

Error analysis of classic colonic transit time estimates

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Bouchoucha, Michel, and S. Randall Thomas. Error analysis of classic colonic transit time estimates. *Am J Physiol Gastrointest Liver Physiol* 279: G520–G527, 2000.—Estimates of colonic transit times (CTT) through the three colonic segments, right colon, left colon, and rectosigmoid, are commonly based on radiopaque markers. For a given segment, CTT is usually calculated from just the number of markers visible in that segment on abdominal X-rays. This procedure is only strictly valid for the theoretical, but unrealistic, case of continuous marker ingestion (i.e., not for a single or once-daily ingestion). CTT was analyzed using the usual estimate of the mean CTT of one marker and also using a new, more realistic estimate based on the kinetic coefficients of a three-compartment colonic model. We directly compared our compartmental approach to classic CTT estimates by double-marker studies in six patients. We also retrospectively studied CTT in 148 healthy control subjects (83 males, 65 females) and 1,309 subjects with functional bowel disorders (irritable bowel syndrome or constipation). Compared with the compartmental estimates, the classic approach systematically underestimates CTT in both populations, i.e., in patients and in healthy control subjects. The relative error could easily reach 100% independent of the site of colonic transit delay. The normal values of total CTT are then 44.3 ± 29.3 instead of 30.1 ± 23.6 h for males and 68.2 ± 54.4 instead of 47.1 ± 28.2 h for females.

compartment model

COLONIC TRANSIT TIMES (CTTs) through successive colonic segments are commonly estimated from the distribution of radiopaque markers visible on successive daily abdominal X-rays taken after a single ingestion of a fixed number of markers (2, 9). This method was useful for objective explanation of constipation and defined three types of delay: right colon (12), left colon (7), and rectosigmoid (8) delays. In previous work (3), to limit radiation exposure, we demonstrated that this method was analogous to daily ingestion of markers over six days followed by a single abdominal X-ray on the seventh morning. Under the assumptions that marker ingestion is continuous and that marker transit has

reached a steady state on the day of the X-ray (3), the usual estimate of mean CTT of a single marker in a segment i is represented by CTT_i (or its reciprocal, the rate constant k_i) and is simply given by

$$CTT_i = \frac{1}{k_i} = n_i \frac{\Delta T}{N} \quad (1)$$

where n_i is the number of markers seen on the X-ray in segment i , N is the number of markers ingested each day ($N = 12$ in the present study), and ΔT is the time interval between consecutive ingestions of markers ($\Delta T = 24$ h in the present study). We call this the classic single-film estimate of CTT_i . It is subject to several kinds of systematic error, of which the following are particularly characteristic, namely, 1) the steady-state assumption may not be respected at the time of X-ray (typically on the seventh day of marker ingestion) in patients with delayed colonic transit (constipated states), 2) in patients with very fast transit (diarrheic states, in which some regions have no markers) the time interval between two ingestions is too great, and 3) this equation is only strictly applicable for continuous ingestion of markers, whereas markers are actually ingested in a bolus once a day.

To overcome these limitations, we previously developed (4) improved estimates of segmental CTT and rate constants for transit between adjacent segments based on a three-compartment model. This method takes account of the bolus nature of the ingestion and does not assume that marker distribution has reached a steady state. We refer to these hereafter as compartmental estimates. Nevertheless, this model was never verified by direct comparison of its predictions with those of the classic techniques in the same patients.

In the present study, we use our more accurate model to evaluate the error in classic estimates, i.e., those based on *Eq. 1*. We also verified the pertinence

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of the model using double-marker studies and daily X-rays on a small group of patients.

METHODS

Double-Marker Test of Model Predictions

Adequacy of our three-compartment model for prediction of marker evolution along the colon was evaluated in a study using two types of radiopaque markers in four women and two men. These patients were given 20 markers of one type on the first day only and 10 markers of a second type every day for 6 days. The only difference between the markers was their shape, and their use was randomized in the different patients to avoid systematic errors. X-rays were taken just before marker ingestion each morning (except *day 1*) until the sixth or seventh day.

Markers were localized and counted in the different segments of the large bowel according to bony landmarks (2). Three zones of interest were defined: the right colon (ascending colon and right part of the transverse), the left colon (descending colon and left part of the transverse), and the rectosigmoid area.

For comparison of our compartmental approach with the classic technique of single ingestion and daily X-rays (2), first-order rate constants of segmental transit were estimated in two ways. First, for the classic single-ingestion technique (as in Ref. 2; see also Eq. 10 below), CTT in compartment i was estimated using

$$\text{CTT}_i = \frac{\Delta T}{N} \sum_j n_{ij} \quad (2)$$

where ΔT is the time between X-rays (24 h), N is the number of markers ingested on *day 1*, and n_{ij} is the number of markers counted in region i (right colon, left colon, or rectosigmoid segment) on day j . The classic single-ingestion estimates of the first-order rate constants are then the reciprocals of these CTT_i values (see Eqs. 8 and 9).

Second, estimates of the rate constants according to our three-compartment model were made by numerical iteration as described in *Compartmental estimates of the rate constants and CTT*. These two sets of rate constants were then used to predict the number of markers that would be present in each colonic segment, and errors were calculated for both methods according to

$$\text{err}_i = \frac{\sqrt{\sum_j (p_{ij} - n_{ij})^2}}{n_{\text{X-rays}}} \quad (3)$$

where n_{ij} is the number of markers counted in region i on day j , p_{ij} is the predicted number of markers, and $n_{\text{X-rays}}$ is the number of X-rays taken on a given patient (i.e., 5 or 6).

Retrospective Study

Population. For the retrospective study, we used data obtained as classic single-film estimates of CTT in patients with irritable bowel syndrome or constipation (1,309 subjects; mean age 45.3 yrs; age range 17–80 yrs; 345 males and 964 females) and subjects used as a control population (148 subjects; 83 males with mean age 36.5 yrs and age range 20–61 yrs and 65 females with mean age 34.5 yrs and age range 18–57 yrs).

Experimental procedure. In all subjects, CTT was estimated using a previously described technique (3). Briefly, 12 radiopaque markers within a gelatin capsule were ingested from *day 1* to *day 6* at 9:00 AM. A plain film of the abdomen

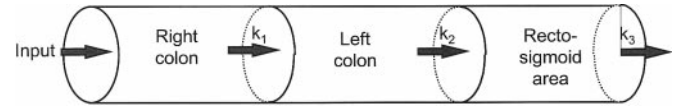


Fig. 1. Diagram of the 3-compartmental model. Three compartments, representing the right colon, left colon, and rectosigmoid area, are used, with 3 constants, k_1 , k_2 and k_3 , representing the net result of propagation and back-propagation between the consecutive compartments.

was taken on the seventh day at 9:00 AM. Markers were counted as described in the previous section.

Segmental and total colorectal classic single-film transit times were calculated using Eq. 1, according to the distribution of markers counted in the different segments of bowel. Total colonic classic transit time was then taken as the sum of the three segmental transit times.

Data Analysis Using a Compartmental Model

In our previous study modeling the transit of markers through the colon, we used a three-compartment model (Fig. 1) representing the right colon, the left colon, and the rectosigmoid area (4). Three rate constants, k_1 , k_2 , and k_3 , represented the net result of propagation and back-propagation between consecutive compartments. Defining N as the number of markers ingested daily and $n_1(t)$, $n_2(t)$, and $n_3(t)$ as the number of markers situated in the right colon, the left colon, and the rectosigmoid area, respectively, as a function of time, the problem can then be formulated as

$$\begin{aligned} \frac{d[n_1(t)]}{dt} &= \text{input}(t) - k_1 n_1(t) \\ \frac{d[n_2(t)]}{dt} &= k_1 n_1(t) - k_2 n_2(t) \\ \frac{d[n_3(t)]}{dt} &= k_2 n_2(t) - k_3 n_3(t) \end{aligned} \quad (4)$$

with initial conditions $n_1(0) = N$, and $n_2(0) = n_3(0) = 0$. With a bolus ingestion [indicated by $\text{input}(t)$] of N markers every 24 h, this system has the following solution (4) for the number of markers in *compartment 1*, the right colon, at a given time t

$$n_1(t) = \text{Integer Part} \left[N \sum_{i=1}^{i_{\max}} e^{-k_1(t-i)} \right] \quad (5)$$

where t is in days and i_{\max} is the greatest integer less than or equal to t . The graphs of this function for two arbitrary values of k_1 (1 day^{-1} and 0.2 day^{-1}) are shown as the stair-step and saw-tooth curves in Fig. 2, in which the stair steps reflect the fact that only integer values of markers can be counted. From Eq. 5, the predicted number of markers visible in *compartment 1* on a film taken on the morning of the seventh day would be

$$n_1(6) = \text{Integer Part} [N(e^{-6k_1} + e^{-5k_1} + e^{-4k_1} + e^{-3k_1} + e^{-2k_1} + e^{-k_1})] \quad (6)$$

Note that since *day 0* is the first day of marker ingestion, the seventh-morning X-ray comes in fact six full days after the first ingestion. Hence the predicted value of markers at the time of the X-ray is $n_1(6)$. Using this equation, the large dots on the two Fig. 2 graphs (i.e., the two graphs show the behavior for different values of the true rate constant k_1)

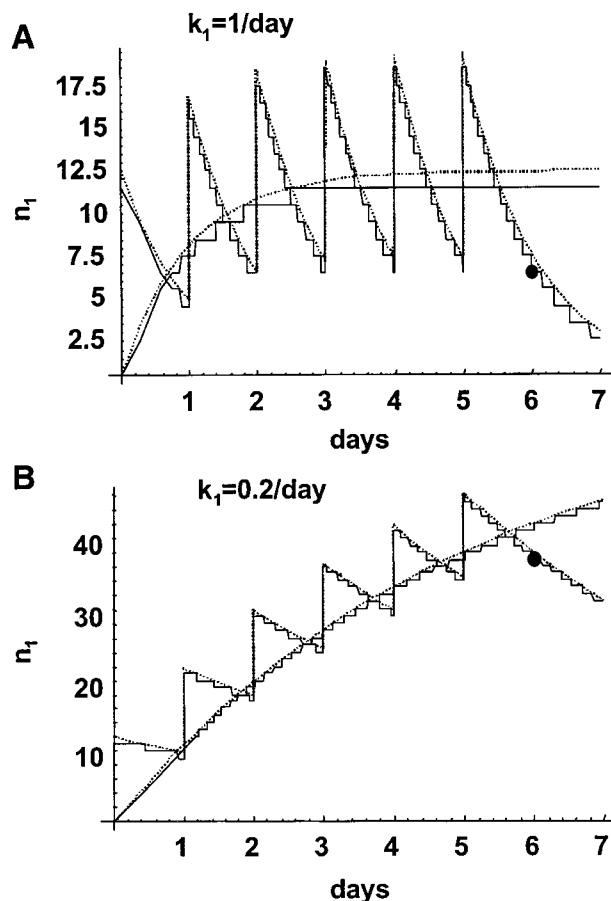


Fig. 2. Right colon marker kinetics. For the right colon, *compartment 1*, this shows marker kinetics predicted by our compartmental model for both continuous and once-daily ingestion of 12 markers per day for 2 values of true rate constant k_1 . Large dots indicate that 6 and 37 markers would be counted on the 7th morning's X-rays in A and B, respectively. Classic predictions of colonic transit time (CTT) through *compartment 1* (CTT_1) based on these numbers would be 0.5 days (12 h) for A and 3.1 days (74 h) for B, whereas the true CTT_1 values are 1 day and 5 days, respectively. Thus classic predictions are underestimates even for fast transit, when steady state is attained by the 7th morning (A). The dotted lines show "envelope" curves that ignore the fact that the number of counted markers is an integer.

indicate the predicted numbers of markers to be counted in *compartment 1*.

If ingestion were continuous instead of as a bolus (for the same number of markers per day), then in *Eq. 4* input = N , with N a constant, and for the number of markers in the right colon, we would have the solution

$$n_1(t) = \text{Integer Part} \left[\frac{N(1 - e^{-k_1 t})}{k_1} \right] \quad (7)$$

This is shown in Fig. 2 as the smooth curves running through the middle of the saw-tooth curves.

For the left colon and rectosigmoid segment (*compartments 2 and 3*), for particular values of k_1 , k_2 , and k_3 , the equations for $n_2(t)$ and $n_3(t)$ (in the set of *Eq. 4*) were solved numerically using the built-in function NDSolve in the software program Mathematica, in which $n_1(t)$ is given by *Eq. 5* and with initial conditions $n_2(0) = n_3(0) = 0$. Figures 3 and 4 show graphs of the solutions to *Eq. 4* for selected combinations of rate constants. As explained in the Mathematica

documentation, NDSolve switches between a non-stiff Adams method and a stiff Gear method based on LSODE.

Compartmental estimates of the rate constants and CTT. The three rate constants were estimated from the number of markers counted in each compartment on the films (designated nx_1 , nx_2 , and nx_3 , respectively) using a specific software program written in the C language (4). Two sets of estimates were made: classic estimates kc_1 , kc_2 , and kc_3 , which were based on *Eq. 1*, i.e.

$$kc_i = \frac{1}{CTT_i} \quad (8)$$

and compartmental estimates kr_1 , kr_2 , and kr_3 , which were based on the pulsed analysis that gives *Eq. 6* and the corresponding equations for the other two compartments: kr_1 was deduced by nonlinear fit of *Eq. 6* to nx_1 [i.e., $n_1(6) = nx_1$]; kr_2 was then deduced from nx_2 and the fitted values of kr_1 and kr_3 were deduced from nx_3 , kr_1 , and kr_2 . For these estimates, we assumed that segmental CTT was at least 1 h for each compartment, a reasonable assumption except in extreme diarrhea, which was never the case for the patients during this study.

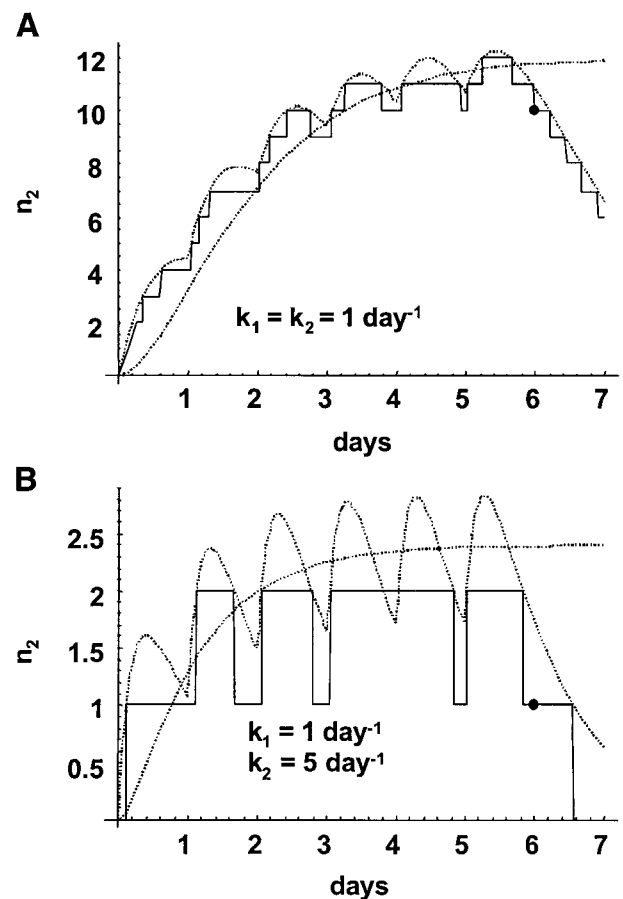


Fig. 3. Left colon marker kinetics. Marker kinetics for the left colon, *compartment 2*, are shown. Assuming continuous or once-daily ingestion of 12 markers, this shows marker kinetics for $k_2 = 1/\text{day}$ and $k_2 = 5/\text{day}$ ($k_1 = 1/\text{day}$ in both panels). As for the right colon, the classic method would yield underestimates of CTT_2 ; classic CTT_2 in A and B [based on $n_2(6)$ values of 10 and 1, respectively, shown as •] would be 0.8 days (20 h) and 0.08 days (2 h), respectively, whereas true values are 1 and 0.2 days.

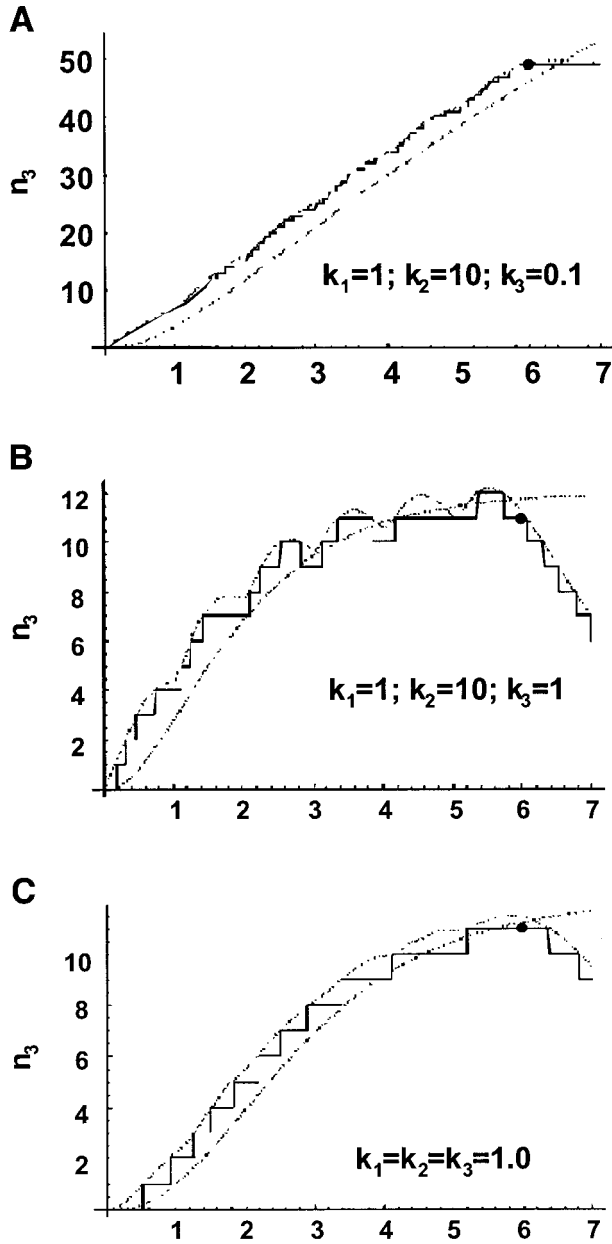


Fig. 4. Predicted marker kinetics in the rectosigmoid area. Marker kinetics for the rectosigmoid segment, *compartment 3*, are shown. Assuming continuous or once-daily ingestion of 12 markers, 3 combinations of rate constants are illustrated, as indicated on the graphs. The classic method would yield underestimates of CTT_3 ; $n_3(6)$ (shown as large dots) is 49 for A and 11 for B and C, so classic CTT_3 estimates would be 4.1 days (98 h) for A and 0.92 days (22 h) for B and C, whereas true values are 10 days in A and 1 day in B and C.

Using these fitted estimates of kr_1 , kr_2 , and kr_3 , compartmental segmental transit times were calculated as

$$CTTr_i = \frac{1}{kr_i} \tag{9}$$

In both the classic and compartmental cases, total CTT was taken as the sum of the three segmental transit time estimates.

Relationship between the two measures. Using the definitions given in Eqs. 8 and 9, the relationship between classic and compartmental estimates was taken as the ratio

$$\frac{CTT_r}{CTT_c} \tag{10}$$

RESULTS

Double-Marker Results

Figure 5 shows a comparison, in one subject, of actual marker counts in each segment to predicted

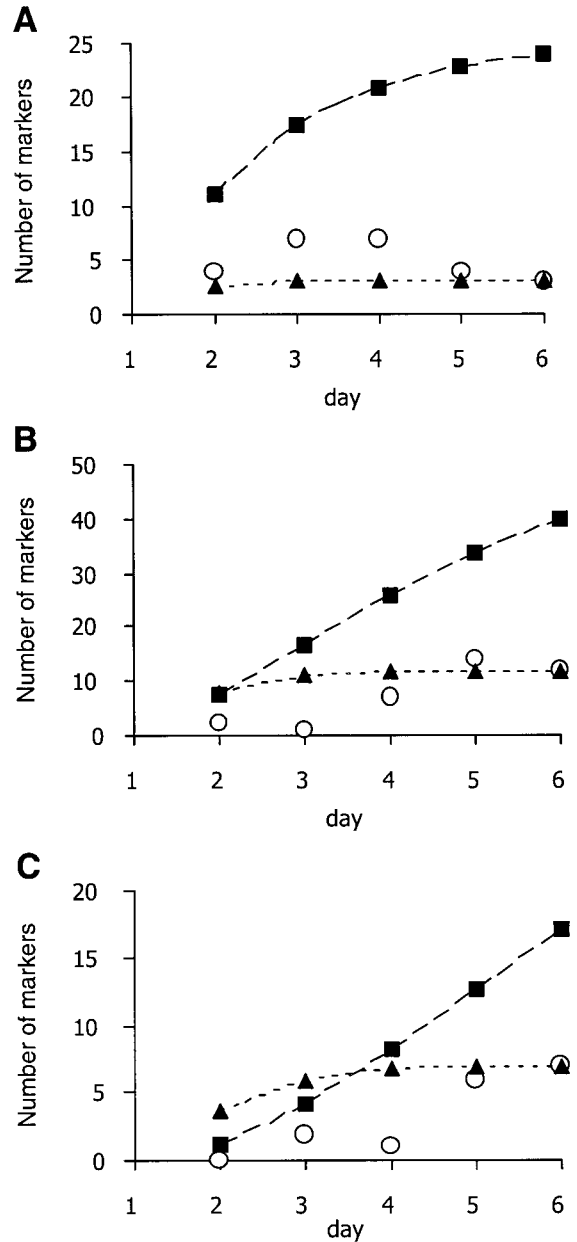


Fig. 5. Predictions of daily X-ray marker counts by classic vs. compartmental model. For the right colon (A), left colon (B), and rectosigmoid segment (C) of 1 patient, these 3 graphs show the actual number of markers counted in each segment (○) and predicted counts using the classic 1-time ingestion/daily X-ray technique (■) and our 3-compartment model (▲).

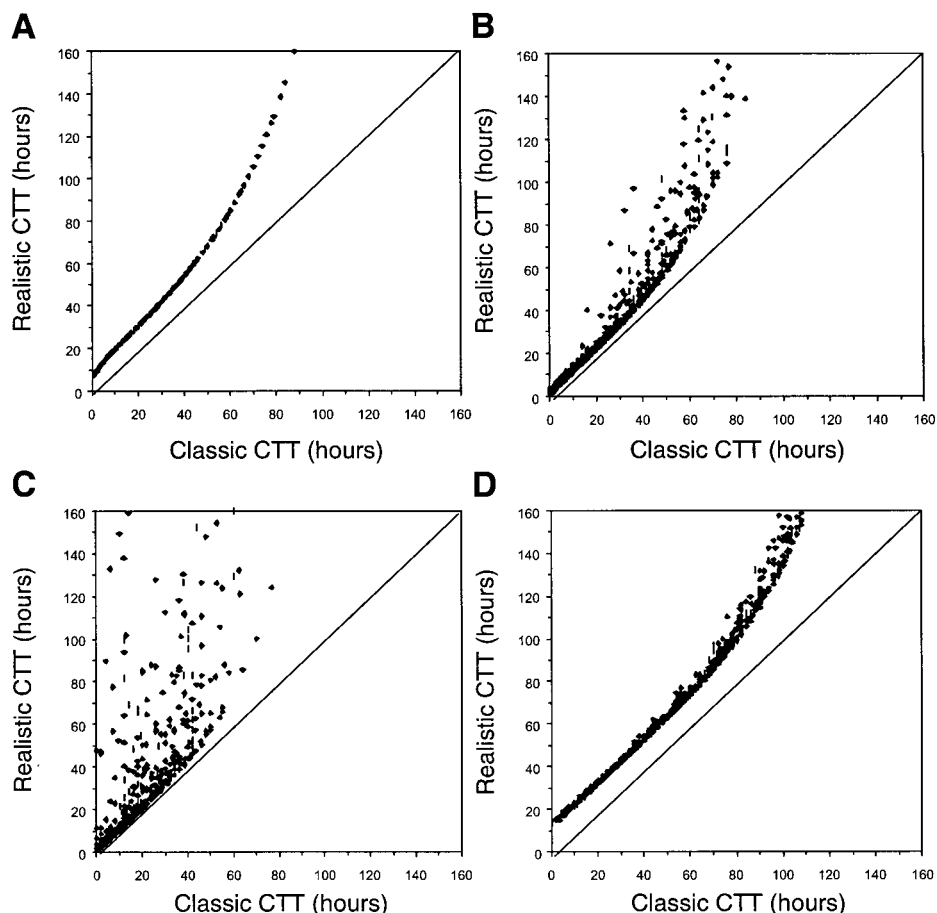


Fig. 6. Compartmental vs. classic estimates of CTT. In these figures, classic and compartmental estimates of segmental and total CTT in 1,309 subjects who complained of constipation or symptoms of irritable bowel syndrome are plotted vs. the classic estimates. *A*: right colon; *B*: left colon; *C*: rectosigmoid area; *D*: entire colon. In all colonic segments, compartmental estimates of CTT were higher than classic estimates, as shown by the absence of data under the line $y = x$.

counts using both the classic single-ingestion/multiple X-ray technique and our compartmental analysis. The compartmental model is clearly a better predictor of marker counts over the course of the study. This pattern is similar to that of the other patients in this study, except that for the rectosigmoid segment the compartmental model predictions were not systematically better than classic predictions. For these six patients, the means of the errors (*Eq. 3*) for the classic vs. compartmental model estimates were 3.75 vs. 1.25 ($P < 0.05$ by paired *t*-test) for the right colon, 4.15 vs. 2.00 ($P < 0.05$ by paired *t*-test) for the left colon, and 1.28 vs. 1.19 (not significant) for the rectosigmoid segment. The finding that the compartmental model provides no improvement over the classic method for description of rectosigmoid kinetics probably reflects the influence of voluntary control over the emptying of the terminal intestine.

Retrospective Study Results

Patients. In all colonic segments, the compartmental CTT estimates were significantly higher than classic estimates ($P < 0.0001$; Fig. 5). The difference between the classic and compartmental estimates in the right colon was higher than the differences in the other segments ($P < 0.0001$; Fig. 6). It was minimal for CTT of 43 h in the right colon, 26 h in the left colon, 15 h in the rectosigmoid area, and 68 h for the entire colon.

The offset between compartmental and classic single-film CTT seen in Fig. 5 at low transit times (high transit rates) for the right colon is a direct result of the bolus rather than continuous marker ingestion regimen. For high transit rates (high k_1 values), right colon transit will have time to reach a steady state by the seventh morning, but even once steady state is reached, the number of markers present each morning before marker ingestion will be inferior to the number that would be predicted in the theoretical case of continuous, rather than once-daily, ingestion. Figure 2A shows an example of this. Since the classic estimate of CTT was derived on the assumption of continuous ingestion, it leads to a systematic underestimate in the steady state, manifested here as the asymptotic offset for low CTT.

Healthy subjects. In healthy subjects, similar results were obtained (Table 1), namely, compartmental transit time estimates were greater than classic estimates in both genders.

DISCUSSION

The double-marker study shows that the three-compartment model is an improvement over classic techniques for characterization of colonic transit. In addition, the retrospective study shows that the classic implementation of the single-film method underesti-

Table 1. *Classic one-film and compartmental estimates of total and segmental colonic transit time in healthy subjects*

| | Males, 83 subjects | | | Females, 65 subjects | | |
|--------------|--------------------|-------------|---------------|----------------------|-------------|---------------|
| | n_i | Classic CTT | Realistic CTT | n_i | Classic CTT | Realistic CTT |
| Right colon | 5.7 ± 5.4 | 11.4 ± 10.9 | 20.8 ± 13.0 | 7.5 ± 5.1 | 14.9 ± 10.3 | 24.8 ± 11.9 |
| Left colon | 4.3 ± 5.2 | 8.5 ± 10.3 | 11.3 ± 12.1 | 8.8 ± 7.8 | 17.7 ± 15.6 | 21.7 ± 20.8 |
| Rectosigmoid | 5.1 ± 5.9 | 10.2 ± 11.8 | 12.2 ± 14.6 | 7.3 ± 7.1 | 14.6 ± 14.1 | 21.6 ± 36.0 |
| Total | 15 ± 12 | 30.1 ± 23.6 | 44.3 ± 29.3 | 23.5 ± 14 | 47.1 ± 28.2 | 68.2 ± 54.4 |

Values are means ± SD expressed in hours; n_i = no. of markers seen in each segment i . CTT, colonic transit time.

mates CTT mainly for long transit times, and the error is greatest for the right colon. The underestimate of CTT by classic techniques has been pointed out using scintigraphic measurements (11) and also using radiopaque markers (3).

In the initial description (2), the measurement of CTT was merely the measurement of the mean transit time of a single marker, defined as the integral

$$\int_0^{\infty} n(t) dt \quad (11)$$

where $n(t)$ is the number of markers present in the colon at time t .

This was applied to a protocol of a single ingestion of 20 radiopaque markers followed by 7–12 daily X-rays. The impossibility of continuously recording marker movement led Arhan et al. (2) to propose the approximation

$$\int_0^{\infty} n(t) dt \approx \sum_{i=1}^{p-1} n_i \left(\frac{t_{i+1} - t_{i-1}}{2} \right) \quad (12)$$

where p is the number of daily films and t_i the time of film number i , counted from the time of marker ingestion ($t = 0$).

The alternative method of daily ingestion, single film, using six daily ingestions of radiopaque markers and an X-ray on the seventh morning, corresponds to the mean of six measures of CTT performed using the method of daily films (3). However, this daily-ingestion single-film protocol has its own limits: 1) CTT is considered as a discrete and not a continuous phenomenon; 2) there is a limited number of marker ingestions; and 3) CTT is underestimated, especially when transit is delayed.

All recent studies of CTT using radiopaque markers (1, 5, 10) used the approximation defined in Eq. 12. Nevertheless, the absence of markers in one film could signify that the last marker was expelled any time during the previous day. Although propulsion of colonic contents is not a continuous phenomenon (6), modeling it with first-order kinetics allows derivation of a continuous law of variation of the number of markers at one site (4). We can then use this law to describe the number of markers at a given site at any time. For

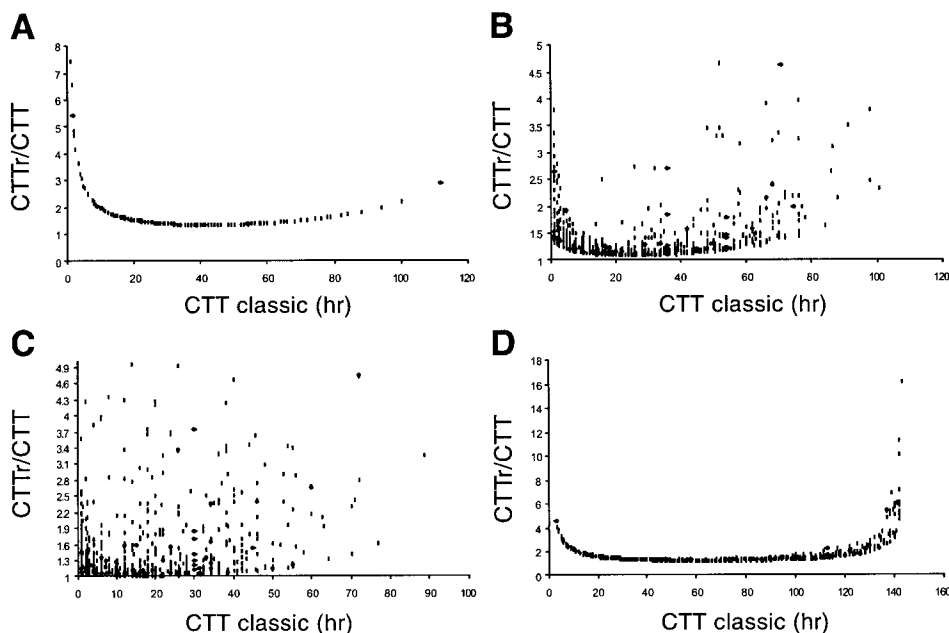


Fig. 7. Compartmental vs. classic estimates. The ratio $CTT_r:CTT_c$ is plotted against classic CTT estimates. A: right colon; B: left colon; C: rectosigmoid area; D: entire colon. For the right and the entire colon, this ratio is higher for lower values of colonic transit time (rapid transit) and higher values of colonic transit time (slow transit). For the left colon and the rectosigmoid area, a high ratio could be observed for all values of segmental CTT.

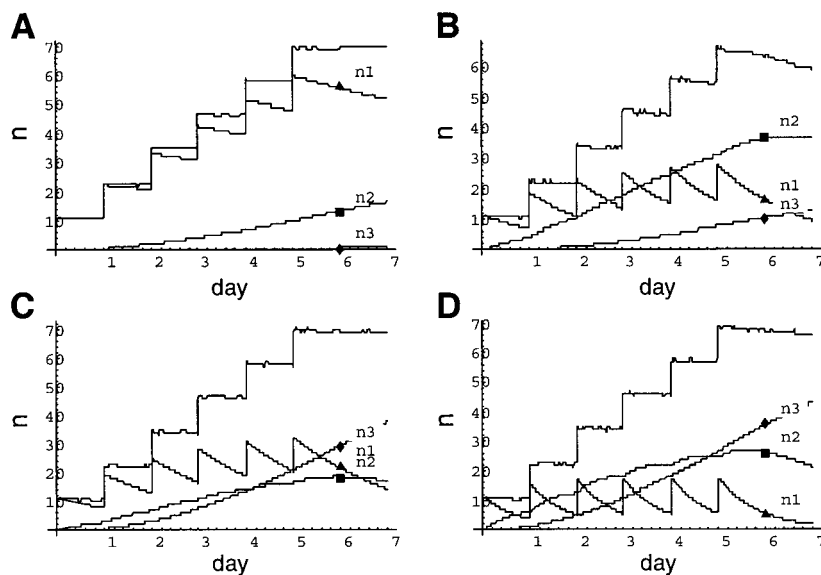


Fig. 8. Values from actual patients (all showing a total of ~ 70 markers). We selected 4 constipated patients with similar total marker counts (~ 70) but in whom the marker distributions were quite different, indicating colonic motility blocks in different segments. Table 2 gives actual segmental marker counts, the resulting classic estimates of CTT (from Eq. 1), compartmental rate constants (calculated as best fits to our 3-compartment model), and the corresponding compartmental estimates of CTT (reciprocals of k_i , converted from days to hours). Besides noting the flagrant classic underestimates of segmental CTT, we can make the following observations on closer inspection. For the case of right colon block (A), all 3 compartments are far from the steady state, which accounts for the quite dramatic classic underestimates of segmental CTT, e.g., the classic estimate of rectosigmoid CTT is 2 h here, whereas the more realistic compartmental estimate is almost 2 days. For the left colon block (B), only the right colon has attained steady state. The classic method suggests identical transit times for the right colon and rectosigmoid segments, since they show equal numbers of markers, but the compartmental analysis reveals the much slower transit in the rectosigmoid. For the 2 cases of rectosigmoid block (C and D), both right and left colon have attained steady state, but the rectosigmoid has not. We thus see that the kinetic analysis gives a much clearer notion of colonic transit over time, even from a single, 7th-day X-ray.

example, if N is the number of markers ingested and k_1 the transfer coefficient from the right colon to the left colon, the number of markers on *day 1* in the right colon is Ne^{-k_1} . Then after six daily ingestions of N markers, the predicted number of markers in the right colon on *day 7* at the time of the film, $n_1(6)$, given by Eq. 6, is set equal to the observed number, nx_1 , and we solve for kr_1 . The compartmental estimate of right colon transit time, $CTTr_1$, is then the reciprocal of kr_1 . In the same fashion, the reciprocals of kr_2 and kr_3 (calculated by numerical fits using nx_1 , nx_2 , and nx_3 and the upstream fitted kr_i values) give the compartmental estimates $CTTr_2$ and $CTTr_3$.

In the three colonic segments and for the colon as a whole, and for all the patients in the present study, Fig. 6 shows classic and compartmental estimates of CTT vs. the classic single-film estimates. Figure 7 shows the relative errors, based on Eq. 10. The considerable scatter seen here for the compartmental estimates in *compartments 2 and 3* is easily understood; consider two patients for whom the number of markers counted in the left colon is identical but whose films show different numbers of markers in the right colon, i.e., nx_2 is identical in both patients, but nx_1 is different, a common observation easily understood to result from different relative motility patterns of the two segments. By the classic method, one would erroneously conclude that CTT_2 is identical in these two

Table 2. Classic one-film and compartmental estimates of total and segmental CTT in four constipated patients with similar total marker counts

| | n_i | CTT _c | kr_i | CTT _r |
|----------------------|-------|------------------|--------|------------------|
| Right colon block | | | | |
| Right colon | 56 | 112 | 0.074 | 324 |
| Left colon | 14 | 28 | 0.061 | 392 |
| Rectosigmoid | 1 | 2 | 0.520 | 46 |
| Total | 71 | 142 | | 762 |
| Left colon block | | | | |
| Right colon | 17 | 34 | 0.515 | 47 |
| Left colon | 37 | 74 | 0.163 | 147 |
| Rectosigmoid | 17 | 34 | 0.030 | 800 |
| Total | 71 | 142 | | 994 |
| Rectosigmoid block 1 | | | | |
| Right colon | 22 | 44 | 0.403 | 60 |
| Left colon | 19 | 38 | 0.482 | 50 |
| Rectosigmoid | 30 | 60 | 0.016 | 1,493 |
| Total | 71 | 142 | | 1,603 |
| Rectosigmoid block 2 | | | | |
| Right colon | 6 | 12 | 1.098 | 22 |
| Left colon | 27 | 54 | 0.370 | 65 |
| Rectosigmoid | 36 | 72 | 0.037 | 653 |
| Total | 69 | 138 | | 740 |

Values are means expressed in hours. Total marker counts in all 4 patients were ~ 70 . Kinetics are shown in Fig. 8. CTT_c, CTT as determined from the classic model; CTT_r, CTT as determined from the compartmental model; kr_i , rate constant in the compartmental model for segment i .

patients, whereas the more realistic method, based on the three-compartment model, easily distinguishes the two. Obviously, the dispersion is increased further downstream in the rectosigmoid segment for exactly the same reason.

This approach thus overcomes the usual errors due to studies over a limited number of days of marker ingestion, since CTT using the present definition accounts for the kinetics of marker transit. Moreover, using the previous methodology of daily films, counting of markers was frequently stopped after 8 or 10 days in constipated patients with high delayed transit. The method used in the present study overcomes this problem and furnishes improved estimates of CTT without prolonging marker ingestion. The large errors resulting from the classic approach are evident in the four examples illustrated in Fig. 8 associated with Table 2.

In conclusion, our improved kinetic estimate of CTT could be useful in clinical or pharmacological analysis, yielding more accurate values of CTT in constipation and better evaluation of the action of prokinetic drugs. The problems of classic methodology hindered the determination of mechanisms of drug action. Our improved estimates allow distinction between patients having similar classic total CTT but with large differences in segmental transfer coefficients, as seen in Fig. 2.

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