LACK OF INTERACTION BETWEEN MUCUS GLYCOPROTEINS AND ANTIBIOTICS

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Mucus glycoproteins (GP) have been shown to impair drug diffusion even at concentrations below the gelling point (Marriott et al 1984) and the ability of GPs to undergo extensive changes in macro- and micro-conformation has also been demonstrated (Cheema et al 1985). This leads to inadequate penetration of antibiotics into mucus and this may be due to binding of the drug to the GP molecules or via an indirect effect that leads to a change in the physical properties of the gel. This work has measured the binding of a range of antibiotics to mucus glycoproteins and also their effect on the viscoelasticity of the mucus gel.

Binding studies were carried out using centrifugal ultrafiltration of ligand/GP solutions at 1100 g for 5 minutes at 20°C to produce 200 µl of filtrate. Binding to apparatus was negligible. Scatchard analysis of the data (Table 1) assuming two classes of binding site provides the number of molecules per binding site (n) and the intrinsic binding constant (k mol^{-1}). The viscoelastic parameters G' and G", the elastic and viscous moduli respectively were measured by the method described by James & Marriott (1982). The G' value at 10 Hz is reported in Table 2 since this approximates to lung ciliary beat frequency. Antibiotics of clinical relevance were used at 0.2 - 100 mmol l^{-1} for binding studies and 10 and 50 µg ml^{-1} for rheological studies.

Table 1

Ligand	Site 1		Site 2		
	n	k	n	k	
Benzylpenicillin	430.0	5.97	-	-	
Ticarcillin	31.1	77.27	118.5	10.12	
Cefsulodin	9.3	193.50	59.6	20.13	
Cefotaxime	20.5	115.20	77.2	16.90	
Mezlocillin	26.2	91.60	156.0	9.48	
Carbenicillin	387.3	3.61	-	-	(n = 8)

Table 2

	G' Nm^{-2}			
	Control	10 µg ml	50 µg ml^{-1}	
Benzylpenicillin	17.0 (2.7)	18.2 (1.8)	15.4 (4.6)	
Cefsulodin	16.7 (2.9)	15.6 (1.1)	10.9 (3.0)	
Cefotaxime	25.0 (7.3)	23.5 (6.2)	30.5 (6.5)	
Carbenicillin	19.9 (8.4)	29.1 (13.4)	27.1 (2.0)	
Gentamycin	17.3 (4.2)	17.1 (7.5)	15.9 (1.8)	
Ceftazidime	17.2 (3.4)	13.6 (4.1)	17.7 (4.0)	
Ticarcillin	19.6 (7.7)	8.8 (0.7)	19.4 (0.4)	
Clavulanic acid	12.1 (1.9)	22.3 (5.9)	14.9 (2.0)	(SD) n = 3

The results indicate no significant binding or changes in rheological properties of the mucus ($p = 0.05$ Mann Whitney) and consequently these mechanisms do not play a role in impaired diffusion through mucus in disease states. Poor penetration of antibiotics into mucus gels must therefore be due to other reasons and changes in the GP conformation which may not be detected by the viscoelasticity studies could in turn lead to reduction in the availability of free water (Cheema et al 1985) which appears crucial to the diffusion process.

Marriott, C. et al (1984) 2nd Euro. Cong. Biopharm. and Pharmcokinetics, 176
Cheema, M.S. et al (1985) J. Pharm. Pharmacol. 37: 9P
James, S.L., Marriott, C. (1982) J. Phys. E: Sci. Instrum. 15: 179-180