SHORT TERM FATE OF PULMONARY DELIVERED TECHNETIUM-99m LABELLED LIPOSOMES

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The therapeutic effect of aerosolised bronchodilator drugs following deposition within the conducting airways of the lung is rapid but frequently short lived as the drug is removed to the systemic circulation. Liposomes have been shown to confine the distribution of pulmonary administered cytosine arabinoside to the respiratory tract (Juliano and McCullough, 1980), and therefore may prove beneficial in sustaining the effect of locally active drugs. However, the determination of liposomal pulmonary clearance is necessary to evaluate the effect of vesicle encapsulation on the pharmacokinetics of inhaled drugs.

In this study, for which ethical approval was obtained, multilamellar vesicles (MLVs) composed of dipalmitoyl phosphatidylcholine (DPPC) were prepared by hydrating a lipid film with 0.9% $^{w}/_{v}$ saline at 55°C. Small unilamellar vesicles (SUVs) were prepared by probe sonication of an MLV suspension. The liposomes (40mg DPPC in 1 ml) were labelled with ^{99m}Tc (20-25 MBq) as pertechnetate (Farr et al, 1983) before dilution to 8 ml and transfer to an air jet nebuliser (Hudson). Each of a group of 4 healthy male volunteers (aged 27-40) inhaled the nebulised product while remaining undisturbed in a supine position above a wide angle γ camera. The volunteers were encouraged to maintain deep, slow inspirations with breath holding before exhalation (breathing frequency 6-8 cycles min^{-1}) for sufficient time (approx. 13 min) to accumulate lung burdens of 3.5 to 4 MBq. Clearance was calculated from the corrected activity within defined regions of interest of images taken at intervals of up to 8 h post inhalation. Size analysis was conducted on the liposomes (Coulter counting for MLVs, photon correlation spectroscopy for SUVs) and on the aerosol product (multistage liquid impinger).

Short term clearance profiles for MLVs and SUVs were indicative of mucociliary transport and were very different from the fate of a nebulised pertechnetate solution, where rapid absorption from the lung was apparent ($t_{\frac{1}{2}}$ = 0.35 h). Mucociliary transport becomes progressively faster from the peripheral to the central airways (Foster et al, 1980). The statistically equivalent 6 h retentions for MLVs and SUVs (table) infer that pulmonary penetration of both liposome types was similar and therefore, a function of droplet size of the nebulised product rather than liposome size; mean liposome size was 2.9 μm and 0.07 μm, MMAD and σg of the aerosol products were 3.7 μm and 1.54 and 3.2 μm and 1.53 for MLVs and SUVs respectively.

VOLUNTEER	6 h LUNG RETENTION (%) MLVs	SUVs
A	86	82
B	90	83
C	91	78
D	83	64
Mean (±SEM)	87.5(2.1)	76.8(5.1)

Inter- and intra-volunteer variation was probably dependent on small differences in initial deposition pattern, highlighted in volunteer D where the rapid clearance of SUVs occurred as a result of significant amounts of activity depositing within the perihilar zones of the lung, regions predominant in the central airways. In conclusion, this study has elucidated that short term clearance of inhaled liposomes occurs via the mucociliary escalator. Individuals suffering from chronic lung disease may demonstrate slower clearance profiles which, prospectively, may be of benefit to sustained bronchodilator therapy.

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