MICROENCAPSULATION OF MITOMYCIN-C WITH ETHYLCELLULOSE. DISSOLUTION STUDIES AND PHARMACOKINETICS IN PATIENTS WITH LIVER METASTASES

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Regional chemotherapy is an attempt to increase the therapeutic index of the drug by increasing the concentration within the organ harbouring the metastatic deposits, with decreased concentration of drug in the systemic vascular compartment.

The value of intra-arterial chemotherapy is limited by systemic toxicity. Microencapsulation of cytotoxic agents can give particles in the size range 50-300μm which show sustained release of drug. Particles in this size range will be trapped in the capillary bed of the liver following intra-arterial administration. Increased exposure of the tumour in the target organ to the cytotoxic drug occurs with a reduction in systemic drug levels and side-efects in animal models (Kerr et al., 1988). This process has been termed chemoembolization. The sustained release of microencapsulated water soluble drugs can be readily achieved using ethylcellulose, a non-toxic, inert material

The aim of this study was to measure systemic drug exposure following hepatic arterial administration of microencapsulated mitomycin C in patients with liver metastases.

Mitomycin C was microencapsulated by the method of Kato et al (1985). Two types of mitomycin C were used: (a) pure mitomycin C powder and (b) a mixture of mitomycin C and sodium chloride.

A range of coating to core ratios were used: a typical preparation involved 100mg of mitomycin C dispersed in 50 ml of cyclohexane containing polyisobutylene (0.8%) plus ethyl cellulose (250mg). The mixture was stirred under reflux at 80°C and cooled slowly to room temperature over a period of 2 hrs with continuous stirring.

Release rate studies were performed using U.S.P. Method II and HPLC assay.

Table 1.

	Free MMC	Microencapsulated MMC
Peak drug Concentration (ng/mL)	812±423	80±75
Area under curve (ng/mL h) (A_{o-24h})	438±126	143±42
Clearance (L/h)	46±8	140±31
Half-life (h)	0.11±0.02	0.39±0.03
Volume distribution (L)	33±4	246±23

Uncoated mitomycin C dissolved instantaneously. Microencapsulated mitomycin C plus NaCl showed a limited sustained release effect which increased with increasing coating to core ratio e.g. with 500mg ethylcellulose the time for 90% release was 10 min, this could be increased to 30 min using 5g of ethylcellulose. These limited sustained release effects with the microenecapsulated mitomycin C plus NaCl were however sufficient for these systems to be used in the clinical situation, i.e. no significant amount of mitomycin C was released during the short period required to re-suspend and inject the microencapsulated material. The smaller particle size and the free flowing nature of the microencapsulated mitomycin C plus NaCl were significant advantages compared to the microencapsulated pure mitomycin C.

The microencapsulated pure mitomycin C showed much greater sustained release effects e.g. times for 50% release were 25 min (250mg ethylcellulose), 115 min (500mg ethylcellulose) and 170 min (750mg ethylcellulose).

The pharmacokinetic results for two detailed studies performed six weeks apart in six patients are shown in Table 1. 20mg mitomycin C in solution and 20mg mitomycin C in microencapsulated form were administered as a bolus via the hepatic artery. 10 ml peripheral venous blood samples were obtained from an indwelling venous cannula before microcapsule administration and at regular intervals afterward (5, 15, 30, 60 and 120 minutes, 6, 8, 12 and 24 hours).

The results show that very little systemic exposure is associated with the administration of the microencapsulated form of mitomycin C. Dose escalation should be feasible without increasing systemic toxicity.

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