J. Pharm. Pharmac., 1976, **28**, 117–126 *Received September* 1, 1975

Gastrointestinal absorption of carbenoxolone in the rat determined *in vitro* and *in situ*: deviations from the pH-partition hypothesis

J. W. BRIDGES, J. B. HOUSTON, M. J. HUMPHREY, W. E. LINDUP, D. V. PARKE, J. S. SHILLINGFORD AND *D. G. UPSHALL

*Department of Biochemistry, University of Surrey, Guildford, Surrey, GU2 4XH and *Chemical Defence Establishment, Medical Division, Porton Down, Nr Salisbury, Wiltshire, U.K.*

The absorption of [^{14}C] carbenoxolone from everted rat ileum *in vitro* and from rat stomach and ileum *in situ* has been examined. The rate of its mucosal to serosal transfer *in vitro* increases as pH increases from 5 to 8 whereas the amount bound to ileum tissue decreases with increased pH; absorption closely parallels the drug's solubility. The uptake of carbenoxolone *in situ* is bi-exponential and the rate constants for the two processes, have been calculated. Absorption *in situ*, and biliary excretion, of the drug increases with increasing pH from 5·0 to 7·4. Tissue binding to the ileum *in situ* is not dependent on pH except below pH 5·0 when extensive tissue accumulation of carbenoxolone occurs because of its low solubility. Tissue binding to the stomach increases markedly with decrease of pH from 7·4 to 6·5 and at pH 6·5 is 80 times greater than binding to the intestine. The rate of absorption from the stomach, at pH 6·5–7·4, was much less than that from the intestine *in situ*. When allowance is made for the binding of carbenoxolone to the stomach, contrary to the pH-partition hypothesis, correlation is apparent between its absorption and the amount present in the ionized form.

Carbenoxolone (3-O-β-carboxypropionyl-11-oxo-18β-olean-12-en-30-oic acid), is a highly lipophilic, highly protein bound, weak dibasic acid, with approximate pKa values of 6·7 and 7·1 (Parke, 1968). According to the pH-partition hypothesis, (see Schanker, 1964 for refs) the drug should be efficiently absorbed from the stomach since it is largely undissociated at pH values below 6·0; on the other hand the free acid is only sparingly soluble in aqueous systems. However, the orally administered drug has been shown to be well absorbed (Downer, Galloway & others, 1970; Lindup, Parke & Colin-Jones, 1970) and is excreted as conjugates, almost exclusively via the bile in both man and animals (Downer & others, 1970; Parke, Hunt & Iveson, 1972; Iveson, Lindup & others, 1971).

Downer & others (1970) showed that the maximum plasma concentration of carbenoxolone in man occurred 1 to 2 h after dosage and as this corresponded to 60% of the dose in the plasma compartment they concluded that substantial absorption of the drug occurred from the stomach; a second plasma maximum 3 to 6 h after dosage was attributed to enterohepatic circulation. They also showed, in two men that absorption did not occur when the gastric contents were maintained at neutral pH with bicarbonate-citrate buffer, and concluded that carbenoxolone was absorbed from the stomach in its non-ionized form, in accordance with the pH-partition hypothesis. In contrast to these observations in man, only poor evidence has been obtained for the gastric absorption of carbenoxolone in animals (Iveson & others, 1971; Lindup, 1971).

As only unchanged carbenoxolone has been found in the circulating blood of patients (Baron, Gribble & others, 1974) it has been assumed that the drug is absorbed unchanged in man being subsequently conjugated with glucuronic acid in the liver (Downer & others, 1970). In the rat, hydrolysis of carbenoxolone to enoxolone and succinate may occur before absorption, the hydrolysis being effected by enzymes of the gastrointestinal microflora and not by mammalian enzymes (Iveson & others, 1971).

The site and characteristics of the absorption of orally administered carbenoxolone are probably closely related to the therapeutic efficacy of the drug. The original findings of Doll, Hill & others (1962) that the drug when orally administered heals gastric but not duodenal ulcers has been attributed to a topical action and its extensive gastric absorption (Parke, Pollock & Williams, 1963).

Carbenoxolone is much more lipophilic than any of the compounds used in the development of the pH-partition hypothesis and in view of the lipophilicity parabola established for the gastrointestinal absorption of carbamates (Houston, Upshall & Bridges, 1974) it is conceivable that the drug may be absorbed faster in its ionized form. Its site of absorption, and the nature of the absorbed species, have therefore been investigated using an *in situ* technique with rat stomach and by *in vitro* and *in situ* methods with rat small intestine. The rate of bilary excretion of the drug has also been measured to correlate with the absorption studies.

MATERIALS AND METHODS

Animals. Female Wistar albino rats, ~200 g, bred and housed in the University's Animal Unit had free access to Spiller's Small Animal Diet and water. Before use the rats were fasted overnight but were allowed water.

Chemicals. [Carboxypropionyl-1, 4-$^{14}C_2$] carbenoxolone (0·1 mCi g^{-1}) was prepared (Iveson & others, 1971). Other reagents were of the appropriate grade and used as supplied.

Determination of radioactivity. Samples were counted in either a dioxan based scintillator (Iveson & others, 1971) or in a Tritox X 100–toluene (1 : 2 by volume) scintillator containing 1% w/v butyl PPD. Radioactivity was measured by scintillation spectrometer and counting efficiency determined using [^{14}C]toluene as internal standard.

Procedure for everted gut sac studies. The general procedure was that of Wilson & Wiseman (1954) using the serial sampling modification of Crane & Wilson (1958). The rat was killed by a blow on the head and a length of ileum removed, everted and cut into four 5 cm segments which were maintained in ice-cold isotonic saline gassed with 5% CO_2 in oxygen. After the segments were rinsed with isotonic saline, sacs 4 cm in length were filled with 1 ml of 0·154 M citrate–Na_2HPO_4 buffer containing 0·5% w/v glucose and incubated at 37° in 8 ml of 0·15 M Krebs-Henseliet buffer solution containing 100 μl of an ethanolic solution of [^{14}C]carbenoxolone (10 mg ml^{-1}) Duplicate experiments in each of 3 rats were performed at various pH values between 8·0 and 5·0, and samples (50 μl) of serosal fluid were removed for analysis at suitable intervals for up to 1 h, at the end of which the volume of serosal fluid was measured, the gut washed in buffer at pH 7·4, and the surface area of the opened sac measured. Samples of gut, serosal and mucosal fluid were analysed for [^{14}C]carbenoxolone and metabolites (Iveson & others, 1971).

Although the validity of this technique has been questioned because of the loss of structural and physiological integrity of the preparation (Levine, McNary & others,

1970), only slight loss of integrity after incubation for 90 min was reported by Fischer & Millburn (1970) and no loss of tissue viability or change in absorption rate was detected over 2 h by Houston & others (1974). We found no change with time in the rates of absorption of carbenoxolone, at any of the pH values studied.

Procedure for in situ *absorption studies.* The procedure of Doluisio, Billup & others (1969) and Doluisio, Crouthamel & others (1970) was used. Rats, fasted overnight but with access to water, were anaesthetized with sodium pentobarbitone (60 mg kg^{-1}; i.p.) and maintained at 37°, a midline abdominal incision was made and the small intestine isolated and cannulated at the duodenal and ileal ends with polyethylene cannulae i.d. 2·5 mm; o.d. 3·5 mm). A 50 ml syringe, with a three-way tap (Rocket Ltd., London, U.K.) and containing perfusion solution at 37°, was attached to the duodenal cannula and the intestinal lumen flushed. The stomach and ileum were ligatured, and the bile duct was cannulated using polyethylene tubing (Portex PP25; i.d. 0·4 mm; o.d. 0·8 mm). A duplicate 50 ml syringe was affixed to the ileal cannula and by this means 0·15 M Sørensen phosphate buffer (10 ml for intestinal or 5 ml for gastric studies) at various pH values (7·4–5·0 at 37°), and containing 100 μl of an ethanolic solution of [^{14}C]carbenoxolone (10 mg ml^{-1}), was introduced into the intestine. For gastric studies the stomach was isolated and cannulated at the oesophageal and the antral-duodenal junctions with polythene cannulae (i.d. 2·5 mm; o.d. 3·5 mm). At 3 min intervals (for up to 1 h duodenal and 2 h gastric) the solution in the intestine was pumped into either syringe and a 100 μl sample removed for determination of radioactivity, and the volume of the perfusate measured. Finally the gut was rinsed with phosphate buffer pH 7·4 and the amount of radioactivity determined. Four rats were studied at each of three pH values. The amount of carbenoxolone and its conjugates in bile was determined by measurement of total radioactivity of samples taken every 10 min. The drug is excreted in rat bile as its glucuronides (Iveson & others, 1971).

The solubility of the drug was determined by dissolving [^{14}C]carbenoxolone in citrate-phosphate buffer, pH 5 to 8 and 37°, depositing the insoluble drug by centrifugation, and measuring the radioactivity of the supernatant. Its partition coefficient between n-octanol and 0·15 M citrate–phosphate buffer was measured over the pH range 5 to 8. The organic solvent and buffers were presaturated with the relevant aqueous or organic phase. [^{14}C]Carbenoxolone (1 mg) dissolved in 20 ml of n-octanol was added to an equal volume of aqueous buffer in a stoppered flask, and the solutions mixed at 37° for 1 h and the concentration of [^{14}C]carbenoxolone in aliquots (1 ml) of each phase determined by liquid scintillation counting.

RESULTS

Intestinal absorption

Carbenoxolone is a large molecule (mol. wt 571) whose apparent partition coefficient between n-octanol and aqueous buffer varies by two orders of magnitude over a pH range of two units either side of its pKa of 6·7 (see Table 1).

The transfer rate of carbenoxolone from mucosal to serosal fluid in the intestinal sac (%cm^{-2} h^{-1}) increased as the pH value increased from 5 to 8, the rate at pH 8 being more than seven times that at pH 5 (see Table 2). Conversely the percentage of carbenoxolone tissue bound cm^{-2} after 1 h decreased as pH increased but was always much higher (for 1 h) than the absorption rate at the same pH. Ratios of % tissue bound to % transferred varied from 2 at pH 8 to nearly 50 at pH 5 when the drug's

Table 1. *Correlation of the apparent partition coefficients between octanol and buffer and the ionization of carbenoxolone at various pH values.*

pH	Apparent partition coefficient (octanol/buffer)	Fraction unionized
8·0	14	0·05
7·4	27	0·17
7·1	60	0·29
6·8	214	0·44
6·5	350	0·61
6·2	484	0·76
5·6	679	0·93
5·0	908	0·98

0·1M-Citrate-phosphate buffer was used to maintain the pH values. The fraction unionized was calculated assuming a pKa of 6·7 for carbenoxolone.

low solubility may have caused precipitation in the intestinal wall, or adsorption onto the mucosal surface, thus elevating the tissue bound figures. Measurement of the amount of carbenoxolone in true solution at the start of each experiment (Table 2) endorsed this view. Analysis of the serosal fluid according to Iveson & others (1971) showed that no metabolism of carbenoxolone had occurred during passage through the gut wall.

The relation between the concentration of ionized and unionized carbenoxolone, its solubility, and the rate of absorption from the intestinal sac at various pH values indicate that both ionized and unionized forms of the drug are absorbed (Fig. 1), and that absorption closely parallels solubility. Using the *in situ* perfusion technique we found the concentrations of drug administered at pH values above 5 were below the true aqueous solubility and unlikely to precipitate whereas the concentration of carbenoxolone at pH 5 was in excess of its aqueous solubility at that pH value.

Typical plots of the fraction remaining in the lumen *in vivo* with increasing time for pH values 5·0 and 7·4 are shown in Fig. 2. At each pH value a bi-exponential loss was observed indicating that two processes were involved in the removal of the drug from the lumen. Separation of the two processes was achieved by "feathering" (Mayersohn & Gibaldi, 1971). The fast disposition stage (α) and the slow disposition phase (β) rate constants are listed in Table 3. A similar second process has been described for intestinal absorption of other drugs (Doluisio & others, 1970) who suggested that it results from accumulation of the drug in the intestinal tissue.

Table 2. *The absorption of carbenoxolone from everted sacs of small intestine at various pH values.*

pH	Carbenoxolone transferred (% cm^{-2} h^{-1})	Carbenoxolone tissue bound at 1 h (% cm^{-2})	Carbenoxolone in solution at start of expt. (%)
8·0	0·52 ± 0·01	1·1 ± 0·03	100
7·4	0·47 ± 0·01	1·4 ± 0·03	100
6·8	0·43 ± 0·06	1·6 ± 0·2	83
6·2	0·20 ± 0·01	2·8 ± 0·1	16
5·8	0·10 ± 0·04	3·0 ± 0·1	2·1
5·0	0·07 ± 0·02	3·3 ± 0·1	0·9

Values given are the means for 4 animals ± s.e.m.

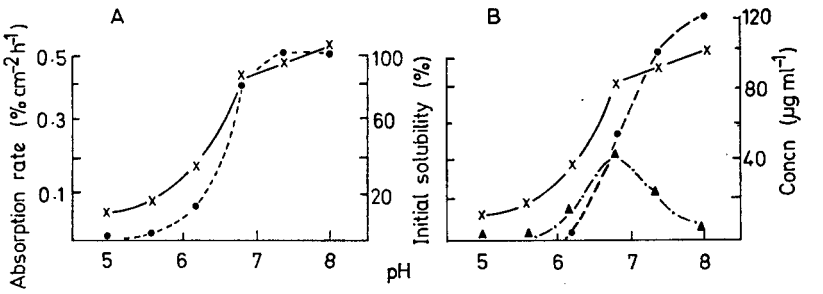

FIG. 1. Rate of absorption of carbenoxolone from rat intestine *in vitro* and the relation to its solubility and the concentration of ionized and unionized species at different pH values. Mean values of 3 experiments are shown for A) rate of carbenoxolone transferred (x——x) and initial solubility (● - - - - - ●) and B) rate of carbenoxolone transferred (x——x), ionized carbenoxolone (● - - - - - ●) and unionized carbenoxolone (▲-·-·-▲) at different pH values.

The following kinetic model may be envisaged:

$$\text{Lumen} \underset{K_{TL}}{\overset{K_{LT}}{\rightleftharpoons}} \text{Tissue} \xrightarrow{K_A} \text{Blood System}$$

where K_{LT} and K_{TL} are the rate constants for transfer from lumen to tissue and tissue to lumen respectively, and K_A is the true absorption rate. Mathematically the loss from the lumen (L) may be described by the two-exponential equation:

$$L = Ae^{-\alpha t} + Be^{-\beta t}$$

The values of A, B, α and β are determined from the semilog plots (see Fig. 2), and the rate constants (see Table 3) for this two compartment model were calculated as outlined by Doluisio & others (1970).

The absorption rates as measured by β and K_A, decreased regularly as the pH was lowered . However the rate constants for tissue accumulation (α, K_{LT} and K_{TL}) and the tissue/lumen ratios (obtained from K_{LT}/K_{TL}) at pHs 7·4, 7·1, 6·8 and 6·5 remained fairly constant. This indicates that the processes of tissue binding and absorption can

Table 3. *Rate constants to describe the bi-exponential disappearance of carbenoxolone from the intestinal and gastric lumen at various pH values using the* in situ *method.*

pH	Carbenoxolone concn (μg ml^{-1})	Fast disposition phase (α) (min^{-1})	Slower disposition phase (β) (min^{-1})	K_A (min^{-1})	K_{LT} (min^{-1})	K_{TL} (min^{-1})	T/L*
a) *Intestine*							
7·4	120	0·20 ± 0·03	0·052 ± 0·004	0·090	0·046	0·115	0·40
7·1	69	0·28 ± 0·01	0·045 ± 0·004	0·078	0·086	0·164	0·52
6·8	90	0·24 ± 0·01	0·039 ± 0·005	0·069	0·074	0·135	0·55
6·5	36	0·22 ± 0·01	0·032 ± 0·002	0·057	0·070	0·127	0·55
5·0	120	0·22 ± 0·01	0·011 ± 0·003	0·020	0·100	0·115	0·87
b) *Stomach*							
7·4	120	0·00947 ± 0·0006	0·00314 ± 0·0003	0·005	0·003	0·006	0·42
6·8	120	0·0163 ± 0·0015	0·00318 ± 0·0003	0·006	0·006	0·011	0·55
6·5	120	0·0366 ± 0·0021	0·00266 ± 0·00026	0·005	0·050	0·020	2·48

* Ratio of the rate constants for accumulation in tissue-lumen. The fast (α) and slow disposition (β) phase rate constants are calculated as described in the text and shown in Fig. 2. Mean values ± s.e.m. for 4 animals are given.

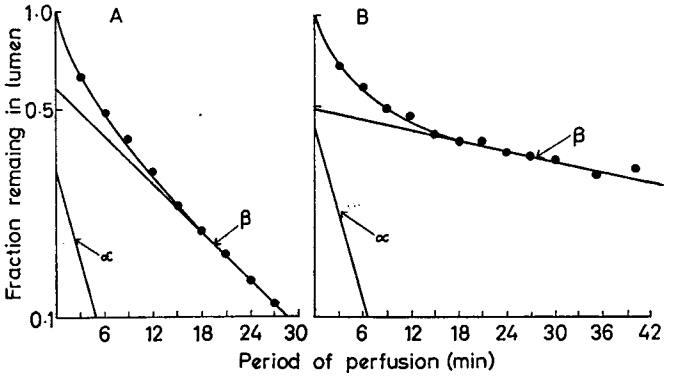

FIG. 2. Semi-log plots of the fraction of carbenoxolone remaining after various periods in the rat intestinal lumen after *in situ* perfusion. Mean values of 4 experiments are plotted for A) pH 7·4 α, $t\frac{1}{2}$ = 3·0 min, β, $t\frac{1}{2}$ = 11·3 min and B) pH 5·0 α, $t\frac{1}{2}$ = 3·0 min, β, $t\frac{1}{2}$ = 65·0 min.

be considered separately and that only the absorption process is pH sensitive. This assumption does not hold at pH 5 where extensive tissue accumulation occurs due to decreased solubility.

The amount of carbenoxolone found in the tissue at the completion of each experiment was much greater at pH 5·0 than at higher pH values (see Table 4). The biliary excretion rates of total radioactivity were found to decrease progressively as the pH was lowered from 7·4 to 5·0 confirming the decreased rates of absorption found (Table 4 and Fig. 3).

Plots of the absorption rates (β and K_A) and biliary excretion rates against the fraction of carbenoxolone unionized at the different pH values studied showed a negative dependence on the fraction unionized (U), as illustrated in the following regression equations:

$$K_A = -0{\cdot}726\ (\pm 0{\cdot}0052)U + 0{\cdot}101\ (\pm 0{\cdot}0022) \quad (1)$$
$$n = 4 \quad r = 0{\cdot}995 \quad s = 0{\cdot}00176$$

$$\beta = -0{\cdot}0431\ (\pm 0{\cdot}0028)U + 0{\cdot}0584\ (\pm 0{\cdot}0012) \quad (2)$$
$$n = 4 \quad r = 0{\cdot}996 \quad s = 0{\cdot}00095$$

$$\text{Biliary excretion rate} = -11{\cdot}66\ (\pm 1{\cdot}26)U + 16{\cdot}69\ (\pm 0{\cdot}520) \quad (3)$$
$$n = 4 \quad r = 0{\cdot}989 \quad s = 0{\cdot}424$$

where n, r and s are respectively the number of data points, the correlation coefficient and the standard deviation.

Table 4. *Percentage carbenoxolone tissue bound and biliary excreted at various pH values using the* in situ *method with rat intestine and stomach.*

pH	% tissue bound at t = 42 min	% biliary† excreted h^{-1} Intestine	% tissue bound at t = 42 min	% biliary† excreted h^{-1} Stomach
7·4	22·2 ± 0·1	15·0 ± 1·2	11·2 ± 8·6	1·32 ± 0·04
7·1	1·0 ± 0·1	12·9 ± 1·4		
6·8	1·4 ± 0·2	11·8 ± 0·9	18·3 ± 7·4	1·02 ± 0·03
6·5	0·5 ± 0·1	9·5 ± 0·7	38·7 ± 10·3	0·78 ± 0·03
5·0	11·6 ± 3·8	2·3 ± 0·5		

The percentage carbenoxolone tissue bound was determined at termination of the experiment i.e. intestine (60 min), stomach (120 min).

Results are the means values ± s.e.m. for 4 rats.

† calculated from the linear portion of the excretion curve.

According to Crouthamel, Tan & others (1971) the intercepts of these equations at U = O (totally ionized) and U = 1 (totally unionized) should correspond to the rates for the absorption of the ionized (K_i) and unionized (K_u) species, respectively. The value of ratio K_i/K_u is very similar (3·6–3·9) using the three different methods of evaluating the absorption rate.

Comparison of the theoretical rate constants for *in situ* absorption with experimentally determined values (using equations 1, 2 and 3) confirmed that at pH 5·0 the rate of absorption of carbenoxolone at a concentration of 120 μg ml^{-1} is limited by its low aqueous solubility the % reduction between observed and theoretical values being 34, 30 and 52% for β phase, K_A and biliary excretion respectively.

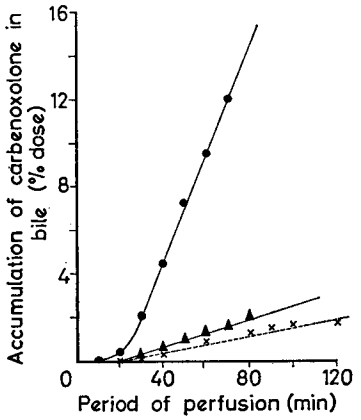

FIG. 3. Cumulative percentage of carbenoxolone excreted in bile after intestinal and gastric administration using *in situ* methods in the rat. The results of mean values for 4 rats are plotted for intestinal perfusion, pH 5·0, intestine (▲——▲), and pH 7·4, intestine (●——●); and for gastric perfusion at pH 7·4, stomach (x - - - - - x).

Gastric absorption

The *in situ* disappearance rates of carbenoxolone from the rat stomach, as measured by β and K_A, were very low compared with those for the intestine at the same pH. A bi-exponential disappearance similar to that for the intestine was found (Table 3). The rate constant K_A governing the true absorption rate shows little change between pH 6·5 and 7·4. On the other hand the rate constants for tissue accumulation (α, K_{LT} and K_{TL}) and the tissue/lumen ratios increased markedly with lowering of pH, implying that this leads to extensive tissue accumulation.

The amount of carbenoxolone in the tissue at the completion of each experiment was much greater at pH 6·5 than at higher pH values (see Table 4). The biliary excretion rates after gastric administration were much lower than those from gut, but had in common a progressive decrease as the pH was lowered from 7·4 to 6·5 (see Table 4). When allowance is made for the increase in stomach wall binding of carbenoxolone with decreasing pH a reasonably direct correlation is apparent between the carbenoxolone disappearing through absorption and the amount in the ionized form. This view is supported by the good correlation between biliary excretion of carbenoxolone and stomach pH.

DISCUSSION

Preliminary studies using everted rat intestinal sacs indicate that the solubility of carbenoxolone and its pKa are the prime determinants for the rate of absorption of

the drug from the intestine. In contrast to many acidic drugs (Schanker, 1960), carbenoxolone appears to be absorbed faster at pH values where the ionized form predominates. The gut sac findings were confirmed using an *in situ* procedure and employing carbenoxolone at concentrations below its limits of aqueous solubility. No evidence of metabolism during absorption was obtained using either method, both for stomach and intestine. The rates of biliary excretion of the drug after *in situ* perfusion followed the same pattern as the disappearance rates from the intestinal lumen, thus indicating that absorption is the rate-limiting step regulating systemic concentrations of carbenoxolone *in vivo*.

Extensive tissue binding of the drug was observed *in vitro*. The ratios of percentage tissue bound to percentage transferred were much higher than those observed for a series of aliphatic carbamates (Houston & others, 1974) where the highest ratio was approximately 1 for n-octyl carbamate (a compound with a partition coefficient of the same order as that of carbenoxolone at pH 5·0). Although it is known that the drug is strongly bound to albumin (Parke & Lindup, 1973), it is unlikely that the high percentage of carbenoxolone which accumulated in the tissue was due entirely to binding to tissue proteins and lipids. The solubility-determinations confirmed these doubts and suggested that precipitation in, or adsorption to, the gut sac epithelium was significant. The difficulty was overcome in the *in situ* studies by using lower concentrations of carbenoxolone at pH 7·4 to 6·5 such that solubility was not rate-limiting and the process of tissue binding could be analysed separately from absorption. The results for rat intestine showed that there was little relation with change of pH of the lumen indicating that the tissue binding process should not compete with the absorption process which is pH-dependent. This was confirmed since the K_A values showed good agreement with the β values. The latter is a hybrid rate constant which includes the rate constants for tissue accumulation and absorption. Low concentrations of carbenoxolone were found in the tissues at the end of each experiment showing that the binding is reversible.

Regression equations were used to calculate theoretical values of the rate constants for pH 5. Comparison with the observed values showed that the rate of absorption is limited by the aqueous solubility of the drug. It is surprising that the differences between observed and theoretical values are not larger, considering that the true aqueous solubility is only 1% of the dose. However, the tissue binding parameters are markedly higher at pH 5·0 than at the other pH values studied. Carbenoxolone bound in the intestinal tissues at the end of each experiment at pH 5·0 averaged 11·6% whereas at higher pH values figures of 0·5%–2·2% were found. Much higher binding to the wall of the stomach was experienced (11·2–38·7%). It would therefore appear that some true binding to the mucosa had occurred.

Although the pH of the rat stomach is 3–4, studies of gastric absorption of carbenoxolone *in situ* were performed at pH values of 7·4–6·5 only, so that solubility was not rate-limiting. Binding to the stomach also increased as the pH was lowered from 7·4 to 6·5, the degree of binding being much greater than for the intestine (see Table 4). When allowance is made for the increased tissue binding with decrease in pH, some degree of correlation is found between the amount of carbenoxolone present in the ionized form, and the rate of its disappearance from the stomach and its biliary excretion implying that, as for the intestine, carbenoxolone is preferentially absorbed in the ionized form or, at least, that the ionized and unionized forms are comparably absorbed. The implication must then be that at pH values characteristic of the

stomach even less carbenoxolone would be absorbed due to more extensive tissue binding, and increased precipitation from solution. This impaired ability of the stomach to absorb carbenoxolone compared with the intestine, may result from the differences in surface structure and area of the absorptive surfaces of the two organs, and the relatively poor blood supply of the stomach. The results conclusively demonstrate that in the rat the gastric absorption of carbenoxolone is of minor importance compared with the absorption from the intestine, but, conversely, the tissue binding of the drug is very much greater in the stomach and furthermore increases substantially as the pH becomes more acidic. Although these results may be considered to cast serious doubt on the previous suggestion that the stomach is the primary route of carbenoxolone absorption in man (Downer & others, 1970; Parke, 1972), it is possible that because of the high degree of tissue binding much of the administered carbenoxolone is adsorbed or precipitated onto the gastric mucosal surfaces so that a relatively small portion of the dose is available for subsequent absorption from the duodenum. Sodium taurodeoxycholate has been shown to increase the permeability of rat small intestine (Feldman, Reinhard & Willson, 1973) so that biliary reflux, which is quite common in gastric ulcer patients (Cocking & Grech, 1973) might further promote gastric absorption.

Contrary to the pH-partition hypothesis (Schanker, 1964) carbenoxolone is absorbed from the intestine, and perhaps also from the stomach, at a greater rate when ionized than in its unionized form, and although Downer & others (1970) found that bicarbonate-citrate buffer (pH 2·0) inhibited absorption of orally administered carbenoxolone in man, a more recent study by Baron & others (1975) has shown that antacid (magnesium trisilicate mixture) has no effect on the absorption rates of this drug, as measured by plasma concentration. Other drugs have been shown to be absorbed to some extent in their ionized state, for example salicylic acid (Nogami & Matsuzawa, 1961), barbitone and sulphaethiodole (Crouthamel & others, 1971), but in these cases the ratio of the rate constants for the absorption of the ionized and unionized forms (K_I/K_U) was less than 1 (K_I/K_U for carbenoxolone is 3·8) indicating that absorption in the undissociated form was still favoured. The absorption behaviour of carbenoxolone is therefore very unusual and requires further study and explanation. It remains uncertain whether the carbenoxolone anion is absorbed as such or in the form of an ion pair. Possibly this drug possesses chelating properties which would enhance absorption of the ionic form, or possibly the conformation of carbenoxolone in its ionic form tends to mask the negative charge.

It has been suggested (Houston & others, 1974) that an optimal partition coefficient exists for the intestinal absorption of xenobiotics, which for the octanol/aqueous buffer system was found to be in the region of 10. As carbenoxolone becomes fully ionized, its octanol–aqueous buffer partition coefficient approaches this value. Therefore carbenoxolone appears to conform to this hypothesis that drug absorption is determined both by the hydrophilic as well as the lipophilic nature of the drug. The partitioning properties of ionized carbenoxolone allow easy passage through the hydrophilic and lipoidal membrane barriers, whereas passage of the unionized form is hindered by its low solubility in the hydrophilic barrier. Smolen (1973) has suggested that although the pH-partition hypothesis is "an excellent rule of thumb" it cannot justify the assumption that biological barriers such as the gut wall are generally impermeable to ions. It is possible that other highly lipophilic, weakly acidic drugs may exhibit this phenomenon like carbenoxolone.

Although it has been shown that in the rat carbenoxolone is not readily absorbed from the stomach, the drug is nevertheless seen to be extensively bound to this tissue. In view of the suggested topical action of this drug (Parke, 1972) and its known effects on the synthesis of mucus by the gastric mucosa (Shillingford, Lindup & Parke, 1973, 1974; Johnston, Lindup & others, 1975), the binding of the drug to the stomach is probably of far greater importance to its therapeutic efficacy than is its systemic absorption. In fact, since the adverse mineralocorticoid side-effects of the drug are believed to be due to potentiation of aldosterone (Parke, 1972), it is possible that this drug is further unique in that its plasma concentration is likely to show a closer parallel with adverse side-effects than with therapeutic efficacy.

Acknowledgements

We wish to thank Biorex Laboratories Ltd. for the supply of carbenoxolone and for financial support of Drs. M. J. Humphrey and J. S. Shillingford. We are also grateful to the Ministry of Defence for the support of Dr. J. B. Houston.

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