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TRICLABENDAZOLE RESISTANT *FASCIOLA HEPATICA*: PHARMACOKINETIC AND EFFICACY ASSESSMENTS OF A DRUG COMBINED TREATMENT

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The altered drug influx/efflux and enhanced metabolic capacity identified in triclabendazole (TCBZ)-resistant *Fasciola hepatica* contributes to the development of resistance to TCBZ. The aim of this work was to evaluate the pharmacokinetics (PK) and clinical efficacy (CE) of TCBZ administered alone or co-administered with ivermectin (IVM, drug efflux inhibitor) and methimazole (MTZ, metabolic inhibitor) in TCBZ-resistant *F. hepatica* parasitized sheep. Sheep infected with TCBZ-resistant *F. hepatica* were divided into three groups (n= 4): untreated control, TCBZ-treated and TCBZ+IVM+MTZ treated sheep. Plasma samples were collected (PK study) and analysed by HPLC. In the CE study, the animals were sacrificed at 15 days post-treatment to evaluate the comparative efficacy against TCBZ-resistant *F. hepatica*. The presence of IVM and MTZ did not affect the plasma PK behaviour of TCBZ metabolites. The combined drug treatment was not sufficient to enhance the poor efficacy of TCBZ against resistant *F. hepatica*. Finally, the enhancement of TCBZ concentrations in *F. hepatica* induced by both IVM and MTZ in *ex vivo* assays, did not reach a measurable effect under the current *in vivo* experimental conditions.