XXXIX ANNUAL SCIENTIFIC MEETING
ARGENTINE SOCIETY
OF EXPERIMENTAL PHARMACOLOGY

November, 27-30, 2007

BUENOS AIRES, ARGENTINA

80

Enzymatic pathways involved in flubendazole liver biotransformation

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Flubendazole (FLBZ) is a benzimidazole anthelmintic widely used in poultry and swine, which may be an alternative drug for parasite control in ruminants. The objective of this work was to characterise the main enzymatic pathways involved in the hepatic biotransformation of FLBZ. Liver cytosols and microsomes were obtained from control and phenobarbital (PB)-induced female Wistar rats, and from untreated male Corriedale x Merino cross breed sheep. Subcellular fractions were incubated with 40 μM of either FLBZ or its reduced chiral metabolite (red-FLBZ) in presence of NADPH. Incubation mixtures were analysed by HPLC. Liver microsomes from control rat reduced FLBZ to red-FLBZ and oxidised the later back to the parent molecule. Microsomes obtained from PB-induced rats displayed higher cytochrome (CYP) 3A and 2C-mediated N-demethylase activities, which correlated with an enhanced ability to convert red-FLBZ into FLBZ. CYP-mediated oxidative metabolism of red-FLBZ to FLBZ was absent in sheep liver. Both cytosolic and microsomal fractions obtained from sheep liver were able to reduce FLBZ into red-FLBZ at the same rate; the reduction of FLBZ led to the prevalent (~98%) stereospecific formation of one of the enantiomeric forms of red-FLBZ. A NADPH-dependent ketone-reductase may be involved on FLBZ reduction in sheep liver. The study of drug metabolising enzyme activities may help to predict drug-drug metabolic interactions in Veterinary Therapeutics.