

Special Section on Pediatric Drug Disposition and Pharmacokinetics

Examining Small Intestinal Transit Time as a Function of Age: Is There Evidence to Support Age-Dependent Differences among Children? [§]

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ABSTRACT

The small intestine represents the region where the majority of drug and nutrient absorption transpires. Among adults, small intestinal transit kinetics is well delineated; however, the applicability of these values toward children remains unclear. This article serves to examine the relationship between age and mean small intestinal transit time (SITT) based on the available literature. In addition, the influence of alterations in intestinal transit time was explored among children using a model-based approach. Primary literature sources depicting SITT from children to adults were ascertained via the PubMed database. Data were limited to subjects without pathologies that could influence intestinal motility. Random-effect meta-regression models with between-study variability were employed to assess the influence of age on SITT. Three separate models with age as a linear

or higher-order (i.e., second- and third-order polynomial) regressor were implemented to assess for the potential of both linear and curvilinear relationships. Examination of the influence of altered intestinal transit kinetics on the absorption of a sustained release theophylline preparation was explored among children between 8 and 14 years using physiologically based pharmacokinetic (PBPK) modeling. Age was not found to be a significant modulator of small intestinal transit within either the linear or higher-order polynomial meta-regression models. PBPK simulations indicated a lack of influence of variations in SITT on the absorption of theophylline from the examined sustained release formulation in older children. Based on the current literature, there is no evidence to suggest that mean SITT differs between children and adults.

Introduction

Estimation of bioavailability following oral compound administration is an inherently complex procedure, requiring a fundamental understanding of the interplay between compound and formulation properties and the dynamic nature of the alimentary canal. Within the gastrointestinal (GI) tract a multitude of physiologic parameters can exert an influence on both the rate and extent of compound absorption, including gastric emptying time, small intestinal transit time (SITT), regional differences in pH and permeability, relative abundances of intestinal transporters and enzymes, and GI fluid volumes. Since developmental changes in any of the aforementioned parameters may impart differences in oral absorption between children and adults, there is an inherent need to identify which parameters change as a function of age and by how much. The small intestine is of particular importance because it represents the region where the majority of nutrient and xenobiotic absorption transpires (Lin et al., 1999). This is due to the presence of several morphologic features on the luminal surface, such as folds (valves of Kerckring), villi, and microvilli, which serve to

significantly expand the absorptive surface area (Wilson, 1967). Correspondingly, knowledge of the time a xenobiotic spends traversing the small intestine is essential toward fostering predictions of oral compound absorption. This is particularly true for poorly absorbed compounds, where the extent of absorption is highly mediated by the time of contact between the compound and the small intestinal epithelium (Burton et al., 2002).

Conceptually, the widely used maximum absorbable dose equation as proposed by Johnson and Swindell (1996) offers a simplistic overview of how SITT can influence the extent of compound absorption. Equation (1) utilizes the absorption rate constant (k_a), compound specific saturation solubility (C_s), small intestinal water volume (SIWV), and SITT to garner estimates of the maximum absorbable dose (MAD) following oral compound administration.

$$\text{MAD} = k_a \times C_s \times \text{SIWV} \times \text{SITT} \quad (1)$$

Based on eq. 1, shorter SITT (i.e., ↓SITT) would translate to lower compound availability following oral administration; whereas, longer SITT (i.e., ↑SITT) would result in the opposite. Owing to the influence of intestinal transit on oral drug disposition, there exists an inherent need to identify specific subpopulations exhibiting differences in SITT (Levy et al., 1972).

In humans, estimates of SITT have been determined using a variety of techniques including lactulose hydrogen (H_2) breath tests, scintigraphy

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ABBREVIATIONS: GI, gastrointestinal; H_2 , hydrogen; LITT, large intestinal transit time; OCTT, orocecal transit time; PBPK, physiologically based pharmacokinetic; PK, pharmacokinetic; SITT, small intestinal transit time; SR, sustained release.

and wireless pH/pressure monitoring devices (Christensen et al., 1985; Miller et al., 1997; Maqbool et al., 2009). However, scintigraphy is generally regarded as the gold standard for SITT assessment. Among adults, SITT is generally assumed to be independent of feeding state, age, gender, weight, and compound formulation (i.e., tablet versus solution) (Yu et al., 1996). In an analysis of over 400 adult SITTs compiled over multiple investigations utilizing scintigraphy, Yu et al. (1996) estimated the average (\pm S.D.) SITT to be 199 ± 78 minutes. However, since data pertaining to children were not formally assessed by the analysis, the applicability of these values toward pediatric subjects, who are developmentally immature, remains questionable.

Based on previously published literature reviews, which are non-quantitative in nature, it has been postulated that older children may possess shorter (i.e., faster) intestinal transit times compared with adults (Strolin Benedetti and Baltes, 2003; Bartelink et al., 2006). This assertion originates, in part, from clinical investigations in asthmatic children administered sustained-release (SR) theophylline. Children frequently demonstrated large interindividual differences in the percent fluctuation between maximum and minimum steady-state theophylline plasma concentrations [i.e., $(C_{\text{peak}} - C_{\text{trough}}/C_{\text{trough}}) \times 100$] (Isles and Newth, 1985; Rogers et al., 1985). As such, they generally require more frequent dosage administration times to maintain appropriate therapeutic concentrations (Weinberger et al., 1981). In addition to higher weight-normalized clearances compared with adults (Grygiel et al., 1983), the etiology of this variability among children has also been attributed to inconsistent theophylline SR absorption due to variability in parameters such as intestinal transit time (Szefer, 1986).

Since intestinal transit has the capacity to influence the extent of absorption (i.e., bioavailability) of certain xenobiotics (Jamei et al., 2009), an understanding of the differences in SITT between children and adults is critical for deriving age-appropriate dosage regimens. This paper examines the relationship between age and mean SITT based on available literature and provides a current assessment of intestinal transit in children and adults. In addition, the pharmacokinetic (PK) influence of alterations in intestinal transit among children will be examined using a model-based approach for the compound theophylline.

Materials and Methods

Literature-Based Assessment of SITT as a Function of Age. Primary literature sources documenting SITT from children to adults were acquired from the PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>, last accessed June 2015). In addition, secondary (McConnell et al., 2008; Yuen, 2010) and tertiary (Edginton and Fotaki, 2010) literature sources were used as focal points from which further primary investigations were obtained. Data were limited to subjects free of pathologies that may influence intestinal motility. As such, subjects with GI disorders (such as diarrhea, constipation, ileus, and Crohn's disease) were excluded. The analysis included data pertaining to various formulations (solutions, single unit capsules, and multi-unit pellets) as well as different feeding states (i.e., fasting and fed).

Methods employed to measure SITT were wide ranging and included H_2 breath tests, scintigraphy, wireless pH/pressure capsules, lactose- ^{13}C ureide breath tests, fluoroscopy (X-ray), and magnetic tracking systems. Upon initial evaluation of the data, two separate investigations reported by Fallingborg et al. (1989, 1990), in which fluoroscopy (X-ray) was used, purported the two longest SITT compared with other investigations (7.5 and 8 hours). Transit times recorded by this method traced the GI movement of an orally administered capsule through the use of bony landmarks and gaseous outlines. Consequently, subtle movements such as displacement of the dosage form from the ileum to the cecum may not have been easily discerned. In addition, since the use of fluoroscopy was exclusively confined to these two investigations from the same research group, supplementary studies conducted by separate investigators were unable to assess the validity of these findings. As a

result, data pertaining to the two aforementioned studies were removed from the analysis.

Lactulose H_2 breath tests report intestinal transit in terms of orocecal transit time (OCTT) rather than an exact measurement of SITT. Furthermore, among adults, lactulose has been demonstrated to dramatically accelerate normal small intestinal transit while reducing associated intersubject variability (Miller et al., 1997). Since the focus of this analysis was to define the effects of age on SITT under normal conditions, inclusion of studies where intestinal transit was altered would appear counterintuitive. Unfortunately, a large majority of pediatric investigations exclusively employed lactulose H_2 breath testing. Exclusion of such data would notably decrease the power of the analysis toward recognizing developmental differences in intestinal transit among the youngest cohort of patients. As a result, the analysis did not exclude studies in which intestinal transit was measured via lactulose H_2 breath tests; however, data from these investigations were segregated and analyzed separately.

To discern the influence of age on SITT based on separate investigations acquired from the literature, the analysis used meta-regression (Borenstein et al., 2009). Briefly, meta-regression is a technique by which weighted data from separate investigations can be combined to provide an assessment of the influence of specific covariates on a given outcome or effect. Unlike the more familiar regression analyses typically employed within primary investigations, which examines relationships at the level of individual subjects, meta-regression examines the relationship between study-level covariates (i.e., age) and aggregated measures of effect (i.e., mean intestinal transit time) among separate investigations. In this context, mean intestinal transit time parallels the concept of a dependent variable used in conventional linear regression.

For each study, the aggregated measure of effect was recorded as the mean SITT, or mean OCTT for studies employing breath tests. Variances associated with each measure of intestinal transit were calculated based on the following formula:

$$\text{Variance}_i = (\text{SD}_i / \sqrt{n_i})^2 \quad (2)$$

where SD_i is the study-specific S.D. associated with intestinal transit and n_i is the number of subjects examined within the specific study. Since the analysis compiles SITT (or OCTT) data as measured among separate subject groups by different investigators, heterogeneity of intestinal transit between studies was expected. Therefore, a random-effects model with between-study variability was adopted. Using this method, weights associated with each intestinal transit measure were tabulated as the reciprocal of the sum of within-study variance (i.e., Variance_i) and between-study variance. Between-study variance was approximated using a restricted maximum likelihood estimation technique (Thompson and Sharp, 1999).

Since meta-regression requires study-specific effect measures (e.g., SITT) to be summarized in the form of mean and S.D., supplementary estimation techniques were employed for studies that summarized data using alternative statistics. In studies where the SITT (or OCTT) values were represented by the median, maximum, and minimum, estimates of mean and S.D. were computed as described by Hoza et al. (2005). In studies where SITT values were summarized using the interquartile range (i.e., 25th percentile, median, and 75th percentile), the estimation techniques denoted by Wan et al. (2014) were employed. In several investigations multiple SITT determinations were conducted on the same participants under various conditions (i.e., fasted versus fed or transit of tablet versus transit of solution). In such cases, data provided by each treatment arm were considered to be highly correlated (i.e., Pearson's correlation coefficient $r \approx 1$). Inclusion of correlated data into the analysis as if they represent separate independent entities would inappropriately bias parameter estimates. To circumvent this issue, the analysis aggregated data in order to provide a single estimate of SITT (or OCTT) represented by the mean and pooled S.D. (eq. 3) between separate treatment conditions for such studies (Borenstein et al., 2009)

$$\text{SD}_i = \frac{1}{2} \sqrt{s_1^2 + s_2^2 + (2r \cdot s_1 \cdot s_2)} \quad (3)$$

Equation 3 depicts the formula for the pooled standard deviation (SD_i), where s_1 is the S.D. associated with the first treatment arm, s_2 is the S.D. associated with the second treatment arm, and r is the correlation coefficient between measures of intestinal transit from each treatment arm (assumed to be 1 for this analysis).

Examination of the influence of age on mean intestinal transit time was conducted using two separate analyses. The first analysis was restricted to studies that employed lactulose H₂ breath tests, where intestinal transit was postulated to be accelerated due to the effects of lactulose. A random-effect meta-regression was conducted using age as the sole modulator. For the remaining studies that employed scintigraphy, wireless pH/pressure capsules, lactose-[¹³C]ureide breath tests, H₂ breath tests (without lactulose), and magnetic tracking systems, data were also analyzed using a random-effect meta-regression model but with both age and measurement method as modulators. Since scintigraphy represents the anecdotal gold standard method, the variable measurement method was coded as either 0 or 1, where 0 pertains to studies utilizing scintigraphy and 1 pertains to studies employing other measurement techniques. Age was quantified by the mean age as depicted from each investigation. If mean values were not specified but alternative summary statistics were available, the mean age was estimated in a similar manner as depicted for intestinal transit times. For some adult investigations, only the range (i.e., minimum and maximum) of ages of the study participants were described. In these studies age was denoted by the middle of the age range. In two adult investigations (Ishibashi et al., 1998; Brun et al., 2011) no ages were specified. For these studies a mean of 45 years was used, which represents the approximate middle of the adult age range from our collected cohort of studies. Both linear and curve-linear relationships between age and intestinal transit were investigated based on the following models:

Linear

$$SITT = B_0 + (\text{measurement method} \times B_1) + (\text{age} \times B_2) \tag{4}$$

Second-order polynomial

$$SITT = B_0 + (\text{measurement method} \times B_1) + (\text{age} \times B_2) + (\text{age}^2 \times B_3) \tag{5}$$

Third-order polynomial

$$SITT = B_0 + (\text{measurement method} \times B_1) + (\text{age} \times B_2) + (\text{age}^2 \times B_3) + (\text{age}^3 \times B_4) \tag{6}$$

where the estimated regression coefficients for the model intercept, binary variable measurement method, and continuous variables age, age², and age³ are denoted by B₀, B₁, B₂, B₃, and B₄, respectively.

To reduce collinearity and mitigate computational errors associated with polynomial regression models, the explanatory variable, age, was centered (i.e., x_i - \bar{x}) within each analysis (Bradley and Srivastava, 1979). Tables 1,2, and 4 are subsequently presented using centered data; however, Figures 3–5 are presented using actual age (i.e., uncentered) to ease interpretation. In addition to the models depicted previously, models that included interaction terms between age and measurement method were also explored for studies where intestinal transit was measured by scintigraphy and other auxiliary techniques. All analyses were conducted using the metafor package (Viechtbauer, 2010) in conjunction with the R statistical software (version 3.1.2) (R Foundation for Statistical Computing, Vienna, Austria). Modulating variables (age and measurement method) were

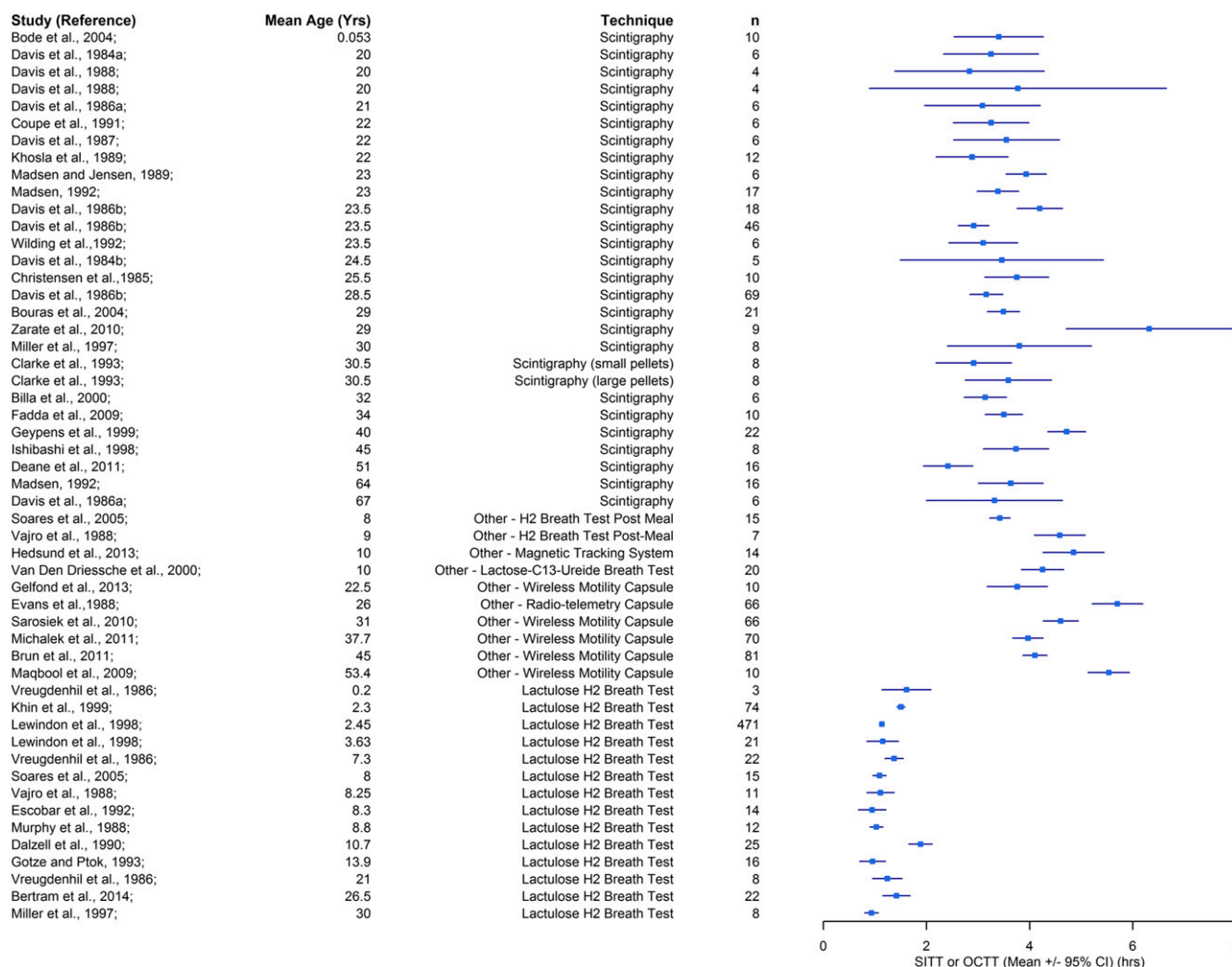


Fig. 1. Mean intestinal transit time (SITT or OCTT) estimates pertaining to each study group included within the analysis. Data are reflective of transit values from normal subjects, free of GI disease.

deemed significant contributors to the model if associated parameter estimates attained $P \leq 0.05$. For studies where results were presented graphically, data were quantified using GetData Graph Digitizer (version 2.26) [http://getdata-graph-digitizer.com].

Model-Based Assessment of the Influence of Intestinal Transit on Theophylline Pharmacokinetics in Children. To assess the impact of alterations in intestinal transit on the PK of theophylline among children, a physiologically-based PK (PBPK) modeling approach was used. Simulations were parameterized based on a previously conducted in vivo PK study conducted by Pedersen and Steffensen (1987). Briefly, the study investigated the absorption of a SR once-daily theophylline preparation in children ranging from 8 to 14 years. Plasma concentration values were ascertained from 14 children on days 6 and 7 following multidose administration.

Simulations were conducted using PK-Sim version 5.2 (Bayer Technology Services, Leverkusen, Germany). Development of pediatric-specific PBPK models followed a well-accepted modeling paradigm (Leong et al., 2012) whereby adult models are first developed and evaluated prior to scaling models toward a younger population. The adult model was parameterized utilizing drug-specific properties obtained from the literature (e.g., molecular weight, log P, pKa, and solubility). System-specific parameters (e.g., organ weights and blood flows) were provided within the software platform. Tissue:plasma partition coefficients were estimated using in silico tissue composition-based algorithms published by Rodgers et al. (2005a,b) and Rodgers and Rowland (2006). Albumin was denoted as the principle binding protein of theophylline in plasma with an average fraction unbound of approximately 0.58 in healthy adults (Buss et al., 1983; Leopold et al., 1985). Human intestinal permeability was estimated for theophylline by scaling from in vitro Caco-2 data (Parrott et al., 2009). Correspondingly, simulations used an intestinal permeability of 4.4×10^{-4} cm/s, a value that is qualitatively associated with high-permeability compounds (Lennernäs, 2014).

In adults, theophylline clearance is a combination of hepatic metabolism (CYP1A2 and CYP2E1) and glomerular filtration (Ginsberg et al., 2004; Edginton et al., 2006). Utilizing the PBPK model framework, literature-based PK studies depicting concentration-time profiles following administration of theophylline either intravenously (Aslaksen et al., 1981; Horai et al., 1983) or orally (Rovei et al., 1982) as an immediate release formulation (assuming fraction absorbed = 1) were used to obtain specific estimates of hepatic and renal clearance in healthy adults. This method of parameter obtainment has been previously described in the literature (Maharaj and Edginton, 2014). In addition,

using a similar modality, tissue:plasma partition coefficients were refined using a single global scalar value to ensure simulated results from the adult PBPK model adequately represented observed PK data.

Following development and refinement of the adult model, pediatric model development commenced. A population of $n = 50$ was generated (Willmann et al., 2007) in order to match the demographics (age, weight, and % females) of children examined by Pedersen and Steffensen (1987). Simulations used an oral dose of 15.5 mg/kg every 24 hours, representing the average dose administered during the study. Plasma sample time points within the simulation were congruent to those depicted by the study. In vivo release characteristics of the SR theophylline preparation were simulated based on fraction absorbed versus time data obtained from PK evaluations following single dose administration to a similar subset of children investigated within the same study. Using this approach, it was inherently assumed that theophylline release from the formulation was the principle rate-limiting factor for absorption. To explore the influence of intestinal transit on theophylline PK, pediatric models were parameterized using separate intestinal transit rates: 1) SITT and large intestinal transit time (LITT) were held at the reference adult values; 2) SITT was decreased by 25% compared with adult values (i.e., faster), while LITT was held at the reference; 3) SITT was decreased by 50% compared with adult values (i.e., faster), while LITT was held at the reference; 4) both SITT and LITT were decreased by 25% compared with adult values (i.e., faster); and 5) both SITT and LITT were decreased by 50% compared with adult values (i.e., faster). Simulated estimates of C_{max} , C_{min} , and percent fluctuation between peak and trough plasma concentrations $[(C_{max} - C_{min})/C_{min}]$ after 1 week of dosing were compared with observed data presented by Pedersen and Steffensen (1987).

Results

Estimates of SITT and OCTT were compiled from over 40 separate investigations obtained from the literature (Fig. 1) and pertained to subject groups ranging in average age between 20 days and 67 years. OCTT was measured via lactulose H_2 breath testing in 14 subject groups, while estimates of intestinal transit time were ascertained via scintigraphy in 28 groups and other measurement techniques in 10 subject groups. Correspondingly, 52 subject groups were included within the analysis.

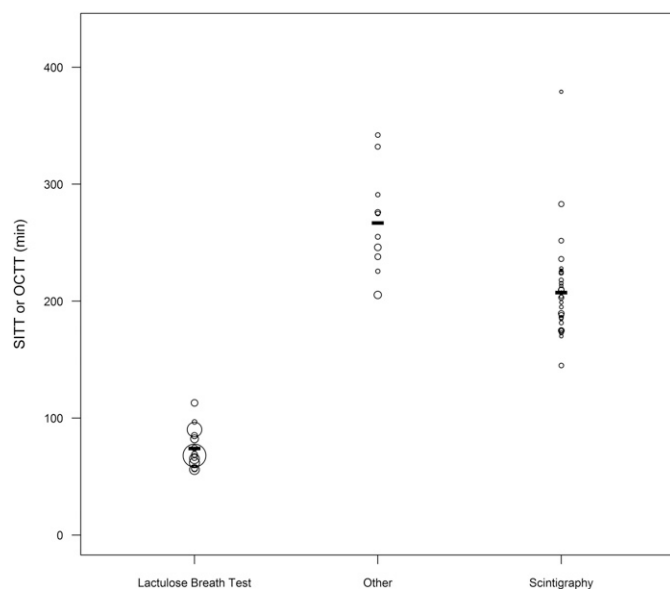


Fig. 2. SITT or OCTT segmented according to measurement method for all investigations (i.e., all age groups) documenting intestinal transit in normal subjects free of GI disease (open circles). The diameter of each circle is proportional to the $1/(\text{Variance}_i)^{1/2}$, where Variance_i represents the within-study variance. Mean values, as estimated according to a meta-regression model employing measurement method as the sole modulator, are displayed for reference (—).

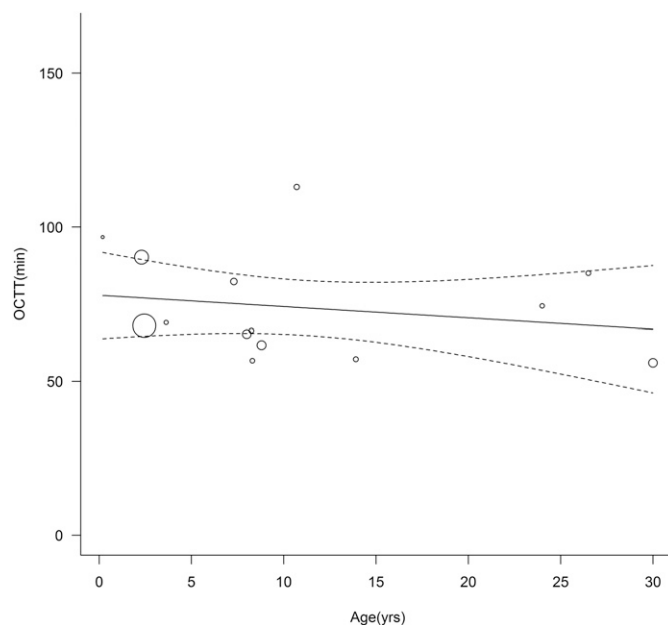


Fig. 3. OCTT as a function of age for investigations employing lactulose H_2 breath testing in normal subjects free of GI disease (open circles). The diameter of each circle is proportional to the $1/(\text{Variance}_i)^{1/2}$, where Variance_i represents the within-study variance. Estimates of OCTT based on a meta-regression model with age as a linear regressor have been superimposed for reference (mean, solid line; 95% confidence interval, dotted lines).

TABLE 1
Lactulose H₂ Breath Tests—Linear Meta-Regression Model

Summary Statistics	$k^a = 14$	$Q_M (df=1)^b = 0.5296$ ($p = 0.4668$)	$I^2^c = 92.53\%$	$R^{2d} = 0.00\%$	
	Estimate	Standard Error	p-Value	95% CI (lower)	95% CI (upper)
Fixed Effects					
Intercept (B_0)	73.8142	4.5321	*	64.9315	82.6969
Age (B_1)	-0.3663	0.5034	0.4668	-1.3529	0.6203
Random Effects					
Between study variance (τ^2)	239.7203	116.7795	—	—	—
Tau (τ)	15.4829	—	—	—	—

^a k = number of subject groups;

^b Q_M = heterogeneity statistic (Cochran's Q) – tests whether any coefficient (not including the intercept) is significantly different than 0;

^c I^2 = % of total variability due to heterogeneity;

^d R^2 = % of total heterogeneity explained by the covariate(s);

*p-Value < 0.0001; CI, confidence interval; —, value does not need to be determined.

The analysis included 11 investigations (Davis et al., 1984a,b, 1986a, 1987; Khosla et al., 1989; Madsen and Jensen, 1989; Coupe et al., 1991; Madsen, 1992; Billa et al., 2000; Bouras et al., 2004; Fadda et al., 2009), where estimates of intestinal transit were pooled between test conditions (e.g., fasted versus fed). For each of these investigations, mean intestinal transit times were not found to be significantly different between treatment arms as either denoted by the authors' results or independently confirmed using a paired Student's t test ($P > 0.05$; two-tailed test). One investigation by Clarke et al. (1993) examined GI transit kinetics of pellets of varying sizes (0.5 and 4.75 mm) and densities (1.5 and 2.6 g/cm³) in a single group of adult subjects using scintigraphy. A statistically significant difference in SITT was denoted between pellets of different sizes ($P \leq 0.05$). Consequently, data concerning this study were analyzed as two separate subject groups pertaining to each pellet size rather than combining data across both formulations.

As an initial assessment, differences between the separate measurement methods were examined with a preliminary meta-regression run with the entire data set using measurement technique (i.e., lactulose H₂ breath test versus other versus scintigraphy) as the sole modulator of mean intestinal transit time (Fig. 2). Compared with investigations employing the gold standard measurement technique scintigraphy, studies utilizing lactulose H₂ breath tests displayed mean intestinal transit times that were approximately 133 minutes faster (i.e., smaller). This result is consistent with a previous study denoting lactulose's ability to accelerate intestinal transit (Miller et al., 1997). Moreover, intestinal transit time estimates determined using other measurement methods—i.e., wireless pH/pressure capsules, lactose-[¹³C]ureide breath test, H₂ breath tests (without lactulose), and magnetic tracking systems—were on average 60 minutes slower (i.e., greater) when compared with investigations utilizing scintigraphy.

Data pertaining to intestinal transit studies employing lactulose H₂ breath tests are displayed as a function of age in Fig. 3. Fitted estimates based on a linear meta-regression model are superimposed and depict a negative correlation between age and OCTT. However, the estimated parameter associated with age did not attain statistical significance, indicating a lack of evidence to support the notion that age influences OCTT (Table 1). Second- and third-order polynomial models (Supplemental Fig. 6) exhibited slightly more complex relationships between age and OCTT; however, similar to the linear model, age was not considered a significant modulator (Supplemental Tables 5 and 6).

For studies utilizing scintigraphy in addition to other measurement techniques, data are displayed in Fig. 4. Separate regression lines based on a linear meta-regression model have been superimposed according to the measurement technique employed (higher-order polynomial models are displayed in Supplemental Fig. 7). Parameter estimates pertaining to the linear model are given in Table 2, while those pertaining to the

second- and third-order polynomial models are given in Supplemental Tables 7 and 8, respectively. For all tested models (linear, second-order polynomial, and third-order polynomial), the coefficient associated with measurement method was found to be a significant modulator of mean small intestinal transit. However, similar to the previous assessment, age was not found to be significantly associated with mean intestinal transit time. For models that included interaction terms between age and measurement method, parameter estimates associated either age or the interaction term(s) were not significant modulators of mean SITT within the linear and second-order polynomial models (Supplemental Figs. 9 and 10; Supplemental Tables 11 and 12). For the third-order polynomial model, the interaction term associated with the age³ × measurement method did attain statistical significance ($P = 0.0391$) (Supplemental Fig. 11; Supplemental Table 13). However, this result was not thought to convey a meaningful relationship between age, measurement technique, and SITT since the adjusted R^2 (R^2_{adj}), which normalizes for the effects of the additional interacting parameters, was similar between third-order

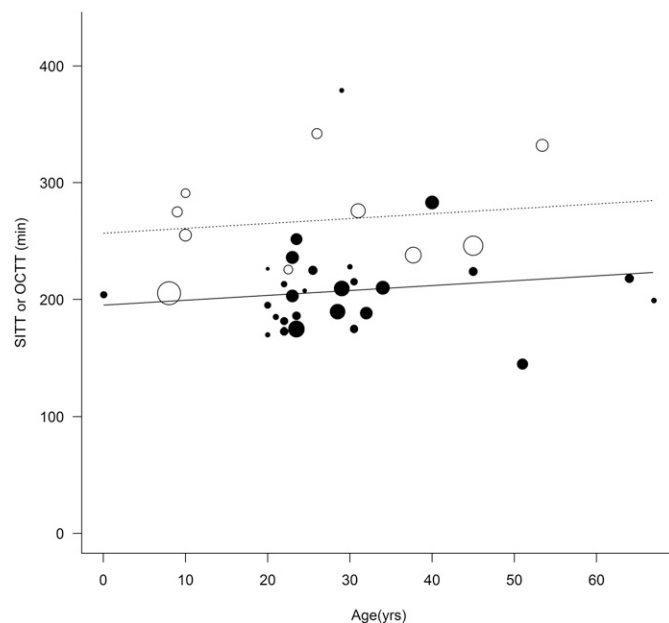


Fig. 4. SITT or OCTT as a function of age for investigations employing scintigraphy (black circles) and other measurement techniques (open circles) in normal subjects free of GI disease. The diameter of each circle is proportional to the $1/(\text{Variance}_i)^{1/2}$, where Variance_i represents the within-study variance. Estimates of mean intestinal transit time based on a meta-regression model with age as a linear regressor have been separately superimposed for studies utilizing scintigraphy (solid line) and other measurement techniques (dotted line).

TABLE 2
Scintigraphy and Other Techniques—Linear Meta-Regression Model

Summary Statistics	$k^a = 38$	$Q_M (df=2)^b = 19.1664 (p < 0.0001)$	$I^2^c = 84.57\%$	$R^{2d} = 39.63\%$
	Estimate	Standard Error	p-Value	95% CI (lower) 95% CI (upper)
Fixed Effects				
Intercept (B_0)	206.9675	7.8990	*	191.4857 222.4493
Measurement Method (B_1)	61.5907	14.0951	*	33.9648 89.2166
Age (B_2)	0.4183	0.4689	0.3723	-0.5006 1.3373
Random Effects				
Between study variance (τ^2)	1165.4337	370.2652	—	— —
Tau (τ)	34.1384	—	—	— —

^a k = number of subject groups;

^b Q_M = heterogeneity statistic (Cochran's Q) – tests whether any coefficient (not including the intercept) is significantly different than 0;

^c I^2 = % of total variability due to heterogeneity;

^d R^2 = % of total heterogeneity explained by the covariate(s);

*p-Value<0.0001; CI, confidence interval; —, value does not need to be determined.

polynomial models with and without interaction terms (R^2_{adj} 0.266 versus 0.259, respectively). In addition, highly parameterized models, such as the aforementioned interaction models, increase the risk of type I errors (false positives) (Higgins and Thompson, 2004), and as such covariates that display significance within this context should be interpreted with caution.

Simulations of theophylline SR in children (8–14 years) utilizing adult intestinal transit values provided a mean C_{max} along with an associated estimate of variability, as denoted by the % CV, that were similar to those observed by Pedersen and Steffensen (1987) (Table 3). However, simulations overpredicted the mean C_{min} by approximately 1.2 mcg/ml, whereas the percent fluctuation between C_{max} and C_{min} was under-predicted by approximately 20% when compared with observed data. Changes to SITT in isolation (i.e., without changes to LITT) did not appear to affect simulated outcomes since C_{max} , C_{min} , and the percent of fluctuation were essentially identical to those simulations where SITT was held at adult values. The C_{max} , C_{min} , and percent fluctuation were also unchanged in simulations where total intestinal transit time was

decreased by 25% (i.e., both SITT and LITT). However, a decrease in total intestinal transit by 50% resulted in a notable decrease to all indices.

Discussion

Owing to the importance of the small intestine toward the absorption of nutrients and xenobiotics, knowledge of its transit kinetics is of key interest to pharmaceutical researchers. Although estimates of small intestinal transit have been conducted by several investigators, typically subjects are confined to a specific demographic cohort (e.g., children, adult, and elderly). The presented work sought to summarize the literature pertaining to small intestinal transit to assess for differences between children and adults. The analysis included data from several studies employing a variety of measurement techniques (i.e., lactulose H_2 breath tests, scintigraphy, wireless pH/pressure capsules, etc.). To evaluate the influence of age on SITT across the diverse array of collected

TABLE 3
Simulated vs. Observed Theophylline Absorption PK at 1 Week Following Daily Administration of a Sustained Release Formulation in Older Children (8-14 yrs)

Source	Mean C_{max} [mcg/mL] (CV% ^a)		Mean C_{min} [mcg/mL] (CV%)		Mean Percent Fluctuation (%) ^b (CV%)	
	i ^c	ii ^d	i	ii	i	ii
Observed						
Pedersen and Steffensen, 1987	12.86 (24.84%)	12.18 (26.07%)	6.79 (33.03%)	7.29 (31.69%)	95.78 (26.77%)	72.80 (40.34%)
Simulated-PBPK						
SITT (adult)	12.53 ^e		8.48		52.39	
LITT (adult)	(27.15%)		(37.68%)		(25.60%)	
SITT (↓ 25%) ^f	12.53		8.48		52.38	
LITT (adult)	(27.16%)		(37.68%)		(25.63%)	
SITT (↓ 50%)	12.53		8.48		52.38	
LITT (adult)	(27.15%)		(37.68%)		(25.63%)	
SITT (↓ 25%)	12.53		8.48		52.40	
LITT (↓ 25%) ^g	(27.14%)		(37.68%)		(25.65%)	
SITT (↓ 50%)	11.15		7.81		46.91	
LITT (↓ 50%)	(29.01%)		(38.66%)		(24.49%)	

^acoefficient of variation;

^bpercent fluctuation between peak and trough plasma concentration values over a given dosing interval (i.e. [peak – trough]/trough);

^cData reported by Pedersen and Steffensen on Day 6 following oral maintenance (q24h) therapy with a sustained release theophylline formulation (Noctelin – Riker Labs Inc, Loughborough, UK) [n = 14];

^dData reported for 10 of 14 children investigated by Pedersen and Steffensen on Day 7 following oral maintenance (q24h) therapy with a sustained release theophylline formulation (Noctelin – Riker Labs) [n = 10 – same study group as depicted above; data for 4 children was unavailable];

^ePBPK models were not parameterized to include intradose variability. (i.e. once steady-state was achieved, concentration-time values were congruent between dosing intervals). As such, simulated data is only provided as a single value obtained on day 7 of theophylline maintenance dosing [n = 50];

^f25% reduction in small intestinal transit time (SITT) from adult values. SITT for normal adults was parameterized as 2.1h - the default PK-Sim® v5.2 value. This represent the time span between gastric emptying of 63% of a nonabsorbable marker and localization of 90% of the marker within the caecum.

^g25% reduction in large intestinal transit time (LITT) from adult values. LITT for normal adults was parameterized as 44.2h - the default PK-Sim® v5.2 value. This represent the time span between 90% of a nonabsorbable marker reaching the caecum and localization of 70% of the marker within the feces;

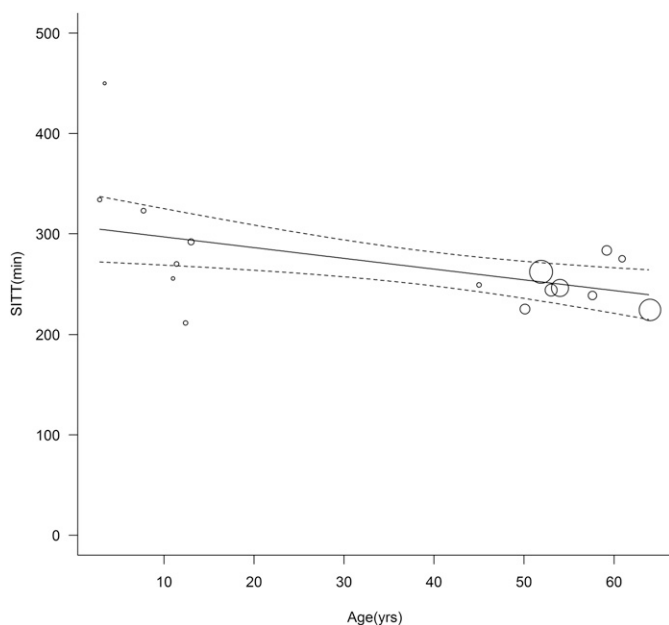


Fig. 5. SITT as a function of age for investigations employing capsule endoscopy (open circles). The diameter of each circle is proportional to the $1/(\text{Variance}_i)^{1/2}$, where Variance_{*i*} represents the within-study variance. Estimates of SITT based on a meta-regression model with age as a linear regressor have been superimposed for reference (mean, solid line; 95% confidence interval, dotted lines).

investigations, meta-regression was used. Based on this analysis of the current literature, age was not found to significantly influence SITT.

Within the analysis, studies were specifically confined to subjects free of GI pathology to mitigate the potential effects of disease or altered health statuses on intestinal transit. This criterion ensured the analysis provided an assessment of the influence of age on mean SITT within the context of normal human development. To provide an example of the potential bias that can be introduced into such an analysis if patients were not stratified accordingly, a separate evaluation of SITT was conducted using data derived from capsule endoscopy investigations. Capsule endoscopy is a diagnostic procedure that can obtain images of the small bowel while minimizing the degree of invasiveness and patient discomfort typically associated with traditional endoscopic procedures. Subjects are required to swallow a wireless video transmitting capsule that transverses the GI tract through the actions of intestinal peristalsis. Images are transmitted to a portable recording device and capsule location is determined using the obtained images (Iddan et al., 2000). Literature data pertaining to capsule endoscopy are

primarily focused toward disease diagnosis with information regarding GI transit commonly reported as a secondary outcome. Such studies typically include patients with known or suspected GI disease for indications such as obscure GI bleeding, undiagnosed abdominal pain, suspected Crohn's disease, ulcerative colitis, celiac disease, and small bowel tumors (Fireman et al., 2007). Based on 11 capsule endoscopy studies (Fireman et al., 2005, 2007; Velayos Jiménez et al., 2005; Ge et al., 2007; Tokuhara et al., 2010; Nuutinen et al., 2011; Robinson et al., 2011; Westerhof et al., 2012; Yazici et al., 2012; Oikawa-Kawamoto et al., 2013; Ou et al., 2014), which provided information on 16 unique subject groups with mean ages ranging from 2.9 to 64 years, a meta-regression was performed using a similar methodology as described previously. The analysis depicted a negative correlation between age and mean SITT using a linear model (Fig. 5). In contrast with the previous analyses that focused on healthy/normal subjects, this analysis denoted age to be a significant modulator of mean SITT (Table 4). In addition, second- and third-order polynomial regression models also found parameters associated with either age, age², or age³ provided significant contributions toward reducing the heterogeneity associated with SITT (Supplemental Fig. 8; Supplemental Tables 9 and 10). The etiology of this association is unclear, but may be linked to differences in disease prevalence between children and adults.

The results of the analyses in healthy/normal subjects, which indicate no significant effect of age toward SITT, are in contrast with previously held assertions that older children exhibit faster intestinal transit times than adults (Strolin Benedetti and Baltes, 2003; Bartelink et al., 2006). This notion has been linked to previous PK investigations of SR theophylline in asthmatic children who typically display large degrees of interindividual variability in terms of systemic concentrations (Isles and Newth, 1985; Rogers et al., 1985). However, large degrees of intersubject variability in absorption have also been denoted in adults administered SR formulations of theophylline (Sommers et al., 1992). Within our analysis, theophylline absorption among older children was examined using a model-based approach. From this assessment it was found that alterations of SITT lacked influence on the oral absorption of SR theophylline. Of note, discernable changes in theophylline absorption were only observed when total intestinal transit time (i.e., SITT and LITT) was greatly altered (i.e., ↓50%). Consequently, the results of these simulations downplay decreased SITT as a primary factor contributing to PK variability of SR theophylline in older children.

Although not formally addressed in this investigation, simulations in younger pediatric cohorts provided a similar outcome to those depicted for older children (i.e., changes in SITT failed to influence the PK of SR theophylline). The reasons behind this observation are 2-fold. First, mechanistic pediatric oral absorption models are rather underdeveloped due to limited information surrounding age-specific differences in

TABLE 4
Capsule Endoscopy Studies—Linear Meta-Regression Model

Summary Statistics	$k^a = 16$	$Q_M (df=1)^b = 7.6931 (p = 0.0055)$	$I^2^c = 93.76\%$	$R^{2d} = 41.58\%$
	Estimate	Standard Error	p-Value	95% CI (lower) 95% CI (upper)
Fixed Effects				
Intercept (B_0)	270.3442	8.8046	*	253.0875 287.6009
Age (B_1)	-1.0695	0.3856	0.0055	-1.8252 -0.3137
Random Effects				
Between study variance (τ^2)	908.1523	432.9293	—	— —
Tau (τ)	30.1356	—	—	— —

^a k , number of subject groups;

^b Q_M , heterogeneity statistic (Cochran's Q) – tests whether any coefficient (not including the intercept) is significantly different than 0

^c I^2 , % of total variability due to heterogeneity;

^d R^2 , % of total heterogeneity explained by the covariate(s);

*p-Value < 0.0001; CI, confidence interval; —, value does not need to be determined.

intestinal permeability, luminal fluid volumes and composition, and abundance of intestinal transporters. As a result, pediatric oral absorption models are commonly parameterized in a similar manner to those of adults. Second, theophylline is considered to be Biopharmaceutics Classification System class I compound (high solubility and high permeability) with adequate levels of absorption attainable throughout the entire GI tract (i.e., small bowel and colon) (Staib et al., 1986). When formulated as a SR preparation, the limiting factor modulating theophylline absorption can be attributed to its rate of release. Consequently, simulations fail to depict any changes in oral absorption of SR theophylline except in extreme cases where total intestinal transit time is shorter than formulation release time (i.e., total intestinal transit time \downarrow 50%).

In studies where the effects of separate formulations (solution versus tablet) or different feeding conditions (fasted versus fed) were explored in the same study participants, the analysis assumed SITT estimates were highly correlated (i.e., $r \approx 1$). This permitted SITT to be summarized between treatment arms using the overall mean and pooled S.D. Similarity of intestinal transit kinetics between separate dosage forms and different feeding conditions was assumed based on data presented by Davis et al. (1986b). The study examined 201 SITT estimates as measured by scintigraphy among normal adult subjects for single unit dosages, pellets, and solutions under various feeding conditions. The results conveyed no statistical difference in the transit behavior between formulations and a lack of effect of feeding status.

The current investigation segregated data measured by lactulose H₂ breath testing due to the propensity of lactulose to accelerate intestinal transit. In addition, lactulose H₂ breath tests typically report reduced degrees of intersubject variability in transit times compared with subjects where lactulose was not administered (Miller et al., 1997). These findings prevented the amalgamation of intestinal transit data obtained from scintigraphy and other auxiliary techniques with lactulose H₂ breath tests into a single analysis, since reductions in intestinal transit time variability due to lactulose may have unfairly weighted the meta-regression analysis toward these investigations. Dissimilar to scintigraphy, which provides isolated measures of small bowel transit, lactulose H₂ breath tests provide composite estimates of oral to cecal transit. Thus, to assess the effects of age on SITT using such studies, both esophageal and gastric transit must be considered. For liquids, esophageal transit transpires in the realm of seconds and is not considered to vary with age (Bowles et al., 2010). However, gastric emptying varies between fasted and fed states and can be influenced by factors such as feed composition and osmolality (Edginton and Fotaki, 2010). In a recent assessment of gastric transit data from neonates to adults, it was found that gastric emptying was not significantly influenced by age (Bonner et al., 2015). In addition, the time at which increased levels of H₂ are first detected in expired air (denoted as the OCTT) correlates with the foremost portion of lactulose reaching the cecum rather than a specific quantity (i.e., 10% of lactulose entering the cecum) (Edginton and Fotaki, 2010). Consequently, for breath testing, differences in gastric emptying times (i.e., fasted versus fed states) should not exert a substantial influence on OCTT. Based on this assessment, OCTT as measured by lactulose H₂ breath testing should provide a suitable surrogate for SITT, albeit in an accelerated state.

The analysis included data pertaining to 52 normal/healthy subject groups, 16 of which were representative of children less than 18 years old. The frequencies of pediatric subject groups stratified according to specific developmental age ranges were as follows: one neonate (0–30 days); one infant (1 month to 2 years); three young children (2–5 years); 10 children (6–12 years); and one adolescent (12–18 years). Accordingly, it can be seen that data pertaining to young children, especially those less than 2 years of age, are disproportionately underrepresented

within the analysis. This pattern is concerning since the youngest subjects (i.e., neonates) are considered to be the most functionally immature, and therefore the most likely to display developmental differences in comparison with adults. Consequently, the findings presented by this analysis are contingent on currently available literature, and as such are malleable to change if additional investigations, especially in neonates and infants, are prospectively conducted.

In one investigation, SITT within a single subject group was found to be statistically different ($P \leq 0.05$) between administration of pellets of varying size (0.5 versus 4.75 mm pellets) (Clarke et al., 1993). Rather than combine the measurements into a single outcome, the data were analyzed as separate groups. Although this clearly introduces a small degree of bias into our analysis, the presented results are similar to that if the aforementioned investigation was simply excluded from the analysis altogether. A major limitation associated with meta-regression or any other technique where data are summarized over trials as opposed to individual subjects is aggregation bias (i.e., ecological fallacy). This bias describes the loss of information that occurs when data are averaged across trials, resulting in an inability to detect correlations that would be present if individual study subjects were assessed (Thompson and Higgins, 2002). Unfortunately, the majority of literature investigations summarize data over all study subjects as opposed to denoting individualized measures of age and SITT. Consequently, despite the potential for aggregation bias, meta-regression was still deemed the most appropriate analysis technique.

Conclusion

The essential role of the small intestine toward facilitating absorption of nutrients and xenobiotics highlights the inherent need to appropriately define its transit kinetics. Within the literature, SITT has been reported using a variety of measurement methods by several research groups. Previous investigations have summarized SITT reflective of adult subjects, but the relevance of these values toward children remained questionable. The present study employed meta-regression to summarize the effect of age on SITT. Based on this analysis, there is no evidence to suggest that mean SITT differs between children and adults.

Authorship Contributions

Participated in research design: Maharaj, Edginton.

Performed data analysis: Maharaj.

Wrote or contributed to the writing of the manuscript: Maharaj, Edginton.

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