THE RELEASE AND CLEARANCE OF AN I.M. ADMINISTERED LIPOSOME FORMULATION OF STEROIDS

M. Arrowsmith, J. Hadgraft and I.W. Kellaway*, Department of Pharmacy, University of Nottingham, NG7 2RD. *Welsh School of Pharmacy, U.W.I.S.T., Cardiff.

The advantages in using liposomes as sustained release devices are (1) the low toxicity of lecithins, and (2) their complete biodegradability. The preparation of C21 ester derivatives has been shown to prolong liposomal retention of corticosteroids (Shaw et al 1976). We have previously reported the in vitro release characteristics of a homologous series of such derivatives of cortisone, from dipalmitoylphosphatidylcholine (DPPC) liposomes (Arrowsmith et al 1980). We now report the in vivo release behaviour of two esters of this series and the clearance of liposomal material from the intramuscular injection site.

The plasma ^{3}H level/time profiles of liposomally encapsulated ^{3}H-cortisone palmitate and ^{3}H cortisone octanoate, and non-entrapped cortisone palmitate, were determined following injection by the i.m. route. 0.125mls of a 12.5%w/v suspension of DPPC containing 9 mole% of the ester was injected into the upper thigh muscle of 3 rabbits. Plasma samples were collected and assayed by scintillation counting. When the plasma radioactive content was insignificant the animal was sacrificed and the injected muscle removed. The % of the dose non absorbed was determined by assay of the homogenised muscle. From anlaysis (Wagner and Nelson 1963) of the plasma/time profile and i.v. clearance data of a solution of ^{3}H-cortisone, the kinetics of drug absorption from the i.m. site were determined.

Using a monochloride technique (Lubran and Pearson 1958) egg lecithin was labelled with ^{131}I and this material included in tracer quantities in cortisone palmitate loaded liposomes. Using the administration procedure detailed above, the clearance of liposomal components from the i.m. site was followed by gamma scintigraphy.

Preparation	$t_{\frac{1}{2}}^{\Delta}$ in vitro release (days)	$t_{\frac{1}{2}}^{\Delta}$ muscular clearance (days)
^{3}H-cortisone palmitate in DPPC liposomes	2.92	4.70
^{3}H-cortisone octanoate in DPPC liposomes	1.21	0.68
^{3}H-cortisone palmitate suspension	-	0.79
^{131}I-liposomes	-	8.48[/]

$^{\Delta}$All release kinetics were first order, except / which was zero order.

A comparison of the data obtained from the cortisone ester liposomal preparations shows that the same rank order of release rate is seen, in vitro and in vivo. While following i.m. injection the release rate of the octanoate was faster than in vitro, for the palmitate the opposite was true. Liposomal material is cleared slowly following i.m. injection and such formulations may be of use in future sustained release products. It would appear that in vitro data are only partially useful in predicting in vivo release characteristics from liposomes.

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