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The gastrointestinal transit investigation of a controlled release aminophylline formulation

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Summary

The gastrointestinal transit and release of a radiolabelled marker from an orally administered controlled release preparation has been evaluated in vivo in a group of 6 subjects using the technique of gamma-scintigraphy. Excellent agreement between in vitro and in vivo release rates was obtained. Release of aminophylline was found to be constant throughout the gastrointestinal tract and was independent of changing pH and degree of gastrointestinal motility. Absorption of aminophylline is controlled by its rate of release from the tablet matrix.

Introduction

The transit of a drug formulation through the gastrointestinal (GI) tract can have an important bearing on the drug release and the subsequent bioavailability of the drug. The resultant blood level–time profile can be dependent on such factors as gastric emptying time and intestinal transit time as well as the in vivo disintegration and dissolution characteristics of the dosage form (Rowland and Tozer, 1980). Controlled release systems represent an important group of dosage forms where knowledge of transit through the GI tract is necessary for the design of a good product.

Controlled release dosage systems can take different forms, but the two main categories are multiple and single unit systems. Both have advantages and disadvantages and recently there has been discussion about relative merits with regard to transit in the gastrointestinal tract.

The modern technique of gamma-scintigraphy now makes it possible to follow the transit behaviour of dosage forms in human volunteers in a non-invasive manner. The dosage can be labelled with a small amount of a gamma-emitting radionuclide and by placing the subject in front of a gamma-camera the position of the dosage form and its integrity can be ascertained. It is not normally possible to use a labelled drug with the scintigraphic technique, since the gamma emitting isotopes of carbon, oxygen and nitrogen are

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short-lived. Instead, a radiolabelled marker that has similar release properties to the drug can be included in the formulation and an in vivo release profile can be determined. The behaviour of the drug in vivo can be followed by conventional pharmacokinetic measurements and the absorption rate obtained by deconvolution methods. If the absorption of the drug is controlled by the rate of release from the dosage form, the absorption rate constant can be taken as the in vivo release constant. It is possible to correlate position within the gastrointestinal tract with the pharmacokinetic profile and to investigate gastrointestinal absorption of the drug. Previously, we have studied a wide variety of controlled release systems using the method of gamma-scintigraphy (Daly et al., 1982; Wilson et al., 1984; Davis et al., 1984; Christensen et al., 1985). Here we describe the in vivo properties of aminophylline formulated within a controlled release system. This system of controlled release depends on a delicate balance between the hydration of hydrophilic cellulose(s) subsequently incorporated within a higher aliphatic alcohol to produce the desired rate of release for each particular drug (Leslie, 1986). This controlled release system is designed to provide a constant delivery of drug regardless of the change in pH and degree of motility of the GI tract.

Experimental

Study design

A single period open assessment of gastrointestinal transit and pharmacokinetic profile of aminophylline was carried out in 6 healthy volunteers using a single oral dose of labelled Phyllocontin Continus tablets. The tablet cores were labelled with [technetium-99m-ethyl]HIDA. The position of the unit within the gastrointestinal tract, its release characteristics and integrity were evaluated. Blood samples were collected at suitable time intervals for analysis of aminophylline.

Labelling of the Phyllocontin Continus tablets

A radiolabelled marker was included in the formulation so that the in vivo profile could be determined. In vitro experiments were used to confirm that the release of the marker and the drug were similar.

The tablets were labelled by adding the marker as the granulating fluid in the manufacture of the granules. The granules were prepared according to the Company's own procedure. Tablets were compressed using an instrumented Manesty F3 machine at a compaction pressure that resulted in tablets with a crushing strength of 4–6 kgF. A minimum batch of 30 tablets was prepared on each occasion.

Preliminary investigations were carried out with the marker DTPA (diethylenetriaminepentaacetic acid) labelled with indium-III (half-life 2.7 days).

Dissolution tests were carried out using a 6-station USP dissolution apparatus with a rotating paddle speed of 100 rpm at 37 °C using pH 6.5 citric acid/phosphate buffer. One station of the dissolution apparatus contained a standard solution of aminophylline.

The quantity of aminophylline released from each of 5 tablets was determined by direct measurement of the UV absorbance of the dissolution medium at 294 nm using a Kontron Uvikon 810 spectrophotometer. The mean percent released over time was then calculated.

During the same dissolution test the release of radioactive marker from the 5 tablets was also determined by removing 2 ml samples (replaced by 2 ml of buffer) and then counting on a gamma-counter (Intertechnique CL4000). The results were corrected for background and decay and the percent released was calculated on the basis that the activity in the dissolution vessel after 23 h represented 100% release.

The dissolution profiles of radiolabelled DTPA and aminophylline were found not to be similar, probably because of the more polar nature of the marker. A second marker, ethyl-HIDA (EHIDA), labelled with technetium-99m was therefore employed. EHIDA is an iminodiacetic acid analogue of lignocaine (*N*-[*N'*-{2,6-dimethylphenyl}]carbomoylmethyl iminodiacetic acid), a more lipophilic compound. Using the procedure described above, the in vitro results showed that [^{99m}Tc](EHIDA)$_2$ mimicked the in vitro release of aminophylline quite closely.

Dosage and administration

The volunteers, who were fully informed of the nature of the study, reported to the trials unit having fasted since midnight. Following a standard light breakfast of approximately 1500 kJ (one slice of lightly buttered toast, one glass of orange juice) each volunteer was given the radiolabelled tablet together with 100 ml of water. A standard lunch was provided 3 h into the investigation. No xanthine-containing food or beverages were allowed during the study but a non-xanthine beverage was allowed after lunch. Alcohol consumption was forbidden during the study.

Procedure

Blood samples were obtained by indwelling cannulae, predose and at the following times: 1, 2, 3, 4, 5, 6, 8, 10, 12 and 23 h. The samples were transferred to heparinised tubes and then centrifuged to provide plasma. Plasma samples (stored at $-20\,^{\circ}C$) were subsequently assayed for aminophylline by an HPLC method (Napp Laboratories, unpublished observations). Scintigraphic images were obtained at times corresponding to blood sampling and at additional times to provide data on gastrointestinal transit behaviour. The volunteers were placed in front of a General Electric gamma-camera (field of view 40 cm diameter). Static images of 60 s duration were recorded from anterior and posterior positions. The position of the dosage form in the GI tract was determined with reference to an external marker. Regions of interest of constant size were created around the releasing tablet and the activity recorded. The data for anterior and posterior views obtained in this way were corrected for background and radioactive decay and expressed as the geometric mean.

Results and Discussion

Gastrointestinal transit

The pattern of transit of the tablets in the gastrointestinal tract is shown in Table 1. The times for gastric emptying, small intestine transit and arrival at the colon are provided.

The gastrointestinal transit profiles for the 6 volunteers were quite variable as would be expected for the administration of a single unit dosage form after a light breakfast. Four of the volunteers demonstrated gastric emptying within 2.5 h while two others retained the tablet in the

TABLE 1

Gastrointestinal transit of the radiolabelled Phyllocontin Continus tablets (225 mg)

Key: S = stomach; SI = small intestine; ICJ = ileocaecal junction; SF = splenic flexure; AC = ascending colon; HF = hepatic flexure; TC = transverse colon; SC = sigmoid colon; (B) = matrix began to disintegrate.

Time (h)	Position in gastrointestinal tract					
Subject:	1	2	3	4	5	6
0	S	S	S	S	S	S
0.5	S	S	S	S	S	S
1.0	S	S	S	S	S	S
2.0	S	SI	S	ICJ	S	SI
3.0	SI	TC	S	AC	S	SI
4.0	SI	TC	S	HF	S	ICJ
6.0	AC	SC	S	SC	S	AC
8.0	AC	SC	S	SC	S	AC
10.0	TC	SC	S(B)	SC(B)	S(B)	HF
12.0	TC	Out	SC	SC(B)	TC(B)	TC
	Approximate transit times (h)					
Gastric emptying times	2.5	2.0	> 8	1.0	> 8	1.5
Small intestine transit times	3.5	1.0	–	1.0	–	4.0
Colon arrival times	6.0	3.0	–	2.0	–	5.5

stomach for 8 h. The emptying of a single unit from the stomach is controlled amongst other factors by the fed state of the subject. Matrix tablets, larger than about 10 mm in size, will be retained in the stomach while it is in the digestion mode and will only be emptied when this is completed (Davis et al., 1986). Hereupon, the third phase of the migrating myoelectric complex (sometimes called the housekeeper wave) will move undigested material from pylorus to ileocaecal junction in about 2–3 h. If the stomach remains fed then a single unit can remain in the stomach

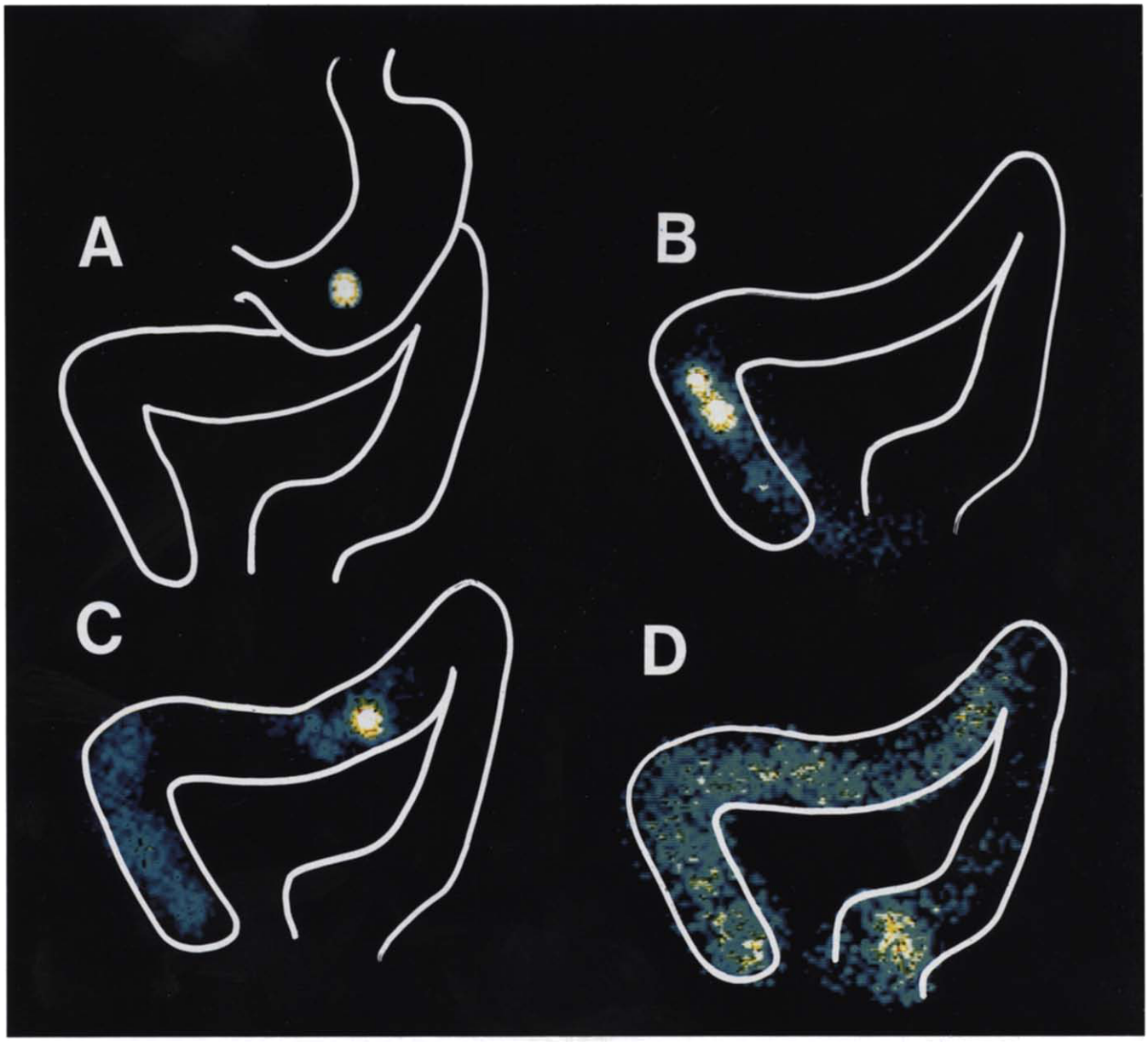

Fig. 1. Radionuclide images showing Phyllocontin Continus tablet (225 mg) in different regions of the gastrointestinal tract. A: 15 min after dosing. B: 2.5 h after dosing. C: 3.5 h after dosing. D: 8 h after dosing.

for a longer period of time. Thus, the data in Table 1 reflect the somewhat different individual digestive patterns for the subjects. The individuals 3 and 5 clearly received the subsequent meals (lunch or dinner) before the end of the digestive phase or before the arrival of the "housekeeper wave" that would clear the tablet from the stomach. Notwithstanding these observed patterns of gastric emptying it should be appreciated that even if the dosage form itself remained in the stomach, released drug, in solution or as small particles, would have been emptied into the small intestines for absorption.

Scintigraphic images

Scintigraphic images showing the dosage forms in the stomach and intestines are given in Fig. 1. In the images the intact tablet and released activity are evident.

Release of radiolabelled marker

Mean data for the release of the radiolabelled marker in vitro and in vivo are given in Fig. 2. In some cases it was not possible to follow the release of activity over the full-time profile because of difficulties in characterising multiple images caused by the disintegration of tablets towards the end of the study. The correlation between the in vitro and in vivo data is excellent. This is to be expected since the release process is independent of pH.

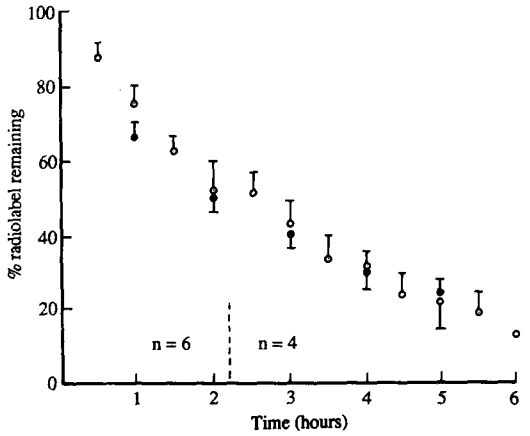

Fig. 2. In vitro–in vivo correlation. Release of [^{99m}Tc]EHIDA from Phyllocontin Continus tablets (mean ± S.E.M.) (in vitro $n = 5$; in vivo $n = 4$ or 6).

TABLE 2

Summary of non-linear regression parameter estimates for the one-compartment model following administration of radiolabelled Phyllocontin Continus tablets (225 mg)

Key: V = volume of distribution; K_a = absorption rate constant; K_e = elimination rate constant; t_{lag} = lag time to absorption; S.E.M. = standard error of mean.

Parameter	Estimates	S.E.M.
V	62.0	13
K_a	0.300	0.110
K_e	0.0939	0.0271
t_{lag}	0.173	0.263

Relationship between in vivo release of labelled marker and absorption of aminophylline

Mean aminophylline plasma concentration data were obtained. A non-linear regression program (PCNONLIN) was used to fit the parameters of a one-compartment open model with a lag time to the data. The applicability of the model to describe the data was judged by the correlation coefficient, the weighted residual of squares and visual inspection of residual plots. The 'best fit' parameters are summarised in Table 2. Good agreement between the predicted curve and observed points was seen. From this model and with the data available, absorption of aminophyl-

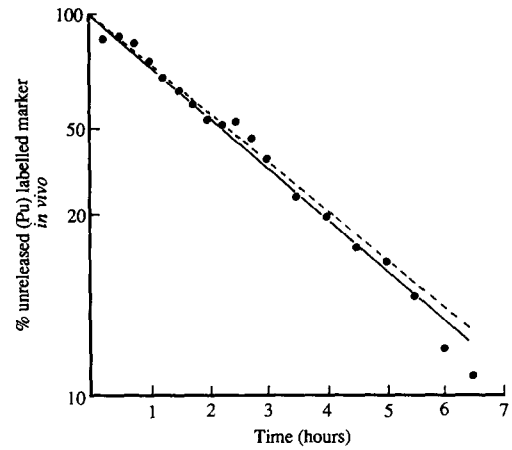

Fig. 3. Mean percent marker unreleased (●) as assessed by scintigraphy in 6 subjects. Solid line ($P_u = 100 \cdot e^{-0.31t}$) is the regression line through data points. Broken line ($P_u = 100 \cdot e^{-0.30t}$) is the simulated line assuming the rate constant for release is equal to the absorption rate constant measured in vivo.

line appears to be adequately described by a monoexponential process having a rate constant of 0.300 h^{-1}.

Using the scintigraphic data, a graph of percent labelled marker unreleased in vivo, was plotted on semilogarithmic axes against time (Fig. 3). Visual inspection of this curve suggests that the data are described by a single exponential process. The line of best fit conforming to this model derived by PCNONLIN had the form:

$$P_u = 100 \cdot e^{-0.310t}$$

where P_u is the percent labelled marker unreleased, the first-order rate constant has units h^{-1} and t is time in hours. It is interesting to note that this derived value for the in vivo release rate of the labelled marker corresponds almost exactly with the independently estimated first-order absorption rate constant for aminophylline or Phyllocontin Continus tablet. This provides strong evidence to support a claim that the absorption of aminophylline from the wax/cellulose formulation in vivo is controlled by its release from the matrix assuming:

(a) the release of the labelled marker from the matrix in vivo accurately reflects the release of aminophylline;
(b) the applicability of the pharmacokinetic model. For example, a rigorous mathematical description of absorption from a controlled release form may require two sequential input functions. It is debatable if any single sampling protocol would provide sufficient in vivo data to support such a model; and
(c) the approximation of first-order processes are not introducing bias into the overall data analysis.

TABLE 3

Mean percent aminophylline released in vitro and percent aminophylline absorbed in vivo

Time (h)	% Released in vitro	% Absorbed in vivo [a]
1	38	26
2	51	46
3	60	60
5	75	78
6	78	84

[a] Calculated from model derived absorption rate constant using the formula:
% absorbed $= 100 - (100 \cdot e^{-Kat})$

Relationship between in vivo absorption rate and in vitro dissolution rate

The mean results of 5 dissolution profiles are presented in Table 3. Good agreement can be seen between the measured in vitro dissolution release rates and the calculated absorption rates.

Conclusion

This study has shown the value of the technique of gamma-scintigraphy in the investigation of gastrointestinal transit of controlled release formulations. It has also shown that an excellent correlation exists between the in vitro dissolution release rate and in vivo absorption of aminophylline released from Phyllocontin Continus tablets. It can be seen that the rate of aminophylline released and the in vivo absorption is constant throughout the gastrointestinal tract regardless of changing pH and gastrointestinal motility.

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