PRESYSTEMIC METABOLISM OF ALBENDAZOLE: EXPERIMENTAL EVIDENCE OF AN EFFLUX PROCESS OF ALBENDAZOLE SULFOXIDE TO INTESTINAL LUMEN

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ABSTRACT:

Albendazole (ABZ) presystemic clearance was studied in rat by perfusion of a 25 μM ABZ solution in isolated intestinal loops. Significant secretion of the active metabolite, ABZSO, into the lumen was observed. The metabolite was also present in mesenteric blood. After 30 min of intestinal perfusion, 64% of the ABZ dose had disappeared from lumen. The total amount of ABZSO measured was 0.341 ± 0.04 nmol/cm with 0.176 ± 0.03 nmol/cm in mesenteric blood. The metabolite secretion to intestinal lumen was 0.165 ± 0.05 nmol/cm. Intestinal sulfoxidation was induced by repeated administration of ABZ and ABZ coadministered with surfactants, especially polysorbate 80. The enantioselectivity of the in vitro intestinal sulfoxidation of ABZ showed that the relative contribution of P-450 and flavin-containing monoxygenase was quite similar, but after the induction by ABZ coadministered with polysorbate 80, the cytochrome P-450 system contribution was significantly increased. The appearance of ABZSO in mesenteric blood clearance was also increased under these conditions.

Albendazole (ABZ, 1-methyl(5-pro pylthio)H-benzimidazole-2yl) carbamate is one of the most important benzimidazole derivatives used against liver flukes, tapeworms, and lung and gastrointestinal roundworms. It is effective in the treatment of human hydatidosis (Gil-Grande et al., 1993) and microsporidial species, emerging agents as opportunistic pathogens in persons infected with the human immunodeficiency virus (HIV) (Kelly et al., 1996; Didier, 1997).

After oral administration, ABZ is oxidized to a sulfoxide (ABZSO), which is in part further oxidized to a sulfone (ABZSO2); albendazole sulfoxide is the main metabolite in vivo. The formation of ABZSO is directly associated with two different microsomal enzymatic systems, cytochrome P-450 and flavin-containing monoxygenase (FMO). Previous studies into liver and intestine microsomes of rat (Moroni et al., 1995; Villaverde et al., 1995) have shown that both systems are similarly involved. ABZSO has two enantiomers (−) and (+), produced from the chiral thioether albendazole, which can be separated by HPLC; (+)ABZSO is associated with the activity of FMO, whereas the P-450 system participates in the production of (−)ABZSO (Delatour et al., 1991).

The low aqueous solubility of albendazole influences its absorption. Recently, we obtained results on the coadministration of ABZ with surfactants, which modify the pharmacokinetic profile of ABZSO, increasing the area under curve (AUC). When ABZ was administered to rats in a formulation that included surfactants sodium taurocholate at 5 and 10 mM and polysorbate 80 (P80) at 0.0022% (0.016 mM), ABZSO mean residence time values showed longer-lasting levels, particularly for the 0.016 mM P80 treatment (Redondo et al., 1998).

The liver has been considered a predominant organ of drug bioconversion. However, recent research has suggested a significant role of intestinal metabolism that contributes to the presystemic clearance for orally administered drugs such as cyclosporine (Kolars et al., 1992; Watkins, 1992).

To determine the contribution of the gut to the first-pass metabolism of ABZ, we decided to use the rat jejunum by means of the in situ physiological model of intestinal absorption. The method described by Doluisio et al. (1969) was partially modified by a surgical technique allowing us to collect the mesenteric blood drained by that segment. The experimental approach maintained the perfused intestinal segment under proper physiological conditions, with the possibility of isolating the enterocyte metabolism from the systemic (liver) metabolism. The simultaneous disappearance of ABZ and formation of its metabolite are aspects not covered in a previous study on the biotransformation of ABZ in isolated rat intestine, where the perfusion procedure was performed in vitro (Lawrenz et al., 1992). The isolated loop model has been previously used to characterize the absorption and/or intestinal metabolism of different xenobiotics (Goon and Klaassen, 1989; Albers and Rosenberg, 1991; Choi et al., 1995). Nevertheless, one disadvantage of this method is the need to determine the water reabsorption rate when the loss is greater than 10% (Martín-Villodré et al., 1986).

The aim of the present study was to investigate the role of the intestine in the presystemic biotransformation of albendazole in rat. The experimental preparation was an isolated intestinal loop with complete venous collection. Because the biotransformation process can be induced by long-term ABZ administration, the study was carried out after having administered different formulations of ABZ for 21 days. To elucidate the enzyme system involved under each condition, the enantioselectivity of the microsomal sulfoxidation by rat intestinal microsomes was studied.
Materials and Methods

Chemicals. Albendazole (mw 265), albendazole sulfoxide (mw 281), and albendazole sulfone (mw 297) used to carry out the study and to prepare the standard solutions were kindly supplied by Smith-Kline & Beecham S.A. (Madrid, Spain). Albendazole used as internal standard was supplied by the laboratory of Dr. Esteve (Barcelona, Spain). Sodium taurocholate (mw 537.7) and P80 (polyoxyethylene sorbitol mono-oleate; mw 1309.68) were purchased from Sigma Chemical Co. (St. Louis, MO). Other analytical-grade chemicals were obtained from the following sources: methanol and acetic acid from Merck (Darmstadt, Germany), acetonitrile from BDH (Poole, UK), and ethyl acetate from Sigma-Aldrich (Dorset, UK).

Animals and Experimental Protocol. Male Wistar rats (250 ± 10 g), purchased from IFFA CREDO (Barcelona, Spain), were housed, three per cage, in a temperature-controlled room (21–23°C), with 40–60% humidity and 12:12 h light/dark cycles. Rats were accustomed to these conditions for at least 1 week before any experimentation. Standard rodent diet (Panlab SA, Barcelona, Spain) and water were available ad libitum.

The study of intestinal metabolism of ABZ was carried out in four experimental groups. A control group included animals not receiving ABZ pretreatment (group 1). For induction studies, rats were treated by oral administration with ABZ (5 mg/kg) for 21 consecutive days with the following formulations: ABZ administered in saline (1% dimethyl sulfoxide; group 2), ABZ plus 10 mM sodium taurocholate (STC; group 3), and ABZ plus 0.016 mM P80 (P80; group 4).

Intestinal Biotransformation In Situ. The preparation of isolated intestinal loops in situ and implantation of the mesenteric venous cannula was performed as described by Doluisio et al. (1969) and Goon and Klaassen (1989), respectively.

Before surgery, the animals underwent a fasting period of 16 to 18 h, but drinking water was available. Rats were anesthetized with urethane solution 30% (by i.p. injection of 1 ml/250 g b.w.t.) and cannulas (filled with saline containing 100 IU heparin/ml) were introduced into the right jugular veins. Rectal temperature was monitored and kept at 37°C.

The small intestine, caudal to the ligament of Treitz, was exposed through a midline abdominal incision. An intestinal segment with a single mesenteric vein was isolated by two ligatures; then, two L-shaped glass cannulas (input and output) were inserted through small openings and secured by ligation with silk thread and connected by a three-step stopcock to a glass syringe as described by Doluisio et al. (1969). Afterwards, warm isotonic saline buffered to pH 6.4 was infused to wash the internal surface of the gut. The mesenteric vein was cannulated by inserting a 23-gauge needle attached to Silastic tubing filled with heparinised saline. The cannula was anchored by applying a drop of α-cyanoacrylate adhesive at the entry point.

An ABZ solution (1% dimethyl sulfoxide), was introduced into the lumen of isolated loop (length, 10.5 ± 0.6 cm) in a volume of 1.5 ml. The range of measured dose concentrations was 10.07 ± 4.10 μM.

All mesenteric venous blood from the loop was continuously collected for 30 min at 5-min intervals. A constant blood volume of the rat was maintained by infusing an heparinized blood-saline mixture (4:1 v/v) into the jugular vein at a rate approximately equal to the rate of blood drained from the mesenteric cannula (12 ml/h). Replacement blood used to perform the infusion was collected from ether-anesthetized donor rats by retroorbicular puncture.

Blood samples were collected in preweighed tubes and the volume of each sample was gravimetrically determined (specific gravity of 1.054). After 30 min, the intestinal loop was excised and measured and the luminal contents collected. It was necessary to determine the reabsorption of water when the loss was greater than 10% (Martin-Villodre et al., 1986) to avoid the excessive distortion of the final concentration of the remaining perfused solution. In our study, the method used to correct the final concentrations of solutes was the determination of phenol red concentration (a nonabsorbable dye) in relation to its initial perfused concentration (Miller and Scheld, 1972). Five animals were used for each of the experimental groups studied.

Intestinal Biotransformation In Vitro. The intestinal bioconversion of ABZ was calculated by measuring the sulfoxidase activity through the amount of ABZSO produced by intestinal microsomes.

Cells from the upper and midvillus regions were used as a source of intestinal material. The method used to isolate the enterocytes include evertion of the gut and incubation in chelating medium with EDTA and dithiothreitol, substances that removed the enterocytes from the gut (Weiser 1973). Microsomes from enterocytes were prepared essentially by methods developed for liver microsomes.

The sulfoxidase activity corresponding to the different experimental groups was obtained in incubations with 25 μM ABZ in a volume of 1 ml containing the microsomal fraction (1 mg of microsomal protein). ABZ was dissolved in methanol (10 μl). The incubations (15 min) were performed in an oscillating bath at 37°C, according to the technique of Galtier et al. (1986). After incubation, ABZ and its metabolites were extracted with dichloromethane. Six animals were used for each of the experimental groups studied.

Analytical Method. Plasma and luminal samples were analyzed for the concentration of ABZ and the two known metabolites (ABZSO and ABZSO2) using reversed-phase HPLC. The extraction method has been previously described by Alvinerie and Galtier (1984). The HPLC parameters and the quantitation method used for the analysis is described by Redondo et al. (1998).

Samples of in vitro experiments were extracted by the addition of 3 ml of dichloromethane to the incubation mixture, shaking in a vortex and evaporating the organic phase to dryness under a nitrogen atmosphere. The residue was then dissolved in 100 μl of methanol and analyzed as before.

Enantiomeric Analysis. During the chromatographic analysis of in vitro samples, the ABZSO fraction was collected, extracted, and evaporated under a nitrogen stream. The subsequent residue was then chromatographed on a chiral column in which stationary phase was an α1-glycoprotein immobilized on silica (Chiral AGP; ChromTech AB, Högsersten, Sweden) using the conditions previously described by Delatour et al. (1991). This step provided the relative proportions of both (−)ABZSO and (+)ABZSO enantiomers. Results were expressed as enantiomeric excess (e.e.), which is defined as:

\[
e.e.(%) = \frac{\text{concentration (−)ABZSO} - \text{concentration (+)ABZSO}}{\text{concentration of ABZSO}} \times 100
\]

Statistical Analysis. Data are presented as mean ± S.D. Mean values for each experimental group were compared by ANOVA. When a significant F value was found, a Newman-Keuls multiple range test was performed to test the difference between means.

Results

Intestinal Biotransformation In Situ. Table 1 shows the percentage of disappeared ABZ from lumen intestinal after an experimental period of 30 min. The range of measured ABZ dose concentration initially perfused was 10.07 ± 4.10 μM.

The percentage of the ABZ dose removed from the lumen was increased in the experimental groups of rats pretreated 21 days with ABZ plus surfactants in comparison with rats without pretreatment. Table 2 shows the sulfoxide production (nmol/cm) after intestinal perfusion of ABZ in the control group (rats without treatment) and in animals treated for 21 consecutive days with ABZ in different formulations. Data for sulfoxide production (ABZSO) are expressed in nanomoles per centimeter of intestine, taking into account the different length of the intestine (Ravis et al., 1983). ABZSO3 was not detected in any sample. ABZSO was quantified in mesenteric blood.

### Table 1

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>% of Dose Disappeared</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>63.71 ± 15.82</td>
<td>5</td>
</tr>
<tr>
<td>ABZ pretreatment</td>
<td>5 mg/kg</td>
<td>64.47 ± 4.31</td>
</tr>
<tr>
<td></td>
<td>+ STC 10 mM</td>
<td>84.73 ± 3.88</td>
</tr>
<tr>
<td></td>
<td>+ P80 0.016 mM</td>
<td>84.90 ± 8.01</td>
</tr>
</tbody>
</table>
and lumenal fluid. The total amount of ABZSO produced was obtained as the addition of ABZSO in mesenteric blood and lumenal fluid.

With regard to dose-mass balance recovery, the percentage of ABZ that was converted into sulfoxide was between 25 to 50%, taking into account that the absolute mass of disappeared ABZ ranged from 0.3 to 0.9 nmol/cm. The remaining amount could have been trapped in intestinal villi or in blood and remains to be elucidated.

In control animals the total ABZSO formed by intestinal mucosa was 0.341 ± 0.04 nmol/cm. In the groups that received ABZ for 21 days with surfactants, the formation of ABZSO was significantly different (1.042 ± 0.18 nmol/cm in the STC group; 1.214 ± 0.13 nmol/cm in the P80 group). The sulfoxide in mesenteric blood significantly increased after 21 days of treatment with ABZ plus surfactants. The intestinal efflux of ABZSO produced in the enterocytes is shown by the amount of metabolite present in lumenal fluid. This value in control rats was 0.165 nmol/cm, very similar to that in mesenteric blood. The administration of ABZ for 21 days in the formulation with surfactants increased the amount of ABZSO in both the intestinal lumen and blood. However, the ratio of ABZSO in mesenteric blood/intestinal lumen increased from 1.202 ± 0.67 (52/48) in control to 3.118 ± 1.14 (75/25) with the administration of the polysorbate formulation (Fig. 1).

Cumulative amounts of ABZSO transferred to the mesenteric vein and metabolite appearance rate constant calculated over 30 min are shown in Fig. 2 and Table 3. Both of them summarize the increase of ABZSO in mesenteric blood. Rate constant (min⁻¹ cm⁻¹) significantly increased with respect to control rats when ABZ was administered with surfactants, whereas the administration of ABZ without surfactants did not alter the formation and passage of ABZSO through the intestinal mucosa to systemic blood.

**Microsomal Metabolism: Sulfoxidase Activity.** Table 4 summarizes the sulfoxidase activities (nmol·mg⁻¹·min⁻¹) of rat intestinal microsomes. The sulfoxidation was 0.147 ± 0.03 nmol/min/mg in control rats. However, the activity significantly increased (0.324 ± 0.043 nmol/min/mg) in rats treated with ABZ plus P80.

The production of (-)ABZSO, (+)ABZSO, and e.e. was obtained from the total sulfoxidase activity. From these data we estimated the percentage of involvement of the enzymatic systems P-450 and FMO, respectively. The ratio of (-)ABZSO/(+)ABZSO in control rats was 48.07/51.92, which corresponded to an e.e. of −4.13% (favorable to FMO). When ABZ was administered with P80, the ratio of both was 71.60/28.40, with an e.e. of 43.20%, favorable to P-450.

**Discussion**

**ABZSO Intestinal Formation.** The intestine is considered to be an absorptive organ but some drugs are excreted from the systemic circulation to the intestinal lumen through an active transport. This same efflux process can be considered as causing presystemic elimination of an orally dosed drug, influencing drug bioavailability (Yahara et al., 1984; Lennernäs and Regårdh, 1993). The process becomes more evident when the enterocyte takes part in the metabolism of a drug orally administered.

The distribution of the metabolites in mesenteric blood and intestinal lumen after intestinal biotransformation has been described for different xenobiotics such as 7-ethoxycoumarin (Albers and Rosenberg, 1991) and cyclosporine (Kolars et al., 1992).

The excretion of ABZSO from the enterocyte to the lumen, at least in a proportion similar to the one transferred to the blood, means an important modification in the theory stating that the low bioavailability of the ABZ in blood is due to their low absorption. The presence of ABZSO in the lumen is highly beneficial to the treatment of the intestinal parasitoses because the metabolite is more active than the parent compound.

The results expressed in Table 2 show the importance of intestinal metabolism of albendazole. The total amount of ABZSO in control rats was 0.341 ± 0.04 nmol/cm of intestine, and when the percentage of ABZ disappeared in the lumen at the same time it was 63.71 ± 15.82%, as shown in Table 1.

In our experimental conditions, the lack of the sulfone metabolite in the analyzed samples suggests that the biotransformation of the ABZ by the intestine may be limited to its first step, the sulfoxidation. Owing to the fact that ABZSO was collected continuously, drained by mesenteric vein, it is not possible to completely discount sulfonation.

**TABLE 2**

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>ABZSO Total</th>
<th>ABZSO Mesenteric</th>
<th>ABZSO Lumenal Fluid</th>
<th>ABZSO Blood/Lumen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nmol/cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.341 ± 0.04</td>
<td>0.176 ± 0.03</td>
<td>0.165 ± 0.05</td>
<td>1.202 ± 0.67</td>
</tr>
<tr>
<td>5 mg/kg ABZ</td>
<td>0.467 ± 0.15</td>
<td>0.289 ± 0.10</td>
<td>0.177 ± 0.06</td>
<td>1.693 ± 0.48</td>
</tr>
<tr>
<td>5 mg/kg ABZ + STC 10 mM</td>
<td>1.042 ± 0.18**</td>
<td>0.653 ± 0.10**</td>
<td>0.388 ± 0.10**</td>
<td>1.725 ± 0.32</td>
</tr>
<tr>
<td>5 mg/kg ABZ + P80 0.016 mM</td>
<td>1.214 ± 0.13**</td>
<td>0.899 ± 0.03***</td>
<td>0.314 ± 0.11***</td>
<td>3.118 ± 1.14*</td>
</tr>
</tbody>
</table>

* Significantly different from control p ≤ 0.05.
** Significantly different from control p ≤ 0.01.
However, the absence of sulfonation by intestine was also one of the conclusions drawn from the work by Lawrenz et al. (1992), after recirculating 1000 ng/mL through isolated intestinal segments.

The observed increase in the total production of ABZSO (Table 2) in the experimental groups treated with ABZ for 21 days, with statistically significant differences when coadministered with surfactants (10 mM STC, 1.042 ± 0.04 nmol/cm) and in the intestinal lumen in a similar proportion (0.165 ± 0.05 nmol/cm).

The reasons of the luminal excretion from the enterocyte could be due to the hydrophilic nature of the formed metabolites and to the existence of carriers. In the specific case of the metabolism of the 7-ethoxycoumarin, the free and sulfated metabolites are equally distributed between blood and lumen, without the participation of active transport, but the glucuronide conjugate metabolites are liberated into mesenteric blood by a carrier in the basolateral membrane of the enterocyte (Albers and Rosenberg, 1991).

A slight modification in the ratio of ABZSO in blood and luminal perfusate takes place when ABZ is administered for 21 days (Table 2 and Fig. 1), producing a greater transference of the sulfoxide to the mesenteric blood. This was particularly evident when ABZ was administered with polysorbate vehicle. This excretion of ABZSO toward the enterocyte basal membrane could be related to the intracellular distribution of the biotransformation enzymes involved in the ABZ sulfoxidation.

Microsomal Intestinal FMO and P-450 Contribution. Differential enantioselectivity of ABZSO was used in our study to determine the P-450 and FMO contribution to ABZ sulfoxidation. Specific inhibitors such as clotrimazole (P-450) and methimazole (FMO) have been used by some authors with the same purpose (Galtier et al., 1986, Villaverde et al., 1995; Moroni et al., 1995).

Our results show that both systems (P-450 and FMO) are involved in the microsomal intestinal ABZ sulfoxidation in a similar way. The mean ratio (ABZSO)/(+)-ABZSO obtained is 48.07±51.92 being 4.13% the e.e. of the S(+)-enantiomer (Table 4). These data agree with the results of Villaverde et al. (1995). In liver the contribution of the enzymatic systems is different because P-450 in liver sulfoxidation is more relevant than FMO. The mean ratio (+)-ABZSO/(−)-ABZSO 55.75:43.36, corresponds to an e.e. of 13.33% for (−)-ABZSO (Moroni et al., 1995).

In the rat and in the human the major enterocyte P-450 appears to be a member of the P-450A subfamily and it could be involved in the sulfoxidation process (Watkins et al., 1987; Fasco et al., 1993). FMO1 is present in the intestinal system but the enzymatic activity measured by the oxidation of thiourea is lower in intestine than in liver (Larsen-Su and Williams, 1996).

Effects of Administration of Surfactants. Surfactants, especially P80, operated at the intestinal level by increasing the metabolic conversion rate of ABZ into ABZSO and also caused marked changes in the kinetic disposition of the latter.

The increase in the sulfoxidase activity when ABZ was administered with 0.016 mM P80 was due predominantly to P-450, because it correlates well with the stereoselective production of (−)-ABZSO (enantiotmeric ratios: 71.6/28.4 versus 48.07/51.9 in the control). The surfactants increased the intestinal absorption of ABZ (del Estal et al., 1991), which could enhance the cytochrome transcriptional mechanisms (Aix et al., 1994). Because in our work the gastrointestinal tract is repeatedly exposed to ABZ, long-term oral administration could not contradict the important increases observed with the use of surfactants because they facilitate the ABZ absorption and the passage into enterocyte. To explain these increases, some aspects must be considered. First, the long-term administration of the drug could modify the composition of the enterocyte membrane (Miyamoto et al., 1983; Joes, 1992), which favors the absorption of ABZ. Even if such effect is reversible, it may influence the absorption process (Kakemi et al., 1970) and the apparent rate of sulfoxidation. Secondly, the surfactant itself could exert an inductive effect on the biotransformation system. This point will be discussed below.

Another interesting observation reflected in Table 2 and Fig. 1 is that ABZSO was quantified in the mesenteric blood (0.176 ± 0.03 nmol/cm) and in the intestinal lumen in a similar proportion (0.165 ± 0.05 nmol/cm).

Table 3

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Appearance Rate Constant (min⁻¹ cm⁻¹)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.71 ± 0.01</td>
<td>5</td>
</tr>
<tr>
<td>5 mg/kg ABZ</td>
<td>0.89 ± 0.14</td>
<td>4</td>
</tr>
<tr>
<td>5 mg/kg ABZ + STC 10 mM</td>
<td>1.36 ± 0.19*</td>
<td>4</td>
</tr>
<tr>
<td>5 mg/kg ABZ + P80 0.016 mM</td>
<td>1.25 ± 0.24*</td>
<td>4</td>
</tr>
</tbody>
</table>

* Significantly different from control p ≤ 0.05.
modulate the metabolizing enzyme at the site of a primary entry point of the systemic circulation.

Intestinal microsomal activity could be modified by increased ABZ absorption, but considering that the increase in ABZ absorption from 64% under the control condition to 85% of the administered dose in the presence of surfactants seems very slight in comparison with the increase in ABZ sulfoxidation in vitro and in situ, the possibility that the surfactants have a direct P-450 inductive effect must be considered. Also, the membrane perturbation produced by detergents increased microsomal hæmox-6-phosphate dehydrogenase (Kulkarni and Hodgson, 1982) and glucuronyltransferase activities (Berry et al., 1975), possibly due to an increased cofactor or substrate accessibility for a functional conformation of P-4501A2. With the phospholipid molecules surrounding P-4501A2 its important to modulate the metabolizing enzyme at the site of a primary entry point of the systemic circulation.

### Acknowledgments

We thank Smith-Kline & Beecham S.A. (Madrid, Spain) for the free supply of ABZ, ABZSO, and ABZSO2 and to the Dr. Esteve Laboratory (Barcelona, Spain) for supplying the mebendazole. We are also grateful to María Luisa Fernández Rojo for translating the manuscript.

### References


### Table 4

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>ABZSO Production</th>
<th>% of Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.147 ± 0.043</td>
<td>0.081 ± 0.014</td>
</tr>
<tr>
<td>5 mg/kg ABZ</td>
<td>0.128 ± 0.004</td>
<td>0.062 ± 0.003</td>
</tr>
<tr>
<td>5 mg/kg ABZ + STC 10 mM</td>
<td>0.175 ± 0.024</td>
<td>0.081 ± 0.037</td>
</tr>
<tr>
<td>5 mg/kg ABZ + P80 0.016 mM</td>
<td>0.324 ± 0.047</td>
<td>0.092 ± 0.010</td>
</tr>
</tbody>
</table>

*Significantly different from control p < 0.01.


