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The effect of sleep on the gastrointestinal transit of pharmaceutical dosage forms

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Summary

The gastrointestinal (GI) transit of pharmaceutical dosage forms was studied during sleep in eight, healthy, male volunteers. Each ingested five 7-mm radiolabelled tablets and a pressure-sensitive radiotelemetry capsule (RTC) following a light meal on two separate occasions, administered either at night (22:00) or in the morning (08:00). Transit of the tablets was monitored by gamma scintigraphy and the RTC detected contractile activity within the GI tract. Oro-caecal transit of the 7-mm tablets was longer for night-time dosing compared to morning administration, although the difference did not reach statistical significance. Gastric residence time and small intestinal (SI) transit time of the RTC were also extended after night time dosing. Total transit times of the RTC were similar following both morning and night-time administration. These results may be explained by alterations in the periodicity of the fasting migrating myoelectric complex (MMC) at night.

Introduction

Circadian variation has been documented for several orally administered drugs (Reinberg and Smolensky, 1982). For example, aspirin has a higher bioavailability when administered at 06:00 rather than at 22:00 (Ritchel, 1984). Similarly, oral dosing of hexobarbital leads to a 2.5-times higher plasma level at 02:00 than at 18:00 (Ritchel, 1984). The cause of the observed effects is not well established but is clearly related to chronopharmacological behaviour. For a number of drug substances, it is advantageous to make use of these temporal variations. Best known is the early morning delivery of drugs used in the treatment of nocturnal asthma, and in cardiovascular therapy (Scott et al., 1981; Theeuwes, 1989). Controlled release technology is now available which provides pulsatile release of drug at a predetermined time after administration (Wilding et al., 1991) which may allow optimization of plasma levels in the morning for a given circadian response. The rationale behind the design of these devices is valid provided that the transit of such dosage forms in the GI tract does not differ from

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day to night. It has previously been shown that gastric emptying (GE) of solid meals is slower in the evening than in the morning (Goo et al., 1987). Many studies have been performed on the GI transit of pharmaceutical dosage forms (Davis et al., 1984; Mojaverian et al., 1989) but the majority of these have involved morning dosing and little is still known of the night-time transit. Studies to date on circadian variation in GI transit of pharmaceutical dosage forms and test meals have investigated both evening administration and evening transit (Goo et al., 1987; Davis et al., 1991), however, little is known regarding night-time administration and transit during sleep. Motility patterns of the GI tract, in particular interdigestive activity, have a circadian pattern (Kumar et al., 1986) and correlations between migrating myoelectric complex (MMC) activity and sleep stages have been published (Finch et al., 1982). A recent study (Davis et al., 1991) involving patients with ulcerative colitis showed an extended colon arrival (CA) time for 5-mm tablets when the patients were dosed at 20:30, as opposed to 08:30. Other factors such as posture (Moore et al., 1988), exercise (Moore et al., 1990) and stress (Kaus and Fell, 1984) have been shown to affect GI transit, all of which will be different at night compared to the day.

Gamma scintigraphy has been widely used to monitor the GI transit of dosage forms, but this technique has inherent problems for nocturnal imaging. It is clearly unphysiological if volunteers are awoken during the night for data acquisition since the normal sleep pattern will be disrupted. We have utilised the technique of pressure radiotelemetry, in conjunction with gamma scintigraphy, to gain information on the transit of dosage forms at night. Ingestible pressure-sensitive radiotelemetry capsules (RTC) provide a non-invasive method for the assessment of motility (Evans et al., 1982). The position of the RTC within the GI tract can be positively identified by the motility pattern of intraluminal activity and the transit behaviour of the RTC will also model that of a large non-disintegrating single-unit dosage form. The objective of our study was to investigate the effect of sleep on the GI transit of five 7-mm tablets and an RTC.

Materials and Methods

Subjects

The study was performed in eight, healthy males (age range 19–27 years) who were non-smokers and who were not on any medication. Each subject gave written informed consent to participate in the study. The experimental protocol was approved by the University of Nottingham Ethics Committee and conducted in accordance with the Declaration of Helsinki guidelines for Ethics in Research. Approval to administer radiopharmaceuticals was obtained from the Department of Health, London.

Radiolabelling of dosage forms

Non-disintegrating tablets (7 mm diameter, 140 mg weight) were prepared from ethylcellulose (BDH, Poole, Dorset) using a Manesty F3 tablet machine. Each tablet contained a small amount (2.8 mg) of Amberlite IR-120 (BDH, Poole, Dorset) resin radiolabelled with ^{111}In to give a total activity per volunteer at the time of administration of 1 MBq. The tablets were coated to prevent leaching of the radiolabel and in vivo disintegration. A more detailed description of tablet preparation can be found elsewhere (Coupe et al., 1991a).

The RTC (Remote Control Systems, London) was radiolabelled by placing a sealed source of ^{99m}Tc in the battery compartment to give an activity of 1 MBq at the time of administration. The RTC was enclosed within a rubber sheath and allowed to stabilize for 12 h at 37°C and was then calibrated before ingestion (Reynolds et al., 1989). After administration, signals transmitted from the RTC were detected by an aerial worn around the subject's waist. For study period 1 (morning administration), the radio signal was processed and then recorded onto a chart recorder. Study period 2 (night-time administration) was performed using a portable receiving and recording system worn around the subject's waist (Slater et al., 1982). The system consisted of a battery-operated FM receiver recording onto a magnetic tape using a miniature 24 h cassette recorder (Oxford Medilog 4-24, Oxford Medical Systems).

Procedure

A cross-over study was performed comprising one morning and one night-time administration. There was a period of at least 7 days between the study periods.

Morning administration Volunteers fasted overnight and were given a light breakfast (1200 kJ) at 08:00 consisting of one radiolabelled scrambled egg (^{99m}Tc sulphur colloid (3 MBq)), one piece of lightly buttered toast and a cup of tea. Immediately after breakfast, each volunteer received a RTC and five 7-mm tablets together with 100 ml of water. Anterior and posterior images of 60 s duration were recorded using a gamma camera having a 40 cm field of view, fitted with a medium energy (300 keV) parallel-hole collimator. Images were taken every 3 min until all the preparations had left the stomach, then images were recorded at approx. 15-min intervals for the remainder of the day. The images were recorded using a Nodecrest computer system and stored on magnetic tape for subsequent analysis.

Night-time administration Volunteers fasted from 14:00 on the study day and were given the same light meal as per the morning administration at 22:00. Immediately after the meal, each received a RTC and five 7-mm tablets together with 100 ml of water. Anterior and posterior images of 60 s duration were taken every 4 min for 30 min and the volunteers then retired to bed. On waking at 08:00, a single image was taken, breakfast was then given (two pieces of toast, margarine and marmalade and one cup of tea). Imaging then proceeded for the remainder of the day at frequent intervals approx. 20 min apart. The study was terminated at 20:00.

Data analysis

GE and CA of both the tablets and the RTC is an all-or-nothing process, the images were therefore analysed by noting the time of the image in which the tablet had emptied from the stomach or entered the colon. Coadministration of the radiolabelled meal with the formulations enabled delineation of the stomach and colon and the subsequent position of the tablets and RTC to be identified.

Morning administration GE times and CA times for 50% ($T_{50\%}$) of the 7-mm tablets were estimated and SI transit times were calculated by subtracting the GE from the CA time.

Examination of the motility traces allows the GI transit time for the RTC to be estimated as described previously (Coupe et al., 1991b). Each trace was analysed manually by an investigator, who was without prior knowledge of the scintigraphic data, and the GE time and CA time derived. Again SI transit time was calculated by subtracting the GE time from the CA time.

Night-time administration The night-time administration period did not permit data on the GE (and in most cases CA) to be collected via scintigraphy. The data were analysed by recording the position of the individual tablets and displaying these as histograms of transit vs time plots to provide information on position within the GI tract and the extent of tablet spreading. Motility was recorded continuously throughout the night and analysis of the traces permitted the determination of the GE and CA times and the subsequent calculation of the SI transit time of the RTC.

Results

Table 1 shows the $T_{50\%}$ times for the 7-mm tablets to transit the different regions of the GI tract following morning administration. The time for 100% of tablets to enter the colon following morning and night-time dosing is presented in Table 2. In four of the subjects, entry of 100% of the tablets into the colon occurred during the night which prevented the median value being calculated. The longest CA time after morning dosing was 486 min and the shortest was 96 min. In the remaining subjects CA times of the tablets were considerably longer following night-time administration, i.e., 610, 637, 660 and 857 min. Table 3 presents GI transit data for the RTC. The data indicate that both GE and SI transit times are extended following night-time administration, however, the differences were not statistically significant at the 5% level (Wilcoxon's signed rank test). Figs 1–3 present the GI transit data of

TABLE 1

$T_{50\%}$ for the 7-mm tablets to transit the different regions of the gastrointestinal tract (min), following morning administration

Subjects	Tablets (5 × 7 mm)		
	Gastric emptying	Colon arrival	Small intestinal transit
1	73	350	277
2	5	240	235
3	205	385	180
4	23	270	247
5	11	96	85
6	117	323	206
7	124	392	268
8	225	323	98
Mean	98	297	200
SD	85	97	74
Median	95	337	221
Range	5–225	96–392	85–268
n	8	8	8

the RTC from Table 3 diagrammatically (only subject data where positive identification of transit times are presented); the apparent trend being that GI transit is extended following night-time administration. Fig. 4 shows representative tablet versus time histograms following night-time dosing. The data for each subject are presented with the position of each tablet at the time of the last image at night and first image in the morning. In

TABLE 2

Colon arrival time for 100% of the tablets (min)

Subject	Morning dosing	Night-time dosing
1	393	610
2	486	660
3	385	857
4	270	< 581
5	96	637
6	369	< 581
7	407	< 583
8	350	< 580
Mean	345	
SD	117	
Median	377	
Range	96–486	
n	8	

TABLE 3

Gastrointestinal transit data for the RTC (min)

Subject	Gastric emptying	Colon arrival	Small intestinal transit	Total transit (h)
Morning dosing				
1	290	575	285	24
2	258	581	323	36
3	> 720	– [b]	– [b]	36
4	195	499	304	24
5	108	390	282	34
6	431	– [c]	> 373	28
7	264	454	190	24
8	259	652	393	24
Median	262	537	295	26
Range	108– > 720	390–652	190–393	24–36
Night-time dosing				
1	375	563	188	21
2	450	888	438	62
3	275	563	288	34
4	163	588	425	18
5	450	875	425	44
6	513	913	400	34
7	153	562	409	13
8	–[a]	–[a]	–[a]	24
Median	375	588	400	29
Range	153–513	562–913	188–438	13–62

[a] Data lost due to equipment malfunction.
[b] RTC remained in the stomach during the study period.
[c] RTC remained in the small intestine during the study period.
NB: Time of awakening for subjects following evening dosing was approx. 500 min.

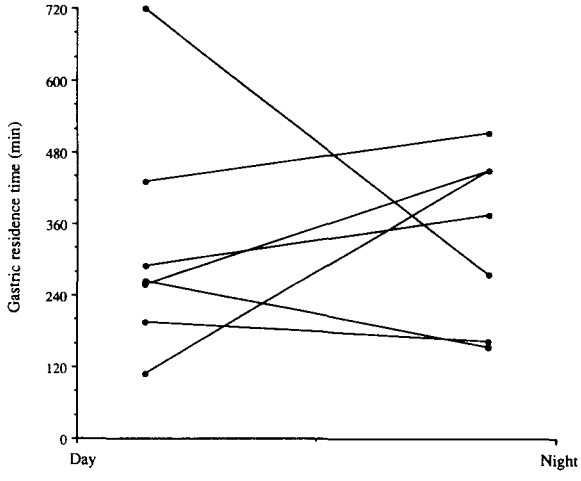

Fig. 1. Gastric residence time of the RTC.

four of the eight subjects tablets still remained in the SI, at the first morning image, after a period of approx. 9.7 h.

Discussion

GI transit of the formulations, although not statistically different, does appear to be extended following night-time administration. The mean GE time for the RTC was 258 min for those dosed at 08:00 and 340 min for those dosed at 22:00, a difference of 82 min, the observed difference being greater than that expected due to natural variation in GI transit of dosage forms (Coupe et al., 1991a).

Two reasons have been postulated for extended gastric residence at night. It is known that the MMC runs more slowly at night (Kumar et al., 1986). This is of direct consequence for the GE of the RTC, since the emptying of the RTC is dependent upon phase 3 contractions of the MMC (Coupe et al., 1991b). The RTC may, however, resist clearance by the phase 3 contractions and remain in the stomach until the propagation of a further MMC approx. 2 h later. An example of this was seen with subject 3 following morning dosing, the RTC remaining in the stomach for the whole of the study period. If this phenomenon was seen during the night, it too would

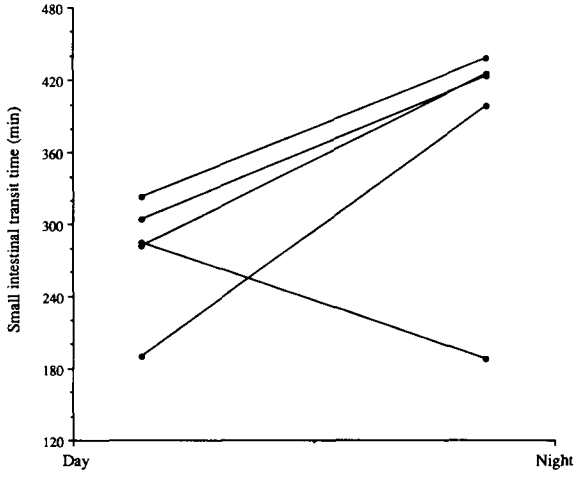

Fig. 2. Small intestinal transit time of the RTC.

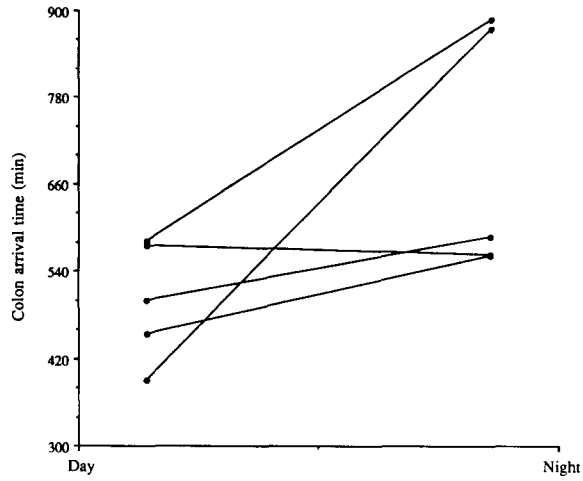

Fig. 3. Colon arrival time of the RTC.

lead to extended gastric residence times. However, examination of the motility traces indicated that for each subject the RTC emptied with the first series of phase 3 contractions following night-time administration. Secondly, Finch et al. (1982) showed that phase 3 of the MMC was detected in the stomach less than in the duodenum during sleep thereby suggesting that phase 3 was absent in the stomach and that it appeared to originate distal to the pylorus on several occasions. This reduction in gastric phase 3 activity could also lead to the extended gastric residence time, as observed in this study.

SI transit time of the RTC was extended after night-time administration in four of the subjects. No significant difference was observed between morning and night-time dosing, however, the mean SI transit time was 296 min (median 295 min) following morning dosing compared to 366 min (median 400 min) after night-time administration. In four of the subjects dosed at night the CA of the tablets was over 600 min, with tablets remaining in the SI at the first morning image. This infers longer transit times than is normally observed following morning administration. Tablets of the size used in this study (7 mm) are known to empty the fed stomach and those that do not empty with food are retained in the stomach until phase 2 and phase 3 contractions of the MMC occur, whereupon they empty into the SI

Subject	Time (mins)	Stomach	Small Intestine	Ileo-caecal Junction	Ascending Colon	Hepatic Flexure	Transverse Colon	Splenic Flexure	Descending Colon	Sigmoid Colon
1	31										
	No overnight images									
	580												
2	30										
	No overnight images									
	582												
3	32										
	No overnight images									
	583												
4	22										
	No overnight images									
	581													
5	31										
	No overnight images									
	584													
6	20										
	No overnight images									
	581													
7	29										
	No overnight images									
	583													
8	32										
	No overnight images									
	580												

Fig. 4. Gastrointestinal transit of five 7-mm tablets for eight subjects. Evening dosing. Each tablet is represented as a vertical bar.

(Coupe et al., 1991b). GE of all the individual tablets would be expected to range from 0 to 240 min following a light breakfast. If the average SI transit time of 180 min (SD 60) (Davis et al., 1986) is added to this, a CA time of between 120 and 480 min is predicted. The longest CA time is 486 min and the shortest 96 min for the tablets dosed in the morning (Table 2). For the night-time administration, tablets were dosed at 22:00 which would give a maximum expected CA time of 06:00, assuming a 480 min transit.

It is known that interdigestive activity during sleep is different to awake activity. The MMC runs more slowly at night (Kumar et al., 1986) and also phase 2 contractions are diminished at night (Ritchie et al., 1980; Kumar et al., 1990); both could result in extended SI transit times. Stagnation of the formulation at the ileo-caecal junction (ICJ) has been reported in subjects after morning administration (Khosla and Davis, 1989; Khosla et al., 1989). Tablets that had spread in the SI were observed to re-group at the ICJ before entering the caecum. If this was to occur during the night then extended SI transit times would be recorded.

It is interesting to note that for all subjects, the RTC only entered the colon after the volunteer had awoken in the morning. It has been observed previously that there is an increase in SI and colon activity during the 1 h preceding awakening (Reynolds et al., 1989). It is possible that the stimulus of awakening might elicit contractions within the small bowel which cause the RTC to pass across the ICJ, however, this requires further investigation.

The total transit time of the RTC was not affected by the time of dosing, the average time from administration to defaecation was approx. 30 h (Table 3). In three of the volunteers the total transit time following night-time dosing was less than 24 h.

Conclusions

The GI transit of 7-mm tablets and a RTC was extended when these preparations were administered just prior to retiring to bed. Both the GE and SI transit appear to be extended but total transit time was not. The precise reason for this is unknown but it is thought to be related to alterations in the contractile activity of the MMC during the night.

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