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Effect of dosing time on the total intestinal transit time of non-disintegrating systems

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Abstract

The total gastrointestinal transit time of nondisintegrating tablets may be affected by dosing time; available literature on this topic is inconclusive. OROS® systems are nondisintegrating osmotically driven tablets that release drug over a period of time during their transit through the gastrointestinal tract and are excreted intact in the feces. Total transit times following morning administration of OROS® systems pooled from various studies ($n = 1163$ systems) showed a distribution with peak frequencies clustering around 24 and 48 h and following night administration ($n = 80$ systems) was found to cluster around 12 and 36 h. The total transit time distribution appears to be different following morning and night administration. However, on reanalyzing the data considering clock time when the tablet was collected rather than time post-administration, most of the difference between the distribution patterns disappeared. This suggested that total transit times after morning or night administration may be related to the bowel movement habits of the study population. Therefore, OROS® systems total transit time were compared to the intrinsic bowel movement pattern of the general population reported in the literature and indeed a good correlation was seen between the two. The total transit time appears to be determined by two factors: the defecation frequency and the probability of its inclusion in the defecation event which is related to its location in the GI tract. A tablet is more likely to be excreted if it is further down in the GI tract. The total transit time data for OROS® systems suggest that with the morning dosing the tablet is more likely to be excreted in the bowel movement the next morning. With the night time dosing the tablet may not be far enough in the colon to be excreted in the next morning bowel movement and therefore, it is more likely to be excreted the following morning. © 2000 Published by Elsevier Science B.V.

Keywords: Transit time; OROS® systems; Non-disintegrating tablet

1. Introduction

OROS® systems are nondisintegrating osmotically driven tablets that release drug over a period of time during their transit through the gastrointestinal tract and are excreted intact in the

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feces. Transit time of these tablets through the gastrointestinal (GI) tract could be affected by several factors including dosing time. The total intestinal transit time of nondisintegrating markers and tablets has been reported in several studies (Coupe et al., 1992a,c; Price et al., 1993a) and has been reviewed by Coupe et al. (1992b). These studies report a very high degree of inter and intra-subject variability in the total transit time. Most of these studies reported the total transit time following morning administration and few studies have compared morning and night administration. The effect of dosing time (morning vs. evening) was explored in two studies by Coupe et al. (1992a,c) with nondisintegrating tablets and radiotelemetric capsules. These studies showed that with nighttime dosing both gastric emptying and colon arrival time was slower compared to morning dosing. The diurnal difference in the total intestinal transit, however was not conclusive with only one study demonstrating statistically significant difference between night and morning administration. These studies were conducted with small number of subjects ($n = 6$ and 8) and statistical inferences from the results could be misleading due to low power. Due to high inter- and intra-subject variability, a large number of subjects are needed to properly characterize and compare the distribution pattern. Several studies have also evaluated the effect of dietary intake and have reported contradictory results. Price et al. (1993a,b) observed high variability in the transit time despite identical diets and suggested that this variability to be probably due to some intrinsic factor. In this report, we present the total transit time data of OROS@ systems administered in the night compared to morning administration. Also the OROS® systems total transit time relation to the intrinsic bowel movement pattern of the general population will be examined.

2. Methods

Two-open label, randomized, crossover studies were conducted in healthy male volunteers. In Study 1, 12 subjects (21–42 years) were given a single OROS® system on three separate occasions. In this study two formulations (differing in drug release pattern) were studied; formulation A was administered in the morning (08:00 h) or at night (22:00 h) and formulation B was administered only at night (22:00 h). In Study 2, 14 subjects (18–45 years) were administered OROS® system C at night (22:00 h) for 5 consecutive days.

Before dosing, each OROS® system was uniquely marked. All subjects received the same dinner at 17:00 h and a light snack 15 min prior to dosing. All stools were collected for 72 h after OROS® system administration, and the date and time of each defecation were recorded. As soon after defecation as possible, each stool was carefully searched in an airflow hood to recover the OROS® systems. Total transit time was calculated as the difference between the dosing time and the time the OROS® system was excreted.

2.1. Results and discussion

In Study 1, of the 36 systems administered, 30 were recovered; all 12 of those administered in the morning and only nine of each formulation administered at night. The total transit times for the morning dosed OROS® systems were clustered around 24 h (median 26.5 h; range 20–32 h). However, the total transit time of the systems administered at night showed greater variability compared with morning administration (median 21 h; range 7–61 h) (Fig. 1A).

In Study 2, a larger number of OROS® systems were given at night. Of the 70 OROS® systems administered at night, 62 were recovered. The total transit time ranged from 9 to 64 h (median 31 h), and the transit time distribution curve had two peak frequencies at 9–11 and 34–36 h. The night administration data pooled from Study 1 and Study 2 ($n = 80$ tablets) are shown in Fig. 1B; peak frequencies clustered around 12 and 36 h post dosing.

As expected degree of variability in the total intestinal transit time was high. Therefore, to evaluate the effect of dosing time on total transit time, the combined (Study 1 and 2) night administration data were compared with the larger ALZA data base of OROS® system total intestinal transit

times pooled from various studies following morning administration ($n = 1163$ tablets) (Fig. 2A). The total transit time distribution pattern following morning OROS® system administration appeared to be consistent with that reported in the literature (Hinton et al., 1969) for other non-disintegrating systems. Similar to the night administration data, the morning administration data also exhibited a distribution with two peak frequencies. The peak frequencies for the morning dosing were clustered around 24 and 48 h post dosing versus 12 and 36 h for the night-time dosing. The transit time distribution pattern therefore appears clearly different following morning and night administration (Fig. 2A). Interestingly, when the same data were reevaluated considering the clock time instead of hours post dosing (Fig. 2B), the high-frequency peaks from two dosing times overlapped.

Several studies have evaluated the effect of dietary intake on transit times and have reported contradictory results (Coupe et al., 1992b). Price et al. (1993a,b) observed high variability in the total transit time despite identical diets and suggested that this variability to be probably due to some intrinsic factor. To explore whether the total intestinal transit time is related to some intrinsic factor, the OROS@ system transit time in relation to intrinsic bowel movement was examined. An epidemiology survey was conducted in 1987–1989 (Heaton et al., 1992), in which men and women were questioned about their bowel habits in terms of defecation timing and frequency. In terms of defecation timing, the majority of defecations (50%) occurred in the early morning between 06:00 and 09:00 h; very few defecations occurred at night, especially between 01:00 and 05:00 h. In general the OROS® system total transit time data appear to be related to the bowel movement habits of the study population — regardless of the dosing time, about 50–60%, of the OROS@ systems were collected in the morning hours. Fig. 2B shows the similarity between 24 h defecation data from the survey and the OROS@ system total transit time frequencies.

It has been reported that there is decreased motility in all parts of the GI tract during sleep and on awakening in the morning there is significant increase in small intestine and colonic motility that is responsible for the morning bowel movement (Reynolds et al., 1989; Narducci et al., 1987). Consistent with this Coupe et al. (1992a,c)

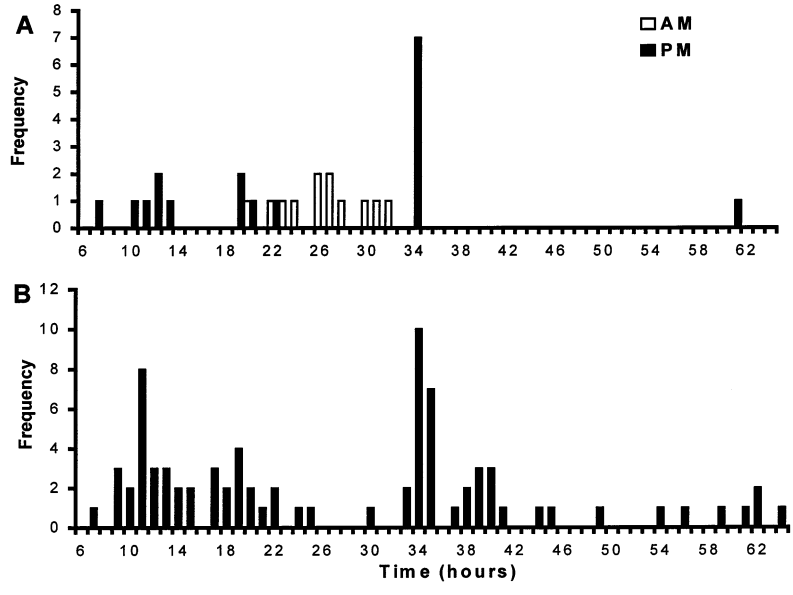

Fig. 1. OROS@ system total transit time frequency from (A) Study 1 following morning ($n = 12$ systems) and night (n = 18 systems) administration; (B) Study 1 and Study 2, night administration pooled together ($n = 80$ systems).

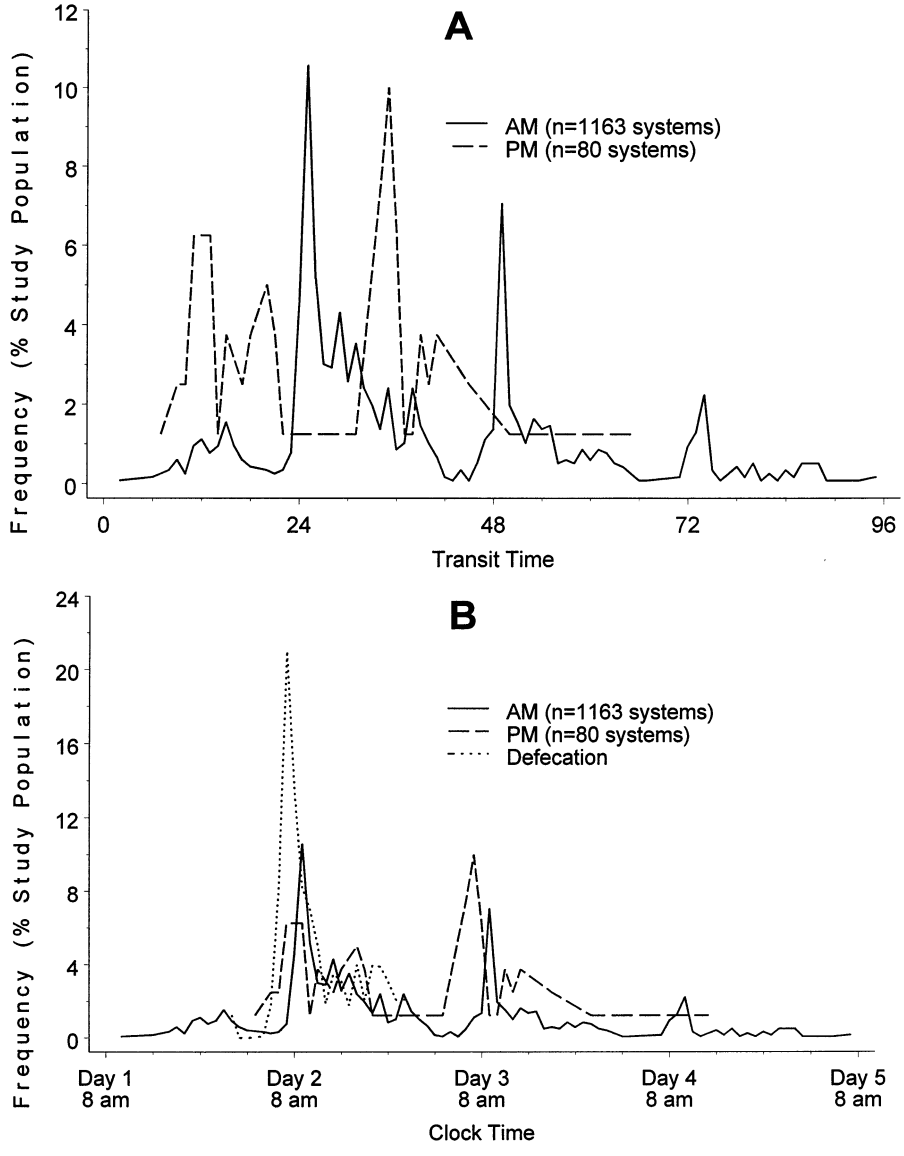

Fig. 2. OROS® system total transit time frequency following morning ($n = 1163$ systems) and night ($n = 80$ systems) administration with respect to (A) total transit time and (B) clock time; defecation frequency from a population survey (Heaton et al., 1992) is also shown in B.

observed slowing of gastric emptying and prolongation of colonic arrival time following nighttime dosing. The increased motility in the morning may cause a tablet present in the colon to be excreted during the bowel movement in the morning. However, the total transit time, i.e. time of tablet's ingestion to its excretion in the feces is determined by two factors: the defecation frequency and the probability of its inclusion in the defecation event. Defecation frequency in a large population has been studied; in self reported bowel habit surveys (Heaton et al., 1992; Everhart et al., 1989), 60–70% of the study population reported once daily defecation. About 20–25%

reported less frequent defecations and a small percentage (about 5%) reported more than one defecation a day. The probability of a tablet's inclusion in a defecation event is related to its location in the GI tract; a tablet is more likely to be excreted if it is further down in the GI tract. Thus the probability is higher if the tablet was ingested several hours before the defecation. In addition, the timing of the last defecation prior to tablet ingestion is also important since it would affect the timing of the next defecation and therefore the total transit time. It appears that the total transit time data would be more meaningful if the defecation events prior to tablet ingestion and up to tablet excretion are also reported. In Fig. 2, the first peak frequency at 24 h is larger than the second peak at 48 h for the morning dosing and the second peak at 36 h is larger than the first peak at 12 h for the evening dosing. This is consistent with the notion that probability of the tablet being excreted is higher if it was ingested several hours before the defecation. With the morning dosing the tablet is more likely to be excreted in the bowel movement the next morning (approximately 24 h after dosing). With the night time dosing the tablet may not be far enough in the colon to be excreted in the next morning bowel movement given the slowing of the gastrointestinal tract and therefore, it is more likely to be excreted the following morning (approximately 36 h after dosing).

In two studies conducted by Coupe et al. (1992a,c), with morning administration the median total transit times were 24 h (range 12–30 h) and 26 h (range 24–36 h). After night administration, the median total transit times were 35 h (range 15–41 h) and 29 h (range 13–62 h). Based on these median values, a significant difference in total transit time between morning and night administration was reported in only one of the studies (Coupe et al., 1992c). Comparison of median values following morning and night administration in Study 1 (which had comparatively small number of subjects, $n = 12$) as done by Coupe et al. (1992a,c) would have concluded that dosing time has no effect on total transit time. To fully characterize the total transit time distribution pattern, a small number of subjects are not sufficient and comparison of the mean or the median value does not reflect the different distribution patterns following the morning and night administration.

In conclusion, the distribution of total transit times of the non-disintegrating OROS® systems following morning and night dosing are different. If dosed in the morning, a tablet is more likely to be excreted the next morning and if dosed in the night, it is more likely to be excreted in the morning the day after. The total transit times distribution pattern following both morning and night administration appears to be related to the bowel movement pattern in the general population.

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