Dissolution Rate and Transit Times of Technetium-99m DTPA-Labeled Tablets

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In this study we demonstrate that the dissolution rate and gastroduodeno-cecal transit time of radiolabeled tablets of theophylline can be determined in vivo using technetium-99m (^{99m}Tc). Six healthy male volunteers ingested a tablet containing 300 mg of theophylline mixed with 3.7 MBq of [^{99m}Tc]DTPA. Anterior and posterior scintigraphic views of the abdomen were collected serially over 8 hr, after which a 200-ml solution containing 37 MBq of [^{99m}Tc] pertechnetate was ingested in order to visualize the contours of the stomach. The in vivo activity contained in the tablet was calculated from the scintigraphic views after correction of background activity, radioactive decay, and depth attenuation. The dissolution rate of [^{99m}Tc] DTPA was also measured in vitro and compared with the dissolution rate of theophylline. The results showed close dissolution rates between [^{99m}Tc]DTPA and theophylline in vivo ($T_{1/2}$ 184 min and 176 min, respectively), and a faster early dissolution rate of [^{99m}Tc]DTPA in vitro ($T_{1/2}$ 92 min versus 156 min for theophylline). The mean gastroduodenal and duodenocecal times were 72 ± 25 min (m ± s.d.) and 245 ± 15 min, respectively. Scintigraphic imaging of labeled formulations with ^{99m}Tc present useful applications in pharmaceutics and pharmacology.

J Nucl Med 28:1199–1203, 1987

The emergence of new pharmaceutical formulations has raised interesting questions in the study of kinetics of release and absorption of drugs. In vitro dissolution tests can be easily performed, but their results do not necessarily apply to in vivo conditions, especially for gastrointestinal formulations. For instance, the release can be pH-dependent or a succession of degradations can occur prior to the absorption. Therefore, in vivo studies appear to be highly desirable. Because technetium-99m DTPA ([^{99m}Tc]DTPA) can be incorporated easily into tablets, it becomes possible to monitor in vivo the anatomic position and the release of activity of a labeled tablet (*1–6*).

In this study we compare the dissolution rates of [^{99m}Tc]DTPA-labeled tablets of theophylline in vitro and in vivo. We also show that during the same experiment the absorption kinetics of theophylline can be calculated as well as the transit time of the tablet in the stomach and in the small intestine using ^{99m}Tc as the sole radionuclide.

Received Jul. 15, 1986; revision accepted Dec. 9, 1986.

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MATERIALS AND METHODS

Preparation of Tablets

After adsorption with an aliquot part of lactose, a 3-ml solution of [^{99m}Tc]DTPA was dried for 15 min in an oven at 90°C. The resulting powder was mixed with theophylline monohydrate (300 mg), hydroxypropylmethylcellulose (two different grades), lactose, silicon dioxide, and magnesium stearate. Tablets of nominal weight 535 mg were compressed on an alternative Korsch Eko, using adequate oblong punches, just before time of administration, resulting in tablets with a nominal activity of 100 μCi (3.7 MBq) and a 16.4 × 7.3 × 5.1 mm size.

In Vitro Dissolution Tests

The USP paddle method was used with a rotation speed of 120 rpm in a phosphate buffer at pH 7.2. The dissolution rate of theophylline from the labeled tablets was compared with theophylline release from the conventional commercial product (Theostat R300®) by measuring the absorbance value at 272 nm. The dissolution rate of DTPA was also evaluated by counting in a gamma well-counter the activity of periodically withdrawn samples.

In Vivo Studies

Six healthy male volunteers (age 24–28) were included in the study after signing an informed consent. Approval of the protocol was obtained from the committee on ethics at our institution.

In order to facilitate repositioning during the study, two radioactive markers were taped on the skin of each volunteer's flank. After overnight fasting, each subject (while standing upright) swallowed a radioactive tablet with 200 ml of water. One-minute anterior and posterior scintigraphic views were collected with a large field-of-view scintillation camera equipped with a high resolution low energy parallel-hole collimator. The spectrometry was set on the 140 keV gamma peak with a 20% window. During the first 4 hr views were taken at 15-min intervals in each volunteer. Then a 1-hr break was allowed during which a standard light lunch was served. The study resumed with sequential views taken every 30 min then every 60 min until the end of the study, 8 hr after starting time. At 24 hr a view of the stomach was taken after drinking 200 ml of water labeled with about 37 MBq of [^{99m}Tc]pertechnetate.

All views were stored as 64 × 64 matrices in a dedicated computer. The focal activity of the tablet could be easily seen on all views until it reached the colon. In order to calculate the amount of activity present in the tablet, the surrounding background activity had to be subtracted (*7*). The tablet activity was calculated within a 4 × 4 region of interest positioned over the tablet image. It was corrected for background activity calculated within a surrounding 11 × 11 region of interest. This process was performed on both the anterior and posterior views. Finally the "true" tablet activity was obtained after correction for the gamma ray depth attenuation by calculating the geometric mean (GM) value on the corresponding anterior and posterior views (*8*). All values were corrected for radioactive decay.

Blood samples for theophylline dosage were taken at 1-hr intervals during the entire experiment. From these values the absorbed dose and then the in vivo kinetic of release of theophylline were calculated.

RESULTS

The in vitro dissolution of DTPA and theophylline were in good agreement with a mathematical model of hydrophilic matrix release. The in vitro and in vivo kinetics of release of theophylline were highly correlated ($r = 0.996$, $n = 9$) (Figs. 1 and 2) with $T_{1/2}$ of 176 and 156 min, respectively. In vitro, the early release of DTPA was faster than theophylline; then both remained parallel. $T_{1/2}$ was 92 min for DTPA.

With the help of (a) the two skin markers used to realign all the views, (b) the image of the stomach as shown by the solution of pertechnetate ingested at 24 hr, and (c) the colonic activity seen at 8 hr, the anatomical position of the tablet (i.e., in the stomach, small intestine, or colon), could be retrospectively traced during the entire study. Thus, it appeared that immediately after swallowing, the tablet was deposited at the bottom of the stomach, close to the pyloric antrum (Fig. 3). It did not move inside the stomach until it was suddenly expelled into the duodenum. The mean gastroduodenal time was 72 ± 25 min (mean ± s.d.; Table 1). Movement in the small intestine was hectic. During the 1-min acquisitions the tablet was usually still but sometimes rapid displacement could be observed. After entering the cecum (Fig. 3) all tablets deposited a large spread of activity, unveiling the colic borders. In most cases the ascending colon was clearly seen but only in three cases did the activity reach the left colic flexure. The duodenocecal time was 245 ± 15 min (Table 1).

DISCUSSION

This study shows that the in vivo dissolution rate of a radiolabeled tablet and its gastroduodenal and duodenocecal times can be calculated by scintigraphy. Measurements of the digestive transit times has been performed previously, using radio-opaque pellets (*9*). In these conditions only the overall transit time could be measured and the radiation dose was not negligible.

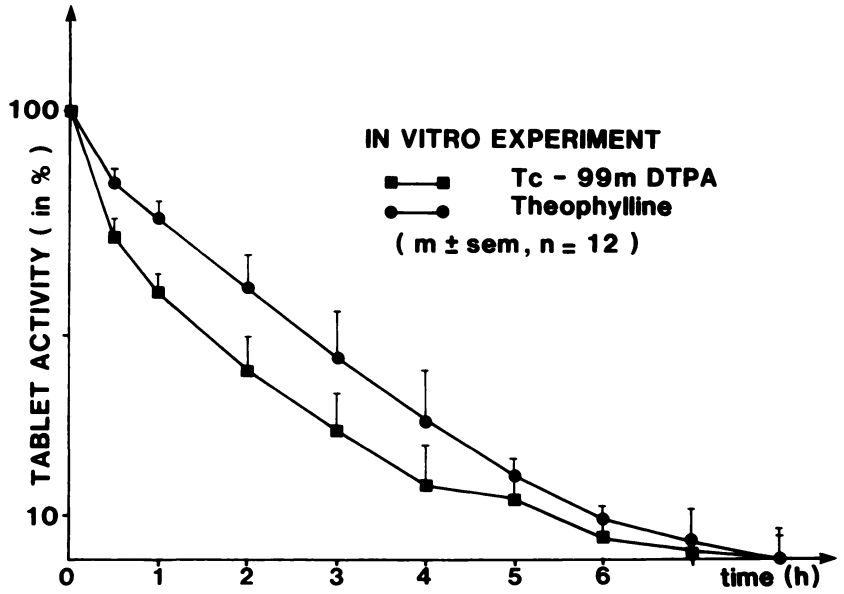

FIGURE 1
Kinetic release of [^{99m}Tc]DTPA and theophylline in vitro.

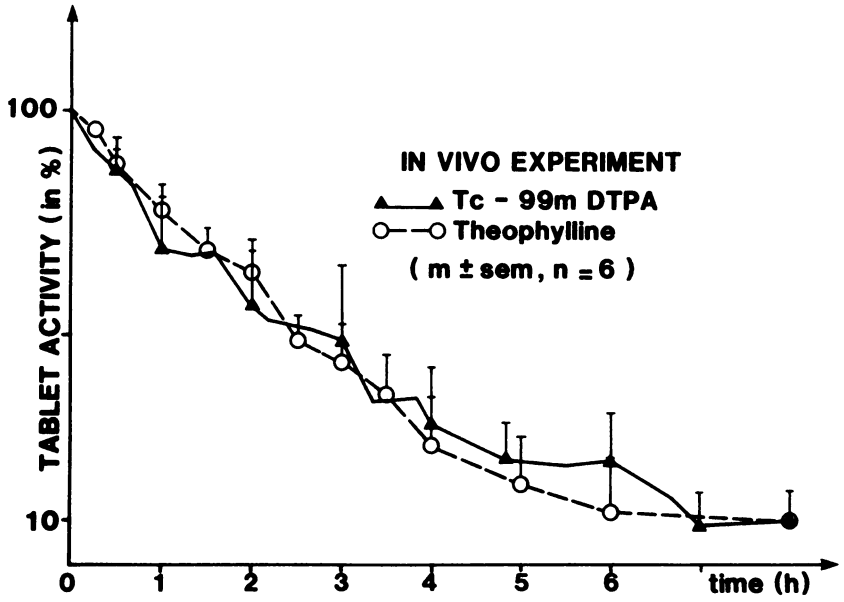

FIGURE 2
Kinetic release of [^{99m}Tc]DTPA and theophylline in vivo. [^{99m}Tc]DTPA activity was calculated on the scintigraphic images. 100% value is the activity immediately after ingestion. For theophylline, the values were computed from the blood samples measurements.

Moreover, the high density of this material affects the transit time of the pellets (*10*). Gastroscopy has also been utilized (*9*), although it only provides qualitative results and does not explore the intestine. Scintigraphy is a low-radiation exposure technique that provides quantitative results along the entire digestive tract. It also presents some limitations.

Because most drugs cannot be labeled efficiently with ^{99m}Tc, the assumption is made that the release of [^{99m}Tc] DTPA and of the drug are similar, despite their different solubility properties. In fact, we and other investigators (*2,3*) have observed close correlation between the dissolution rates of [^{99m}Tc]DTPA and the studied drug. Another limitation of the scintigraphic technique is that it cannot differentiate between the solid and liquid forms of the radionuclide. Therefore, the amount of radioactivity calculated from a region of interest drawn around the tablet image is overestimated. This is the reason for the subtraction of background activity, which is estimated by the mean count density inside a square region of interest drawn around the tablet (*7*). This correction, however, does not account for the complex pattern of distribution of activity, especially in the loops of the small intestine, and it probably contributes greatly to the variation in the results. Moreover, some free [^{99m}Tc]DTPA may hang around the tablet like a cloud making perfect correction for background virtually impossible. Therefore, the calculated tablet value is probably always overestimated. Finally, all studies were performed exclusively with ^{99m}Tc, which is attenuated by 50% after 4.5 cm in tissue. This is the reason for the calculation of GM between the anterior and posterior views (*8,9,12*). It is assumed that both views are taken with the tablet at the same location. This is probably not always true when the tablet is in the small intestine where it can move quickly. Furthermore, this correction does not account for the variation in the overall thickness of the abdomen, which is supposed to be constant. This assumption becomes false when the tablet is situated in the lateral parts of the abdomen.

In our study the movements of the tablet along the digestive tract could be easily followed between the

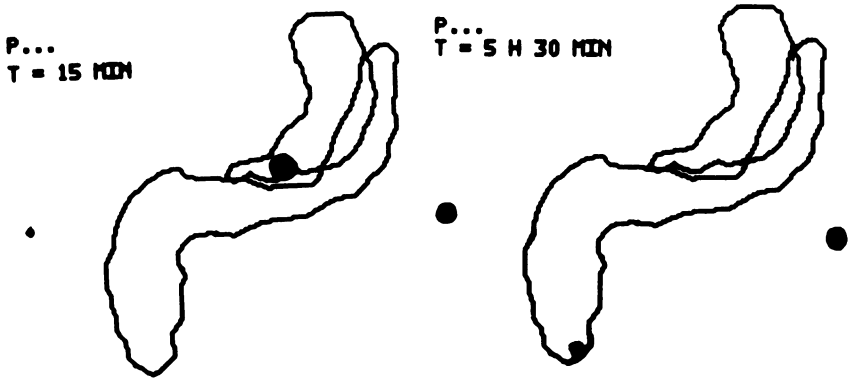

FIGURE 3
These views taken at 15 min (left) and 5 hr 30 min (right) after administration show the tablet located, respectively, in the prepyloric region and in the cecum. The contours of the stomach were obtained at 24 hr with a solution of [^{99m}Tc]pertechnetate. For the colon, contours were obtained from the activity left by the tablet during its displacement between the cecum and the left colic flexure. Notice the dramatic decrease of relative activity of the tablet when compared with the activity of the skin markers.

TABLE 1
Values of the Individual Gastroduodenal and Gastrocecal Times*

Subject	Gastroduodenal (min)	Gastrocecal (min)	Duodenocecal (min)
1	35	270	235
2	100	340	240
3	100	375	275
4	60	300	240
5	66	306	240
6	71	312	241
Mean ± s.d.	72 ± 25	317 ± 36	245 ± 15
± s.e.e.	±10	±15	±6

*The difference between gastrocecal and gastroduodenal times gave the duodenocecal time.

lower portion of the esophagus and the colon. In all the subjects the tablets entered the stomach rapidly and no sticking was observed in the esophagus. Other investigators have noticed the presence of some esophageal sticking in up to 50% of the subjects (*13*). The subject's posture at the time of administration and the volume of water ingested with the tablet largely contribute to this phenomenon (*14–16*). In a preliminary experiment we noted that sticking can occur even in the standing position if no water is taken with the tablet; swallowing the tablet with 200 ml of water prevented esophageal sticking.

Once inside the stomach, the tablets quickly reached the prepyloric portion of the great curvature and stayed here until being swept into the duodenum and small intestine. The initial absence of intragastric movement could be related to the fact that all subjects were fasted. Therefore the tablets were probably sticking to the gastric mucosa in a nearly empty stomach, until the "house-keeping" contractions occurred (*17,18*).

The calculation of the mean gastroduodenal and duodenocecal times requires that at least the stomach and the colon can be localized on the scintigraphic views. Administration of a labeled solution easily displays the stomach. The colon is the area where the remainder of the tablet activity will eventually stand. If the tablet is labeled with ^{99m}Tc, then a ^{99m}Tc labeled solution cannot be administered concomitantly because it would interfere with the localization and counting of the tablet activity. Daly et al. (*2*) solved the problem by labeling the solution with indium-113m (^{113m}In)-DTPA which has a higher energy emission and a shorter half-life than ^{99m}Tc. However, this was at the cost of several disadvantages: (a) additional corrections were required for the calculation of the tablet activity due to crossover counting in the energy window of ^{99m}Tc, (b) a high- or medium-energy collimator had to be used, resulting in poorer resolution and lower count rates, and (c) an expensive generator for ^{113m}In had to be purchased. In our study these complications have all been avoided by having the subjects ingest a solution of [^{99m}Tc]pertechnetate 24 hr after the beginning of the study. By that time there was no detectable activity in the abdomen from the dissolved tablet and the gastric activity could not interfere with the already terminated tablet activity counting. With the help of the two skin markers the gastric image was easily repositioned on the early views on which only the labeled tablet was present, thus, allowing us to follow its movement relative to the stomach, and especially to determine the time it entered the duodenum.

The duodenocecal time of 245 ± 15 min found in this study is close to the values reported by Prokop et al. (*19*) for water (248 ± 58, 240 ± 47, and 232 ± 54 min, on different occasions) and by Christensen et al. (*20*) for labeled pellets (204 ± 31 min) and for a solution of [^{99m}Tc]DTPA (246 ± 28 min). Christensen et al. noticed that although the transit times in the small intestine were not significantly different between liquid and pellet solutions, there was a significant difference in the stomach (18 ± 4 min for the solution versus 99 ± 7 min for the pellets). They suggested that the variations in the overall mouth to cecum transit time observed in earlier studies could be due almost exclusively to differences in the transit through the stomach alone, rather than through the stomach and small intestine. It is interesting to note that our own results show a small relative standard deviation of the duodenocecal time when compared with the gastroduodenal time (6% versus 33% of their means, respectively). This seems to show that for tablets, also, the intestinal transit time is rather constant and similar with that of liquids or pellets, whereas, there are great individual variations in the gastroduodenal times.

In conclusion this simple and inexpensive (although time-consuming) scintigraphic method allows in vivo visualization of the evolution of the anatomical position and the drug release of tablets. Applications of this technique are presently sought for the assessment of the effects of factors such as patient's position or meal composition on the digestive absorption of drugs and the efficiency of new formulations.

NOTE

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