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Gastro-intestinal transit of a multiple-unit formulation (metoprolol CR/ZOK) and a non-disintegrating tablet with the emphasis on colon

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Abstract

The main aim of the present study was to compare the transit through the entire gastro-intestinal channel of a membrane-coated, multiple-unit system containing metoprolol and a single-unit placebo tablet using gamma-scintigraphy. The two formulations were simultaneously administered, together with a breakfast (2800 kJ), to eight healthy male volunteers. The mean gastric emptying time for the pellets was 3.6 (range 1.5–5.0) h on average and the mean gastric emptying time for the tablet was 9.6 (range 3.3–(14–24)) h. This difference was statistically significant. The mean transit through the small intestine, 3.1 (range 1.5–5.7) h and 2.0 (range 1.0–3.3) h for the pellets and the tablet respectively, did not differ significantly between the formulations. The pellets had a longer residence time in the colon in all subjects compared with the tablet. The mean colon transit time was 28 (range 6.0–48) h on average for the pellets and 15 (range 3.8–26) h for the tablet. The tablet was expelled 26 (range 9.5–42) h after intake on average, whereas the pellets remained for a significantly longer time period (mean 35, range 10–55 h). The desired extended-release properties and metoprolol absorption was obtained throughout the entire gastrointestinal (GI) tract.

Keywords: Metoprolol; Gamma scintigraphy; Pellets; Gastrointestinal transit

1. Introduction

Multiple-unit pellets and non-disintegrating, single-unit tablets are two widely used formulation principles for modified-release preparations. The residence time in different parts of the gas-

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trointestinal (GI) tract is often an important feature of such formulations. The gastric emptying and small intestinal transit of single- and multiple-units has been compared in several studies (Christensen et al., 1985; Clarke et al., 1993; Davis et al., 1984; Hardy et al., 1985). Until now the colonic transit of the two types of formulation has, however, been studied on a far smaller scale. The transit through this part of the GI tract is of special importance for modified-release formulations which are designed to utilise the colon for drug absorption or for local treatment in the colon.

Metoprolol, a β_1-selective adrenoceptor blocker used for the treatment of hypertension and other cardiovascular disorders, is a suitable candidate for extended-release (ER) administrations as a result of its good absorption in the entire GI tract, rapid elimination and a well-defined relationship between the beta-blocking effect and plasma drug concentration (Kendall et al., 1991). Such formulations have also been developed, as both multiple-unit pellets and single-unit tablets, which provide similar plasma concentration profiles (Sandberg et al., 1993). The multiple-unit formulation, denoted metoprolol CR/ZOK (Seloken ZOC®, Toprolol XL®), was included in the present study. This formulation provides a continuous and a relatively constant drug release over a period of approximately 20 h, thus resulting in even plasma concentration and effect profiles after dosing once daily (Kendall et al., 1991).

The main objective of the present investigation was to study the transit time in all parts of the GI tract of the metoprolol pellets in comparison with a non-disintegrating tablet. Gamma-scintigraphy, the method of choice for GI transit studies, was utilised for this purpose. The power to detect differences between the formulations was maximised in the present study by the simultaneous administration of the two formulations to each subject. A second objective was to study the absorption of metoprolol in relation to the localisation of the pellets using measurements of metoprolol plasma concentrations.

2. Material and methods

2.1. Study formulations

The metoprolol CR/ZOK formulation contains thousands of membrane-coated metoprolol succinate pellets embedded in a rapidly-disintegrating tablet (Sandberg et al., 1988). Approximately two-thirds of the pellets in the tablets included in the present study contained metoprolol and they were identical to those used in the marketed formulation. Each tablet contained 95 mg of metoprolol succinate. The remaining one-third of the pellets were labelled with ^{51}Cr. These pellets contained no metoprolol but their diameter (0.4–0.6 mm), density (1.2–1.3 g/cm^3) and composition of the outer membrane were essentially the same as those of the drug containing pellets. The labelled pellets were designed to obtain no release of the radionuclide and they were manufactured in specially developed small-scale equipment. This has been described in detail elsewhere (Lundberg et al., 1988). The leakage of ^{51}Cr from the pellets was also tested after compression to tablets to ascertain the suitability of the labelling as a marker for the GI transit of the pellets (Lundberg et al., 1988). The radioactivity of the pellet formulation did not exceed 2 MBq ^{51}Cr at the time of administration.

The non-disintegrating placebo tablet was round (Ø = 9 mm), corresponding to the size of another once daily tablet of metoprolol which is based on the osmotic pump principle. It was labelled with ^{99m}Tc as a complex with diethylenetriaminepentaacetic acid (DTPA). This tablet was coated with an inert and insoluble polymeric material in order to prevent the release of the radionuclide. The leakage of the radionuclide was less than 5% after 24 h in a phosphate buffer at pH 6.8. The radioactivity of the non-disintegrating tablet did not exceed 5 MBq ^{99m}Tc.

The dissolution of metoprolol was measured and compared with unlabelled metoprolol CR/ZOK by using the rotating paddle method (USP II) with a stirring rate of 100 rpm. A phosphate buffer solution (500 ml), pH 6.8 and thermostated to 37°C, was used as the test medium. Metoprolol was measured by UV-spectrometry.

2.2. In vivo study

This study was approved by the Swedish National Board of Health and Welfare and reviewed by the local Ethics Committee at the University of Göteborg and the Isotope Committee at Sahlgren's Hospital, Göteborg. The written informed consent of all volunteers was obtained before the study started.

Eight healthy, young (24–27 years), male subjects of normal weight (67–84 kg) and height (174–190 cm) were included. On the morning of the study day, each subject took two labelled metoprolol succinate CR/ZOK tablets 95 mg and one non-disintegrating placebo tablet simultaneously with 200 ml of tap water. The study drugs were administered immediately after a standardised breakfast of 2800 kJ (bread, butter, cheese, cereals, milk, orange juice). Standardised meals were also served 4 h (lunch), 6 h (snacks), 10 h (dinner), 13 h (snacks), 24 h (breakfast), 28 h (lunch), 30 h (snacks), 34 h (dinner) and 36 h (snacks) after drug intake. No other intake of food or fluid was permitted from 10 h before administration to 48 h after drug intake. The use of tobacco, snuff, alcohol, prescribed and over-the-counter drugs was not permitted prior to and during the study days. Plasma samples and scintigraphic measurements were frequently collected at 0–14 h and 24–36 h after intake. Additional scintigraphic measurements were made at 48, 72 and 96 h. Bowel habits were also registered during the study days.

The scintigraphic measurements were performed by a gamma camera system up to 48 h and by a whole body counter (Alpsten et al., 1985) immediately after dosing, at 72 h and 96 h. The latter measurements were primarily made in order to control the total emptying of radionuclides from the body. Measurements of ^{51}Cr using the whole body counter have been described elsewhere (Alpsten et al., 1985). Gamma camera images of 60–240 s duration were taken with the subjects standing in a standardised position between two cameras. Each image was collected in 4096 pixels (64 × 64 matrix) and medium-energy parallel hole collimators were used. In order to determine the transit of the multiple-units, regions of interest (ROI) were defined for the stomach and the colon in the gamma camera images. The counts from ^{51}Cr were determined for these ROI as the geometric mean of the anterior and posterior image after correction for background activity. The different transit times for the pellets were determined by moment analysis (von Hattingberg, 1984; Podczeck et al., 1995) according to the following formula;

$$MT = \frac{\int \Delta A_i[(t_{i-1} + t_1)/2)}{100}$$

where A is the cumulative percentage of pellets transported from one region to another at different times t, ΔA_i is the difference between time t_{i-1} and t_1 and MT is the mean transit time corresponding to the most probable transit time for an individual pellet. The obtained transit time MT is a mean estimate which takes account of all the obtained data in contrast to single-point estimates such as the time when 50% of the material has been transported from one region to the next ($t50\%$). In a linear process, this equals $t50\%$, but the use of moment analysis is not dependent on the kinetics of the studied process. The mean gastric emptying time (MGET), mean colon arrival time (MCAT) and mean total transit time (MTTT) of the pellets were calculated by moment analysis from the inverted gastric emptying-, colon arrival and inverted colon emptying-time curves, respectively. According to the additivity of mean times determined by moment analysis, the mean small intestine transit time (MSITT) was calculated as the difference between MCAT and MGET and the mean colon transit time (MCTT) was calculated correspondingly from the difference between MTTT and MCAT. The data obtained from the whole body counter was also included in the calculation of MCTT and MTTT. Gastric emptying, small intestinal transit, the time of arrival in the ileocaecal region, colon transit and the total transit time for the non-disintegrating tablet were estimated as the midpoint between the time of the last observation in one ROI and the time of the first observation in the subsequent ROI. Ninety-five percent confidence intervals of the difference be-tween the formulations were calculated for all transit times.

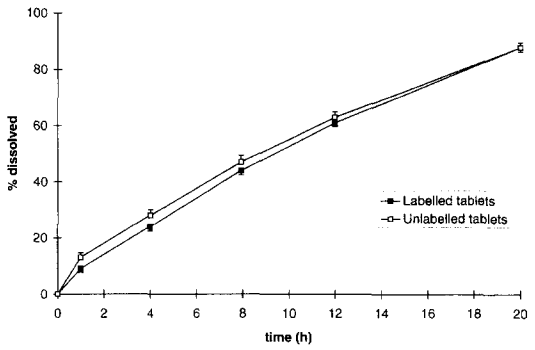

Fig. 1. Mean (SD) cumulative percent metoprolol released at different times for the experimental tablets with labelled pellets and the unlabelled metoprolol CR/ZOC product ($n = 6$).

The determination of metoprolol concentrations in plasma was performed by gas chromatography and electron-capture detection (Ervik et al., 1986). The minimum determinable concentration was 10 nmol/l. The area under the metoprolol plasma concentration-time curve (AUC) was determined from 0 to 36 h using the trapezoidal method and extrapolated to infinity using of the elimination rate constant (K_e) determined by linear regression from the terminal part of the plasma concentration time curve. The cumulative absorption-time profile was calculated from the plasma concentration data according to the Wagner–Nelson method (Wagner and Nelson, 1963).

3. Results and discussion

3.1. In vitro dissolution

The mean in vitro dissolution profiles of metoprolol for the investigational tablets containing labelled pellets and a commercial tablet (Seloken ZOC®) with unlabelled pellets are given in Fig. 1. The drug dissolution proceeded at an almost constant rate up to 20 h. The in vitro release rate of metoprolol from the labelled tablets was essentially the same as that from the unlabelled tablets. The experimental CR/ZOK formulation in this study is thus representative of tablets obtained in full-scale production.

3.2. Gastro-intestinal transit

The mean transit times and the 95% confidence interval for the difference between the pellets and the single-unit tablet in all parts of the GI tract are given in Table 1. The multiple-unit tablets had disintegrated within 30 min after intake, whereas all the single-unit tablets remained intact throughout the entire GI tract.

After an initial period of approximately 2–3 h with no emptying of the pellets in most subjects, the pellets moved rapidly into the small intestine in an approximately zero order rate process. A similar delay in gastric emptying has also been shown for larger pellets (0.8–1.1 mm) given together with a radiolabelled meal (Coupe et al., 1993). In this particular study, it was shown that the pellets were emptied at a different rate thathe food in most cases, despite rapid mixing and location in the distal stomach. This discrimination between ground food and pellets thus also appears to occur in the case of smaller pellets like the metoprolol beads.

The mean MGET for the pellets was 3.6 h. Since the gastric emptying-time curve was approx-

Table 1
Mean (SD) GI transit times (h) for the pellets and the tablet and 95% CI for the differences of the transit times between the two formulations ($n = 8$)

	Gastric emptying (MGET)		Small intestine transit (MSITT)		Colon transit (MCTT)		Total transit (MTTT)	
	Pellets	Tablet	Pellets	Tablet	Pellets	Tablet	Pellets	Tablet
Mean (S.D.)	3.6 (1.2)	9.6 (6.2)	3.1 (1.4)[a]	2.0 (1.0)	28.4 (14.5)	15.2 (8.7)	35.1 (15.6)	26.3 (11.8)
95% CI	−10.7–(−1.3)		−0.3–1.9		5.5–20.9		0.02–17.5	

[a] $n = 6$, small intestinal transit occurred during the night hours in two subjects when no images were recovered.

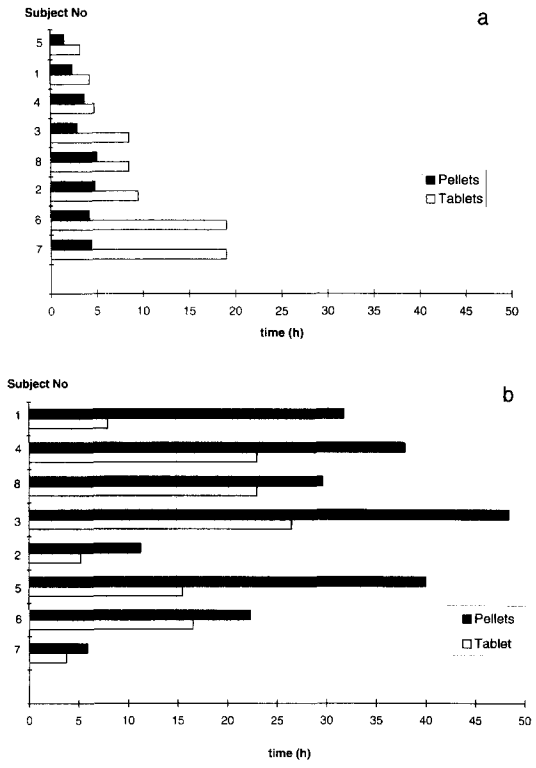

Fig. 2. (a) Gastric emptying (MGET) and (b) colon transit (CTT) of the pellets and the tablet for individual subjects.

imately linear, about 50% of the pellets had been evacuated from the stomach at that time. The mean gastric emptying time for the tablet was 9.6 h. The tablets were emptied from the stomach later than the pellets in all subjects (see Fig. 2a). The variability between subjects was also much greater for the single-unit tablet compared with the pellets. For example, the tablet was emptied between 3 h and more than 14 h after intake, whereas the corresponding range for the pellets was 2–5 h. The faster and less variable gastric emptying of the pellets compared with the tablet was well in line with previous data (Davis et al., 1986). Tablets are most often emptied in connection with the powerful contractile movements of the GI tract which appear under fasting conditions, the housekeeper waves, whereas the emptying of pellets is less dependent on the digestive mode. The very long gastric residence time for the tablets obtained in some subjects can be explained either by the absence of housekeeper waves during the study day due to frequent food intake or to the fact that the tablets were retained in the stomach during one or more housekeeper waves.

The mean small intestinal transit time was 3.1 and 2.0 h for the pellets (MSIT) and the tablet, respectively. This is approximately in accordance with the small intestinal transit times reported for other formulations (Davis et al., 1986). Both formulations appeared to be transported more rapidly through the upper part of the small intestine than through the terminal region. After the transit through the small intestine, the pellets appeared to gather in the ileocaecal region before moving forward in the colon in most subjects. Due to the prolonged gastric residence time, the single-unit tablet arrived in the colon after the pellets in all subjects. The mean colon arrival time was 6.7 and 11 h for the tablet and the pellets, respectively.

In the colon, the pellets were slowly dispersed over a wide area. In contrast, the tablet moved more intermittently in most subjects. After being stationary for several hours, the tablet could move long distances between two measurements, e.g. from the caecum to the descending colon within 2 h. The transport of pellets through the colon was slower in all subjects compared with the tablet (see Fig. 2b). The mean transit time (MCTT) was 15 h for the tablet and 28 h for the pellets, respectively. It has been suggested that the segmenting pattern of motility in the colon causes the retention of smaller particles within the haustra, while larger particles are able to pass more rapidly through the bowel (Steed et al., 1989). Previous experimental evidence of a difference in colonic transit between small multiple-units and single-unit formulations obtained after concomitant administration is very limited. One comparative gamma-scintigraphic study of pellets (0.5–1.8 mm) and a single-unit capsule (23×9 mm) has revealed a similar difference (Hardy et al., 1985). In addition, a study comparing the colon transit of pellets (0.5–1.8 mm) and 6 mm particles also revealed a clear tendency towards slower transit for the smaller particles (Proano et al., 1990). In contrast, in a comparative study of transit through the ascending colon, no difference was found between pellets (0.2 mm) and tablets (5–8 mm)

(Watts et al., 1992). The present study thus provides support for the hypothesis that small particles are transported at a slower rate than larger particles. Other formulation properties such as shape, surface properties and density may also play a role.

The individual results showed a large variability for both types of dosage form in the present study. In the two subjects with very rapid colon transit (4–5 h) for the tablet, the transit of the pellets was also fairly rapid (6 and 11 h). No correlation was found in the present study between the bowel-emptying frequency and colon transit. The physiological reasons for the large inherent variability in colon transit are as yet poorly understood. Factors that have been suggested as having an impact such as meals, especially fatty acid and fibre content, and physical activity (Sarna, 1991) were standardised in the present study.

The mean regional distribution of the pellets in the colon at six different times is shown in Fig. 3. After entry into the colon, the pellets were mainly located in the ascending colon for up to 14 h after intake. Thereafter, the colon transversum stored the main part of the pellets for up to a minimum of 48 h. The similar distribution of small particles (Ø = 0.5–1.8 mm) in the colon has previously been reported and has led to a hypothesis that the ascending and transversal colon are the reservoir for solid material, whereas the more distal parts function mainly as a conduit (Proano et al., 1990). Thus, the ascending and transversal colon are the most important sites with respect to drug delivery and absorption for multiple-unit ER formulations.

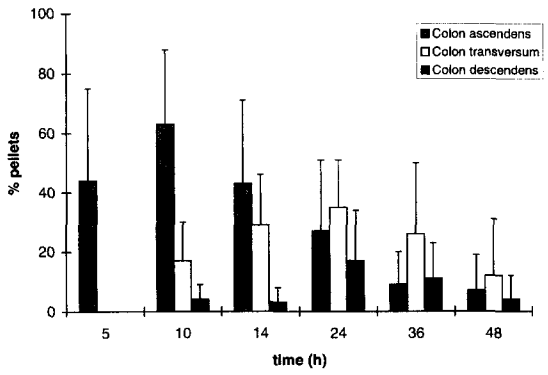

Fig. 3. The mean (SD) distribution of the pellets in different parts of colon at 5, 10, 14, 24, 36 and 48 h after intake ($n = 8$).

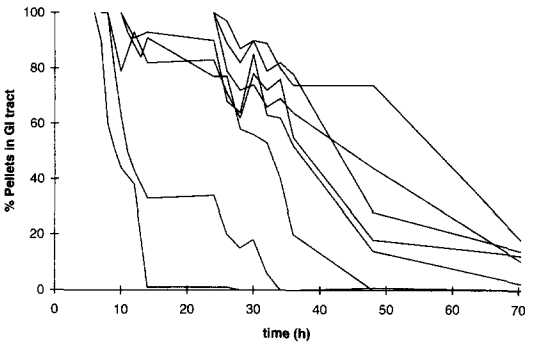

Fig. 4. Percentage pellets remaining in the GI tract at different times for individual subjects.

The mean total transit time was longer for the pellets (MTTT) than for the tablets. The total transit time showed a large interindividual variation with a range of 10–56 h for the pellets and 9.5–42 h for the tablet, mainly as a result of the variable colon transit. In seven of the eight subjects, most of the pellets still remained in the colon at the time of tablet emptying. The individual emptying profiles for the pellets are depicted in Fig. 4. The emptying of the pellets from the GI tract proceeded during several defecations. The emptying of pellets was completed after 96 h in all subjects.

3.3. Drug absorption

The individual absorption-time profiles for metoprolol is shown in Fig. 5 together with depictions of the gastric emptying, colon arrival and colon emptying times for the pellets. The absorption appeared to be independent of the localisation of the pellets. On average, approximately 50% of the drug was absorbed when the pellets were located in the colon, at approximately the same rate as in the more proximal parts. The mean absorption-time profile and the in vitro drug dissolution were very similar, in accordance with previous findings relating to metoprolol CR/ZOK (Sandberg et al., 1991).

The plasma concentration profile was rather even with a mean peak level of 139 nmol/l obtained on average after 11 h and a mean plasma concentration of 83 nmol/l after 24 h. This was well in accordance with previous data for metoprolol CR/ZOC (Sandberg et al., 1988, 1991).

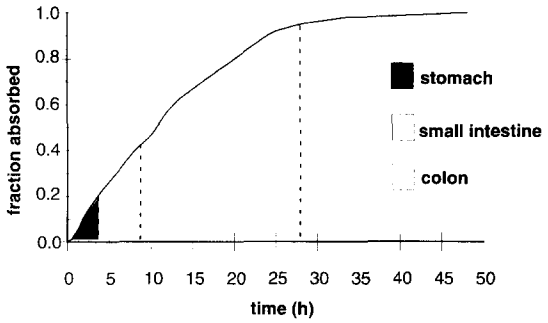

Fig. 5. Individual cumulative fraction of metoprolol absorbed at different times also including depictions of mean transit times of the pellets in the different parts of the GI tract determined by statistical moment analysis ($n = 8$).

4. Conclusions

This study verified that the gastric emptying of a multiple-unit system is faster and more predictable than the emptying of a single-unit tablet when administered together with a meal. Furthermore, small pellets appear to be favourable compared with tablets in terms of residence time in the colon and in cases where a spread of the dose in the colon is important. However, total transit times of less than 24 h can occur for both types of system and the variability in colon transit is of similar magnitude. Finally, metoprolol CR/ZOK is an appropriate once-daily formulation, since the desired drug-release properties and the absorption of metoprolol are obtained throughout the entire GI tract.

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