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Metabolism and Pharmacokinetics of Albendazole in Korean Native Cattle

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Abstract : Metabolism and phamacokinetics of albendazole have been studied in Korean native cattle after oral administration of 5 mg/kg of albendazole. As ABZ is known to be rapidly biotransformed to many metabolites in most animal species, it is very imperative to establish the analytical conditions for its metabolites. LC/MS methods for ABZSO and $ABZSO_2$ met every requirement enough to study the metabolism of pharmacokinetics of albendazole in Korean native cattle. The parent drug (ABZ) was only measured at first two time points of 0.5 h and 1 h, whereas two metabolites were consistently formed between 0.5 h to 48-72 h post-treatment. Formation kinetics for ABZSO and $ABZSO_2$ were similar. Time to peak concentration (Tmax) of ABZ-SO appeared at 12 h post-treatment of ABZ, faster than that of $ABZSO_2$ at 24 h. Cmax of $ABZSO_2$ (1.05 $\pm$ 0.05 ug/ml) was 1.09 times higher than that of ABZSO (0.96$\pm$ 0.15). Elimination half-life of $ABZSO_2$ (4.2 h) was much shorter than $ABZSO_2$ (7.0 h) ($p<0.005$). ABZSO was detected until 48 h post-administration but $ABZSO_2$ was measurable even at 72 h post-dosing. $AUC_{0-\infty}$ of ABZSO was smaller than that of $ABZSO_2$. Regimen of ABZ is advised to take into consideration its metabolite profiles, especially that of ABZSO, an active metabolite.

Key words **:** albendazole, metabolites, pharmacokinetics, Korean native cattle, LC/MS

Introduction

Albendazole (ABZ) belongs to the group of benzimidazoles, and is a broad spectrum anthelmintic drug employed in both human and veterinary medicine, for the control of gastrointestinal roundworms, lungworms, tapeworms and liver fluke[5,16].

ABZ is rapidly biotransformed to many metabolites in most animal species[9,14,21]. However, ABZ, having sulfide in its chemical structure, is mainly oxidized to two metabolites such as sulfoxide (ABZSO), and sulfone ($ABZSO_2$). ABZSO has active anthelmintic activity, which is available as an anthelmintic in the name of ricobendazole[21]. On the other hand, $ABZSO_2$ is an inactive metabolite[21].

ABZ is only available as oral forms including suspensions (drench), granules, pastes, tablets, and bolus preparations[3]. Oral dosing results in low plasma levels of ABZ because of its rapid first-pass metabolism in the liver. Therefore, the practical antiparasitic activity of ABZ is thought to depend on its metabolites[3].

Following oral administration ABZ is present at very low concentrations in plasma samples[6]. Meanwhile, its main and active metabolite, ABZSO, is present at higher concentrations. For this reason bioavailability of ABZ formulations is frequently studied with regard to ABZSO concentrations[7].

Some methods based on the reversed-phase HPLC with UV absorption have been developed for the quantitation of albendazole and its metabolites[1,12,19], but these methods achieved only relatively high detection limits in the range of 20~80 ng/g or ng/ml. In order to get the high sensitivity and low detection limit in the biological fluid, LC/MSD could be a powerful technique for separation, identification and quantitation of albendazole and its metabolites.

Several complete ABZ pharmacokinetic studies have been reported for animals such as cattle, sheep, pigs, dogs[2,17,18,20], but there are not any reported data on the pharmacokinetic and metabolic profiles of ABZ in the Korean native cattle.

The present study was carried out to investigate the pharmacokinetics of ABZ and its metabolites following a single oral administration of the drug to Korean native cattle using LC/MS.

Materials and Methods

Animals and drug administration

Four healthy adult female Korean native cattle (245.50 $\pm$ 6.03 kg) were used. A commercial preparation of ABZ (Valbazen®, Jeil Vetchem, Ansan, Korea) was administered orally at the rate of 5 mg of albendazole per kg.

Sample collection

Blood samples were taken from the jugular vein into sterile Vacutainer® tubes containing heparin (Becton Dickinson, U.S.A.) at 0.5, 1, 2, 4, 8, 12, 18, 24, 36, 48 and 72 h post-treatment. The plasma was obtained by centrifugation at 3,000 rpm and stored at −60 until analyzed.

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Chemicals and reagents

Standard ABZ, ABZSO and $ABZSO_2$ were kindly donated by Smith-Kline Beecham (Worthing, U.K.). HPLC grade acetonitrile, methanol, n-hexane and chloroform were obtained from Tedia (Fairfield, U.S.A.). All other chemicals were purchased from Sigma (St. Louis, U.S.A.).

Apparatus and chromatographic conditions

Samples were analyzed on a Hewlett-Packard 1100 series LC/MSD system. Separation was achieved on XTera® C_{18} (particle size 3.5 μm, 4.6× 150 mm, Waters, U.S.A.). Flow rate was operated at 0.8 ml/min. The mobile phase consisted of 0.05% acetate in D.W. (solution A) and 1 μM acetate in acetonitrile (solution B). The mobile phase was flowed by gradient elution program method. The pressure of nebulizer was 40 p.s.i. and heated to 350°C. The quadrupole was heated to 100°C. The mass spectrometer was run in the positive mode and selective ion monitoring mode.

Quantitative assay of ABZ, ABZSO and $ABZSO_2$

For the determination of ABZ, 5 ml of methanol was added to aliquots of plasma sample (1 ml) to precipitate proteins. Each tube was stoppered, vortexed for 3-5 min and centrifuged for 10 min (4,000 g). The upper layer was dried under a stream of nitrogen gas. The residue was dissolved in methanol and cleared with *n*-hexane. Aqueous layer was evaporated to dryness and the residue was dissolved in 1 ml methanol and then analyzed. For the determination of ABZSO and $ABZSO_2$, the same procedures as for ABZ were employed before the methanol precipitation. The formed residue was dissolved in sodium acetate buffer solution (pH 2.7) and then cleared with *n*-hexane. The buffer solution layer was then partitioned with chloroform. The chloroform layer was evaporated to dryness and the residue was dissolved in 1 ml methanol and applied to a C_{18} column.

Validation

Calibration curves: Standard ABZ, ABZSO and $ABZSO_2$ were used to prepare calibration curves in the range of 0.1, 1, 10, 100 and 1,000 ng/ml, respectively.

Specificity and limit of quantitation: The lack of matrix interference was established by analysis of blank plasma samples (n=3). The chromatograms were visually inspected for peaks from endogenous substances. Limit of detection and limit of quantitation were based on the signal-to-noise ratio based on their areas. The signal-to-noise ratio of 3 was accepted for the limit of detection and that of 10 for the limit of quantitation.

Accuracy, precision and recovery: Samples of ABZ, ABZSO and $ABZSO_2$ at each of three concentrations (0.1 ng/g, 10 ng/g and 1,000 ng/g) were assayed to determine the accuracy expressed as mean relative error (R.E.) and the precision expressed as coefficient of variation (C.V.). The recovery of ABZ, ABZSO and $ABZSO_2$ was assessed in triplicate determinations at three different concentrations (0.1 ng/g, 10 ng/g and 1,000 ng/g). The responses of the extracted samples were compared with those of the same concentrations over the constructed calibration curves.

Pharmacokinetic data analysis

The pharmacokinetic parameters for each metabolite were determined using the time course of drug concentration in plasma by a non-compartmental model with the non-linear pharmacokinetic modelling program PCNONLIN (Statistical Consultants, Lexington, U.S.A.), where the area under the curve (AUC) was zero moment and the mean residence time of a drug in the body (MRT) was the first moment. The AUC was determined by the trapezoidal rule. The terminal elimination slope (k_e) was obtained by a linear least-square regression analysis. C_{max} and T_{max} was graphically estimated. Statistical comparison of mean pharmacokintic parameters was performed by Student's *t*-test at the confidence level of $p<0.05$.

Results

Analytical studies

The validation parameters of LC/MS detection for ABZ, ABZSO, $ABZSO_2$ in fortified Korean native cattle plasma are summarized in Table 1. Specificity of this analysis was confirmed by no matrix interference from the blank plasma samples (Fig. 1). The retention time of ABZ, ABZSO and $ABZSO_2$ were appeared about 20.4, 15.8 and 18.5 min (Fig. 1) and their intensities were increased in proportion to concentrations. All of the calibration lines for ABZ, ABZSO and $ABZSO_2$ in the range of 0.1 through 1,000 ng/g proved high correlation coefficients ($r>0.999$). Precision and accuracy met the accepted criteria (Table 1). Limit of quantitaion and limit of detection of ABZ and its metabolites in the spiked plasma were 0.1 ng/g and 0.01 ng/g, respectively. The recovery means of ABZ, ABZSO, and $ABZSO_2$ were 97.8 ± 5.3%, 97.3 ± 6.8%, and 95.7 ± 4.3% for 1 μg/ml-spiked plasma (Table 1). Since $[M+H]^+$ forms gave the strongest signals for ABZ, ABZSO and $ABZSO_2$, peak ions of ABZ (m/z=266.1), ABZSO (m/z=282.1) and $ABZSO_2$ (m/z=298.1) were easily measured and confirmed qualitatively one another (Fig. 2).

Disposition kinetics of albendazole and its metabolites in Korean native cattle

Time-concentration curves of ABZ, ABZSO and $ABZSO_2$ are shown in Fig. 3. Following oral administration of ABZ to Korean native cattle, the parent drug (ABZ) was only measured at first two time points of 0.5 h and 1 h, whereas two metabolites were consistently formed between 0.5 h to 48-72 h post-treatment (Fig. 3). The plasma disposition kinetic data for ABZSO and $ABZSO_2$ are shown in Table 2. Formation kinetics for ABZSO and $ABZSO_2$ were similar as

Table 1. Detection limit, precision, accuracy, recovery of albendazole and its two metabolites*

		ABZ	ABZSO	$ABZSO_2$
LOQ (ng/ml)		0.1	0.1	0.1
LOD (ng/ml)		0.01	0.01	0.01
Linearity (r)		0.999	0.999	0.999
Precision (CV, %)				
intraday (n=6)	0.1	6.6± 0.1	3.3± 0.0	6.6± 0.1
	10	1.1± 0.0	0.7± 0.0	2.0± 0.0
	1000	1.0± 0.0	2.2± 0.0	2.2± 0.0
interday (n=6)	0.1	6.7± 0.2	2.9± 0.0	6.5± 0.0
	10	1.3± 0.0	1.1± 0.0	1.9± 0.0
	1000	1.1± 0.0	2.2± 0.0	2.1± 0.0
Accuracy (RE, %)				
intraday (n=6)	0.1	0.2± 0.0	0.1± 0.0	0.2± 0.0
	10	5.5± 0.0	3.7± 0.0	9.5± 0.2
	1000	575.5± 9.6	1205.7± 28.4	1187.8± 23.7
interday (n=6)	0.1	0.3± 0.0	0.1± 0.0	0.3± 0.0
	10	6.6± 0.0	5.5± 0.0	10.0± 0.2
	1000	612.0± 12.5	1246.8± 32.1	1187.8± 20.4
Recovery (n=6, %)	0.1	78.3± 5.32	77.3± 4.42	76.0± 2.72
	10	90.5± 4.71	89.7± 5.84	84.2± 6.27
	1000	97.8± 5.34	97.3± 6.83	95.7± 4.35

*Validation results were assessed in spiked plasma (0.1, 10 and 1000 ng/ml) and represented as mean± S.D. with nominated concentrations.

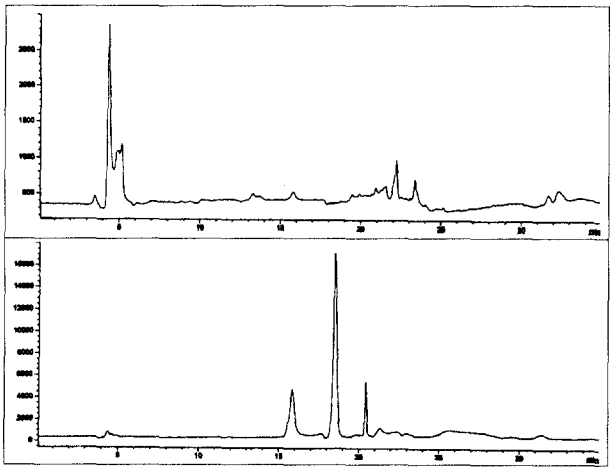

Fig 1. Chromatograms of the Korean native cattle plasma following oral administration of ABZ. Retention times for ABZ, ABZSO and $ABZSO_2$ are 20.4, 15.8, 18.5 min, respectively. Upper panel represents the chromatogram of the blank plasma.

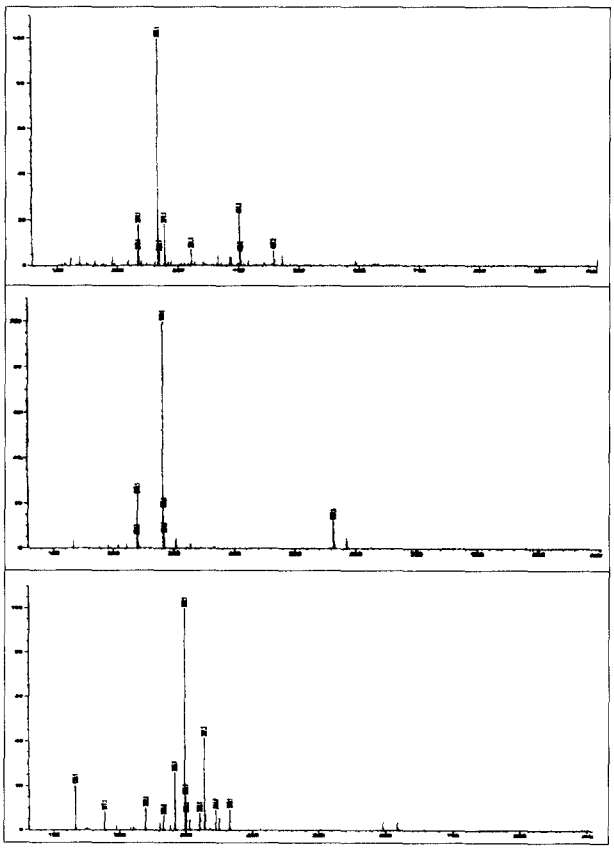

Fig 2. Mass spectra of ABZ (m/z=266.1), ABZSO (m/z= 282.1) and $ABZSO_2$ (m/z=298.1) by collision induced dissociation at 100 V for one ppm of albendazole and its metabolites in water/acetonitrile (v/v) containing 0.05% acetate and 1 μM acetate.

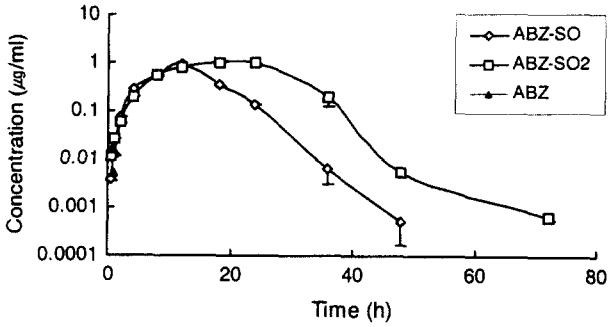

Fig 3. Concentration-time curves for ABZ, ABZSO and $ABZSO_2$ in Korean native cattle after oral adminstration of 5 mg ABZ/kg (n=4). Statistical differences (ABZ vs ABZSO, ABZ vs $ABZSO_2$, ABZSO vs $ABZSO_2$) were highly significant ($p < 0.005$) at all detected time points. *marks are not attached on the graph for the sake of brevity.

shown in the ascending portion of Fig. 3. Time to peak concentration (T_{max}) of ABZSO appeared at 12.00± 0.00 h post-treatment of ABZ, faster than that of $ABZSO_2$ at 22.50± 3.00 h ($p<0.005$). C_{max} of $ABZSO_2$ (1.05 ± 0.05 ug/ml) was 1.09 times higher than that of ABZSO (0.96 ± 0.15). But elimination half-life of ABZSO (4.14 ± 0.30 h) was much shorter than $ABZSO_2$ (6.95 ± 0.36 h) ($p<0.005$). ABZSO was detected until 48 h post-administration but $ABZSO_2$

Table 2. Phamacokinetic parameters of albendazole sulfoxide (ABZSO) and albendazole sulfone ($ABZSO_2$) after oral administration of albendazole at 5 mg/kg in Korean native cattle

Kinetic parameters	ABZSO	$ABZSO_2$	Significance
C_{max} (μg/ml)	0.96± 0.15	1.05± 0.05	0.01<p<0.05
T_{max} (h)	12.00± 0.00	22.50± 3.00	p<0.005
$t_{1/2,\,ke}$ (h)	4.14± 0.30	6.95± 0.36	p<0.005
MRT (h)	13.10± 0.05	21.60± 1.99	p<0.005
$AUC_{0\rightarrow t^*}$ (μg·h/ml)	11.28± 0.65	22.79± 0.25	p<0.005
$AUC_{0\rightarrow\infty}$ (μg·h/ml)	11.29± 0.78	22.80± 0.26	p<0.005
$AUMC_{0\rightarrow t^*}$ (μg·h^2/ml)	147.94± 10.28	492.81± 49.88	p<0.005
$AUMC_{0\rightarrow\infty}$ (μg·h^2/ml)	147.95± 10.27	492.87± 49.89	p<0.005

Each value represents mean± S.D. of four animals

was measurable even at 72 h post-dosing. $AUC_{0\rightarrow t^*}$ to the final detectable time for ABZSO was smaller than that of $ABZSO_2$. $AUC_{0\rightarrow\infty}$ of ABZSO was 11.29 ± 0.78 μg·h/ml and that of $ABZSO_2$ 22.79 ± 0.26 μg·h/ml. Both AUC values of each two metabolites had almost the same each other. Using AUMC and AUC of each metabolite shown in Table 2, the MRT of ABZSO and $ABZSO_2$ were calculated as 13.10± 0.05 h and 21.60± 1.99 h, respectively.

Discussion

Several liquid chromatographic methods have been described for the determination of ABZ and/or its metabolites in biological fluids[12,17,18]. However, the sensitivity of conventional LC methods was not sufficient for the pharmacokinetic study of ABZ and its metabolites: the limits of detection were 20, 50 and 40 ng/ml for ABZ, ABZSO and $ABZSO_2$, respectively. In the present study, a powerful technique for separation, identification and quantitation of ABZ and its metabolites by LC/MSD was developed and has successively employed for the determination of the main pharmacokinetic parameters in the Korean native cattle after oral administration of ABZ at 5 mg/kg.

Benzimidazoles such as albendazole, fenbendazole, flubendazole, mebendazole, oxfendazole, oxibendazole, and thiabendazole have a similar mode of action. They interact with tubulin in the intestinal cells of parasite, resulting in the disappearance of microtubules from the cells and decreased absorption and digestion of nutrients such as glucose[4]. ABZ is a benzimidazole, and is metabolically converted by liver microsomes into active ABZSO. ABZSO are reported to strongly bind to tubulin of parasites, thereby depriving parasites of necessary energy[13]. $ABZSO_2$ binds little or weakly to such tubulins, which is associated with its weak anthelmintic activity.

The pharmacokinetic profiles of ABZSO and $ABZSO_2$ following oral administration of ABZ at 5 mg/kg in Korean native cattle were different from those determined previously in sheep and chicken. ABZ was measured only in 0.5 and 2 h post-dosing, thereafter its measurements were not possible probably due to its poor absorption and rapid first pass effect. Therefore, in this study, the pharmacokinetics of the parent drug ABZ was not possible to estimate due to having only two available time-point concentrations. Many other investigators also reported that ABZ was not detected at any time after oral administration of ABZ in plasma and/or urine of sheep, goats, pigs, humans[2,7,15,22].

In Korean native cattle, ABZ were rapidly metabolized to ABZSO and $ABZSO_2$, whose concentrations were persisted over the long time course. We could detect ABZSO up to 48 h and $ABZSO_2$ up to 72 h. Thus, we analyzed their disposition kinetics of ABZSO and $ABZSO_2$. ABZ parent drug is also known to be rapidly metabolized by two distinct hepatic microsomal enzymatic systems in sheep and cattle: flavin-containing monooxigenase (FMO)[10] for ABZSO and cytochrome P-450 for $ABZSO_2$[8]. Active ABZ sulfoxide (ABZSO) and inactive ABZ sulfone ($ABZSO_2$) are the main metabolites recovered in plasma of sheep and cattle following ABZ administration[11].

Concentration-time curves of ABZ, ABZSO and $ABZSO_2$ were described in Fig. 1. As expected from similar experimentations using other animal species[14,16,21], the parent ABZ was not detected over the whole time range, except at initial two time-points of 0.5 and 2 h after oral administration of ABZ at 5 mg/kg in Korean native cattle. This could be explained by its poor absorption from the intestine and rapid biotransformation into metabolites[3,13]. Temporal ABZSO and $ABZSO_2$ curves showed almost the same pattern. Their formation phases from ABZ were similar in shape as can be seen in the ascending portion of the curves, initially rapidly rising and then slowly reaching the peak concentration. But the T_{max} of 12 h for ABZSO appeared earlier than that $ABZSO_2$ (22.50 ± 3.00 h), indicating the existence of the time-dependent step from ABZ through ABZSO to $ABZSO_2$. C_{max} of ABZSO (0.96 ± 0.15 μg/ml) was not different from that of $ABZSO_2$ (1.05 ± 0.05 μg/ml). These results were in contrast to those of sheep where C_{max} of ABZSO was higher three times than that of $ABZSO_2$ at the same T_{max}[7]. We think there are different metabolic enzyme activity in Korean native cattle as compared to other animal species, especially sheep[7]. Elimination patterns of both metabolites showed mono-exponential decay in Korean native cattle. $AUC_{0\rightarrow\infty}$ of ABZSO (11.29 μg·h/ml) were smaller than that of $ABZSO_2$ (22.80 μg·h/ml) in Korean native cattle at the dosage rate of 5 mg/kg. $AUC_{0\rightarrow\infty}$ of both metabolite were not different form those of $AUC_{0\rightarrow t^*}$, due to the very low concentration at the last measurement. Elimination half-life and MRT of ABZSO (4.14 ± 0.30 h and 13.10 ± 0.05 h) were smaller than $ABZSO_2$ (6.95 ± 0.36 h and 21.60 ± 1.99 h) (p<0.005). The earlier elimination of ABZSO compared to $ABZSO_2$ are reported in many animal species. During the ABZ treatment, ABZSO behaviors in the living body should be con-

sidered for its therapeutic efficacy. Thus, the drug regimen of ABZ in the Korean native cattle should take into account of the smaller AUC of the active metabolite of ABZSO.

In conclusion, ABZ is rapidly metabolized in Korean native cattle, which suggests the efficacy of ABZ does not come from the parent drug. There are at least two metabolites of ABZ formed in Korean native cattle: an active ABZSO and an inactive $ABZSO_2$. Regimen of ABZ is advised to take into consideration its metabolite profiles, especially that of ABZSO.

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한우에서의 Albendazole의 대사 및 약물동태학

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요 약 : 한우에서 albendazole을 경구투여하였을 때의 albendazole의 생체내 대사 및 약물동태학적 특성을 밝히고자 하였다. 거의 모든 가축종에서 albendazole은 투여 후 신속하게 대사산물로 전환되기 때문에 albendazole 대사산물에 대한 분석법 확립이 albendazole의 생체내 거동을 파악하기 위하여 매우 긴요하다. 본 연구에서는 albendazole 및 그 대사산물인 albendazole sulfoxide(ABZSO)와 albendazole sulfone($ABZSO_2$)을 LC/MS를 이용하여 높은 분석능을 획득할 수 있었다. Albendazole을 한우에 5 mg/kg을 경구투여하였을 때 모약인 albendazole은 첫 두 채혈시점인 0.5 h 및 1 h에서만 측정되었을 뿐 그 이후에는 측정되지 않았다. 한편, ABZSO와 $ABZSO_2$은 첫 채혈 시점인 0.5 h부터 측정되어 투여 후 각각 48 h 및 72 h까지 측정이 가능하였다. 두 대사산물의 초기 생성속도는 비슷하였다. 혈중최고농도 도달시간 (T_{max})은 ABZSO가 12.00 h로서 $ABZSO_2$의 22.50±3.00 h보다 빨랐으며 ($p<0.005$), ABZSO의 최고농도 (C_{max})는 0.96±0.15 μg/ml이었고 $ABZSO_2$의 그것은 1.05±0.05 μg/ml를 나타내었다. 소실반감기 ($t_{1/2,\ ke}$)는 ABZSO는 4.14±0.30 h로 $ABZSO_2$의 6.95±0.36 h보다 빨랐으며 ($p<0.005$), MRT (Mean residence time)는 각각 13.11±0.05 h와 21.60±1.99 h로서 $ABZSO_2$가 생체내에 더욱 오래 머물렀다 ($p<0.005$). ABZSO의 $AUC_{0\rightarrow\infty}$는 $ABZSO_2$의 그것보다 작았다. 이러한 사실로 미루어보아 ABZ을 한우에 구충목적으로 투여할 때 구충활성을 가진 것으로 알려져 있는 ABZSO의 생체내 거동을 고려하여 용법용량을 설정하여야 할 것으로 사료된다.