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SIMULATION STUDIES ON THE KINETICS OF INTESTINAL ABSORPTION

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Summary

1. A model has been used to simulate the absorption of solutes from perfused intestines. The model makes possible the numerical solution of the differential equations describing absorption processes along the length of the intestine which cannot be solved analytically. It allows for water absorption and the non-linear fall in solute concentration down the intestine. It can be modified easily to include other features, e.g. a change in V (maximum rate of absorption) or K (solute concentration at $V/2$) along the intestine.

2. 90 perfect data sets have been simulated using the model. The Michaelis-Menten equation was fitted to a quarter of them using different algebraic expressions for the apparent solute concentration. The fit of the equation was very good in every case and it was not possible to explain the poorness-of-fit encountered during an earlier survey (Atkins, G.L. and Gardner, M.L.G. (1977) Biochim. Biophys. Acta 468, 127—145) in terms of the fall in solute concentration described above.

3. The equation was also fitted to all the data sets in order to compare the use of several algebraic expressions for the apparent solute concentration. It has been shown that the current practice of using either the initial concentration or the effluent concentration can lead to estimates of V and K up to almost twice their true value. It has been shown that in one situation (glucose absorption by perfused rat intestine) it is possible to use an empirical expression that will reduce the errors considerably.

4. It is also possible, and perhaps preferable, to use a computer program to fit the model directly to data from the simulated experiments and obtain precise estimates of V and K.

5. In order to show that the model can be easily modified to incorporate

other characteristics of perfused intestines, simulations were performed in which V decreased linearly down the intestine. In this example, it was concluded that an inhomogeneity due to non-constancy of V cannot be detected by single-pass perfusions.

Introduction

Much work has been published on the kinetics of intestinal absorption. In particular, the Michaelis-Menten equation is frequently used to calculate two parameters, V (maximum rate of absorption) and K (solute concentration at $V/2$). However, the application of this equation to the perfused intestine is not strictly valid because (i) the solute concentration changes along the length of the intestine as water and solute are absorbed, and (ii) the intestine is not uniform along its length (e.g. Refs. 1 and 2).

During a recent survey on the calculation of parameters for intestinal absorption [3], it was noted that in many cases the goodness-of-fit of the Michaelis-Menten equation to experimental data produced by various authors was bad or poor, even though the Michaelis-Menten equation appeared to be the 'best-fit' model. The reasons for this were not clear, but may be associated with the two factors mentioned above.

In order to explore this I have devised a model with which to simulate the kinetics of absorption in a perfused intestine. The approach I have used was suggested by that of Nimmo and Bauermeister to model gel filtration [4]. In my model the intestine is considered as a large number of consecutive segments, the properties within each being uniform. The absorption properties of each segment can, however, be different so that I can simulate absorption of solutes and water from a tube whose characteristics vary in a defined way along its length. The differential equations of the model are not capable of analytical solution and the integrations have to be performed numerically.

I have used this model to examine four related questions:

(i) Can the poorness-of-fit of the Michaelis-Menten model to published data be attributed to the neglect of the two assumptions described earlier?

(ii) Since the solute concentration is not constant along the length of the intestine, would some algebraic function of perfusate input concentration (s_0) and effluent concentration (s_n) give more meaningful parameter estimates in the Michaelis-Menten equation? Two empirical algebraic equations have been used to date, the arithmetic mean $[(s_0 + s_n)/2]$ and the geometric mean $\sqrt{s_0 \cdot s_n}$ [5–7].

(iii) Is it possible to fit to the data a model which takes account of the fall in solute concentrations?

(iv) Can the model be modified easily to incorporate other features of the perfused intestine? To answer this point I have incorporated the observation of Fisher and Parsons [1] that the value of V, for glucose absorption, fell linearly down the intestine. I have then simulated single-pass perfusions both down and up the intestine to determine what differences there might be in effluent concentration (s_n).

Methods

Model. The model used in this study is shown in Fig. 1. In order to perform the numerical integrations, the medium within the intestine is considered to be a series of segments. Each segment is momentarily stationary while absorption occurs, then the segments are moved instantaneously to their next positions (Fig. 1a). The intestine is assumed to be a linear tube whose surface area per unit length is constant, although there is evidence that this is not so [8]. The total length is l cm and the luminal volume V_g ml. Perfusion medium is assumed to flow through at a constant rate, V_p ml/min. If each segment is of length Δx cm, then there are n segments ($n = l/\Delta x$), and the volume of each is V_g/n ml. The contents of each segment are assumed to be homogeneous, i.e. well stirred, and there is no longitudinal diffusion.

Consider the ith segment (Fig. 1b). The concentration of solute at the start of absorption is s_i μmol/ml. Absorption occurs during a time Δt min, $\Delta t = V_g/(n \cdot V_p)$, and the amount of solute absorbed is Δp_i μmol. During the time Δt, absorption of water and solute may be defined by any chosen mathematical function. The water absorption rate, whenever used in this study, has been made constant although in practice this may not be so. The amount of water absorbed during time Δt is therefore $\Delta w = K_w \cdot \Delta t \cdot \Delta x$ ml, where K_w is a constant with units of ml $\cdot$ min^{-1} $\cdot$ cm^{-1} of intestine. Initially the volume of the first segment will be Δv ml ($\Delta v = V_g/n$) but at each absorption position this will decrease by Δw. The cross-sectional area of the tube will decrease to allow for the change in volume, but this will not affect the model equations or the results obtained by the simulations. In all the models studied here, the rate of solute absorption is assumed to follow Michaelis-Menten kinetics because (i) most authors use it, and (ii) a recent survey showed this to be often the 'best' func-

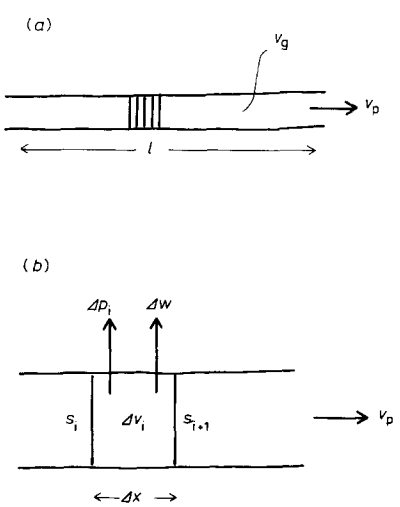

Fig. 1. Model used to simulate intestinal absorption. The perfusate is divided into small segments of volume Δv_i. At each absorption step, the initial solute concentration is s_i and after absorption of solute (Δp_i) and water (Δw) the final concentration is $s_i + 1$.

tion [3]. However, this approach can readily be applied to other equations. Thus

$$\frac{dp_i}{dt} = -\frac{V \cdot s_i}{K + s_i} \cdot \Delta x \qquad \mu\text{mol/min}$$

where V (the maximum rate of absorption) is $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{cm}^{-1}$ and K (the solute concentration at $V/2$) is μmol/ml. The amount absorbed is Δp_i μmol, then

$$\Delta p_i = \left[\frac{dp_i}{dt}\right]_0^{\Delta t} = -\int_0^{\Delta t} \frac{V \cdot s_i}{K + s_i}\, dt \cdot \Delta x = -V\left[\frac{s_i}{K + s_i}\right]_0^{\Delta t} \cdot \Delta x$$

$$= \frac{V \cdot s_i \cdot \Delta t \cdot \Delta x}{(K + s_i)} \qquad \mu\text{mol}$$

The amount of solute initially present in the segment is $s_i \cdot \Delta v_i$ and this falls to $(s_i \cdot \Delta v_i) - \Delta p_i$ μmol. Likewise for the water content, this falls from Δv_i to $\Delta v_i - (K_w \cdot \Delta t \cdot \Delta x)$ ml. Thus the final concentration of solute, which is the initial concentration when the segment moves to its next position, is

$$s_{i+1} = \frac{[(s_i \cdot \Delta v_i) - \Delta p_i]}{[\Delta v_i - (K_w \cdot \Delta t \cdot \Delta x)]} \qquad \mu\text{mol/ml}$$

In the model and in the computer program the solute concentrations run from s_1 to s_{n+1}, but for convenience in the description elsewhere within this paper I have used s_0 and s_n.

In using this model l and K_w, which would normally be experimentally determined, are constant parameters; and s_0 and V_p would be fixed by design. V_g was given an arbitrary, but realistic, value although its magnitude had no effect on the results. When used in simulation studies V and K were assigned particular values, but in model fitting these were the two parameters to be estimated. The number of segments n was large enough so that the flow appears to be continuous. The n calculations were performed and the results obtained were: the total amount of solute absorbed ($\Sigma \Delta p_i$ μmol) and the concentration of solute (s_n μmol/ml) in the outflowing perfusate.

Initial simulations. The objectives were (i) to determine a satisfactory value for n, and (ii) to demonstrate that the results were independent of the luminal volume, V_g, as expected. The values of l, V, and K used in this section, and in most subsequent simulations, were for glucose absorption by rat upper small intestine and were taken from Fisher and Gardner (Ref. 9, Tables I—III). They were $l = 40$ cm, $V = 0.463$ $\mu\text{mol} \cdot \text{min}^{-1} \cdot \text{cm}^{-1}$ and $K = 16.0$ μmol/ml. Other values used were: $K_w = 0$, $s_0 = 4, 8, \ldots 36$ or 40 μmol/ml, $V_p = 1, 2, \ldots 9$ or 10 ml/min, $V_g = 20, 25, 30, 35$ or 40 ml and $n = 100, 300$ or 1000. The differences between the calculated values of the output concentration (s_n) when using $n = 100$ and $n = 300$ were less than 0.1%. For future work it was decided to set $n = 400$ by putting $\Delta x = 0.1$ cm.

The calculated values of s_n were the same regardless of the value used for V_g. This was expected and in all subsequent work V_g was set at 20 ml.

Subroutine for model. The model was incorporated into a subroutine with $V_g = 20$ ml and $\Delta x = 0.1$ cm. The data supplied were K_w, l, V_p, s_0, V and K

and the subroutine calculated values of s_i, Σp_i and $\Sigma(K_w \cdot \Delta t \cdot \Delta x)$.

Main simulations. 90 'experiments' were simulated by setting K = 1.6, 16.0 or 160.0 μmol/ml; V = 0.0463, 0.463 or 4.63 μmol · min^{-1} · cm^{-1}; and V_p = 1, 2, 3, . . ., 9 or 10 ml/min. The absorption rate was calculated at ten values of s_0 = 4, 8, . . ., 36 and 40 μmol/ml (v_{obs}).

Parameter estimations. The standard method for the estimation of V and K in intestinal absorption work is to fit the Michaelis-Menten equation to values of absorption rate at a series of solute concentrations. Thus the equation was fitted to data in which the independent variable was a value for substrate concentration and the dependent variable was absorption rate. The values used for substrate concentrations were either s_0 (input solute concentration), s_n (effluent concentration), s_a (the arithmetic mean of s_0 and s_n), s_g (the geometric mean of s_0 and s_n) and s_e (an empirical function of the form $s_e = (s_0 + s_n + 4.0\sqrt{s_0 \cdot s_n}/6.0)$). The equation was fitted using the non-parametric method of Cornish-Bowden and Eisenthal [10].

The parameters V and K were also estimated by fitting the above model directly by non-linear regression. In this situation the independent variable was always s_0 and the dependent variable was s_n. Four methods were tried: the program of Atkins [11], the method of Marquardt [12], a Fibonacci search method [13] in which V and K were estimated alternately (c.f. Atkins [14]) and the simplex method of Nelder and Mead [15].

Results

The goodness-of-fit of the Michaelis-Menten equation

The Michaelis-Menten equation was fitted to about 25% of the 90 'experimental' data sets. The ones chosen were for K = 1.6 and 160.0 μmol/ml and V = 0.0463 and 4.63 μmol · min^{-1} · cm^{-1} (i.e. the four extreme sets) and for K = 16.0 μmol/ml and V = 0.463 μmol · min^{-1} · cm^{-1}. (i.e. the central one). The equation was fitted to 'observed' absorption rate versus (in turn) s_0, s_n, s_a, s_g and s_e. Except for those experiments where K and V were high, so that all or most of the solute was removed from the luminal fluid, the Michaelis-Menten equation was always a very good fit. The differences between the observed absorption rate (v_{obs}) and the calculated rate (v_{calc}), were expressed as percent difference/v_{obs}. Most of the points had differences less than 0.5%, although six (out of about 200 points) were between 0.5 and 4.7%. For many points the differences were zero. On the other hand, in our previous survey the range of the differences was between about 0.8% and 80% with a median of 7—9%. It was unnecessary, therefore, to apply the statistical tests for goodness-of-fit as used previously [3].

Use of Michaelis-Menten equation to estimate V and K

The results of the simulations with K = 16.0 μmol/ml, V = 0.463 μmol · min^{-1} · cm^{-1} and with K_w either zero or 0.0027 ml · min^{-1} · cm^{-1} [9] were plotted to show how the solute concentrations changed along the intestine. Figs. 2 and 3, respectively, show these results at several values of s_0 and V_p. It is apparent that the changes were quite considerable and, especially at low solute concentrations and low perfusion rates, the fall in concentration was not linear with distance.

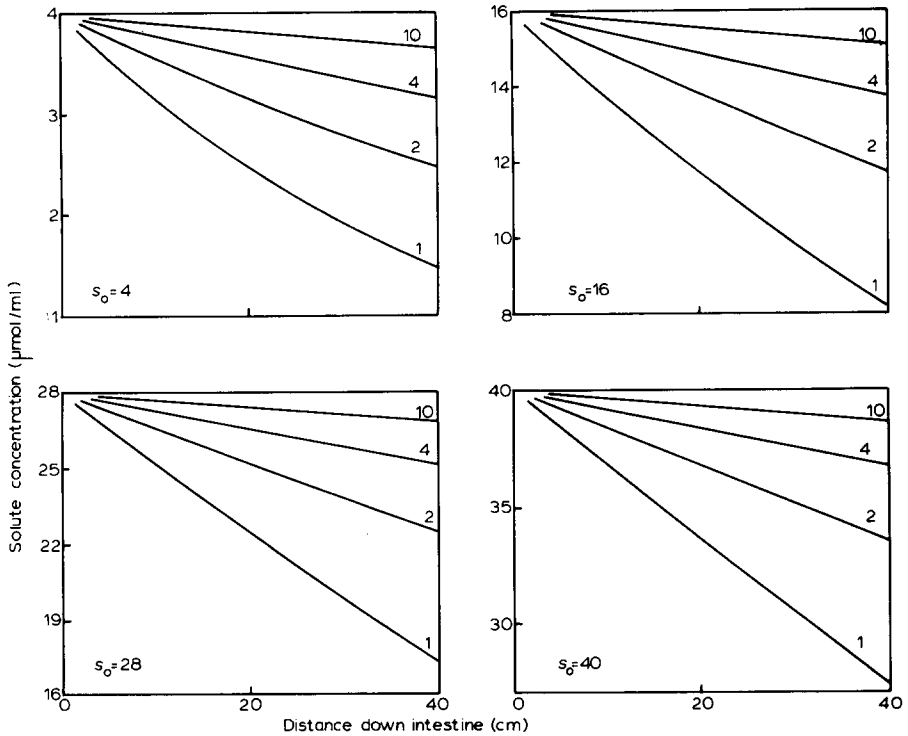

Fig. 2. Solute concentration down a perfused small intestine. Solute concentration is shown as a function of distance down the intestine. The four plots are for initial solute concentrations (s_0) of 4, 16, 28 and 40 μmol/ml. At each concentration, curves are shown for perfusion rates (V_p) of 1, 2, 4 and 10 ml/min. There is no water absorption.

Also, at each perfusion rate the Michaelis-Menten equation was fitted to values of absorption rate (where s_0 = 4, 8, 12, . . ., 36 and 40 μmol/ml) versus s_0, s_n, s_a, s_g or the empirical function s_e as the independent variable.

Table I shows the error in K caused by using these several expressions for solute concentration when $K_w = 0$. When s_0 or s_n was used the error was always greater than 5%. The arithmetic mean and the geometric mean reduced it, but with the empirical expression the error is almost negligible. Similar results were obtained for V. When $K_w = 0.0027$ ml · min^{-1} · cm^{-1} again the results were very similar. None of these are therefore shown.

The review was extended to include the other 80 'experiments'. At each perfusion rate, the Michaelis-Menten equation was again fitted using the several algebraic expressions for solute concentration. For 12 out of the 90 experiments, the values of K and V were such that the absorption rates were fast and (particularly at low perfusion rates) all or most of the solute was absorbed during passage down the intestine. Therefore, the Michaelis-Menten equation could not be fitted to these data.

The successful results are summarized in Table II. Use of the empirical expression (s_e) resulted in a higher proportion of accurate estimates than when the other expressions were used. For an accuracy of 1% or better there was no

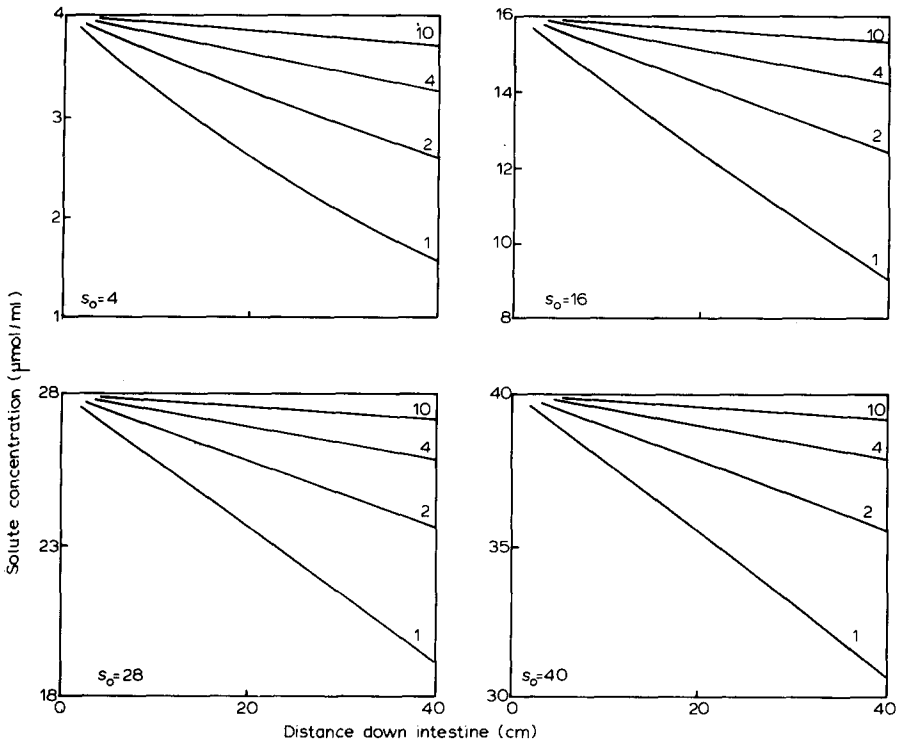

Fig. 3. Solute concentration down a perfused small intestine. As for Fig. 2, except that water absorption is present.

TABLE I

ERROR IN K AS A RESULT OF FITTING A MICHAELIS-MENTEN EQUATION ACCORDING TO CURRENT PRACTICE

K has been estimated by fitting a Michaelis-Menten equation to data for absorption rate vs. solute concentration at different perfusion rates, V_p. The values below are the percentage errors in K when different algebraic expressions for the solute concentrations (s_0, s_n, s_a, s_g and $s_e = (s_0 + s_n + 4.0\sqrt{s_0 \cdot s_n})/6.0$)) were used with the Michaelis-Menten equation for estimating K.

V_p	s_0	s_n	Arithmetic mean s_a	Geometric mean s_g	Empirical value s_e
1.0	81.4	—45.5	9.30	—4.60	—0.15
2.0	32.0	—24.7	2.03	—1.19	—0.17
3.0	20.1	—16.7	0.89	—0.50	—0.07
4.0	14.5	—12.6	0.44	—0.33	—0.05
5.0	11.3	—10.3	0.23	—0.20	—0.00
6.0	9.4	—8.5	0.31	—0.06	0.07
7.0	8.0	—7.3	0.11	—0.14	—0.05
8.0	6.8	—6.5	0.11	—0.13	—0.05
9.0	6.0	—5.8	0.14	—0.00	0.05
10.0	5.5	—5.2	0.06	—0.07	—0.03

TABLE II

ERRORS IN K AND V WHEN THE SURVEY WAS EXTENDED TO WIDER RANGES OF THE TWO PARAMETERS

The Michaelis-Menten equation fitted to 78 simulated experiments using, as the independent variable, the five algebraic expressions for solute concentration (see text). For each algebraic expression used, the 78 results are classified according to the percent difference between the estimated parameter and its true value.

	Solute concentration	Number of results within each error group		
		<1%	1—5%	>5%
K	s_0	22	8	48
	s_n	15	13	50
	s_a	37	18	23
	s_g	38	20	20
	s_e	55	13	10
V	s_0	36	15	27
	s_n	33	19	26
	s_a	55	9	14
	s_g	56	10	12
	s_e	66	4	8

statistical difference between the use of s_a, s_g or s_e. On the other hand, s_a and s_g produced significantly more estimates of K with an error over 5%. It is apparent therefore, that the probability of obtaining a more accurate value for K and V is increased by the use of s_e.

Parameter estimation using the model. The objective of this section was to determine whether the proposed model could be fitted to data directly using non-linear regression methods. If so, K and V would be estimated without any error arising from the two problems discussed earlier: (i) s is not constant down the length of the intestine, and (ii) the choice of a suitable expression for s to use with the Michaelis-Menten equation. Four parameter estimation programs were used in turn. The fixed parameters were: l = 40 cm and K_w = 0.0027 ml · min^{-1} · cm^{-1}. The ten sets of perfect data with V = 0.463 μmol · min^{-1} · cm^{-1} and K = 16.0 μmol/ml were used. At each perfusion rate, V_p = 1, 2, 3, . . ., 9 or 10 ml/min, values of s_n had been calculated for s_0 = 4, 8, 12, . . ., 36 and 40 μmol/ml. For each parameter estimation, corresponding to one value of V_p, the model was fitted to values of s_n versus s_0 as opposed to rate versus an approximate (invalid) value of s.

The first two programs used descent methods [11,12], but neither of them was successful at finding the minimum sum of squares. In order to determine why these programs failed, a plot of sum of squares of residuals versus V and K was drawn. From inspection it was obvious that a long, narrow and flat valley was present and that the descent methods could not follow it in order to find the minimum.

Next a Fibonacci search method was tried (cf. Ref. 14) in which one parameter was kept constant while the optimum value of the other was found. By searching the parameters alternately, the program was able to find the minimum. Lastly the simplex method [15], in which both parameters were

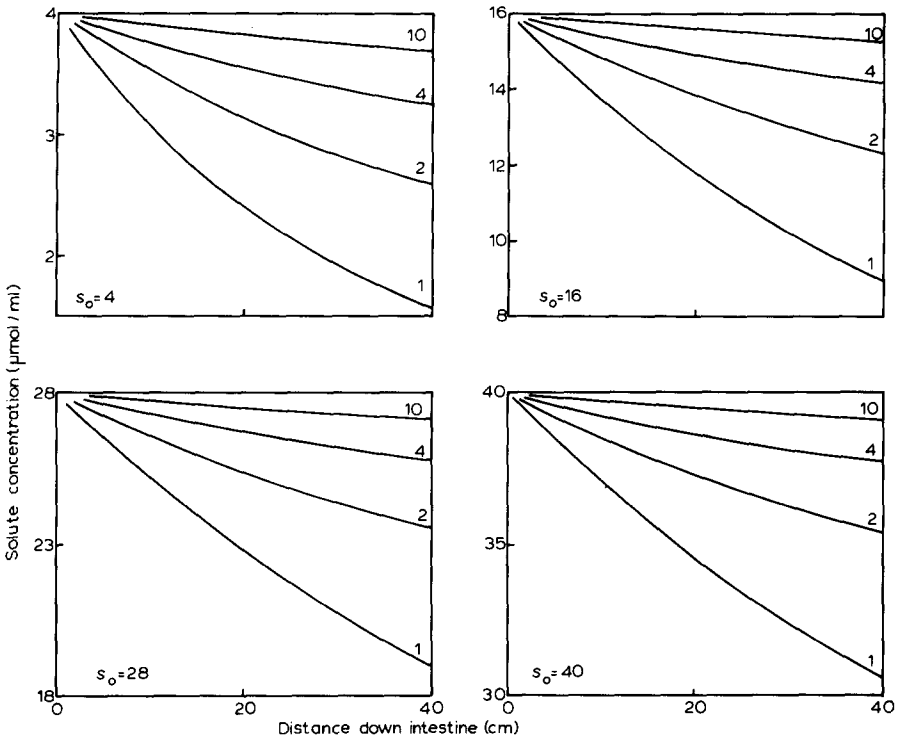

Fig. 4. Solute concentration down a perfused small intestine. As for Fig. 2, except that V decreases as a function of distance down the intestine.

optimised simultaneously, was used successfully to find the minimum. The latter program used only one quarter of the computer time of the former program. It is therefore possible to fit the model to perfect data using a simplex search technique.

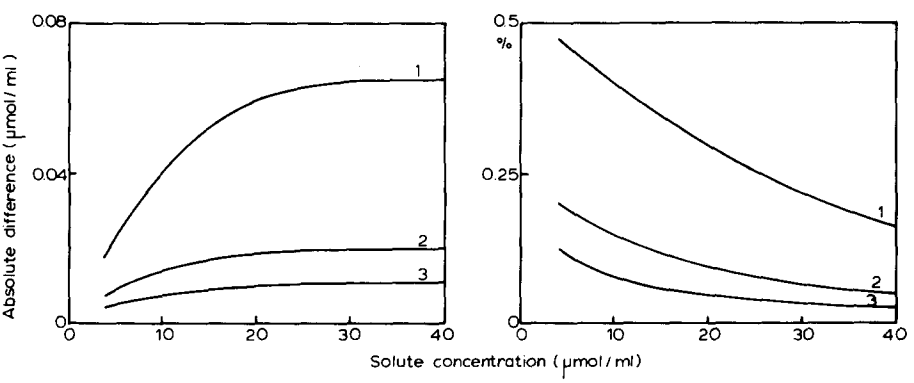

Fig. 5. Detection of non-homogeneity in single-pass perfusions. The differences in final solute concentration (s_n) between downward and upward perfusion are shown. (a) The absolute difference in μmol/ml and (b) is the percentage difference. Results are given for the three slowest perfusion rates, V_p = 1, 2 and 3 ml/min.

An example where the model is extended. To illustrate how easily the model can be extended to include more complex situations, it was decided to perform simulations were V decreased down the intestine. The model was modified to incorporate the linear function of Fisher and Parsons [1] by using $V = 0.5950 - 0.0066 \cdot x$, where x was the distance in cm from the top of the intestine. Simulations were done for various perfusion rates, V_p = 1, 2, 3, . . ., 9 or 10 ml/min, either down or up the intestine, at values of s_0 = 4, 8, 12, . . ., 36 and 40 μmol/ml.

Fig. 4 shows the changes in solute concentration as the intestine is perfused downwards at different rates and at various values of s_0. It is apparent, by comparison with Fig. 3, that the lines are more curved when the intestine is non-homogeneous. Fig. 5 shows the differences due to the two perfusion directions. Fig. 5a gives the absolute differences between the two s_n in μmol/ml and Fig. 5b gives the differences relative to s_0. Both these types of difference are probably too small to be detected experimentally.

Discussion

Although Parsons and Prichard [16] and Parsons [17] have demonstrated that modelling has an important place in intestinal absorption, their approach has never been applied to these particular problems. My model was used to study kinetics of the whole transport process in perfused intestines, whereas Parsons was more concerned with 'black-box models' of the mechanisms of transport at the luminal and serosal cell surfaces.

I am aware that my model is an oversimplification of the processes that are probably present in and near the mucosal cells. For example, it is known that the intestine is not a uniform tube, but that the surface area decreases along its length [8]. It is also claimed that both V [1] and K [2] likewise change with distance, but different authors have different opinions and it appears to depend on the solute (e.g. Ref. 18). It is also likely that an unstirred layer exists close to the mucosal surface, and Fisher has shown how this can have a large effect on the measured K for some transport processes [19]. Winne and coworkers show how corrections may be made for this effect [20,21]. For many kinds of absorption experiment a Michaelis-Menten equation would be the 'best-fit', but the K would be biased towards high values [19,21]. Although Winne and coworkers use a complex equation to calculate the thickness of unstirred layers, it should be noted that a Michaelis-Menten term plus a linear term can be fitted to much of their data [21]. For many solutes there may also be return from the intestine to the perfusate (e.g. Ref. 22), passive diffusion (probably through the junctions of the mucosal cells) and adsorption of the solute onto the cell surfaces. Recently Lewis and Fordtran have shown that many parameters of the absorption process (surface area, thickness of the unstirred layer and the rate constant for passive diffusion) may not be constant but probably increase as the perfusion rate is increased [23]. However, I have demonstrated the usefulness of my type of model for the simplest case, and shown how it can be modified readily to include more detail if necessary (water absorbance and decrease of V with length).

In a previous survey it was noted that the Michaelis-Menten equation,

although the 'best' of three models studied, was a poor fit in a large number of instances (various solutes and various species) [3]. The original authors had used it without formal tests of goodness-of-fit. In this present study I have investigated two problems: (i) the solute concentration changes along the length of the intestine, and (ii) the intestine is not uniform along its length. I have simulated absorption where these characteristics are included and where the range of K and V has been wide. It is quite clear from Figs. 2 and 3 that not only does the solute concentration fall down the intestine but, especially at low flow rates, the decrease with distance is far from linear.

I have also used several algebraic expressions of solute concentration for the independent variable. However, the results show that for a wide range of K and V, and regardless of the expression used for solute concentration, the Michaelis-Menten equation was always a good fit to the data. Therefore one can rule out the two problems discussed in this work as a cause of the poor fits. This still leaves other possibilities to be investigated in the future. Chief among these are the presence of an unstirred layer, passive diffusion through this layer and through the cell junctions, and solute adsorption.

It is apparent from the results in Tables I and II that the current practice of estimating parameters by fitting the Michaelis-Menten equation to absorption rate versus apparent value of s can lead to very inaccurate results. When s_0 and s_n were used for the solute concentration a high proportion of the estimates were in error by over 5% and in many instances they were more than 100%. The errors are smaller at high solute concentrations and high perfusion rates, but under these experimental conditions the relative changes in solute concentrations during passage through the intestine become much smaller and their estimation may itself lead to increasing inaccuracy. The flow rate has therefore to be chosen so that a compromise is achieved between these considerations. The problem has been noted earlier. Fisher and Gardner, studying the absorption of glucose by perfused rat intestine [9], calculated K = 19 mmol/l (using s_0, the initial concentration) and K = 14 mmol/l (using s_n, the luminal effluent concentration). This is a range of approximately 15% about the mean.

Use of the arithmetic or geometric mean of these concentrations may reduce the error, but they do not eliminate it. However, it has been possible, for the example chosen in this study, to use an empirical function for s (a weighted mean of s_a and s_g) that will allow K and V to be better determined. It is doubtful whether it would be of value for other species and other solutes but I suggest that in these situations trials should be made to determine suitable functions.

The above simulations and the measurements of Fisher and Gardner [9] show that the calculated values of K and V are dependent on the algebraic expression used for solute concentration. It has also been commented that these values are greatly dependent on the methodology employed [24]. It should perhaps be noted that a similar problem also arises with incubation experiments when the final and initial solute concentrations are not equal. In addition the rate of decrease of concentration with time may not be linear.

The current work has also demonstrated that of several methods available for model fitting, or non-linear regression analysis, one of them will fit my simple model to perfect data from the simulation of perfused small intestines.

Thus it should be possible in future to fit my model, or some other more complex but plausible model, to experimental data in order to calculate more precise values of K and V.

The last section of this study shows that it is easy to modify my model to incorporate other known characteristics of the small intestine. In this example I have asked the simple question: is there a detectable difference in the effluent solute concentration between single-pass experiments in which the intestine is perfused downwards then upwards? It is clear that the differences are small and probably difficult to detect experimentally. However, one valuable result is apparent by comparing Figs. 4 and 5 with Figs. 2 and 3. It can readily be seen that when the intestine is not uniform, the decrease in solute concentration along the length is even more non-linear than for the homogeneous case. This means that errors in estimating V and K, as discussed above, would also be much greater. There seems to be no reason why my model could not also be modified to include any of the other properties mentioned earlier: an unstirred layer, passive diffusion, solute adsorption or change of parameters with perfusion rate. It would be necessary, though, that adequate mathematical functions for these properties have been previously determined.

Many intestinal perfusions are performed using a recirculated perfusion medium. I have not yet modelled this situation but it should be possible to do so, both for simulation and parameter estimation. The model of the system would have two compartments. The first compartment would be a homogeneous one to represent the reservoir of medium. The second compartment would represent the intestinal absorption and would consist of the model I have presented above. They would be connected by two fluxes with the return flux subject to a time delay dependent on the rate of perfusion.

In conclusion it must be re-emphasised that the parameters K and V are not analogues of K_m and V of the Michaelis-Menten equation, and will probably not represent the actual kinetics of an absorption process [25,26]. Restrictions must therefore be placed on their interpretation, e.g. in terms of carrier mechanisms, counter transport phenomena, etc. (and should not be used, for example, as Crane et al. [27] have done). Nevertheless K and V are valuable as operational constants and may be used for purely descriptive purposes or when comparing the transport characteristics of different solutes [28].

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