Poster Session 2 – Pharmacokinetics

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Dispersion model of hepatic elimination: studies on salicylic acid in hepatic cirrhosis

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The aim was to study the influence of hepatic cirrhosis on membrane permeability and uptake of a hydrophilic model substance, salicylic acid. Using five non-eliminated markers (erythrocytes, albumin, sucrose, urea, and water), the permeability and exchange in the isolated perfused control and cirrhotic rat livers were characterised. After injection into the portal vein of markers and salicylate, outflow data were collected and analysed using moment analysis and the dispersion model (DM). Various parameters, including hepatic volume of distribution (V_H), mean transit time (MTT), the relative spreading (CV^2), dispersion number (D_N), influx rate constant (k_{12}), perfusate-tissue distribution coefficient (K_p), permeability (PS), fraction unbound in cells (f_{uc}) and throughput component (%TC), were calculated (Table 1).

Table1 Disposition kinetics of salicylate in hepatic cirrhosis in rats

	MTT	CV^2	V_H	D_N	k_{12}	f_{uc}	%TC	K_P	PS
Control	86	0.58	2.6	0.08	0.29	0.29	5	3.7	8.2
Cirrhotic	49*	0.96*	1.3*	0.30*	0.12*	0.58*	18*	1.5*	3.2*

*$P < 0.005$, vs control; analysis of variance. MTT (s); V_H ($mL\,g^{-1}$); k_{12} ($L\ s^{-1}$); PS ($mL\,min^{-1}g^{-1}$)

The observed changes in the output profiles of markers in cirrhotic livers implied that due to parenchymal and microcirculatory alterations, the blood–liver exchange is progressively limited in cirrhosis. These findings were confirmed by histological evaluations. The overall distribution of salicylate in the cirrhotic liver is influenced by intracellular binding plus permeability barrier. The increase in f_{uc} is an indication of decreased intracellular binding capacity in cirrhosis. The profound change in the outflow profile of salicylic acid in cirrhotic livers is indicative of change in the distribution to non-equilibrium conditions. The appearance of a fast eluting sharp peak suggests that the hepatic uptake of salicylate has been decreased. The reduced PS value of salicylate suggests that the permeability of hepatocyte membrane, as a consequence of reduced diffusion in the space of Disse, is reduced substantially. The formation of this new barrier further impedes the non-instantaneous cellular transport of salicylate, reducing its MTT whilst increasing CV^2. Of the mechanisms that may account for the observed changes (change in protein binding, metabolism, membrane permeability, diffusion), reduced permeability leads to a decrease in k_{12} and a relatively smaller amount of material can access the peripheral compartment during organ transit. Thus a large fraction appears in the hepatic outflow without having left the central compartment. Hence, the output profile is composed mainly of the throughput component and the shape of the profile is similar to that of a non-eliminated tracer that is confined to the extracellular space. The two-compartmental axial dispersion model introduced by Rowland et al (1984) and Rowland & Roberts (1985, 1986) still describes adequately the output profile of salicylate.

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Rowland, M., Roberts, M. S. (1986) *J. Pharmacokinet. Biopharm.* **4**: 227–260
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