Altered jejunal surface pH in coeliac disease: its effect on propranolol and folic acid absorption

G. KITIS, M. L. LUCAS, H. BISHOP, A. SARGENT, R. E. SCHNEIDER, J. A. BLAIR AND R. N. ALLAN

The General Hospital, Birmingham, Chemistry Department, University of Aston in Birmingham, and Department of Therapeutics, University of Birmingham, Birmingham, U.K.

(Received 14 December 1981; accepted 13 May 1982)

Summary

1. Propranolol and folic acid absorption were studied separately in healthy subjects, non-coeliac patients and patients with treated and untreated coeliac disease.
2. The surface pH of jejunal biopsy samples was measured with a pH electrode.
3. When compared with values found in healthy subjects, plasma propranolol levels were elevated in coeliac disease and, in contrast, serum folic acid levels were depressed after oral administration of the drug. Jejunal surface pH was more alkaline in the coeliac groups than in the healthy and non-coeliac subjects.
4. Pharmacokinetic analysis of the plasma drug levels allowed evaluation of the rate constants associated with absorption and elimination. The absorption rate constant was decreased for folic acid in the coeliac group, but increased for propranolol. These changes correlated with variation in surface pH.
5. Although the changes in drug disposition in treated and untreated coeliac disease are the result of several factors, it is suggested that jejunal surface pH may affect the rate of absorption and therefore the plasma concentration–time profile of drugs which undergo dissociation.

Key words: coeliac disease, drug absorption, folic acid, jejunal surface pH, propranolol, rate constants.

Introduction

According to the pH-partition hypothesis [1], the absorption of dissociable drugs is influenced by the degree of ionization at the pH in the intestinal lumen, the un-ionized form being preferentially absorbed. As this concept did not explain the satisfactory absorption of certain acidic substances, the authors [1] postulated an area of higher acidity at the surface of the small intestinal cells, an ‘acid microclimate’ with a ‘virtual pH’ of 5.3. This surface pH has been measured with pH-electrodes [2] and found to be 5.9 in biopsy specimens from human intestine. However, in coeliac disease, values for surface pH were considerably less acid. Such a reduction in the acidity of the microclimate should reduce the absorption of acidic drugs and enhance the absorption of basic substances. Two substances which seem to behave according to this hypothesis are folic acid and the basic drug propranolol (\(pK_a = 9.45\)). Folic acid malabsorption in coeliac disease is well known and elevations of mean plasma propranolol concentrations have also been found in this disease after oral dosage [3]. The present study is concerned with the relationship between the measured surface pH and the absorption of these two substances.

Methods

Groups investigated

(1) Healthy subjects with no clinical signs of illness: four females and six males, age 21–39 years, for the propranolol studies; three females
and seven males, age 21–31 years, for the folate studies.

(2) Miscellaneous non-coeliac patients whose disorders included Crohn's disease, folate deficiency of unknown aetiology, irritable bowel syndrome, gall-stones and non-specific gastrointestinal symptoms: four females and two males, age 22–45 years, for the propranolol studies; two females and three males, age 20–45 years, for the folate studies.

(3) Patients with confirmed coeliac disease who had been treated with a gluten-free diet for more than 6 months and who had shown histological improvement on further jejunal biopsy: six females and four males, age 23–66 years, for the propranolol studies; three males and three females, age 23–57 years, for the folate studies.

(4) Patients with newly diagnosed coeliac disease, before any treatment. The diagnosis was confirmed histologically at the time of the investigation and by subsequent improvement on a gluten-free diet: five females and four males, age 11–57 years, for the propranolol studies; three males and three females, age 12–54 years, for the folate studies.

All subjects had normal values for haemoglobin concentration, leucocyte count, erythrocyte sedimentation rate, blood urea and electrolytes and had normal results from liver-function tests, including serum albumin, globulin, seromucoids, bilirubin, alkaline phosphatase and aspartate aminotransferase. The study was approved by the Ethical Committee of the Central Birmingham Health District. Informed consent was obtained from all participants.

Jejunal surface pH measurements

Jejunal surface pH was measured in vitro in jejunal biopsy specimens obtained with a suction biopsy capsule [4] from all subjects after an overnight fast. The technique has been described elsewhere in detail [2] and was modified only in that a commercially available Pye M405 oesophageal electrode was adapted by the manufacturers and the pH recorded with a Pye–Unicam 9409 digital pH meter.

Drug absorption studies

Propranolol. After the patient had fasted overnight, a single 40 mg tablet of propranolol (Inderal, ICI) was given by mouth with approximately 50 ml of water. Venous blood samples (10 ml) were obtained from an indwelling cannula kept patent with a slow infusion of sodium chloride solution (154 mmol/l: saline) at zero, $\frac{1}{2}$, 1, 1, 2, 4, 6, 8 and 24 h after ingestion of the drug. The samples were put into heparinized tubes, centrifuged and the plasma was removed. This was stored at $-20^\circ$C until total plasma concentrations of propranolol were measured fluorimetrically [5].

Folic acid. Similarly, after an overnight fast, 5 mg of folic acid completely dissolved in 50 ml of water was given to each subject. Venous blood samples were obtained at zero, $\frac{1}{2}$, 1, 1, 2 and 4 h and the serum was assayed for folate activity by a microbiological (Lactobacillus casei) method [6].

Statistical analysis of data

All results are given as the means ± SEM, with the numbers of results in parentheses. Differences between means were tested by Student's unpaired t-test; similarly, linear regression was carried out by standard methods [7].

Pharmacokinetic analysis of data

The plasma concentration curves were analysed in terms of a one-compartment model with two differential equations describing an absorption and an elimination process, whose solution is:

$$C_2(t) = \frac{FD}{V}(K_1/K_2 - K_2) \cdot \exp(-K_2t*) - \exp(-K_1t*)$$

where $FD/V$ is the bioavailability constant, $K_1$ is apparent absorption rate constant, $K_2$ is apparent elimination rate constant, $t* = (real\ time - lag\ time)$. The curve-fitting procedure involved computing the best least-squares fit through the mean data for each group rather than the data for each individual subject. The rate constants associated with the two processes were estimated by graphical methods [8], as were the bioavailability function and the lag time. These then provided initial estimates for an iterative estimation process incorporated in a programme based on the standard Fletcher–Powell algorithm [9], made available by Dr G. Atkins, Biochemistry Department, University of Edinburgh, suitable for the ICL 2976. In order to facilitate direct comparison of these measurements with others in the literature [3] deriving from a different procedure, the same data were processed by this alternative program [10]. The estimated propranolol values did not differ significantly between programs. As the alternative program could not process data where no peak of absorption was available, the first
procedure was preferred in order to maintain internal comparison.

Results

Jejunal surface pH studies

Jejunal surface pH was significantly elevated ($P < 0.001$) in both the treated and untreated coeliac groups (Table 1), when compared with pH in the healthy controls. These results, obtained with a commercially obtained electrode, are similar to those obtained in another study [2] with other types of electrodes made in this laboratory.

Propranolol absorption studies

Plasma propranolol levels were significantly higher in the treated and untreated coeliac groups than in the group of healthy subjects, from 14 to 8 h (Fig. 1). The mean plasma propranolol level in the untreated coeliac group tended to be higher than in the treated group of patients but the difference did not reach statistical significance. Neither the treated nor untreated coeliac groups differed in plasma propranolol concentration from the miscellaneous group. Among 34 patients where surface pH and propranolol absorption was studied (ten healthy controls, nine untreated coeliac patients, ten treated coeliac patients and five others), there was a significant association between jejunal surface pH and plasma propranolol levels at $1\frac{1}{2}$ h ($r = 0.35$, $P < 0.05$), 2 h ($r = 0.368$, $P < 0.05$) and 4 h ($r = 0.372$, $P < 0.05$).

Folic acid absorption studies

Although initial serum folate levels did not differ between the groups, significantly lower serum folate levels after a 5 mg oral dose are found in the treated and untreated coeliac patients than in the healthy controls (Fig. 2). The value in the untreated group was also significantly lower than in the miscellaneous group. In 31 subjects (ten healthy controls, six untreated and six treated coeliac patients, three patients with Crohn’s disease and six others) there was a

| TABLE 1. Jejunal surface pH in normal subjects, hospital controls and treated and untreated coeliac patients |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Series A: observations from propranolol absorption studies. Series B: observations from folic acid absorption studies. Results are expressed as means ± SEM. Statistical comparisons: *$P < 0.05$; **$P < 0.02$; ***$P < 0.01$. |
|                                | Healthy controls | Miscellaneous non-coeliac patients | Coeliac patients |
|                                | $n = 10$ | $n = 6$ | $n = 10$ | $n = 9$ | $n = 19$ |
| Series A                       |                     |                     |                     |                     |
| Buffer pH                      | $6.7 ± 0.05$ | $6.83 ± 0.05$ | $6.81 ± 0.06$ | $6.72 ± 0.07$ | $6.77 ± 0.05$ |
| Surface pH                     | $5.96 ± 0.05$ | $6.05 ± 0.04$ | $6.32 ± 0.07$*** | $6.42 ± 0.06$*** | $6.36 ± 0.05$*** |
| Series B                       | $n = 10$ | $n = 5$ | $n = 6$ | $n = 6$ | $n = 12$ |
| Buffer pH                      | $6.73 ± 0.05$ | $6.82 ± 0.06$ | $6.80 ± 0.07$ | $6.82 ± 0.02$ | $6.81 ± 0.01$ |
| Surface pH                     | $5.96 ± 0.05$ | $6.05 ± 0.05$ | $6.18 ± 0.05$** | $6.27 ± 0.06$*** | $6.23 ± 0.04$*** |
significant inverse association between jejunal surface pH and the serum folate levels at 1, 1½ and 2 h and at peak values (all $r < -0.472$, $P < 0.01$).

**Pharmacokinetic analysis of absorption curves**

The absorption curves were analysed in terms of a one-compartment model (Table 2) in order to derive absorption and elimination constants for the process, lag times for the onset of absorption and estimates of the bioavailability function ($FD/V = \text{systemically available dose/compartmental volume of distribution}$). Lag times, of the order of 17–25 min, showed no consistent trend for the two drugs within the studied groups. The bioavailability function was lower for both drugs for the untreated coeliac groups, significantly so ($P < 0.001$) for propranolol. There was a significant decrease in the propranolol elimination

![Image: Graph showing folate absorption in coeliac disease.](image)

**FIG. 2. Folate absorption in coeliac disease.** □, Controls, $n = 10$; ○, miscellaneous non-coeliac group, $n = 5$; ▲, coeliac, gluten-free diet, $n = 6$; ■, coeliac, normal diet, $n = 6$. Curves were fitted to data points by computer-assisted least squares best fit of mean values. See also Fig. 1 for further details of results.

![Image: Graph showing relation of drug absorption rate constant ($K_1$) to surface pH by linear regression.](image)

**FIG. 3. Relation of drug absorption rate constant ($K_1$) to surface pH by linear regression. Data points are mean rate constant and mean surface pH for the four groups: ●, propranolol; ○, folate.**

<p>| Table 2. Estimates of absorption model parameters for propranolol and folic acid absorption in normal subjects, hospital controls and patients with coeliac disease |
|-------------------------------------------------|-------------------------|----------------------|-------------------------------|-----------------|
| FD/V, systemically available dose/compartmental volume of distribution. Statistical comparisons: $*P &lt; 0.05$; $**P &lt; 0.02$; $***P &lt; 0.01$; $****P &lt; 0.001$ (comparison with normal control). Results are expressed as means ± SEM. |</p>
<table>
<thead>
<tr>
<th>$\text{FD/V} (\text{ng/ml})$</th>
<th>$\text{Lag time (min)}$</th>
<th>$\text{Propranolol disposition parameters}$</th>
<th>$\text{Folate disposition parameters}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-1}K_1(\text{entry})$ (min$^{-1}$)</td>
<td>$10^{-1}K_1(\text{exit})$ (min$^{-1}$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal controls</td>
<td>6.6 ± 0.58</td>
<td>10.7 ± 0.7</td>
<td>19.56 ± 3.77</td>
</tr>
<tr>
<td>Hospital controls</td>
<td>8.2 ± 8.6</td>
<td>8.1 ± 8.5</td>
<td>22.52 ± 1.64</td>
</tr>
<tr>
<td>Treated coeliac</td>
<td>19.2 ± 6.0$^{****}$</td>
<td>4.24 ± 0.76$^{****}$</td>
<td>22.12 ± 2.20</td>
</tr>
<tr>
<td>Untreated coeliac</td>
<td>47.1 ± 10.6$^{****}$</td>
<td>2.97 ± 0.37$^{****}$</td>
<td>25.59 ± 1.71</td>
</tr>
<tr>
<td>All coeliac</td>
<td>31.6 ± 4.8$^{****}$</td>
<td>3.88 ± 0.32$^{****}$</td>
<td>24.16 ± 1.48</td>
</tr>
<tr>
<td>$10^{-1}K_1(\text{entry})$ (min$^{-1}$)</td>
<td>$10^{-1}K_1(\text{exit})$ (min$^{-1}$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal controls</td>
<td>25.7 ± 6.6</td>
<td>5.69 ± 1.0</td>
<td>19.70 ± 1.72</td>
</tr>
<tr>
<td>Hospital controls</td>
<td>27.9 ± 3.77</td>
<td>7.69 ± 0.8</td>
<td>20.75 ± 0.94</td>
</tr>
<tr>
<td>Treated coeliac</td>
<td>13.5 ± 0.80</td>
<td>8.35 ± 0.5$^{*}$</td>
<td>22.72 ± 0.29</td>
</tr>
<tr>
<td>Untreated coeliac</td>
<td>7.3 ± 2.4$^{**}$</td>
<td>6.83 ± 2.2</td>
<td>16.63 ± 1.4</td>
</tr>
</tbody>
</table>
rate constant for both the treated and untreated coeliac groups and a marginal increase in the folate elimination rate constant in the treated coeliac group. The folate absorption rate constant was depressed ($P < 0.02$) in the untreated coeliac group and the treated group constant was less than that of the miscellaneous group. In contrast, when compared with the healthy subjects, the absorption rate constant of propranolol was elevated in the treated ($P < 0.05$) and untreated ($P < 0.01$) coeliac groups but not in the miscellaneous group. With a similar program [10] used for estimating the propranolol rate constants, much the same values were obtained although this program could not process the folate data. The derived rate constants for absorption correlated significantly (Fig. 3) with the measured surface pH in that the folate constants decreased and those for propranolol increased with an increase in surface pH.

Discussion

The disposition in plasma of an orally administered drug is a complicated process, potentially affected by gastric emptying, hepatic and renal clearance, plasma protein binding and the rate and degree of absorption. Additionally, $\beta$-adrenoceptor-blocking drugs such as propranolol affect their own disposition by reducing hepatic blood flow [11]. The changes in the plasma concentrations of propranolol and folic acid found in this study may be due to a combination of some of these factors, and it is unlikely that any single explanation is exclusive of other interpretations.

The rate of absorption of drugs may be affected by changes in gastric emptying. In coeliac disease, both increased and decreased motility have been claimed [12-15] and, in the present study, lag times, which probably reflect the rate of gastric emptying, showed no definite trend (Table 2). Such contradictory findings make it unlikely that this factor is involved in consistently altering plasma drug concentrations in coeliac disease, especially as propranolol levels were raised, whereas those of folic acid were lowered.

Propranolol is almost entirely eliminated by metabolism in the liver, and plasma concentrations of this drug are known to be raised after oral administration to patients with hepatic cirrhosis [16]. Increased levels of serum aspartate aminotransferase and alanine aminotransferase have been reported in 55% of one series of coeliac patients [17], indicating some measure of hepatic damage, but none of the subjects in the present study had any clinical or biochemical evidence of liver disease. Furthermore, this would not explain the reduced plasma levels of folic acid. Reduced liver blood flow is known to increase systemic plasma concentrations of propranolol, but no evidence of this has been reported in coeliac disease.

Raised plasma propranolol concentrations have been found in patients with inflammatory disease and a raised erythrocyte sedimentation rate [18] and correlate significantly with the serum level of $\alpha_1$-acid glycoprotein [19] to which this drug binds [20, 21]. In the present investigation, however, all subjects had erythrocyte sedimentation rates and serum $\alpha_1$-acid glycoprotein concentrations within normal limits.

The most striking changes to emerge from the pharmacokinetic analysis of the data obtained from this study are the increase in the absorption rate constant for propranolol, and the decrease in the same constant for folic acid, in coeliac disease. These differences would be accentuated if the compartmental volume changes that may occur in coeliac disease are taken into consideration (see the Appendix). Propranolol is a basic drug, which according to the pH-partition hypothesis [1] would be more easily absorbed at the coeliac microclimate pH (6.37), as less of it would be ionized. Whether the mechanism of folic acid absorption is by simple diffusion [22] or by a pH-dependent saturable mechanism of transport for the undissociated form [23], it is clear that an elevated surface pH should decrease absorption. The choice of phosphate buffer meant that the measurement of surface pH was made in the absence of bicarbonate, an anion which may stimulate certain aspects of jejunal function [24]. However, in rat gut in vivo, surface pH values were similar in both phosphate and bicarbonate buffers [25], and resembled those found in the rat jejunum in vitro (M. L. Lucas, unpublished work), provided that glucose (10 mmol/l) was included in the buffer used in vitro. In rat jejunum in vivo, surface pH values of 6.23 + 0.1 [7] and 6.10 ± 0.1 [7] have been found in bicarbonate and phosphate buffers respectively, although no dependence on buffer glucose was noted as adequate substrate was available via the intact blood supply. It thus seemed justified to extrapolate the present human data in vitro to the situation in vivo, and to use a phosphate buffer in the interests of stability.

Correlation can be shown between the log of the absorption rate constant and the jejunal surface pH for both drugs, an inverse relationship for folic acid. The fact that correlation of plasma drug levels with surface pH is modest, though significant at some times, probably reflects the
multifactorial nature of drug disposition. Preliminary calculations have also been made of the fraction of undissociated drug ($f$) available at the measured surface pH values found in the various groups of subjects studied, even though no claim is made that these are the exact values to be found directly at the enterocyte membrane. In the case of propranolol with its single dissociable group, these were straightforward, but with folic acid the $pK_a$ values [26] of the $\alpha$- and $\gamma$-carboxyl groups and of the $N$-1 nitrogen had to be taken into account. Such a calculation shows (Fig. 4) that the apparent absorption rate constant ($K_1$) increases with the apparent fraction of undisassociated or zwitterionic forms, thus supporting the hypothesis that it is the un-ionized form of a weak electrolyte that is preferentially absorbed. Ideally, $K_1$ and $f$ would be calculated for each subject. In practice this would involve calculation of the four disposition parameters from seven data points. Under these circumstances, convergence in the estimation procedure could be achieved only by the prior selection of subjectively chosen constraints, which necessarily vitiates any such best fit procedure. Consequently, an acceptable estimate of $K_1$ could be satisfactorily derived only from grouped data. These calculations, as well as the previously mentioned data, indicated that, in these particular instances, alterations of surface pH were correlated with changes in the rate of drug absorption.

There are other instances in the literature of plasma concentrations of basic drugs being raised in coeliac patients: quinidine [27] and the antimicrobials clindamycin, erythromycin stearate and trimethoprim [28]. Parsons et al. [3] and Schneider et al. [29] claimed the same for propranolol. Impaired absorption of the acidic drugs phenoxymethylpenicillin [30, 31] and sulphafurazole [27] in coeliac patients has also been reported. Benn et al. [32] showed gross impairment of folate absorption in normal subjects when the intraluminal pH had been raised by the oral administration of sodium bicarbonate, and Lucas [33] found that serum folate levels correlated well with the degree of acidity of the intestinal surface. The situation is not quite clear-cut, however, since although subsequent work [23, 34] has been in agreement, Perry & Chanarin [35] failed to confirm the results of Benn et al. [32] and indeed showed augmentation of folic acid absorption when it was given together with bicarbonate. Furthermore, proctolol, which has a similar $pK_a$ to propranolol, and lincomycin, which is closely related to clindamycin, do not have elevated plasma levels in coeliac disease, yet the amphoteric compounds cepahlexin and sulphamethoxazole, together with fusidic acid ($pK_a$ 5-35), do. Parsons et al. [36] investigated the pharmacokinetics of the two acidic, lipid-soluble drugs, aspirin and indomethacin, which have $pK_a$ 3-5 and $pK_a$ 4-6 respectively. No significant differences were found between the areas under the plasma concentration–time curves or between the absorption rate constants of healthy subjects and coeliac patients for either drug, although the salicylate plasma levels were significantly raised in the coeliac patients at the first three sampling times. Thus it seems that factors such as changes in water solubility at different pH values, and lipid solubility, may also exert an effect on plasma drug concentrations.

A factor which is less easily explained is the change in the elimination rate constants for both drugs, that for propranolol being decreased, and that for folic acid increased. It is known that ($\pm$)-propranolol decreases liver blood flow and thus influences its own elimination [11]. If the drug is being absorbed more quickly in coeliac disease, higher concentrations may be delivered to the liver via the portal vein, and thus there will be a greater effect on blood flow and clearance than in normal subjects, even though liver function is normal. In the case of folic acid, the increase in elimination rate constant may be caused by an increase in the volume of distribution, or an increase in tissue avidity, which can occur in subjects who have been folate deficient.
Drug absorption in coeliac disease

Thus it is clear that the absorption step is not the only variable that determines subsequent levels of drug in plasma after an oral dose. In the present study, a group of non-coeliac patients with a variety of diseases, but with normal microclimate pH, histology and erythrocyte sedimentation rates, showed raised plasma pranorolol levels, halfway between those in the coeliac and those in the control groups, and not significantly different from either. The absorption rate constants, however, were only negligibly raised compared with those of the controls, suggesting that it is mainly the rate of absorption of pranorolol which is affected in coeliac disease. In a similar group of patients given folic acid, the non-significant depression in serum folate levels compared with the healthy subjects may again have been due to increased tissue uptake.

The results of the present study are consistent with the concept of an acid surface pH in the jejunum being a controlling influence in the rate of absorption of these drugs. At present it is impossible to rule out, on present grounds, effects of surface pH on absorption by means other than pH-partition: it is possible that changes in surface pH may alter the ionization state of a putative transport protein. Also it may be premature to state that changes in microclimate pH are relevant to all dissociable drugs. However, it would seem to be a factor that should be taken into account when considering changes in drug disposition in disease states.

Acknowledgments

We acknowledge the support of the Birmingham Regional Health Board for a research stipend (G.K.) and the Wellcome Foundation for providing a Biomedical Research fellowship (M.L.L.). Thanks are due to Dr B. Leeming for folate assays, to Dr G. Atkins of the Biochemistry Department, University of Edinburgh, and Professor L. Saunders, Pharmacy Department, University of London, for advice and assistance with curve-fitting procedure, and to Mr Marlow and Mr Holmes of Pye–Unicam, Cambridge, U.K., for producing suitable electrodes on request.

References


APPENDIX

The change in drug concentration in the vascular compartment with respect to time after oral dosage is frequently modelled by a one-compartment system in the pharmacokinetic literature. What this familiar model with first order rate constants obscures is the fact that the measured rate constants, although of dimensions of inverse time, are composites of a rate constant with dimension of flow, i.e. volume per time and a volume term. This follows directly from Fick’s law of diffusion, where:

\[
\frac{dQ_i}{dt} = -k_{ij}C_i(t)
\]

or, since \(Q_i = V_iC_i\),

\[
\frac{V_idC_i}{dt} = -k_{ij}C_i(t)
\]

\(Q_i\) is amount, \(V_i\) is volume, \(C_i\) is concentration and \(k_{ij}\) has dimensions of volume per time. This equation has to be rearranged in order to be solved as a first order differential equation, simply by dividing both sides by the compartmental volume:

\[
\frac{dC_i}{dt} = -\frac{k_{ij}}{V_i} . C_i(t) = -K_{ij}C_i(t)
\]

where the new rate constant \(K_{ij}\) has the familiar dimensions of inverse time but is only appropriate at a given compartmental volume. Consequently this represents information discarded during the solution of the equations. The integrated rate equations are solved to give the familiar bi-exponential term preceded by the proportionality term \(D/V_2(K_{1}/K_{2} - K_{3})\), where \(D\) is dose administered and the rate constants are related to their appropriate compartmental volume. In the case of \(K_{3}\), this is the intraluminal volume.

Two difficulties become immediately obvious, with relevance for the carrying out and interpretation of pharmacokinetic studies. Firstly, scaling of administered dose to the vascular volume or body weight to introduce uniformity will mean that the administered dose will be present in the luminal volume at a lower concentration. Consequently, ‘malabsorption’ will be observed if peak height and other empirical parameters are solely taken into consideration. Secondly, this difficulty is accentuated by the secretory state in untreated coeliac disease, which tends to increase the intraluminal volume. Therefore the absorption rate constant is likely to be reduced in coeliac disease because of the cryptic volume term contained within the constant when expressed as inverse time. This will be without any malabsorption having taken place. Consequently, changes in rate constants have to be interpreted accordingly.