Pharm Res (2013) 30:402–411
DOI 10.1007/s11095-012-0882-6

RESEARCH PAPER

Meta-analysis of Oro-cecal Transit Time in Fasting Subjects

Tohru Kokubo • Shigeyuki Matsui • Makio Ishiguro

Received: 30 May 2012 / Accepted: 5 September 2012 / Published online: 28 September 2012

ABSTRACT

Purpose Computer simulations are utilized during pharmaceutical development in order to design appropriate formulation based on the absorption, distribution, metabolism, and excretion (ADME) and physicochemical properties of target compounds, so that adequate prescriptions are offered to patients. Oro-cecal transit time (OCTT) is an important factor affecting these simulations because the absorption of drug that administered orally and the resultant pharmacokinetic profile are expressed as a function of time. Given the large intra- and inter-individual variance in OCTT, it is unsurprising that an accurate model has not yet been proposed.

Methods We conducted a meta-analysis using subject-level data to construct a statistical model that predicted OCTT. Literature that utilized lactulose to measure OCTT was identified and analyzed using a mixed-effects model.

Results The OCTTs of fasting healthy subjects were expressed using a linear model, with the amount of lactulose as the single significant explanatory factor. We found that this model could statistically distinguish the OCTTs of subjects with altered physical status from those of healthy people. Specifically, cystic fibrosis and celiac disease most significantly affected OCTT.

Conclusion The OCTT models developed herein incorporate inter-subject variations and can contribute to providing more accurate predictions of drug pharmacokinetic profiles.

KEY WORDS computer simulation · gastrointestinal tract · lactulose hydrogen breath test · meta-analysis · oro-cecal transit time

ABBREVIATIONS

ADME	absorption, distribution, metabolism and elimination
FDA	Food and Drug Administration
GET	gastric emptying time
GI	gastrointestinal
LHBT	lactulose hydrogen breath test
OCTT	oro-cecal transit time
PK	pharmacokinetics
SITT	small intestine transit time

INTRODUCTION

Pharmacokinetics (PK) simulations are a crucial step in constructing an effective prescription model for drugs that are under development. With oral dosage formulations, which constitute the most convenient and popular drug delivery method, the drug is designed to be dissolved and absorbed in an appropriate region of the gastrointestinal (GI) tract. Therefore, the transit time of a drug along the GI tract should be closely linked with the drug's absorption behavior, and it is important to obtain an accurate estimate of transit time as it is one of the input values in PK simulations (1). With this aim, Yu

T. Kokubo · S. Matsui · M. Ishiguro
The Graduate University for Advanced Studies
Shonan Village
Hayama, Kanagawa 240-0193, Japan

S. Matsui · M. Ishiguro
The Institute of Mathematical Statistics
10-3 Midori-cho
Tachikawa, Tokyo 190-8562, Japan

T. Kokubo (✉)
Qualicaps Co., Ltd.
321-5, Ikezawa-cho
Yamatokoriyama City, Nara 639-1032, Japan
e-mail: tohru.kokubo@qualicaps.co.jp

et al. (2) proposed a mathematical model using several GI compartments to calculate PK (GastroPLUS™). They used an average value (199 min) for the small intestine transit time (SITT) based on data from more than 400 individuals. Willmann *et al.* (3) constructed a rat model based on the time-dependent movement of orally administered phenol red through the GI tract and applied it in a human PK simulation model (PK-Sim®).

Although these models are promising in terms of PK predictions, substantial inter-subject variations in GI tract transit times mean that further research is necessary for more accurate estimations. It is widely known that transit times can be significantly affected by complex physiological factors such as the peristaltic motion of the stomach/intestine and the nutritional history. In this context, it is very important that during the drug development process, PK simulations take into account the possible impact of disease or altered physical status. However, the precise prediction of inter-subject variation is generally considered to be difficult together with complicated mechanisms of absorption of the tested drug. For example, it is reasonable to imagine that diarrhea affects transit time, but a statistical model offering information on the quantitative difference in OCTT between healthy subjects and those with diarrhea has not been available. Such a model would be extremely useful for approximating the drug absorption in the GI tract for specific diseases. Therefore, new models are needed to clarify the impact of factors related to disease or altered physical status on transit time in the GI tract.

In this study we addressed this issue with a meta-analysis using subject-level data from past medical studies. We identified OCTT to be one of the most important predictors in PK modeling in considering absorption window because it covers the transit time from mouth to cecum, the whole span of the GI tract in which most drugs are absorbed. Several methods are available to assess OCTT; we chose the lactulose hydrogen breath test (LHBT) because of its non-invasiveness and convenience. In addition, the LHBT is the most frequently used test in studies that have measured OCTT in the past such as scintigraphic method (4), magnetic marker method (5) and another breath test using doubly-labeled lactose-[13C, 15N]ureide as a substrate (6). Several important LHBT parameters can potentially affect OCTT results, including the amount of lactulose, the volume of water used as a chaser following lactulose ingestion, and the sensitivity of the method used to detect the hydrogen released by decomposed lactulose. Some authors have provided statistical assessments of this issue using data from small numbers of subjects (7–9). In this paper, the first step in our meta-analysis was to address this issue further by obtaining more reliable statistical evidence with a large subject-level dataset. The second step of our analysis was to evaluate the impact of disease-related factors on OCTT outcomes.

Meta-analysis using subject-level (i.e., individual) data has been considered the gold standard (10) in terms of bias (11) and precision (12), since it offers several advantages over the conventional approach that is based on aggregated data (such as within-study means of OCTTs). We therefore chose to systematically collect subject-level data from medical reports that assessed the OCTTs of 598 adult subjects. For the statistical modeling of OCTT, we employed a mixed model analysis that incorporated both fixed effects, to evaluate influences or effects of interest (i.e., those of disease-related factors), as well as random effects, to take into account unobserved factors that explain the variation across studies. We then derived a simple model for predicting OCTT based on disease-related factors for use as a basic, convenient material that will allow PK simulations to establish optimal dosage and administration data for new drugs in the future.

MATERIALS AND METHODS

Data from previous reports were collected using PubMed (through July 1, 2011), with keywords chosen based on the recommendations of the PRISMA statement (13). We used the basic keywords "lactulose" and "clinical," and limited our results to English articles only. The following additional words were used in combination with the basic keywords: "oroc (a)ecal transit-time" (35 reports found), "oro-c(a)ecal transit-time" (13 reports), OCTT (17 reports), "oral-c(a)ecal transit-time" (five reports), "gastrointestinal transit-time" (seven reports), "hydrogen-breath-test AND transit-time" (32 reports), "mouth-to-c(a)ecum transit-time" (19 reports), and "MCTT" (one report). Results were then limited to those pertaining to OCTT in the fasting state, because it is widely known that food has a significant influence not only on mean OCTT values but also on OCTT variation (14–16). In the next phase of our analysis, we found that 31 of 180 studies included OCTT data. When a report showed only a plot of individual data (21 reports) instead of stating the OCTT value in the text (10 reports), a digitizer (Engage Digitizer, ver4.1, 17) was used to extract the data from the figures. As a consequence, we prepared individual OCTT data from 31 reports (Fig. 1). A summary of these reports is listed in Table I. For subjects who underwent repeat measurements, we used the data from the first measurement only for the analysis.

As stated above, the current report focuses on fasting OCTT only because food significantly affects OCTT. Results from the analysis of non-fasting subjects will be reported elsewhere. Researchers have previously investigated other factors, such as posture during testing or menstrual cycle phase for female subjects, to determine whether or not they influence OCTT, but we excluded these factors from our analysis because the number of reports assessing them is very limited. Also, we did not include age or sex as

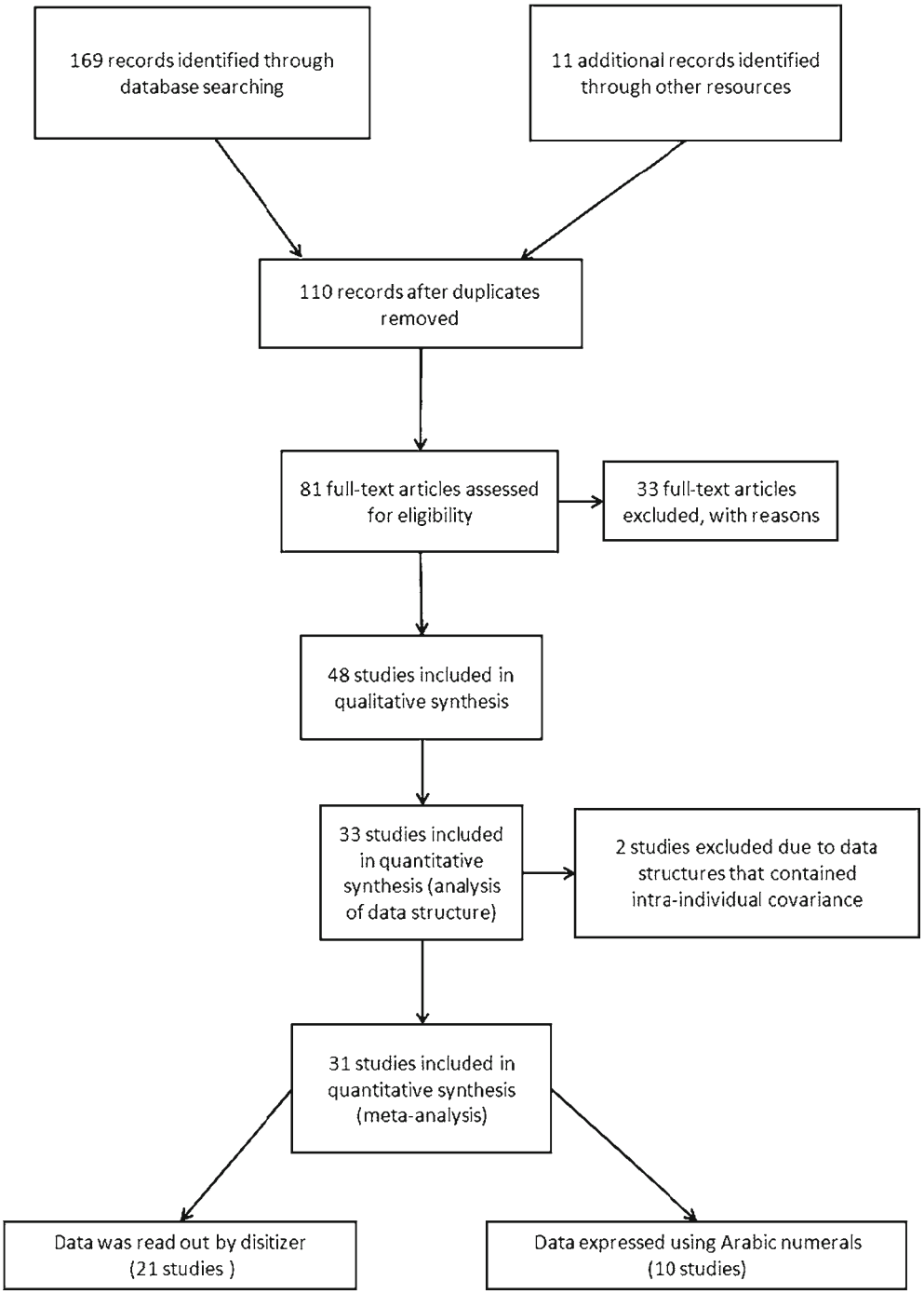


Fig. 1 Flow chart depicting the meta-analysis in this study.

explanatory factors because these data were unclear in most of the reports.

The typical procedure for testing OCTT was as follows. Volunteers were not allowed to take any meals from the night prior to the test. On the day of the test, subjects rinsed their mouths with an antibacterial mouthwash, then ingested varying amounts of lactulose solution followed by a chaser of water. Exhaled air was sampled periodically and the OCTT was determined by the time when there was a sustained rise of the pre-defined hydrogen concentration over basal value.

Our meta-analysis consisted of two stages. In the first stage, we assessed the impact of the three test variables, amount of lactulose, volume of chaser water and hydrogen concentration on OCTT in healthy subjects. In this stage, analyzed data on healthy adult subjects was collected from 31 reports. The number of subjects per report ranged from 6 to 32, for an overall total of 447 individuals.

In the second stage of the analysis we assessed the impact of disease-related factors on OCTT outcomes. In addition to the data used in the first stage, additional

Table I Summary of Reports Cited in OCTT Meta-analysis

PubMed ID	Authors	Year	Cited Figure/Table	Lactulose (g)	Volume (mL)	H_2 level (ppm)[1]	Features of subject group	Number of subjects tested	OCTT Data (min)		
									Mean	Standard Deviation	Reference
6412927	Bali A, *et al.*	1983	Fig 2 on page 112	10	20	30	Healthy Subjects	15	88	25	(22)
							Cystic Fibrosis	7	250	73	
3608730	Basilisco G, *et al.*	1987	Table 1 on page 836	10	100	2	Healthy Subjects	9	86	36	(41)
2702881	Basilisco G, *et al.*	1989	Fig 1 on page 510	10	100	3	Healthy Subjects	22	82	37	(20)
							Obesity	12	136	34	
2026339	Beaugerie L, *et al.*	1991	Fig 1 on page 393	10	100	10	Healthy Subjects	6	93	32	(42)
2778094	Bryson JC, *et al.*	1989	Table 2 on page 735	10	240	10	Healthy Subjects	12	98	53	(37)
3197582	Camboni G, *et al.*	1988	Fig 1 on page 1526	10	100	3	Healthy Subjects	15	85	39	(21)
							Obesity	10	113	25	
6365682	Caride Vj, *et al.*	1984	Table 1 on page 716	10	150	10	Healthy Subjects	13	78	41	(28)
9365142	Chiarioni G, *et al.*	1997	Table 2 on page 2102	10	100	10	Healthy Subjects	20	117	28	(19)
							Celiac Disease	16	243	39	
7297914	Corbett CL, *et al.*	1981	Fig 3 on page 839	10	100	0.25	Healthy Subjects	20	92	28	(24)
							IBS	16	54	26	
8038347	Gorard DA, *et al.*	1994	Fig 2 on page 162	13.4	20	10	Healthy Subjects	28	83	31	(25)
							IBS	10	56	20	
8174987	Gorard DA, *et al.*	1994	Fig 4 on page 498	13.4	20	10	Healthy Subjects	8	70		(43)
8944564	Gorard DA, *et al.*	1996	Fig 2 on page 553	13.4	20	10	Healthy Subjects	21	85	25	(44)
2095341	Lehtola J, *et al.*	1990	Table 1 on page 556	26	200	NA[2]	Healthy Subjects	11	52	18	(30)
1748046	Matsumoto T, *et al.*	1991	Fig 2 on page 1758	18	170	10	Healthy Subjects	12	57	28	(18)
							Amyloidosis	12	141	44	
2604760	Meshkipour H, *et al.*	1989	Fig 1 on page 939	10	150	10	Healthy Subjects	18	69	23	(45)
1439545	Nordgaard I, *et al.*	1992	Fig 1 on page 633	10	100	10	Healthy Subjects	15	92	47	(46)
8491234	Pfeiffer A, *et al.*	1993	Fig 5 on page 222, data of 240 minutes, an outlier, was excluded	10	NA	20	Healthy Subjects	10	112	48	(31)
8541377	Pilotto A, *et al.*	1995	Fig 1 and Fig 2 on page 235	10	200	15	Healthy Subjects	32	92	32	(26)
							Lithiasis	18	112	34	
							Cholecystectomy afetr Lithiasis	14	125	40	
2929556	Rubinoff MJ, *et al.*	1989	Table 1 on page 373	10	200	5	Healthy Subjects	6	90	16	(47)
2753406	Rumessen JJ, *et al.*	1989	Fig on page 812	10	100	10	Healthy Subjects	8	115	60	(48)
990859	Scarpello JH, *et al.*	1976	Fig 1 on page 1226	10	130	NA	Healthy Subjects	8	71	21	(23)
							Diabetes	12	103	46	
3691596	Staniforth DH.	1987	Table 1 on page 56	13.4	50	15	Healthy Subjects	14	107	40	(49)
2703140	Staniforth DH, *et al.*	1989	Table 4 on page 173	13.4	50	15	Healthy Subjects	12	85	36	(16)

8868312	Szilagyi A, *et al.*	1996	Fig1 on page 22	10	100	10	Healthy Subjects	17	63	36	(27)
							Pregnancy	30	99	43	
4074618	Van Wyk M, *et al.*	1985	Table 1 on page 480	10	200	10	Healthy Subjects	8	64	8	(50)
1578101	Vazquez-Olivencia W, *et al.*	1992	Table 1 on page 229	10	150	10	Healthy Subjects	16	92	49	(51)
8612393	Yuan CS, *et al.*	1996	Fig 1 on page 471	10	100	2	Healthy Subjects	12	105	32	(52)
9129564	Yuan CS, *et al.*	1997	Fig 3 on page 472	10	100	2	Healthy Subjects	14	112	35	(53)
10801249	Yuan CS, *et al.*	2000	Fig 1 on page 400 and Fig 2 on page 401	10	100	2	Healthy Subjects	12	106	43	(54)
11752106	Yuan CS, *et al.*	2002	Fig 1 on page 120	10	100	2	Healthy Subjects	6×2	91	37	(55)
15831777	Yuan CS, *et al.*	2005	Fig 1 on page 541	10	100	2	Healthy Subjects	12	101	29	(56)

[1] H_2 level denotes the hydrogen concentration that was used to define OCTT in each report over basal value.
[2] Data not available.

141 data was cited from the reports follows. Matsumoto *et al.* reported the OCTTs of 12 individuals with GI amyloidosis (18). In the case of celiac disease (19), patients had both clinical and biochemical evidence of malabsorption, and all subjects complained of diarrhea, weight loss, and weakness. Data from obese patients were obtained from two studies: Basilisco *et al.* (20) reported a median weight of 130 kg, with a range of 110–160 kg, while Camboni *et al.* (21) investigated 10 patients with nondiabetic obesity (weight range 110–165 kg). For cystic fibrosis, data were obtained from subjects who had been diagnosed on the basis of disease history, clinical examination, and elevated sweat chloride concentrations (22); all patients had a history of recurrent chest infections and sputum production. For diabetes, we included data from insulin-dependent diabetes patients with or without autonomic neuropathy, and our analysis did not distinguish between these two groups (23). OCTT values for irritable bowel syndrome (IBS) were obtained from 16 patients with diarrhea due to IBS (24) and 10 patients with a diagnosis of IBS who were attending a GI clinic (25). In the latter case, patients complained of diarrhea as their predominant bowel habit. For 18 patients with lithiasis, Pilotto *et al.* confirmed the presence of gallstones using ultrasound (26). Our analysis also included data from this same report on 14 subjects who had undergone cholecystectomy for gallstones. OCTT data from pregnant women were obtained during the late second and third trimesters (27).

Statistical Analysis

Given that our meta-analysis used subject-level data obtained from individual studies, we could utilize statistical models for individual subjects. In our statistical modeling we assumed linearity (7,9) and normality (28,29) for the OTCC data, based on previous reports.

The first stage of our meta-analysis of healthy subjects assessed the impact of three test conditions on OCTT outcomes: 1) amount of lactulose, 2) volume of chaser water, and 3) hydrogen concentrations. We assumed the following mixed linear model:

$$Y_{ij} = \mu + a_j + \beta' x_{ij} + \varepsilon_{ij} \quad (1)$$

where Y_{ij} is the OCTT outcome and x_{ij} is a vector of the three test conditions for subject i in study j. The model takes into account two fixed effects—μ, the total mean of Y_{ij}, and β, the effect of the test condition (x_{ij}) on Y_{ij}—while a_j represents the random effect of study j to incorporate unobserved factors that explain the variation across studies. ε_{ij} represents the measurement error of Y_{ij}. We assumed that $a_j \sim N(0, \tau_1^2)$ and $\varepsilon_{ij} \sim N(0, \sigma_1^2)$.

The second stage of our meta-analysis assessed the impact of disease-related factors on OCTT outcomes. We added a fixed effect related to these factors to the model (1):

$$Y_{ij} = \mu + a_j + \beta' x_{ij} + \gamma' z_{ij} + \varepsilon_{ij} \quad (2)$$

where γ is the fixed effect of vector z_{ij} (associated with factors related to altered physical status) on Y_{ij}. We assumed that $a_j \sim N(0, \tau_2^2)$ and $\varepsilon_{ij} \sim N(0, \sigma_2^2)$.

We employed a value of 5% in determining statistical significance of the fixed effects. We conducted sensitivity analyses using non-parametric regression models (PROC GAM) to assess possible deviations from linear fixed effects. In addition, the normality assumption was checked using residual plots. All analyses were conducted using the SAS system, release 9.2.

RESULTS

The first stage of the OCTT meta-analysis consisted of a mixed model analysis of healthy subjects. The second stage investigated the impact of altered physical status by including individuals who suffered from various disorders.

The mixed-effects model in the first stage evaluated data on 447 people from 31 reports. Some reports lacked data regarding hydrogen concentrations (23,30) and water volume (31), and these data were therefore not included for the corresponding analysis. Of the three candidate explanatory factors, only the amount of lactulose was identified as a significant variable (Table II, $p<0.05$), while volume of chaser water and hydrogen concentration were not. Next, the contribution of the lactulose interaction term, as well as its squared and cubed forms, was investigated in the mixed model. None of these was found to be statistically significant. Therefore, we simplified the linear mixed model by removing all terms other than the primary lactulose term. The resultant model equation is as follows:

$$\textit{Model equation}: OCTT(\textit{minutes}) = 125.2 - 3.3 \times \textit{Lactulose}(g) \quad (3)$$

Equation (3) indicates that the amount of lactulose has a significant influence on OCTT, the objective variable, and that OCTT varies linearly with the lactulose term. Since the lactulose term can always be derived when obtaining OCTT values using LHBT, we should be able to estimate intact OCTT (OCTT without the influence of lactulose) using only extrapolation. If we assume that lactulose is 0 in equation (3), we can calculate the estimated OCTT as 125 min. This is the overall OTCC estimate for the healthy subjects evaluated in this paper.

We applied non-parametric regression models to confirm the linearity of the correlation between OCTT and the lactulose term. These demonstrated a significant contribution of the primary lactulose term, and the plot of OCTT *versus* lactulose amount showed clear linearity between OCTT and lactulose amount (data not shown), which was consistent with the results of the analysis based on mixed linear models.

The second stage of the meta-analysis used linear mixed models to investigate the effects of diseases or physical changes that could affect OCTT. We identified previous scientific reports that examined the relationship between physical status and OCTT and that measured OCTT using the LBHT method. A number of physical status impairments have been claimed to affect OCTT, and we included the following (141 people) as candidates: amyloidosis, celiac disease, obesity, cystic fibrosis, diabetes, IBS, lithiasis, cholecystectomy after lithiasis and pregnancy in addition to healthy subjects in the first stage analysis.

In the linear mixed-effects model we considered the lactulose and physical status factors to be covariates with fixed effects, and the studies (reports) to be random effects. The results are summarized in Table III. The mixed model showed that in addition to lactulose, most factors were significant, with the exception of lithiasis. Figure 2 shows the

Table II Results of First-Stage Analysis

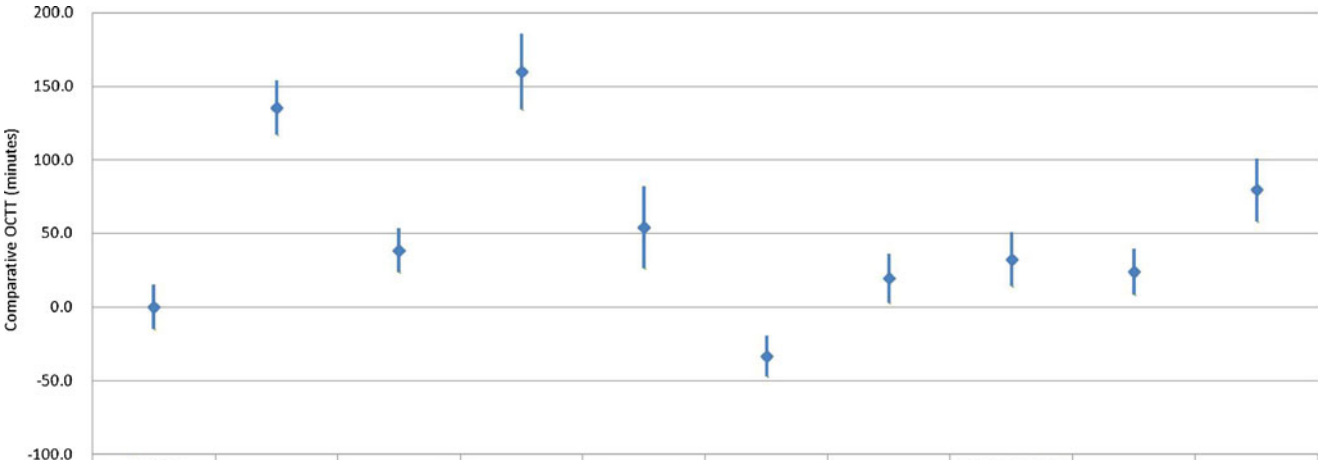
Test Conditions (x_{ij})	Estimate	Standard Error	*p*-value
Intercept	147.0	14.9	<0.0001
Lactulose (g)	−4.4	1.1	<0.0001
Chaser (water) volume	−0.1	0.1	0.1527
Hydrogen level (ppm)	−0.2	0.5	0.6229

Calculations were conducted based on Model 1.

Table III Influence of Disease Factors on OCTT

Test Conditions (x_{ij})	Disease • Status (z_{ij})	Estimate	Standard Error	*p*-value
Intercept		124.5	8.8	<0.0001
Lactulose		−3.2	0.7	<0.0001
	Healthy Subjects	0.0	–	–
	Celiac Disease	135.6	11.1	<0.0001
	Obesity	38.7	9.1	<0.0001
	Cystic Fibrosis	160.2	15.4	<0.0001
	Diabetes	54.3	16.9	0.0014
	IBS	−33.1	8.4	<0.0001
	Lithiasis	19.6	10.2	0.0541
	Cholecystectomy after Lithiasis	32.5	11.2	0.0037
	Pregnancy	24.1	9.5	0.0115
	Amyloidosis	79.7	13.1	<0.0001

Calculations were conducted based on Model 2. Healthy volunteers were configured for the reference group in the mixed model.



	Healthy Subjects	Celiac Disease	Obesity	Cystic Fibrosis	Diabetes	IBS	Lithiasis	Colecystectomy after Lithiasis	Pregnancy	Amyloidosis
Estimate	0.0	135.6	38.7	160.2	54.3	-33.1	19.6	32.5	24.1	79.7
Lower	15.0	154.0	53.7	185.6	82.2	-19.2	36.4	50.9	39.7	101.3
Upper	-15.0	117.2	23.8	134.8	26.3	-47.0	2.9	14.2	8.4	58.1

Fig. 2 Effect of physical status on OCTT (90% confidential interval).

relative OCTT estimates with 90% confidential intervals, allowing for visual comparison of the effect of each factor on OCTT. The OCTT estimate for healthy subjects was set as the default (0 min). A negative effect was observed for IBS. Cystic fibrosis and celiac disease most significantly affected OCTT (more than 100 min). In addition, the deviation of the estimates was especially large for cystic fibrosis, diabetes, and amyloidosis compared with healthy subjects.

DISCUSSION

We have conducted a meta-analysis using subject-level data from past medical studies to construct a statistical model that predicted OCTT. Data variations of OCTT would be affected by that of GET and SITT. However, the value of OCTT has an advantage because it covers both of those parameters. Diggory *et al.* (9) discussed variations of GET could contribute to OCTT with less degree than that of SITT because of the time duration of SITT is longer than GET based on the data using lactulose solutions with different osmolality that could affect GET. Therefore, we consider the discussion on OCTT model should be meaningful in PK/PD simulation of drugs apart from GET. Since understanding of GET variation would be also important especially in evaluating variation of drug absorption, we are planning to propose GET model in another report.

The meta-analytic approach has allowed evaluating the impact of various factors related to disease or altered physical status on OCTT, not covered by any single studies with limited factors investigated and small sample sizes, as well as obtaining more precise estimates regarding the impact of these factors on OCTT. The validity of meta-analysis is related to the nature and degree of unobserved inter-study variation. When comparing with evaluation of effects of therapeutics on clinical outcomes in randomized clinical trials, which is the most popular situation for applying the meta-analytic approach in medical studies, the drug's absorption in a local GI tract would be easier to capture and its procedures are relatively simple and well established. Interestingly, in the second stage meta-analysis, the estimate of the inter-study variance of OCTT (τ_2^2 in the model (2)) was 107.1, which was much less than that of within-study variance (σ_2^2), 1316.3. This would also support the validity of applying the meta-analytic approach to the current situation for evaluating the variation of OCTT.

We have proposed a mixed model for OCTT that includes lactulose as an explanatory variable. The LHBT method was selected for a meta-analysis of OCTT because based on the number of previous reports it appeared to be the most popular clinical diagnostic test for obtaining OCTT data, most likely because of its convenience and safety. The limitation of the LHBT is that it is based on the metabolism of lactulose by bacteria in the colon, and thus accurate OCTT data cannot be obtained from individuals with intestinal bacterial overgrowth (32). According to the Rome Consensus Conference in 2009 (33), obstacles to evaluating OCTT using the LHBT include large variance and low reproducibility, especially when lactulose is administered with a liquid meal. We have shown here that the LHBT can be a useful diagnostic test in fasting subjects even it has some degree of variation. The estimates of the inter-study variance (τ_1^2) and within-study variance (σ_1^2) of OCTT were 112.0 and 1252.1 respectively in the first stage

meta-analysis. This is consistent with the conclusion of the Rome Consensus Conference recommending the LHBT as a viable and useful option in pharmacological studies.

Diggory *et al.* investigated the OCTT in relation with the amount of lactulose and osmolality of the dosing solution (9). They prepared 500, 1000 and 2000 mOsm/kg solution of lactulose and compared OCTT with them and did not find significant change of OCTT (mean and variations) among the test groups while there was a linear relationship between lactulose and the mean OCTT of the groups with different amount of lactulose (5, 10 and 15 g at 1000 mOsm/kg). They speculated that the osmolality of lactulose solution is rapidly converted to the optimal tonicity by influx of water in the upper jejunum. Our result coincides well with their report in terms of significant linear relation of lactulose/OCTT as well as the negligible relationship of osmolality/OCTT that was indicated by the outcome that water amount did not contribute to the OCTT model significantly. It would need to be kept in mind, however, that osmolality of 10 g lactulose in 100 mL water is estimated to be 100 mOsm/kg; therefore, entire ranges of osmolality and lactulose amount in our study are not covered by their study.

Another report investigated the effect of different criteria of hydrogen concentrations on OCTT (34). Because OCTT is determined according to the degree of hydrogen concentrations that increase over basal levels, it was speculated that this factor may affect OCTT measurements. Indeed, the report concluded that increases in hydrogen concentrations prolonged OCTT. We revisited this question to determine whether criteria of hydrogen concentrations also influenced the linear mixed model, and found that they did not. We speculated that the magnitude of concentration differences was not large from a statistical point of view.

Although other factors were considered as candidates for analysis, namely menstrual cycle, age, gender, country of residence, nutritional history and author bias, these were not frequently described in past reports and were not able to analyze in this model, thus excluded. Contribution of these factors should be reviewed when enough data is available in the future.

Many reports have described the effect on OCTT of conditions marked by altered physical status, such as constipation, diabetes, IBS, cholelithiasis, Crohn's disease, obesity, diarrhea, pregnancy, systemic sclerosis and so on. In cases of altered OCTT, it would be meaningful to know during drug development whether the ADME profile of a drug was affected, because PK profiles, bioavailability, and effective duration of drug treatment could vary, especially due to the change in absorption rate. We have shown that OCTT estimation would be available through an OCTT model with a defined state population. Although no rigorous, statistically based investigations have been conducted in the past, we were able to estimate the OCTT for fasting healthy subjects in the first stage of our analysis. In the second stage, we calculated estimated OCTT values for populations with various health conditions, although the statistical power may be low due to the limited number of subjects available with each condition. It would also be noted that because the limited number of reports that were available for our analysis, the generalizability of our results is restricted. The analysis presented here can perhaps be used by future investigators as an example based on currently available information.

The outcome of this report should be useful in simulating the pharmacokinetics of a compound for specific diseases and in prospectively designing bioequivalence studies (35,36). Since the primary interest during development of oral medications is the absorption of the drug in the GI tract, our findings would enable pharmaceutical researchers to design drug formulations by specifying a drug's physicochemical properties and ADME, as well as specific disease state. If a drug's solubility or permeability is low and its absorption window is limited, it would be useful to consider OCTT when formulating the drug. When a sustained-release formulation is planned, OCTT could help define the duration of drug release and help reduce possible variability in drug action (37). In designing bioequivalence studies, interactions on subject-by-formulation and subgroup-by formulation need to be considered. When PK variance is explained by such interactions through OCTT, it would be worthwhile to utilize the OCTT variance in calculating required sample size so that the anticipated clinical study has enough statistical power (38).

In addition, OCTT should be taken into consideration when OCTT values are potentially being altered by either a health condition or the ingestion of a drug that affects OCTT. The latter case is a topic that is relevant to personalized medicine. Hamburg *et al.* (39) argued that diagnostic tests are necessary when customizing a drug to an individual person in the context of pharmacogenetics. If a drug is likely to affect OCTT based on its mechanism of action, a diagnostic test such as LHBT could help determine whether or not the effect on OCTT is clinically significant. If it is, the OCTT-related information should be considered when pursuing a drug's pharmacologic mechanism. This will provide decisive benefits in tailoring pharmacokinetics effectively and appropriately to individual patients. For example, the OCTTs of a population suffering from both cystic fibrosis and diabetes could be predicted by adding both distributions of estimates, resulting in a predicted average OCTT of 338.8 min (124.5+214.3), which is 214.3 min (160.0+54.3) longer than that of healthy subjects, as seen in Table III as the value of intercept of the model. This type of information would be critical when planning a dosage formulation anticipated to have OCTT-dependent absorption, such as a sustained release

formulations or high dose low permeability compounds. The variation of each distribution is expressed as standard error, and thus one would need to consider the sample numbers as well as covariance among studies.

It would be also important to examine the effects of food on OCTT, because drugs can be prescribed with or after meals. With this in mind, the food and drug administration (FDA) is requesting that pharmaceutical companies conduct clinical studies investigating the effects of food early during the development of new drugs (40). We are currently preparing a manuscript in which we analyze OCTT using LHBT performed without fasting and will discuss how this data can be utilized in conjunction with that presented in this report.

CONCLUSION

The developed OCTT models incorporate inter-subject variations regarding the physical status of subjects and can contribute to simulating more accurate predictions of pharmacokinetic profiles for drugs that are under development.

REFERENCES

1. Varum FJ, Merchant HA, Basit AW. Oral modified-release formulations in motion: the relationship between gastrointestinal transit and drug absorption. Int J Pharm. 2010;395(1–2):26–36.
2. Yu LX, Lipka E, Crison JR, Amidon GL. Transport approaches to the biopharmaceutical design of oral drug delivery systems: prediction of intestinal absorption. Adv Drug Deliv Rev. 1996;19(3):359–76.
3. Willmann S, Schmitt W, Keldenich J, Lippert J, Dressman JB. A physiological model for the estimation of the fraction dose absorbed in humans. J Med Chem. 2004;47(16):4022–31.
4. Caride VJ, Prokop EK, Troncale FJ, Buddoura W, Winchenbach K, McCallum RW. Scintigraphic determination of small intestinal transit time: comparison with the hydrogen breath technique. Gastroenterology. 1984;86(4):714–20.
5. Weitschies W, Kosch O, Mönnikes H, Trahms L. Magnetic Marker Monitoring: an application of biomagnetic measurement instrumentation and principles for the determination of the gastrointestinal behavior of magnetically marked solid dosage forms. Adv Drug Deliv Rev. 2005;57(8):1210–22.
6. Wutzke KD, Heine WE, Plath C, Leitzmann P, Radke M, Mohr C, Richter I, Gülzow HU, Hobusch D. Evaluation of oro-coecal transit time: a comparison of the lactose-[13C, 15N]ureide 13CO2- and the lactulose H2-breath test in humans. Eur J Clin Nutr. 1997;51(1):11–9.
7. La Brooy SJ, Male PJ, Beavis AK, Misiewicz JJ. Assessment of the reproducibility of the lactulose H2 breath test as a measure of mouth to caecum transit time. Gut. 1983;24(10):893–6.
8. Ladas SD, Latoufis C, Giannopoulou H, Hatziioannou J, Raptis SA. Reproducible lactulose hydrogen breath test as a measure of mouth-to-cecum transit time. Dig Dis Sci. 1989;34(6):919–24.
9. Diggory RT, Cuschieri A. The effect of dose and osmolality of lactulose on the oral-caecal transit time determined by the hydrogen breath test and the reproducibility of the test in normal subjects. Ann Clin Res. 1985;17(6):331–3.
10. Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. Cochrane Working Group. Stat Med. 1995;14(19):2057–79.
11. Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI, Anti-Lymphocyte Antibody Induction Therapy Study Group. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. Stat Med. 2002;21(3):371–87.
12. Lambert PC, Sutton AJ, Abrams KR, Jones DR. A comparison of summary patient-level covariates in meta-regression with individual patient data meta-analysis. J Clin Epidemiol. 2002;55(1):86–94.
13. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analysis: the PRISMA statement. PLOS Medicine. 2010;6(7)e1000097:1–6.
14. Fadda HM, McConnell EL, Short MD, Basit AW. Meal-induced acceleration of tablet transit through the human small intestine. Pharm Res. 2009;26(2):356–60.
15. Priebe MG, Wachters-Hagedoorn RE, Stellaard F, Heiner AM, Elzinga H, Vonk RJ. Oro-cecal transit time: influence of a subsequent meal. Eur J Clin Invest. 2004;34(6):417–21.
16. Staniforth DH, Rose D. Statistical analysis of the lactulose/breath hydrogen test in the measurement of orocaecal transit: its variability and predictive value in assessing drug action. Gut. 1989;30(2):171–5.
17. Engage Digitizer: 2007. http://digitizer.sourceforge.net/
18. Matsumoto T, Iida M, Hirakawa M, Hirakawa K, Kuroki F, Lee S, Nanbu T, Fujishima M. Breath hydrogen test using water-diluted lactulose in patients with gastrointestinal amyloidosis. Dig Dis Sci. 1991;36(12):1756–60.
19. Chiarioni G, Bassotti G, Germani U, Battaglia E, Brentegani MT, Morelli A, Vantini I. Gluten-free diet normalizes mouth-to-cecum transit of a caloric meal in adult patients with celiac disease. Dig Dis Sci. 1997;42(10):2100–5.
20. Basilisco G, Camboni G, Bozzani A, Vita P, Doldi S, Bianchi PA. Orocecal transit delay in obese patients. Dig Dis Sci. 1989;34(4):509–12.
21. Camboni G, Basilisco G, Bozzani A, Bianchi PA. Repeatability of lactulose hydrogen breath test in subjects with normal or prolonged orocecal transit. Dig Dis Sci. 1988;33(12):1525–7.
22. Bali A, Stableforth DE, Asquith P. Prolonged small-intestinal transit time in cystic fibrosis. Br Med J (Clin Res Ed). 1983;287(6398):1011–3.
23. Scarpello JH, Greaves M, Sladen GE. Small intestinal transit in diabetics. Br Med J. 1976;2(6046):1225–6.
24. Corbett CL, Thomas S, Read NW, Hobson N, Bergman I, Holdsworth CD. Electrochemical detector for breath hydrogen determination: measurement of small bowel transit time in normal subjects and patients with the irritable bowel syndrome. Gut. 1981;22(10):836–40.
25. Gorard DA, Libby GW, Farthing MJ. Influence of antidepressants on whole gut and orocaecal transit times in health and irritable bowel syndrome. Aliment Pharmacol Ther. 1994;8(2):159–66.
26. Pilotto A, Franceschi M, Del Favero G, Fabrello R, Di Mario F, Valerio G. The effect of aging on oro-cecal transit time in normal subjects and patients with gallstone disease. Aging (Milano). 1995;7(4):234–7.
27. Szilagyi A, Salomon R, Smith BE, Martin M, Seidman E. Determinants of prolonged oral cecal transit time during late phase pregnancy. Clin Invest Med. 1996;19(1):20–7.
28. Caride VJ, Prokop EK, Troncale FJ, Buddoura W, Winchenbach K, McCallum RW. Scintigraphic determination of small intestinal transit time: comparison with the hydrogen breath technique. Gastroenterology. 1984;86(4):714–20.
29. Pressman JH, Hofmann AF, Witztum KF, Gertler SL, Steinbach JH, Stokes K, Kelts DG, Stone DM, Jones BR, Dharmsathaphorn

K. Limitations of indirect methods of estimating small bowel transit in man. Dig Dis Sci. 1987;32(7):689–99.
30. Lehtola J, Jauhonen P, Kesäniemi A, Wikberg R, Gordin A. Effect of erythromycin on the oro-caecal transit time in man. Eur J Clin Pharmacol. 1990;39(6):555–8.
31. Pfeiffer A, Schmidt T, Höller T, Herrmann H, Pehl C, Wendl B, Kaess H. Effect of trospium chloride on gastrointestinal motility in humans. Eur J Clin Pharmacol. 1993;44(3):219–23.
32. Dukowicz AC, Lacy BE, Levine GM. Small intestinal bacterial overgrowth: a comprehensive review. Gastroenterol Hepatol (N Y). 2007;3(2):112–22.
33. Basilisco G, Risicato R, Bnazzi P, Di Sario A, Portincasa P. H_2-breath testing for evaluation of oro-caecal transit time. Aliment Pharmacol Ther. 2009;29(Suppl1):1–49.
34. Hirakawa M, Iida M, Kohrogi N, Fujishima M. Hydrogen breath test assessment of orocecal transit time: comparison with barium meal study. Am J Gastroenterol. 1988;83(12):1361–3.
35. Karalis V, Macheras P, Van Peer A, Shah VP. Bioavailability and bioequivalence: focus on physiological factors and variability. Pharm Res. 2008;25(8):1956–62.
36. Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. The role of predictive biopharmaceutical modeling and simulation in drug development and regulatory evaluation. Int J Pharm. 2011;418(2):151–60.
37. Bryson JC, Dukes GE, Kirby MG, Heizer WD, Powell JR. Effect of altering small bowel transit time on sustained release theophylline absorption. J Clin Pharmacol. 1989;29(8):733–8.
38. Zariffa NM, Patterson SD. Population and individual bioequivalence: lessons from real data and simulation studies. J Clin Pharmacol. 2001;41(8):811–22.
39. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010;22, 363(4):301–304.
40. U.S. Department of Health and Human Services, FDA, CDER. Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies. 2002. http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126833.pdf
41. Basilisco G, Camboni G, Bozzani A, Paravicini M, Bianchi PA. Oral naloxone antagonizes loperamide-induced delay of orocecal transit. Dig Dis Sci. 1987;32(8):829–32.
42. Beaugerie L, Burger AJ, Cadranel JF, Lamy P, Gendre JP, Le Quintrec Y. Modulation of orocaecal transit time by hypnosis. Gut. 1991;32(4):393–4.
43. Gorard DA, Libby GW, Farthing MJ. 5-Hydroxytryptamine and human small intestinal motility: effect of inhibiting 5-hydroxytryptamine reuptake. Gut. 1994;35(4):496–500.
44. Gorard DA, Gomborone JE, Libby GW, Farthing MJ. Intestinal transit in anxiety and depression. Gut. 1996;39(4):551–5.
45. Meshkinpour H, Kemp C, Fairshter R. Effect of aerobic exercise on mouth-to-cecum transit time. Gastroenterology. 1989;96(3):938–41.
46. Nordgaard I, Rumessen JJ, Nielsen SA, Gudmand-Høyer E. Absorption of wheat starch in patients resected for left-sided colonic cancer. Scand J Gastroenterol. 1992;27(8):632–4.
47. Rubinoff MJ, Piccione PR, Holt PR. Clonidine prolongs human small intestine transit time: use of the lactulose-breath hydrogen test. Am J Gastroenterol. 1989;84(4):372–4.
48. Rumessen JJ, Hamberg O, Gudmand-Høyer E. Influence of oro-caecal transit time on hydrogen excretion after carbohydrate malabsorption. Gut. 1989;30(6):811–4.
49. Staniforth DH. Effect of drugs on oro-caecal transit time assessed by the lactulose/breath hydrogen method. Eur J Clin Pharmacol. 1987;33(1):55–8.
50. Van Wyk M, Sommers DK, Steyn AG. Evaluation of gastrointestinal motility using the hydrogen breath test. Br J Clin Pharmacol. 1985;20(5):479–81.
51. Vazquez-Olivencia W, Shah P, Pitchumoni CS. The effect of red and black pepper on orocecal transit time. J Am Coll Nutr. 1992;11(2):228–31.
52. Yuan CS, Foss JF, O'Connor M, Toledano A, Roizen MF, Moss J. Methylnaltrexone prevents morphine-induced delay in oral-cecal transit time without affecting analgesia: a double-blind randomized placebo-controlled trial. Clin Pharmacol Ther. 1996;59(4):469–75.
53. Yuan CS, Foss JF, Osinski J, Toledano A, Roizen MF, Moss J. The safety and efficacy of oral methylnaltrexone in preventing morphine-induced delay in oral-cecal transit time. Clin Pharmacol Ther. 1997;61(4):467–75.
54. Yuan CS, Foss JF, O'Connor M, Karrison T, Osinski J, Roizen MF, Moss J. Effects of enteric-coated methylnaltrexone in preventing opioid-induced delay in oral-cecal transit time. Clin Pharmacol Ther. 2000;67(4):398–404.
55. Yuan CS, Wei G, Foss JF, O'Connor M, Karrison T, Osinski J. Effects of subcutaneous methylnaltrexone on morphine-induced peripherally mediated side effects: a double-blind randomized placebo-controlled trial. J Pharmacol Exp Ther. 2002;300(1):118–23.
56. Yuan CS, Doshan H, Charney MR, O'connor M, Karrison T, Maleckar SA, Israel RJ, Moss J. Tolerability, gut effects, and pharmacokinetics of methylnaltrexone following repeated intravenous administration in humans. J Clin Pharmacol. 2005;45(5):538–46.