively 4,5%, 3,5%.

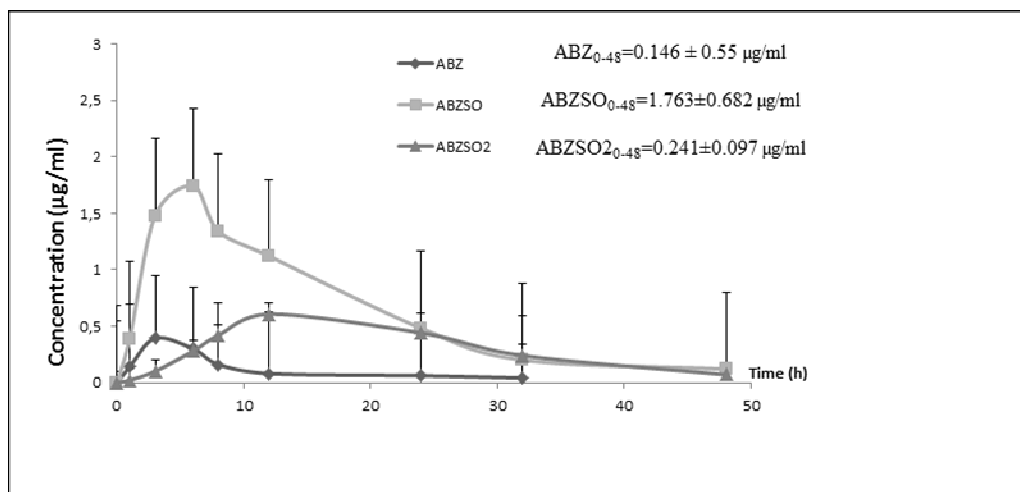
Plasma ABZ and its metabolites (ABZ-SO and ABZSO<sub>2</sub>) versus time data for each local chicken was subjected to pharmacokinetics analysis using the adapted pharmacokinetic software of multi (Yamaoka et al., 1981). Data were analyzed to determine the compartmental parameters of ABZ and its metabolites. The peak concentration (C<sub>max</sub>) and time to reach it (T<sub>max</sub>) were directly read from the experimental data. The area under the concentration versus time curve (AUC) and mean residence time (MRT) were calculated using the arithmetic trapezoidal method (Gibaldi and Perrier 1982).

The mean concentration of albendazole and its metabolites (ABZSO and ABZSO<sub>2</sub>) after single dose were presented in Figure 1 and the pharmacokinetics parameters after single oral doses of Albendazole are summarized in the Table 1. The mean concentration of albendazole sulfoxide and Albendazole sulfone after single

**Table 1** Mean  $\pm$ SD of values pharmacokinetics parameters for albendazole after oral administration of 10mg/kg BW to eight

Parameter	unit	ABZ	ABZSO	ABZSO <sub>2</sub>
C <sub>max</sub>	µg/ml	0.393 $\pm$ 0.557	1.743 $\pm$ 0.682	0.607 $\pm$ 0.097
T <sub>max</sub>	h	3.375 $\pm$ 2.825	6.75 $\pm$ 3.494	16.125 $\pm$ 6.599
AUC <sub>t0-t<math>\infty</math></sub>	µg.h/ml	3.193 $\pm$ 4.129	28.794 $\pm$ 8.307	13.674 $\pm$ 3.239
MRT <sub>t0-t<math>\infty</math></sub>	h	7.849 $\pm$ 3.683	12.943 $\pm$ 3.440	19.308 $\pm$ 4.245

Notes. C<sub>max</sub> : The peak concentration; T<sub>max</sub> :time to reach peak concentration; AUC t0-t $\infty$ : area under the concentration- time curve from 0 to infinity; MRT: mean residue time

**Figure 1** concentration (µg/ml) in plasma following single dose of Albendazole by oral gavage in farm chickens**Table 2:** Mean  $\pm$ SD of values pharmacokinetics parameters for Albendazole sulfoxide (ABZSO) after oral administration of 10mg/kg BW to eight farm chickens

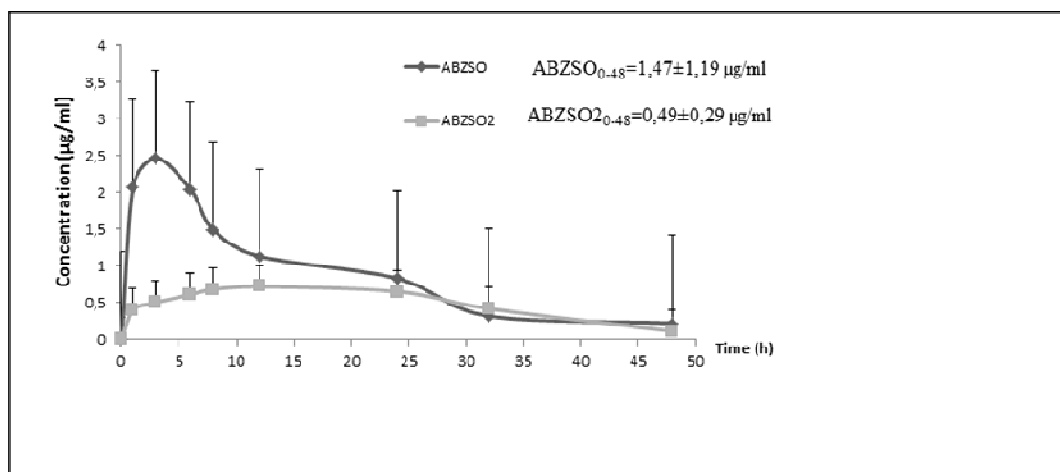
Parameter	unit	ABZSO	ABZSO <sub>2</sub>
C <sub>max</sub>	µg/ml	2.47 $\pm$ 0.80	0.72 $\pm$ 0.19
T <sub>max</sub>	h	4.87 $\pm$ 2.75	17.12 $\pm$ 8.34
AUC <sub>t0-t<math>\infty</math></sub>	µg.h/ml	36.26 $\pm$ 12.59	19.50 $\pm$ 5.81
MRT <sub>t0-t<math>\infty</math></sub>	h	18.16 $\pm$ 16.17	19.08 $\pm$ 2.45

Notes. C<sub>max</sub> :The peak concentration; T<sub>max</sub> :time to reach peak concentration; AUC t0-t $\infty$ : area under the concentration- time curve from 0 to infinity; MRT: mean residue time

dose were presented in Figure 2 and the pharmacokinetics parameters after single oral doses of albendazole sulfoxide are summarized in the Table 2. The ABZ was detected in plasma from the first sample 1h after administration and remains detectable up to 32 h.

The C<sub>max</sub> was observed three hour after administration. The ABZ metabolites appear in succession: albendazole sulfoxide (ABZSO) increases to a peak of 1.633µg / ml during the first 6 hours, then gradually decreases to

0.112µg / ml at 48h after administration of ABZ however the ABZSO was detected from the first time after administration of the single oral dose of ABZSO, indicating a rapid absorption of these antiparasitics via oral route. The C<sub>max</sub> ABZSO was observed 3h after administration, early than the first study with ABZ. For albendazole sulphone (ABZSO<sub>2</sub>), the detection in the blood is not as fast as that of ABZSO as it is observed only 12 h after administration and remains detectable up to 48 h after



**Figure 2** Concentration ( $\mu\text{g/ml}$ ) in plasma following single dose of Albendazole sulfoxide (ABZSO) by oral gavage in farm chickens

administration. Meanwhile, its metabolite was detected in the blood at the first hour to reach a peak of  $0.81 \mu\text{g/ml}$  9h after administration of single oral dose of ABZSO.

Albendazole is one of the most widely used anthelmintics in poultry farming in Morocco. It is too active against most gastrointestinal and respiratory nematodes of cestodes and trematodes in poultry (Mc kellar and Scott 1990). The metabolism of ABZ generates several metabolites including two major ones: albendazole sulfoxide, which is active, and albendazole sulfone which is inactive. In ruminants, ABZ undergoes an intensive first-pass effect at the digestive level and thus, is not detected in the peripheral blood of these species. In poultry, this first-pass effect is not complete and ABZ is detected in peripheral blood (Csiko et al., 1996). In previous works, after oral administration to hens (Bistoletti et al., 2011) and chicken (Csiko et al., 1996), and laying hens (Bistoletti et al., 2012), also ABZ plasma concentrations were measured in plasma.

In the present study, ABZ was detected in the blood, but at low levels, for 32 hours after administration. This result is different from that reported by (Csiko et al., 1996).who detected ABZ only for 9 hours after administration of the same dose ( $10 \text{ mg / kg}$ ).after ABZ oral administration low parent drug concentration were quantified from 30min to 3h to laying hens (Bistoletti et al., 2012) in contrast, ABZ was not measured in several mammalien species after oral administration (Marriner and Bogan 1980; Hennessy et al., 1989; Benchaouiet al., 1993; Alvarez et al., 1996; Sanchez et al., 1997; Sanchez et al., 2000), this difference has been associated with a fast absorption process or as low metabolism in hens compared with ruminants (Csiko et al., 1996).

The gastrointestinal absorption of ABZ is limited by its poor water solubility, which is markedly improved by low pH values this low solubility reduces the dissolution of suspended particles of the drug [9], as we had previously reported [10], the low physiological pH of the poultry muscular stomach, considered a powerful triturating machine may contribute to a better ABZ dissolution in poultry compared to other animal species.

The maximum concentration  $C_{\text{max}}$  of the ABZ obtained in our study ( $0.393 \pm 0.557$ ) is comparable to that reported in broiler chickens ( $0.31 \pm 0.08 \mu\text{g / ml}$ ), whereas its  $T_{\text{max}}$ , which measures the speed of absorption, is longer in farm chicken ( $3.37 \pm 2.82$ ) than in broiler chicken ( $1.62 \pm 0.76\text{h}$ ) (Csiko et al., 1996).

## CONCLUSION

The anthelmintic activity of ABZ is largely attributed to its active metabolite ABZ-SO. Except for the  $T_{\text{max}}$ , which is longer in farm chicken ( $6.75 \pm 3.49\text{h}$ ) than broiler chicken ( $3.74 \pm 0.71\text{h}$ ), the overall pharmacokinetic parameters of ABZ-SO obtained in farm chicken are comparable to those reported in broiler chicken after ABZ administration. The same trend is observed for the sulfone metabolite. At the oral administration of ABZ-SO at a dose of  $10 \text{ mg / kg}$ , the AUC of ABZ-SO was higher ( $36.26 \pm 12.589 \mu\text{g.h / ml}$ ) than at the administration of ABZ ( $28.79 \pm 8.31 \mu\text{g.h / ml}$ ), which reveals a better bioavailability of ABZ-SO.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## SOURCE OF FUNDING- Self

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