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ENHANCED ACTIVITY OF GLUTATHION-S-TRANSFERASE IN THE FLUKE *FASCIOLA HEPATICA* RESISTANT AT TRICLABENDAZOLE

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Fasciolosis is a zoonotic parasitic disease caused by *Fasciola hepatica*. Its control is mainly based on the use of triclabendazole (TCBZ), a halogenated benzimidazole thiol derivative that shows excellent efficacy against both juvenile (immature) and adult stages. The helminth parasites possess different biochemical mechanisms for detoxification; the over-expression of metabolic enzymatic systems is one of them. The resistance of *F. hepatica* to TCBZ is growing worldwide. Hence, the knowledge of detoxification and resistance mechanisms in *F. hepatica* is needed. This preliminary work was aimed to assess the cytosolic enzymatic activity of Glutathion-S-Transferase **(**GST) in adult *F. hepatica* specimens, susceptible (*Cullomptom strain*) and resistant (*Sligo* and *Oberon strains*) to TCBZ. Both resistant strains expressed significant major metabolic activity compared to that measured in the cytosolic fraction obtained from susceptible flukes. GST catalyzes nucleophilic attack by reduced glutathione to a wide array of compounds, including toxic products of lipid peroxidation. TCBZ action may induce secondary oxidative stress in *F. hepatica,* which may explain the observed increment in GST activities as a defensive mechanism. These preliminary results may be useful to further understand the mechanisms underlying the drug metabolism/disposition and activity in target helminth parasites.

B4-89

HEPATIC CYTOCHROME P450 AND FLAVIN-CONTAINING MONOOGYGENASE METABOLIC ACTIVITIES IN MALE AND FEMALE SHEEP

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Xenobiotic metabolizing enzymes play a major role in determining the persistence of therapeutically used drugs in target tissues. Phase 1 oxidative reactions are catalyzed by the cytochrome P450 (CYP) superfamily and the flavin-containing monooxygenase (FMO) system, the most important membrane-bound mixed function oxidases in mammals. The objective of this work was to evaluate CYP- and FMO-dependent activities in liver microsomes obtained from male and female Romney Marsh sheep aged 8-10 months. The involvement of both enzyme systems on the hepatic enantioselective sulphoxidation of the benzimidazole anthelmintic albendazole (ABZ) was also characterized. CYP- and FMO-dependent metabolic activities were measured by using known marker substrates. The total CYP contents in the hepatic microsomes were 0.51±0.18 (males) and 0.53±0.08 (females) nmol/mg of microsomal protein. No gender differences were observed in CYP1A-, CYP2B-, CYP2C-, CYP3A- and FMO-dependent activities. The metabolic ratios FMO/CYP for the total sulphoxidation of ABZ were 3.35 and 3.58 in male and female sheep, respectively. This finding also indicates no gender differences on the contribution of both enzyme systems to the hepatic metabolism of this anthelmintic. Overall, male and female Romney Marsh sheep displayed similar phase 1 metabolic activities in the liver.

B4-90

PK MODEL CONTRIBUTION TO VANCOMYCIN DOSAGE ADJUSTMENT IN RENAL PATIENTS

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Vancomycin dose adjustment in renal patients must be performed in order to avoid more damage of the kidney. Usually, it is done by empirical methods, like Lake & Peterson (Pharmacotherapy 1987; 7: 69-72) and others.

Here, we propose the Giusti-Hayton adjustment method (Drug Intel Clin Pharm 1973; 7: 382-7) to acquire the vancomycin dose interval (tau). Such method is based exclusively on each patient estimated creatinine clearance (ClCr) and easily runs in MS Excel® for Windows®.

Using a sample of patients with moderate renal insufficiency from a published results (Antimcrob Agents Chemother 1984; 25: 433-7), we obtained the following relationship between tau (h) and ClCr (mL/min/1.73 m^2):

$$tau = 592.76 \times ClCr^{-0.788} \quad r^2 = 0.9969.$$

To validate the model we compared this method with others and obtained similar results.

Conclusions, this method provides an easy way to know the correct tau for vancomycin to be applied in each patient. Futher experience could demonstrate if this approach would reduce the renal damage and health costs in vancomycin treated patients.

B4-91

ACETAZOLAMIDE CORNEAL PERMEATION FROM INTERPOLYELECTROLITE-DRUG COMPLEXES.

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Acetazolamide (ACZ) is an inhibitor of carbonic anhydrase used mainly in the management of glaucoma by oral route. Due to its low solubility and poor corneal permeability there is no ocular formulation available. In this work we present interpolyelectrolyte/drug complexes (DIPEC) using two opposite charged polyelectrolytes, Eudragit E100 (EE) and Eudragit L100 (EL) as ACZ potential carriers. Different EE:EL stoichiometric composition in aqueous dispersion were prepared: EE:ACZ:EL (1:0,07:x), where x= 0 to 0,5.

The influence of EE:EL ratio on turbidity, particle size, electrokinetic potential (ζ) and *in vitro* release characteristics of the particles were investigated. *In vitro* release using Franz cells with synthetic membranes, phosphate buffer (pH 7,4) and simulated lachrymal fluid as receptor media were performed. Additionally, permeability assay through rabbit cornea using ringer solution as receptor media was carried out.

As the proportion of EL increased an increment in relative turbidity and a smooth decrease of ζ were observed. Particle size was dependent on EE:EL ratio, varying between 50 and 1500 nm.. These facts could be related to nanoparticles formation. ACZ release rate decreased from 32 to 18 $\mu g.sec^{-0,5}.cm^{-2}$ with the increase of EL proportion and release profiles did not show any difference between both receptor media. Corneal permeability of ACZ from EE:ACZ:EL (1:0,07:0,05) was studied and yielded five folds higher than that from ACZ solution.

DIPEC could be considered as an interesting ACZ carrier to improve glaucoma treatment by ocular controlled delivery. Additionally *in vivo* studies should be performed in order to evaluate efficacy and pharmacokinetic.