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O21

ASSESSMENT OF INTESTINAL DRUG TRANSPORT: DEVELOPMENT AND APPLICATION OF THE USSING CHAMBER TECHNIQUE

Ballent, M.[1,2]; Lifschitz, A.[1,2]; Virkel, G.[1,2]; Sallovitz, J.[1], Maté, L.[1,2], Lanusse, C [1,2]

[1]Lab. Farmacología, FCV, UNCPBA. [2]. CONICET.
Email:mballent@vet.unicen.edu.ar

The role of the transport protein P-glycoprotein (P-gp) in the pharmacokinetics of different drugs used in veterinary medicine has been demonstrated. The goal of the current work was to develop the Ussing chamber technique to characterize the intestinal P-gp-mediated drug transport in rats and sheep. The flat sheets of intestinal mucosa (ileum) were mounted into Ussing chambers. Digoxin (DGX) (200 μM) and Albendazole sulfóxido (ABZSO) (30 μM) were added to mucosal (M) and serosal (S) sides. Samples were taken between 30 and 240 min. DGX and ABZSO were analyzed by HPLC. The efflux rate (P_{eff}) was calculated. The intestinal transport of DGX and ABZSO was corroborated. In rats, the $P_{eff\ S\text{-}M}$ was significantly higher than $P_{eff\ M\text{-}S}$ for both compounds. The $Peff_{S\text{-}M}/Peff_{M\text{-}S}$ ratio ranged between 1.76 and 2.37 for both drugs, indicating a transport process to the intestinal lumen. In sheep, the $Peff_{S\text{-}M}/Peff_{M\text{-}S}$ ratio for ABZSO was 1.49. The presence of PSC833 enhanced the efflux M-S in both species. The $Peff_{S\text{-}M}/Peff_{M\text{-}S}$ ratio decreased to 1.23 (rats) and 1.30 (sheep). The use of the Ussing chamber technique is a useful tool to improve the comprehension of the absorption/excretion mechanisms involved in the transport of drugs therapeutically used in veterinary medicine.

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REGULATION BY ESTROGENS OF MULTIDRUG RESISTANCE-ASSOCIATED PROTEIN 2 (MRP2) IN CACO-2 CELLS.

Arias A., Ruiz ML., Villanueva SSM., Pellegrino JM., Catania VA., Mottino AD.

IFISE-CONICET, Fac. Cs. Bioq. y Farm., UNR, *Suipacha 570, 2000 Rosario, Argentina. E-mail: agoarias@yahoo.com.ar*

In previous studies we observed that repeated administration of the synthetic estrogen ethynylestradiol (EE) to rats reduces the expression of Mrp2 in intestine. Here, we studied whether EE treatment affects MRP2 expression in Caco-2 colon cancer cell line. The cells were treated for 48 hs with EE (5, 30 and 100 μM, n=3), or solvent (DMSO) for the controls (C). When DMEM+10% FBS (medium A) was used as culture medium, EE significantly decreased MRP2 expression at 100 μM, as detected by western blotting. In contrast, the same treatment but using a modified low estrogen medium (phenol red-free, DMEM+10% charcoal-dextran treated FBS) (medium B), showed a significant increase in MRP2 levels by EE (5 and 30 μM). Messenger RNA levels, quantified by Real Time PCR, remain unchanged, indicating post-transcriptional regulation. To confirm that the presence of natural estrogens in the medium conditions EE response, we further treated cells in medium B with estradiol (0.5, 5, and 30 μM, n=3) for 48 hs. The data indicated increased MRP2 levels by estradiol at 5 and 30 μM. **Conclusion:** Estrogens composition of the incubation medium conditions MRP2 expression in Caco-2 cells. Any extrapolation to the pharmacological effects of EE on human intestinal MRP2 has to be cautiously done.