ABSORPTION OF PRACTOLOL AND PROPRANOLOL IN DOG INTESTINAL LOOPS IN SITU

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The absorption of the β-blocking drugs practolol and propranolol in the Doluisio rat in situ gut preparation was described in a previous communication (Taylor and Grundy, 1975). This preparation proved to be an inadequate model of the in vivo absorption of these drugs in rats. This communication describes the absorption of practolol and propranolol in an alternative in situ preparation, in a conscious dog.

Failure of the rat in situ model to reflect in vivo absorption of practolol and propranolol may result from anaesthesia and surgical shock. Changes in ion and water absorption, intestinal pH and mucosal blood flow have been reported under these conditions. As these factors may all be critical in determining the rate of absorption of drugs they should be maintained as near normal as possible in a realistic absorption model. To achieve this, we have adapted the Thiry-Vella dog intestinal loop preparation; this is a chronic in situ preparation which can be used repeatedly, without anaesthetic and under relatively stress-free conditions. Preparation of Thiry-Vella loops, using male Beagle dogs, involved surgically isolating a 20-50cm segment of jejunum or ileum using the procedure described by Markowitz (1964); ends of the loop were exteriorised by means of titanium fistulae. Histological examination of a loop removed 3 months after the initial operation showed no gross abnormalities. Drug absorption was assessed by measuring disappearance of drug from solutions introduced into the loops. Drug solutions, isotonic but not buffered, also contained a non-absorbed marker (^{14}C-polyethylene glycol 4000) to allow correction for water absorption.

Ileal and jejunal loops showed characteristically distinct patterns of pH and volume changes during the course of absorption experiments. Drug solutions in jejunal loops maintained a mean pH of around 7.2 over 60 minutes, but in the ileum rose from pH7 to a resting pH of about 8 after 20 minutes. Water absorption was usually less rapid in the jejunum than in the ileum. Under these conditions the absorption characteristics of practolol and propranolol in jejunal and ileal loops were also quite distinct. Propranolol showed rapid first order absorption from both loops (half-life respectively 15 and 8 min in jejunum and ileum); practolol showed little or no absorption in the jejunum, but rapid absorption (half-life 10 min), after an initial lag period, in the ileum. Despite the identical pKa's of the two drugs, propranolol is apparently absorbed over a much larger area of the small intestine than is practolol. This effect is controlled by the comparative partition coefficients of the two drugs, and the different resting pH of different regions of the small intestine.

The observations in the dog intestinal loops closely reflect results from blood level studies in rat and dog, which show both drugs to be absorbed, propranolol more rapidly than practolol. It is concluded that, compared to the rat in situ model, the dog intestinal loop technique gives a more detailed and realistic indication of the in vivo absorption of these drugs.

Taylor, D.C. and Grundy, R.U. (1975). J.Pharm.Pharmacol., 27, Suppl., 65P.
Markowitz, J., Archibald, J. and Downie, H.G. (1964). Experimental Surgery, 5th. Ed. ,Baltimore, Williams & Wilkins, 143-144.