SUMMARY

Aksit D. Comparative pharmacokinetics of ricobendazole in goat and sheep, and the effect of increased doses on the plasma disposition of ricobendazole in goats.

The aims of this study were to determine and compare the pharmacokinetics and bioavailability of ricobendazole (RBZ) in goats and sheep at dose rate of 5 mg/kg bodyweight and to investigate the effects of increased doses (10 and 15 mg/kg) of RBZ on the plasma disposition of RBZ in goats following subcutaneous administrations. Moreover, the plasma distribution of (-) and (+) enantiomers of RBZ in both animal species was also investigated in the present study.

For these purpose, 12-16-month-old, sixteen (16) goats and eight (8) sheep were used. The study was designed according to two-phase study protocol. In Phase-1, eight sheep were assigned as Group I and 16 goats were allocated into to 2 groups such that the mean gender and weight of animals in each group were similar [Goat Group II: Subcutaneous recommended dose (5 mg/kg), Goat Group III: Intravenous group (5 mg/kg)]. The animals in Group I and II received RBZ subcutaneously and the animals in Group III received intravenously at dose of 5 mg/kg bodyweight. Heparinised blood samples were collected by jugular vein at different times between 1 and 192 hours after drug administrations. A four-week washout period was allowed between the phases of the study.

In Phase-2, the sheep in the group I received RBZ intravenously at dose of 5 mg/kg bodyweight; the goats in Group II and Group III received RBZ subcutaneously at dose of 10 mg/kg and 15 mg/kg bodyweight, respectively. The blood samples were collected in similar fashion of the first phase of the study. The plasma concentrations of RBZ and its sulphone metabolite in plasma were analysed by high performance liquid chromatography (HPLC) following liquid-solid phase (SPE) extraction procedures. The enantiomers of RBZ in extracted samples were re-analysed using chiral chromatography.

It was indicated that the kinetic parameters of RBZ and its main metabolite, $ABZSO_2$ in goats were statistically different compared to those observed in sheep following subcutaneous administration at dose rate of 5 mg/kg. The plasma half-lives ($T_{1/2}$) of RBZ and $ABZSO_2$ in sheep were statistically longer than the values in goats. Although there is no significant difference was observed for peak plasma concentrations (T_{max}) of RBZ in both animal species, the values of area under curve (AUC), mean residence time

(MRT) and time to the last quantifiable plasma concentration (T_{last}) was significantly larger and longer in sheep compared with those in goats, respectively.

Dose-dependent plasma dispositions of RBZ were observed following subcutaneous administration at increased doses (10 and 15 mg/kg) in goats. The parameters of C_{max}, $T_{1/2}$ and AUC of RBZ and its sulphide metabolite were increased almost double and triple in parallel with the increased doses of 10 and 15 mg/kg, respectively.

The plasma disposition of RBZ in goats was also statistically different from sheep after intravenous administration. The plasma clearance (Cl), $T_{1/2}$, MRT and AUC values were significantly faster, shorter and higher in goats compared to those in sheep, respectively. In addition, the bioavailability of RBZ following subcutaneous administration was smaller in goats (82.0%) than in sheep (97.9%), and at increased 10 and 15 mg/kg doses administered in goats the bioavailabilities were 91.18% and 110.01%, respectively.

(-) and (+) enantiomers of RBZ exhibit similar plasma dispositions regardless of the administration routes and animal species. After rasemic RBZ administration (-) enantiomer was higher (55:45%) at the first 2-10 hours and then (+) enantiomer increased and the ratio (-)/(+) changed to almost completely dominant (% 5:95).

RBZ could be used subcutaneously at similar doses in goats compared with sheep, since absorption and peak plasma concentration of RBZ displayed similar disposition in both species. However, the plasma half-life ($T_{1/2}$) and mean residence time (MRT) of RBZ in goats were shorter than sheep and this is probably associated with faster elimination in goats. Moreover, the findings observed after intravenous administration of RBZ in both animal species supports this assumption.

Because of the dose-dependent plasma elevations of RBZ observed after subcutaneous administration at increased doses (10 and 15 mg/kg), RBZ could be used at higher doses to provide higher plasma concentration and longer persistence recommended for some nematodes, thus may provide greater efficiency. However, the dose should be divided into two parts and administered to different regions of animals for subcutaneous application to prevent the adverse reactions that may occur following subcutaneous injection of RCB in goats.

Key words: Ricobendazole, Albendazole sulphone, Pharmacokinetics, Enantiomer, Goat, Sheep.