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On the intestinal transit of a single non-disintegrating object

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Summary

A method is described for the measurement of the rate of transit of a non-disintegrating object through the gastrointestinal tract of human subjects using a gamma camera. A three-dimensional co-ordinate for the object is obtained by reference to external markers placed on the front and side of the body. Passage through the duodenum was very rapid and the rate of transit could not be measured. Thereafter the mean transit rate through the small intestine was measured at 4.2–5.6 cm · min^{-1} and was reasonably consistent between subjects. This is in contrast to the time for the object to leave the stomach which varied from 15 to 197 min.

Introduction

The rate of transport of a dosage form, or drug, down the intestine is of obvious consequence as the major site of absorption of drugs is the small intestine. The recognition that certain drugs may not necessarily be absorbed along the whole of the small intestine but through narrow 'windows' (Koch-Weser and Schechter, 1979), makes the determination of transit rates especially important. If a measurement of transit rate can be established, then the influence of pharmaceutical manipulation can be assessed.

Data on transit rates of pharmaceutical materials, or systems allied to pharmaceuticals is limited, and is often concerned with overall transit times as

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opposed to rates and times in various parts of the gastrointestinal tract (Rosswick et al., 1967; Hinton et al., 1969; Bechgaard and Ladefoged, 1978, 1981). This paper describes a method of measuring intestinal transit rates using gamma scintigraphy to obtain a three-dimensional co-ordinate for an object in the intestine. This technique has been used extensively for measuring gastric emptying (Clements et al., 1978; Hunter et al., 1983) but quantification of intestinal transit has not previously been attempted due to the difficulties of following an object down a coiled structure.

Materials and Methods

Capsules

Perspex capsules measuring 19.54–20.88 mm in length and 6.93–7.49 mm in diameter were used in the study. They were machined to be similar in form to a conventional No. 1 hard gelatin capsule, allowing filling with radioactive material and sealing of the cap on the body with perspex solvent to render them impermeable to liquids. The hollow capsules were filled with either radiolabelled Amberlite resin (CG 400 C1, B.D.H.) or the labelled resin and a stainless steel pellet. The capsule, once filled, was sealed with perspex solvent. Two specific gravities were investigated, one with a range 1.01–1.05, the other with a range of 1.59–1.63.

Labelling and capsule filling

A suitable weight of Amberlite resin was stirred into distilled water. [^{99m}Tc]Sodium pertechnetate, eluted from a generator, was mixed with the ion-exchange resin. The labelled resin was recovered from the suspension by filtration, followed by drying of the filtrate. Weighed amounts of the labelled material were packed by hand into the perspex capsules. 200 ml of fruit (orange) drink (with a calorific value of 70–75 cal.) was labelled with [^{99m}Tc]sodium pertechnetate bound to tin colloid. External markers (1.3 cm in diameter) were made by filling lead wells with ^{57}Co in saline, allowing the solution to evaporate and sealing the radioactivity in the lead wells.

Methods

Four informed healthy male subjects took part in the study. Markers were placed on the body, positioned as shown in Fig. 1. Two additional markers were placed on the right-side of the body on the same level as the subcostal and intertubercular plane. After a 12 h fast, the subject swallowed 200 ml of the labelled orange drink to outline the stomach. The subject then ingested the perspex capsule with 100 ml of water (at 20 °C) and sat in front of a gamma camera (MED 11, Nuclear Data). Once the capsule was seen to leave the stomach, data was accumulated by the on-line computer at 30-s intervals for a total time of 1 h, whilst the subject was standing. The subject rotated every 30 s to obtain alternate views of the front and right-sides. This ensured that a three-dimensional co-ordinate of the capsule's position could be determined relative to the markers, for effectively each minute of the data being recorded.

Each subject repeated the procedure for both specific gravities of the capsule being studied, so that 4 sets of data were collected for each subject. In addition one subject took a perspex capsule of the same specific gravity (1.03 ± 0.02) on 4 separate occasions to assess the reproducibility of the method.

A further study was carried out in a similar manner but for longer time periods. Two subjects took part, ingesting the low specific gravity capsule in the manner described above. After the initial data recording period of 1 h after gastric emptying, the subjects returned at intervals throughout the day for periods of half-an-hour. Food and drink was allowed ad libitum after the initial recording.

Results

The relative positions of the data points obtained were converted to absolute positions by referring to the fixed body markers and an initially recorded frame, named the reference frame. The external marker positions and the capsule position was obtained from each frame by the computer in terms of pixel co-ordinates. Each recorded frame consisted of 64 by 64 pixels. The reference frame was a record of the absolute position of the external body markers in terms of their pixel co-ordinates. The subsequent frames showed the external marker positions to have altered in terms of their pixel co-ordinates and therefore the markers were re-aligned to the initial reference frame in order to obtain the absolute position of the capsule.

The data were quantitated by calculating the distance between the three-dimensional, Cartesian co-ordinates (described in pixels) using Pythagoras' Theorem. Pythagoras' Theorem was used in the determination of the three-dimensional distances travelled, as it was felt that the distance travelled every minute was sufficiently small to describe the path taken by the capsule. The path taken is assumed to be curved, because of the geometry of the intestinal loops. The length of any part of

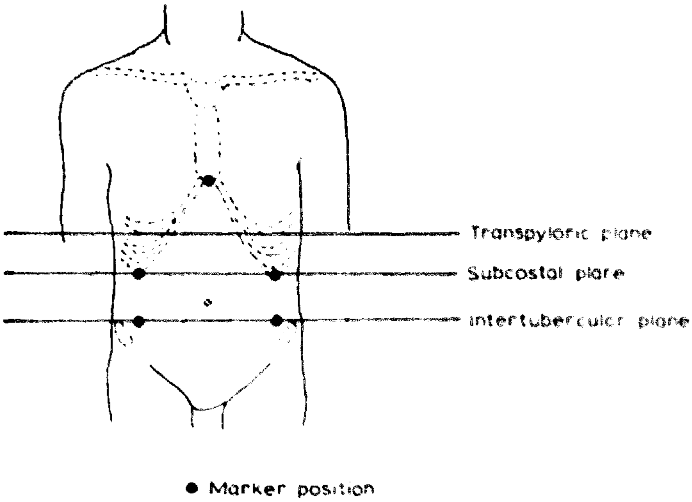

Fig. 1. Diagram showing the external marker positions using landmarks in surface anatomy.

a curve can be divided into a number of elements, each of length δs. The length of these elements is approximately equal to the length of the hypotenuse of a right-angled triangle. If δs is very small, the curvature of each element becomes negligible, the basis of using the Pythagoras' Theorem. The distances travelled in terms of pixels can be converted to absolute distances using a simple calibration procedure. The cumulative distance travelled with time was calculated and examples are shown in Fig. 2. Table 1 shows the results of linear regression analyses of the data points and lists the times for the capsule to leave the stomach. Analyses of variance on the slopes of the plots and the time to leave the stomach showed no significant difference between the two specific gravities ($P > 0.05$). Table 2 shows the results from a single subject who repeated the experiment on 4 separate occasions.

Plots of individual rates of travel against the mean time point are shown in Fig. 3. Although certain peaks of activity in terms of distance travelled in any one minute can be seen, there is no overall pattern of activity.

The results from the extended time studies are shown in Table 3 as slopes of the

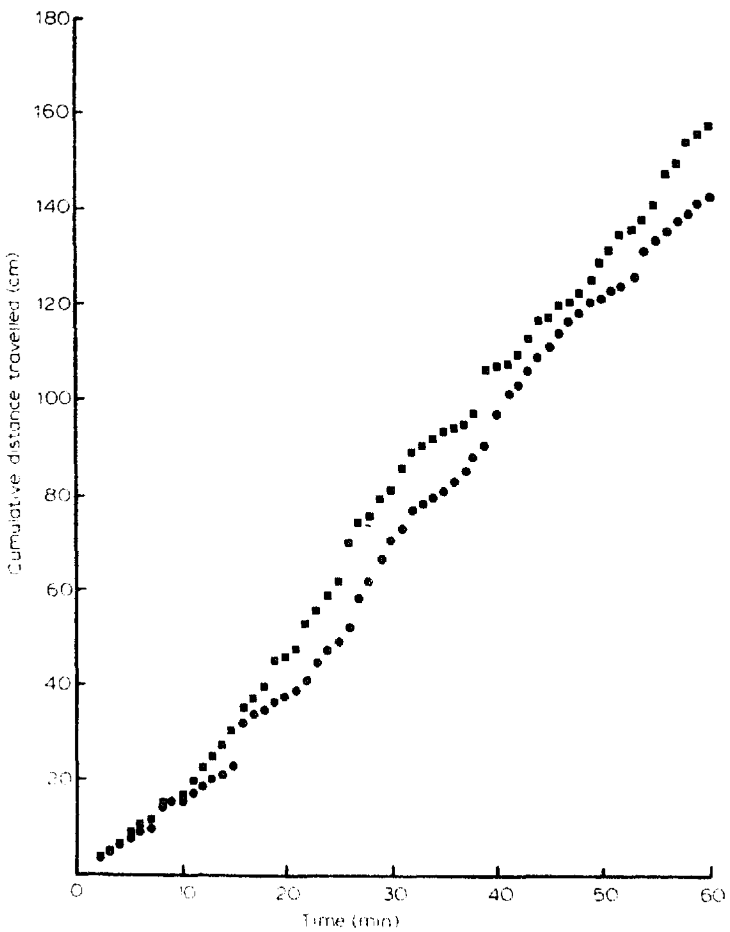

Fig. 2. Cumulative distance travelled down the intestine, against time for Subject 2. ■ = specific gravity 1.03; ● = specific gravity 1.61.

TABLE 1

RESULTS OF LINEAR REGRESSION ANALYSES ON CUMULATIVE DISTANCE TRAVELLED VS TIME DATA

Subject		T.L.S. (min)	Slope ($cm \cdot min^{-1}$) (60 min)	Error variance	Coefficient of correlation
1	A_1	70 min	2.8362	161.8938	0.9985
	A_2	135 min	2.0521	37.1356	0.9935
	B_1	190 min	2.8985	11.0423	0.9990
	B_2	147 min	2.5015	54.4815	0.9935
2	A_1	28 min	2.7598	26.3110	0.9974
	A_2	21 min	2.4114	12.6126	0.9984
	B_1	39 min	2.2916	15.1673	0.997[illegible]
	B_2	82 min	2.6054	27.6355	0.9970
3	A_1	45 min	2.2328	36.9030	0.9945
	A_2	197 min	2.7617	67.5140	0.9934
	B_1	41 min	1.2333	8.0729	0.9960
	B_2	117 min	1.2595	7.6171	0.9964
4	A_1	23 min	2.[illegible]479	32.3965	0.9948
	A_2	92 min	2.4461	17.9023	0.9978
	B_1	138 min	3.6578	100.0193	0.9944
	B_2	15 min	2.3437	89.8821	0.9880

A = Lighter capsule, S.G. 1.03 ± 0.02, repeats 1,2.
B = Heavier capsule, S.G. 1.61 ± 0.02, repeats 1,2.
T.L.S. = time to leave the stomach.

cumulative distance travelled against time for the period of registration of the data. In general there is an overall slowing of the transit rate with time.

Discussion

Current work into gastrointestinal transit and motility distinguishes between the 'fed mode' and the 'fasting mode'. When food enters the stomach regular contrac-

TABLE 2

STATISTICAL ANALYSIS ON REPRODUCIBILITY STUDIES

	Slope ($cm \cdot min^{-1}$) (5–20 min)	Slope ($cm \cdot min^{-1}$) (21–60 min)	Slope ($cm \cdot min^{-1}$) (1–60 min)
Mean	2.5323	2.5887	2.5834
S.D.	0.6840	0.3598	0.1256
C.V. (%)	27.01%	13.90%	4.86%

S.D. = standard deviation; C.V. = coefficient of variance.

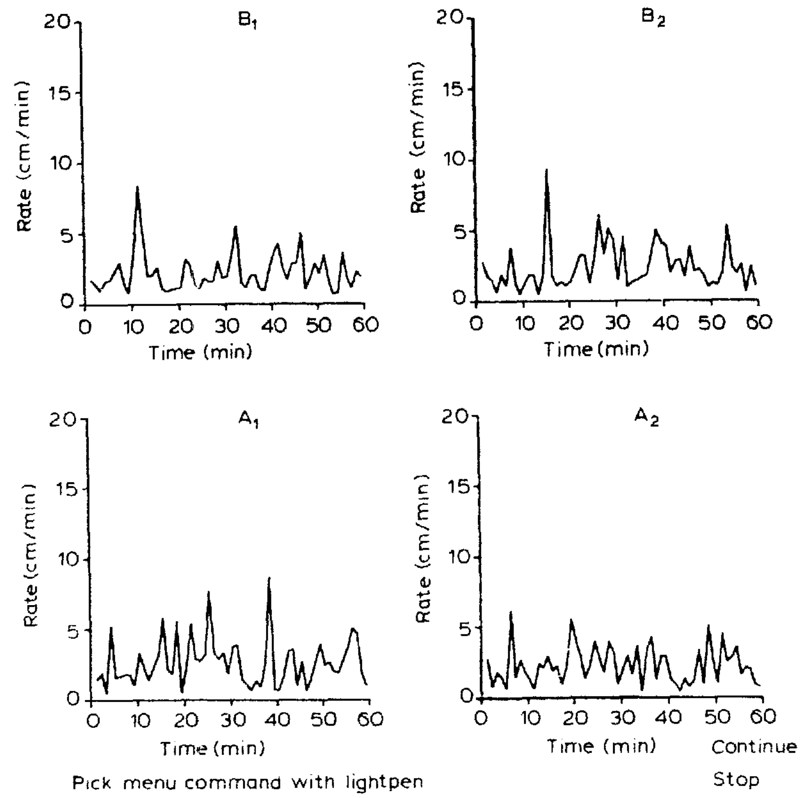

Fig. 3. Graphs of rate of travel of the capsule in the intestine vs time for Subject 2. A = specific gravity 1.03, repeats 1,2. B = specific gravity 1.61, repeats 1,2.

tions occur which move towards the antrum. These not only serve to pass food into the duodenum but also cause retropulsion to occur which ensures thorough mixing and grinding of solid particles. Solids do not normally leave the stomach until they have been reduced in size to less than approximately 2 mm. Liquids are emptied faster than solids (Sarr and Kelly, 1980). Food is moved along the intestine by ring and peristaltic contractions. When most food has left the stomach the fasting mode

TABLE 3

SLOPES FROM LINEAR REGRESSION ANALYSES ON THE DATA FROM THE PROLONGED TIME STUDIES

Subject 7		Subject 8(i)		Subject 8(ii)	
Time of day (h)	Slope ($cm \cdot min^{-1}$)	Time of day (h)	Slope ($cm \cdot min^{-1}$)	Time of day (h)	Slope ($cm \cdot min^{-1}$)
9.29	1.9556	11.36	1.8029	11.34	3.9698
11.31	2.5268	13.34	1.2555	15.00	3.0821
13.31	1.3600	15.05	1.0852	16.39	1.3986
14.36	1.5674	16.46	0.9801	17.15	1.1772
16.04	1.6973	18.00	1.3601	17.31	1.7816

ensues. This is characterized by a quiescent phase followed by increasing contractions leading to intense contractions, the migrating motor complex (MMC), which passes down the intestine and sweeps any remaining contents out of the stomach.

The results showed that the radiolabelled liquid used to outline the stomach was emptied well within half-an-hour (post-ingestion) in all subjects, which is in agreement with the studies of Sarr and Kelly (1980).

The perspex capsule's dimensions were comparable to the 7 mm plastic spheres described in Hinder and Kelly's studies on gastric emptying in dogs (1977). In these experiments, they found that the plastic spheres remained in the stomach up to 4 h post-ingestion, whilst the meal emptied to completeness. Therefore, the perspex capsule ingested by the subjects would be expected to remain in the stomach until the liquids had emptied and left the duodenum. The presence of 'orange squash' in the stomach would have involved the fed mode, but upon its clearance from the stomach and duodenum, the fasting mode would have been instituted. There were no means of establishing in the experiments described the particular 'phase' present at the resumption of the fasting mode.

The retropulsion in the stomach was observed as an oscillating movement of the radiolabelled capsule. Often the capsule's movement was seen as a point source moving progressively upwards towards the pylorus and then being retropulsed back into the pyloric antrum. On one or two occasions the capsule was seen to leave the stomach and travel down the duodenum in a 'gentle' manner, but most often the movement was forceful propulsion of the capsule through the duodenum, often leaving the duodenum before recording of the intestinal data had begun. The duodenum is about 25 cm in length; therefore in less than a minute the capsule has travelled this distance, i.e. the initial rate of travel of the capsule is greater than 25 $cm \cdot min^{-1}$. The rapid transit through the duodenum may be of consequence in the bioavailability of certain drugs such as tetracycline, whose absorption rate is greater in the duodenum and is found to decrease progressively from the small intestine to the lower bowel (Boxenbaum, 1982).

There was a wide range of times taken for the perspex capsule to leave the stomach both within and between subjects, e.g. Subject 4 on one occasion took 15 min for the capsule to leave the stomach and on another occasion 138 min: about a 9-fold increase in time. Also, the mean time taken for capsules to leave the stomach in Subject 2 was 42.5 min, in contrast to Subject 1, who had a mean time of 135.5 min. Therefore, in considering a uni-particulate and non-disintegrating oral dosage form, the time spent in the stomach is unpredictable for the set of conditions described.

In contrast, the mean rate of travel of the capsule down the small intestine was much less variable than the times taken to leave the stomach both within and between subjects. Statistical analysis of the repeat experiments carried out by a single subject also showed the same lack in variability in the intestinal rate of travel of the capsule compared with the times taken to leave the stomach (Table 2).

There was no difference in the rate of travel between the two specific gravities investigated. This contrasts with Hoezel's observations (1930), although he used materials with extremes in specific gravity (spec. grav. 0.9 to 10.53) and the total transit time (mouth-to-stool) was measured. The experimental results also conflict with those of Bechgaard and Ladefoged (1978), who found that the transit time depended on the density of the material ingested. However, it must be stressed that in the latter study pellets were used and not a single object, and the differences in gastric emptying times were not taken into account. In later experiments, Bechgaard and Ladefoged (1981) found that the transit times of single-unit tablets showed great variability both within and between subjects. This variability as shown by these studies is probably accounted for by differences in the time taken for the capsule to leave the stomach and not the variability in the rate of travel which was found to be statistically within the accepted variability of biological systems in general.

The subsequent delay in the time taken for the capsule to leave the stomach, once liquid has been cleared and the fasting mode established is due to the MMC. More specifically, the presence of Phase III is thought to be necessary for the rapid, forceful contractions to 'sweep out' the remaining contents of the stomach, i.e. the capsule. The range of the mean rate of travel of the capsule was 4.2–5.6 $cm \cdot min^{-1}$. The activity front of the MMC (Phase III) is associated with movement of intestinal contents down the gastrointestinal tract (Code and Schlegel, 1978). This range is lower than the figure quoted by Lux et al. (1981) of 10.34 ± 0.85 $cm \cdot min^{-1}$ for the migration of the activity front in the fasting mode in man, but is close to the figure of 4.7 ± 1.8 $cm \cdot min^{-1}$, quoted by Kerlin and Phillips (1982) for the velocity of migration of the MMC along the intestine.

Data from a further subject studied was excluded from the analysis. In this subject, the first part of the duodenal loop was folded back to lie behind the stomach. The oscilloscope display showed the capsule leaving the stomach, travelling along the duodenal loop, before appearing to re-enter the stomach. In fact the capsule was still in the small intestine in the region behind the stomach. The capsule was propulsed and retropulsed in this region and remained in the same vicinity for the duration of the experiment.

The slowing of the rate of transit of the capsule as it moved down the intestine is in keeping with the results of Jian et al. (1982) for radiolabelled meals. Kerlin and Phillips (1982) have shown that the velocity of the MMC decreases distally along the small intestine. The capsule can be adjudged to have entered the ascending colon when it appears over the right iliac fossa. The times taken were 6 h 11 min for subject 7, 6 h 21 min for subject 8(i) but when subject 8 repeated the experiment (8(ii)), the capsule had not reached this point after 9 h. This prolonged time may have been due to a period of intense exercise undertaken by the subject during the study.

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