THE INFLUENCE OF PROTEINS ON THE TRANSPORT OF TETRACYCLINES

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Although in vitro and in vivo studies have indicated that the presence of mucin can affect both the bioavailability (Braybrooks & others, 1975; Banerjee & Chakrabarti, 1976) and penetration of tetracycline (Saggers & Lawson, 1966), no comparative information with a range of tetracycline molecules on the transport across mucus layers is available. Also, the effect of other proteins which are often present in mucus from diseased patients has been ignored. This work describes a method of determining the permeation rates of some tetracyclines through mucoid secretions and bovine serum albumin (BSA), a protein to which the tetracyclines have been shown to bind (Kellaway & Marriott, 1976).

The apparatus consisted of a three compartment Perspex cell, 25.4 mm in diameter. The 15 ml donor and receptor compartments were separated by either a 3.0 mm (I) or 13.0 mm (II) spacer which was fitted on both faces with a visking membrane. The central compartment thus formed was filled with the appropriate protein solution or mucoid gel. The receptor cell was continuously monitored spectrophotometrically for the antibiotics used, which were tetracycline, oxytetracycline, chlortetracycline, demethylchlortetracycline, doxycycline and minocycline. All were dissolved in phosphate buffer (pH 7.0) and controls were carried out with buffer in the central compartment.

All the tetracyclines produced experimental curves which could be characterised in terms of lag time and a permeation rate. The latter was calculated from the slope of a tangent drawn to the permeation curve at a known interval after the lag time.

The presence of BSA in the concentration range 2-10% in the central compartment (II) reduced the rate of transport of all the tetracyclines. For example, in the case of tetracycline, the lag time increased from 14.0 to 42.0 minutes and the permeation rate calculated 60 minutes after the lag phase, decreased from 1.44 to 0.46 $\mu g\ min^{-1}$ for a 10% BSA solution. When homogenised bronchial mucus was placed in the same cell then although the lag time was increased ten-fold, the permeation rate was not markedly reduced. This may be explained by the fact that although tetracycline is bound to the mucus glycoprotein, the degree of binding is much lower than to BSA (Woods, 1977).

The effect of gelation was evaluated using 2.5 to 10% dispersions of hog gastric mucin. With tetracycline a linear decrease in permeation rate with increase in mucin concentration was observed, whereas the lag time produced a curvilinear response. However, when the dispersion was cross-linked by the addition of 0.5% di-sodium tetraborate then although the permeation rate was unaltered, the lag time was considerably increased.

It is concluded therefore that the different transport rates observed for the various tetracyclines may contribute to the variations in peak plasma concentrations which have been observed in man (Sweeney & others, 1959). More significantly, the presence of glycoproteins in the form of a gel network only appears to alter the length of the lag phase of the transport process and not the permeation rate. This would suggest that penetration of mucus layers in vivo could be reduced sufficiently for an initial delay in absorption to occur.

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