NET FLUID TRANSPORT AFFECTS ATENOLOL ABSORPTION IN THE IN-SITU RAT SMALL INTESTINE

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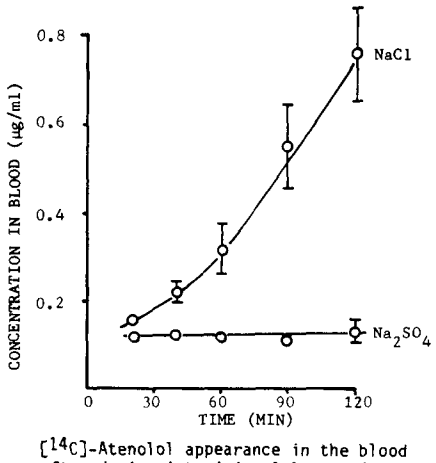
In situ loops of rat small intestine have been used by many workers for the study of drug absorption. However, reports on the presence of simultaneous water absorption in this model have varied and its effect on measured drug absorption rates is unclear. This communication describes experiments designed to clarify this point. They involve measurement of the absorption of the hydrophilic β-adrenoceptor antagonist atenolol in in situ rat jejunum under conditions of different intestinal net water flux.

Absorption measurements were made in halothane-anaesthetised male rats (210-250g) as described previously (Taylor et al 1985). One 7.5 cm loop of upper jejunum was used in each rat and 1 ml of solution containing ^{14}C-atenolol (0.5 mg and 1 μCi/ml) in isotonic (154 mM) NaCl or isotonic (113 mM) Na_2SO_4 was introduced. Blood samples (orbital vein) were removed at 20, 40, 60, 90 and 120 min after administration. In separate experiments, blood samples were taken after intravenous (tail vein) administration of ^{14}C-atenolol (0.5 mg in 0.5 ml saline) in sham-operated rats. Net fluid flux in the intestinal loop was measured by weighing fluid recovered at zero time and 60 or 120 min. Atenolol in blood samples was analysed by scintillation counting; the pH of loop fluid was measured immediately after recovery from the loop. The replacement of NaCl by Na_2SO_4 greatly reduced net water flux; mean values (± SE) were 15.5 ± 0.3 and 4.0 ± 0.1 μl/min respectively ($p < 0.01$). Intestinal pH, however, was not significantly altered [mean values (± SE) = 6.69 ± 0.04 and 6.46 ± 0.06 for NaCl and Na_2SO_4 ($p > 0.05$)]. Mean atenolol blood concentrations (see figure) were up to five times higher after administration in NaCl solution than in Na_2SO_4 solution. The differences are significant at all time points ($p < 0.05$). Estimates from the loop and intravenous data (by numerical deconvolution) show that the 120 min concentrations correspond to 48.5 percent and 10.5 percent absorption, respectively, for NaCl and Na_2SO_4 solutions.



[^{14}C]-Atenolol appearance in the blood after dosing into jejunal loops. Figure shows mean ± SEM except where smaller than symbol (n=6)

The results clearly show that atenolol absorption occurs more rapidly from isotonic NaCl solution than it does from isotonic Na_2SO_4. Jejunal pH is unchanged and therefore the difference in absorption rate most probably results from the change in net water absorption. Fluid transport may affect drug absorption in two ways. Firstly, it will lead to progressive concentration of drug solution in the intestinal lumen (for drugs which are relatively slowly absorbed) and thereby increase the concentration of drug at the gut wall or in the adjacent mucus layer. An increased concentration gradient will increase absorption rate. Secondly, there may be a 'solvent drag' effect resulting in increased drug absorption via paracellular pores or channels (Karino et al 1982). Distinction between these two mechanisms is not possible from the current data.

In conclusion, water absorption from the in situ intestine substantially affects atenolol absorption rate in the rat. This is likely to be a general effect, particularly for slowly absorbed drugs, and may be important in interpreting results from this model. The comparison of absorption rates from isotonic NaCl and isotonic Na_2SO_4 solution is a useful way of identifying this effect.

Karino, A. et al (1982). J. Pharm. Dyn. 5: 670-677.
Taylor, D.C. et al (1985). J. Pharm. Pharmacol. 37: 280-283.