Propranolol absorption in different regions of the rat gastrointestinal tract in situ: implications for sustained release formulations

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Oral sustained-release formulations generally attempt to extend duration of drug activity by retarding dissolution and release in the gastrointestinal tract, thus spreading absorption over a greater length of the tract than with a conventional formulation. A drug normally completely absorbed in the upper small intestine may consequently be presented for absorption throughout the small and large intestine. For this type of formulation, efficient absorption of the drug must not be confined to the small intestine, or bioavailability may be reduced and the prolongation of activity minimal. This aspect has received little attention despite the number of sustained-release formulations introduced.

We have compared the absorption of the β-adrenoceptor blocking drug propranolol in different regions of the rat gastrointestinal tract in situ as part of the development of a sustained-release formulation for propranolol ('Inderal' LA).

Methods. The experimental technique was similar to that of Doluisio et al (1969), which uses rate of drug disappearance from an in situ cannulated segment of rat gut as a measure of absorption. The technique has been claimed as a realistic model of in vivo absorption for the rat (Doluisio et al 1969) and, in some cases, for man (Perrier & Gibaldi 1973). Previous work on β-blocking drugs in the rat (Taylor & Grundy 1975) showed that the in situ–in vivo correlation was poor for practolol, but satisfactory for propranolol.

Male albino rats (Alderley Park strain), 230–250 g, were fasted 18 h before use. Anaesthesia was induced and maintained with halothane ('Fluothane', ICI). The stomach and intestine were exposed with a midline incision, and the segment to be studied cannulated at either end with silastic tubing (5 cm × 0·25 cm internal diameter). Each segment comprised one whole region of the tract, defined as follows: stomach, duodenum (pyloric sphincter to ligament of Treitz), jejunum (ligament of Treitz to mid-point between ligament of Treitz and ileocaecal junction), ileum (from lower point of jejunum, as defined above, to ileocaecal junction), caecum (ileocaecal junction to caecum-colon junction) and colon (caecum-colon junction to rectum). Absorption measurements in each region were made in 4–7 rats, each rat being used for one segment and one experiment only. The drug solution (0·68 mM propranolol in 0·154 M sodium chloride) included [^{14}C]polyethylene glycol 4000 (0·01 mg ml^{-1}) as a non-absorbed marker, and was adjusted to pH7 before use. The cannulated segment was washed through with 0·154 M sodium chloride (37 °C) to remove traces of gut contents, and drug solution (also at 37 °C) was introduced via the proximal catheter; 2–5 ml was introduced depending on the size of the segment. The solution was sampled (0·5 ml) immediately after introduction (zero time) and at 10, 30 and 60 min intervals, using the sampling procedure of Doluisio et al (1969). Withdrawn samples were assayed for propranolol by h.p.l.c., with 4-methyl propranolol as internal standard. The column (0·5 × 10 cm) was packed with 5μ Hypersil ODS (Shandon Southern Products), and the solvent system was methanol–water (80:20%), containing 0·01 M heptane sulphonic acid. Detection was by u.v. absorbance at 290 nm. Each gut segment was excised and weighed at the end of the experiment. Intestinal weight per unit length was approximately uniform throughout the small and large intestine [0·09 (0·01) g cm^{-1}; mean (with s.d.)]. Stomach and caecum are not included in this as they do not approximate to cylindrical form. Concentrations of polyethylene glycol 4000 (as d min^{-1} ml^{-1}) and propranolol (mg ml^{-1}), at each time, were expressed as fractions (f_d and f_c respectively) of their concentrations at zero time.

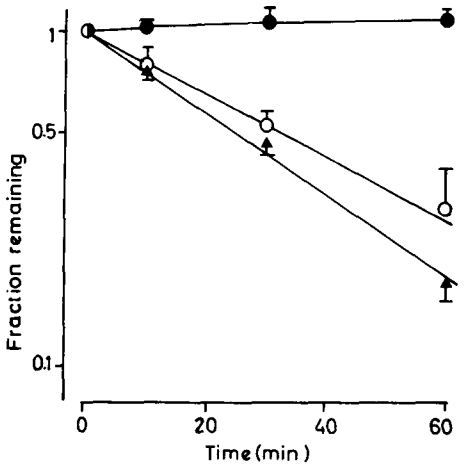

FIG. 1. First-order disappearance of propranolol in in situ rat stomach (●——●), duodenum (○——○) and colon (▲——▲). f_t (on a logarithmic scale) plotted against time; each point is the mean value (n = 4–7), with standard error indicated by a vertical bar. The plot for the caecum is identical to that for the duodenum, and plots for jejunum and ileum fall between those for duodenum and colon.

* Correspondence.

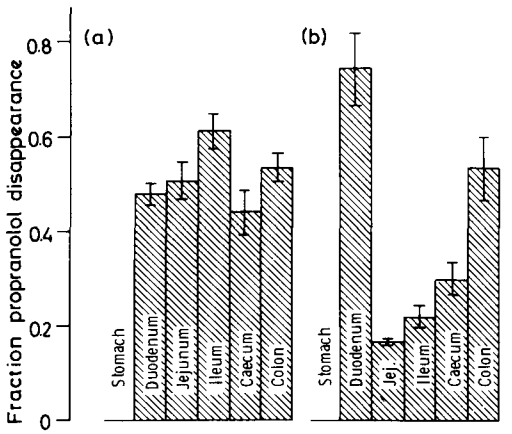

FIG. 2. Fraction propranolol disappearance in 30 min in different regions of rat gastrointestinal tract in situ, compared on the basis of whole segments (a) and per g wet weight of tissue (b). Values plotted are means (n = 4–7), with standard error indicated by a vertical bar.

Correction of propranolol concentrations for changes in drug solution volume was achieved by calculating fc/fd (denoted f_t).

Results. Mean propranolol disappearance plots for whole segments (f_t on a logarithmic scale vs time) are shown in Fig. 1. No disappearance is observed in the stomach, but it is rapid and first order throughout the small intestine (duodenum, jejunum, ileum) and large intestine (caecum and colon). Fig. 2 shows fraction propranolol disappearance in 30 min in the different gastrointestinal regions. As whole segments, all regions except the stomach show a similar ability to absorb propranolol (Fig. 2a). However, correction for wet weight of each segment (Fig. 2b) shows that intrinsic ability to absorb the drug is greater in duodenum and colon than in jejunum, ileum and caecum. A similar pattern is found if length, rather than weight, of the segment is used.

Absorbed propranolol is extensively extracted at first pass through the liver (George et al 1976); gut wall metabolism may also occur (Hayes & Cooper 1971). Consequently, uptake by intestinal tissue only indirectly predicts rate of drug appearance in the systemic circulation. However, the observed equivalent rates of propranolol disappearance in different intestinal regions should give similar systemic availabilities of drug provided that gut wall metabolism does not vary substantially from region to region. Information about this metabolism is not available for propranolol, but work with other drugs shows that gut wall metabolism is usually uniform throughout small and large intestine (Lasker & Rickert 1978) or decreases aborally (Hanninen et al 1968). Therefore, it is fair to assume that the systemic availability of propranolol is similar after absorption from the large intestine and the small intestine.

In the conscious animal, transit rate of a drug or formulation along the gastrointestinal tract decreases aborally. For instance, Varga (1976) found mean transit times in the rat of 0·4 and 2·5 h for upper and lower small intestine, and 14 h for the large intestine. Consequently, an orally-administered solution of propranolol will probably be absorbed to a greater extent in the lower than in the upper small intestine, the longer transit time in the lower segment compensating for its lower rate of drug uptake per unit length of tissue. With a sustained-release formulation this effect is more pronounced, with a major proportion of the dose released in the large intestine. The data presented herein suggest that propranolol released at this site will be absorbed as effectively as that released in the small intestine. This is supported by recent studies in man with a long-acting propranolol formulation (McAinsh et al 1978), where the normal plasma half-life of 6·4 h was extended to an effective half-life of 12·7 h. It is unlikely that this could occur without substantial absorption of the drug in the large intestine.

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REFERENCES

Doluisio, J. T., Billups, N. F., Dittert, L. W., Sugita, E. T., Swintosky, J. V. (1969) J. Pharm. Sci. 58: 1197–1202

George, C. F., Orme, M. L'E., Buranapong, P., Macerlean, D., Breckenridge, A. M., Dollery, C. T. (1976) J. Pharmacokinet. Biopharm. 4: 17–27

Hanninen, O., Aitio, A., Hartiala, K. (1968) Scand. J. Gastroenterol. 3: 461

Hayes, A., Cooper, R. G. (1971) J. Pharmacol. Exp. Ther. 176: 302–311

Lasker, J., Rickert, D. E. (1978) Xenobiotica 8: 665–672

McAinsh, J., Baber, N. S., Smith, R., Young, J. (1978) Br. J. Clin. Pharmacol. 6: 115–121

Perrier, D., Gibaldi, M. (1973) J. Pharm. Sci. 62: 1486-1490

Taylor, D. C., Grundy, R. U. (1975) J. Pharm. Pharmacol. 27: Suppl. 65P

Varga, F. (1976) Digestion 14: 319–324