J. Pharm. Pharmacol. 1983, 35: 814–815
Communicated March 30, 1983

COMMUNICATIONS

The influence of perfusion rate on salicylate absorption in the rat

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The rate of flow of a drug solution down the gastrointestinal tract will influence the residence time at the absorption site and the permeability coefficient governing mass transport across the intestinal wall. Komiya et al (1980) examined the effect of fluid flow on the intestinal absorption of a number of steroids using the in-situ through-and-through rat intestinal perfusion technique. Their steady state results followed the physical model predictions described by:

$$\frac{C(l)}{C(o)} = \exp\left(-\frac{2\pi rl.}{Q} P_{app}\right) \quad (1)$$

where C(l)/C(o) is the fraction of steroid remaining in the intestinal lumen of length l, r is the effective radius, Q is the fluid flow rate and P_{app} is the apparent permeability coefficient. Furthermore the relationship between P_{app} and Q was expressed by

$$P_{app} \propto Q^a \quad (2)$$

with the coefficient a varying from zero, for membrane controlled solutes, to 0.44 for solutes the absorption of which was aqueous boundary layer controlled. These results together with those of Amidon et al (1980), who also used a non-dissociating solute, suggesting that gastrointestinal flow in the rat perfusion technique can be approximated by laminar flow in a cylindrical tube.

Using a similar experimental procedure, we have examined the absorption of salicylic acid, a dissociating solute, under varying flow conditions.

Methods

The technique as described by Komiya et al (1980) was used to determine the absorption of salicylic acid (B.P. grade) at pH 7·4 and 6·5, using flow rates in the range 0·1 to 2.0 ml min^{-1}. Salicylic acid was assayed spectrofluorimetrically (Turner et al 1970). The drug was dissolved in isotonic sodium phosphate buffers of high buffering capacity, one at pH 7·4 (Turner et al 1970), and a similar system at pH 6·5.

To test for the possibility of drug-induced gastrointestinal irritancy a technique based on that outlined by Walker & Wilson (1979) was used. The perfusates from the gut were filtered through a Millipore filter (0·22 μm) to collect any mucosal material removed during perfusion. The residue was then dried in a desiccator and weighed.

Results and discussion

The change in percentage salicylic acid unabsorbed C(l)/C(o) with time at different flow rates and pH 7·4 is illustrated in Fig. 1. The non-steady state sigmoidal region is explained by longitudinal spreading within the perfusion system (Komiya et al 1980). The plateau represents the fraction of drug unabsorbed at steady state. It can be seen that the steady state fraction absorbed is larger at low flow rates, a result which can be explained by an increased residence time (Komiya et al 1980). The slope of a plot of log P_{app} versus log Q was negative giving a value of −0·22 for a (eqn 2). Thus the P_{app} decreased significantly from $0{\cdot}65 \times 10^{-4}$ to $0{\cdot}36 \times 10^{-4}$ cm s^{-1} ($P < 0{\cdot}01$), as the flow rate increased from 0·1 to 2·0 ml min^{-1}. Since salicylic acid is highly ionized at pH 7·4 it was expected that a plot of this form would

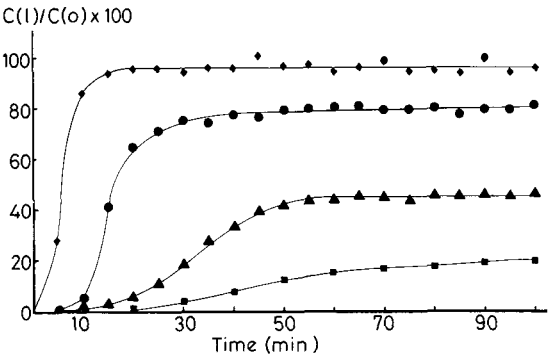

FIG. 1. The percentage of salicylic acid unabsorbed with time at four different perfusate flow rates ◆ 2·0, ● 0·5, ▲ 0·2, ■ 0·1 ml min^{-1}.

* Correspondence.

show log P_{app} to be independent of log Q. Furthermore Desai (1977), using the closed loop Doluisio method, showed that salicylate absorption at pH 7·4 was membrane pore-controlled. Although a buffer with high buffering capacity was used and the technique was such that fresh buffer was flowing continuously through the gut segment, we monitored the pH of the effluent perfusate at the low (0·1 ml min^{-1}) and high (2·0 ml min^{-1}) flow rates. At 2·0 ml min^{-1} the pH of the effluent remained essentially constant but at 0·1 ml min^{-1} the limiting pH of the effluent fell to 6·84. Thus the increase in P_{app} with decrease in flow rate coincided with a fall in pH. The direction of the pH change is such as to increase the proportion of unionized drug.

Literature reports suggest that the physiological pH at the membrane surface is approximately 6·5 (Crouthamel et al 1975; Desai 1977; Schurgers & de Blaey 1982). The absorption of salicylate was therefore studied at pH 6·5 using the low and high perfusate flow rates. Values of $0{\cdot}67 \times 10^{-4}$ and $0{\cdot}45 \times 10^{-4}$ cm s^{-1} were obtained at flow rates of 0·1 and 2·0 ml min^{-1} respectively. Thus both rates were higher than the corresponding values obtained using a perfusate with initial pH 7·4. The trend towards a lower P_{app} at high flow rate was still present, although the difference was not statistically significant at the 5% level. The pH of the perfusate effluent was also measured in the 6·5 pH systems. At the higher perfusate flow rate the pH remained unchanged. However at the low flow rate a slight decrease in pH i.e. from 6·5 to 6·27 was observed.

An alternative explanation considered for the P_{app} changes was the possibility that salicylic acid may cause tissue damage to the gut and thus alter permeability. Musocal loss (mg per 100 min), obtained following perfusion with salicylic acid pH 7·4 and flow rates 2·0 and 0·1 ml min^{-1}, is shown in Table 1. A statistically significant difference ($P < 0{\cdot}01$) was seen in the mucosal loss between the high (2·0 ml min^{-1}) and the low (0·1 ml min^{-1}) flow rates. The mucosal loss decreased with the flow rate, hence the increase in permeability at the lower flow rate is unlikely to be related to an increase in tissue damage. The mucosal loss was also estimated at pH 6·5 and the results are also included in Table 1. No difference was observed between the high and the low flow rates, however the trend was also towards a decrease with decreasing flow rate.

Several studies have shown that the intestine seems to have the ability to change the pH of perfusates towards a physiological value of 6·5. Crouthamel et al (1975) reported that, following perfusion of the rat small intestine with isotonic saline pH 6·0, an equilibrium pH of 6·4 ± 0·1 was obtained in the upper jejunum. Recently, Schurgers & de Blaey (1982) observed that the pH of an isotonic phosphate buffer decreased from pH 7·3 to 6·5 within 60 min when oscillated in the jejunum of the rat. When buffers of high and low buffering capacity and pH of 4·5 and 9·0 were placed in the gut lumen, Desai (1977) found that the bulk pH in both cases tended to converge to pH 6·5. Buffers of initial pH 6·5 did not change pH. The rate of change in the bulk pH depended on the buffer capacity and on the degree of agitation in the system. Furthermore, the pH controlling absorption rate was that at the membrane surface rather than that in the bulk (Desai 1977). This alteration in pH in the direction of less ionization for acidic drugs will enhance transport via the lipodal path. An observed increase in P_{app} as the flow rate decreases could therefore, be explained by an increase in transport related to an increase in the proportion of unionized drug.

Table 1. Muscosal loss (mg per 100 min) following perfusion with salicylic acid (1 g $litre^{-1}$).

Buffer pH	Flow rate (ml min^{-1})	Mucosal loss (mg per 100 min)
7·4	2·0	*4·695
7·4	0·1	*3·285
6·5	2·0	3·710
6·5	0·1	3·242

*$P < 0{\cdot}01$.

In conclusion, therefore, it would appear that the anomalous relationship between P_{app} and Q observed for salicylate in the current work may be explained in terms of the ability of the buffer to influence the membrane surface pH. At the low flow rates physiological buffer secretion is sufficient to maintain the surface pH at 6·5. However, with increasing flow rate the supply of perfusate buffer in the medium is seen to significantly alter the surface pH towards that of the perfusate, thus reducing the proportion of unionized drug absorbed.

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