Does age affect gastric emptying? A model-based meta-analysis of gastric emptying times in premature neonates through to adults

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Background

It has been suggested that gastric emptying is slower and more irregular in neonates, especially premature neonates, than in older children and adults[1,2]. This difference has been largely attributed to immaturity in gastrointestinal motility, although this has not been rigorously tested.

Objective

To assess the effect of age and meal type on gastric emptying in paediatrics and adults

Methods

Data collection Literature databases (PubMed and Embase) were searched using the keywords 'gastric emptying' (all age categories searched), 'gastric emptying AND neonates', and 'gastric emptying AND pediatrics'. The search was limited to 'human' studies published in the 'English' language. Some references were obtained from bibliographies of published papers.

Inclusion criteria Healthy preterm neonatal through adult subjects from studies reporting % of gastric contents remaining at different time points after test meal administration were included.

Exclusion criteria Obese subjects or individuals receiving medication affecting GI motility or having diseases known to influence gastric empting, including gastro-oesophageal reflux, and regurgitation or vomiting were excluded.

Model building and selection Data were modelled using a nonlinear mixed effects approach using NONMEM Version 7.2 (ICON, Dublin, Ireland) with a first-order conditional estimation method with interaction.

Three structural models were tested: exponential decay, exponential decay with lag time, and a double Weibull function[3]. The double Weibull function is described below:

$$GE_{ij} = (100 - PR_i) \times e^{-\left(\frac{t_{ij}}{\gamma_{1,i}}\right)^{\beta_{1,i}}} + PR_i \, e^{-\left(\frac{t_{ij}}{\gamma_{2,i}}\right)^{\beta_{2,i}}}$$

GEij = percentage of test meal remaining in stomach at time t_{ij} for the *i*th publication at the *j*th time point

$\gamma_{1,i}$ and $\gamma_{2,i}$: define scatter

$\beta_{1,i}$ and $\beta_{2,i}$: define shape

PR_i: When $\gamma_{1,i} < \gamma_{2,i}$, PR_i represents the percentage of test meal remaining in the stomach when emptying is temporarily halted. Constrained between 0 and 100.

Model building was guided by analysis of goodness of fit plots in Xpose 4 Version 4.3.5 and changes in the Akaike Information Criterion calculated based on the objective function values obtained from NONMEM and the number of model parameters.

Mean gastric residence times (MGRT) were calculated using the following equation[3]:

$$MGRT_i = \frac{(100 - PR_i) \times {\gamma_{1,i}}^2 \times {\beta_{1,i}}^{-1} \times \Gamma\left(\frac{2}{\beta_{1,i}}\right) + PR_i \times {\gamma_{2,i}}^2 \times {\beta_{2,i}}^{-1} \times \Gamma\left(\frac{2}{\beta_{2,i}}\right)}{(100 - PR_i) \times {\gamma_{1,i}}^2 \times {\beta_{1,i}}^{-1} \times \Gamma\left(\frac{1}{\beta_{1,i}}\right) + PR_i \times {\gamma_{2,i}}^2 \times {\beta_{2,i}}^{-1} \times \Gamma\left(\frac{1}{\beta_{2,i}}\right)}$$

Covariate selection Covariates tested were postnatal age, gestational age, and meal type. Test meals were divided into five categories: aqueous solutions, breast milk, formula, semi-solid and solid meals.

Validation External validation was performed on a validation dataset and visual predictive checks were performed using PLT tools Version 4.0 (PLTsoft, San Francisco, CA).

Simulations based on final model The final model was coded in MATLAB Version 2010.2 (MathWorks, Natick, MA) for further investigation. The % remaining *versus* time plots were simulated for 1000 individuals ranging in age from 0.01 to 800 months for the five different meal types.

Results

The initial dataset consisted of 49 gastric emptying studies (representing 1991 individuals) covering an age range from preterm neonates of 28 weeks' gestation to adults. The validation dataset consisted of 17 studies (representing 386 subjects). The % of test meal remaining *vs.* time for all studies used in the meta-analysis is shown in Figure 1.

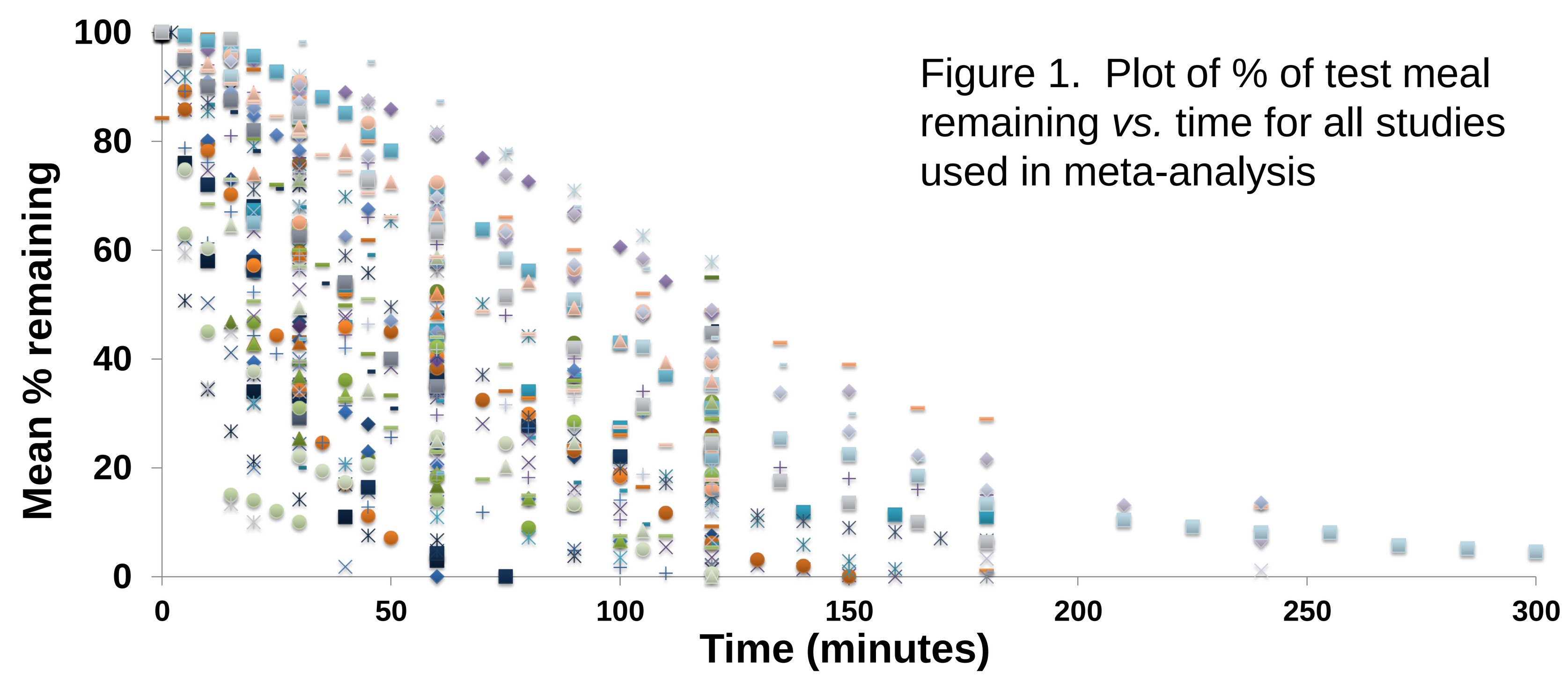

Figure 1. Plot of % of test meal remaining *vs.* time for all studies used in meta-analysis

Based on the objective function values and the goodness of fit plots, the double Weibull function was selected as the final model. The performance of the final model is shown in Figure 2 as a visual predictive check plot based on the initial dataset.

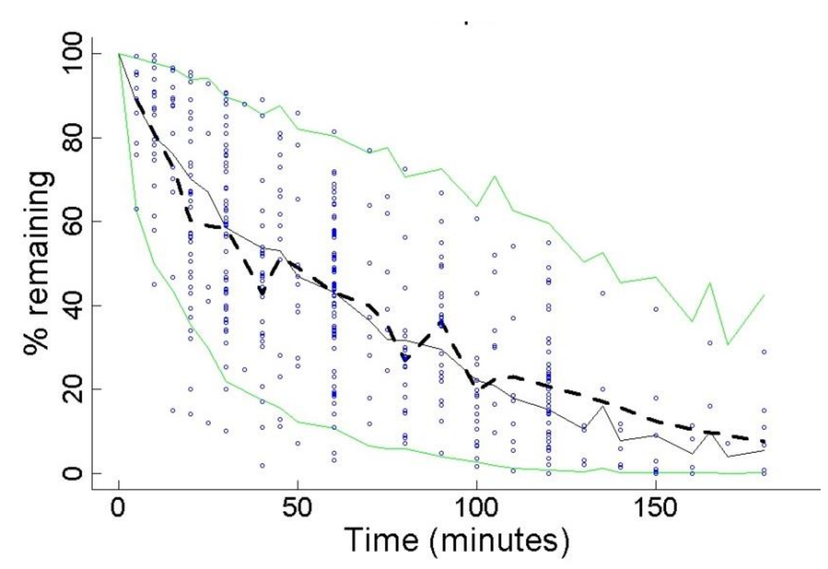

Figure 2. Visual predictive check plot based on initial dataset shows good predictability of the model. Green lines represent 2.5[th] and 97.5[th] percentiles of model-predicted data. Solid grey line represents 50[th] percentile. Dashed black line represents median of the observed data.

Test meal type had a significant influence on mean gastric residence time. Age and gestational age were not significant covariates.

Simulations show influence of food type on MGRT (aqueous<breast milk<formula<semi-solid<solid) (Figure 3a). Simulated data also show lack of relationship between MGRT and age (Figures 3b, 3c).

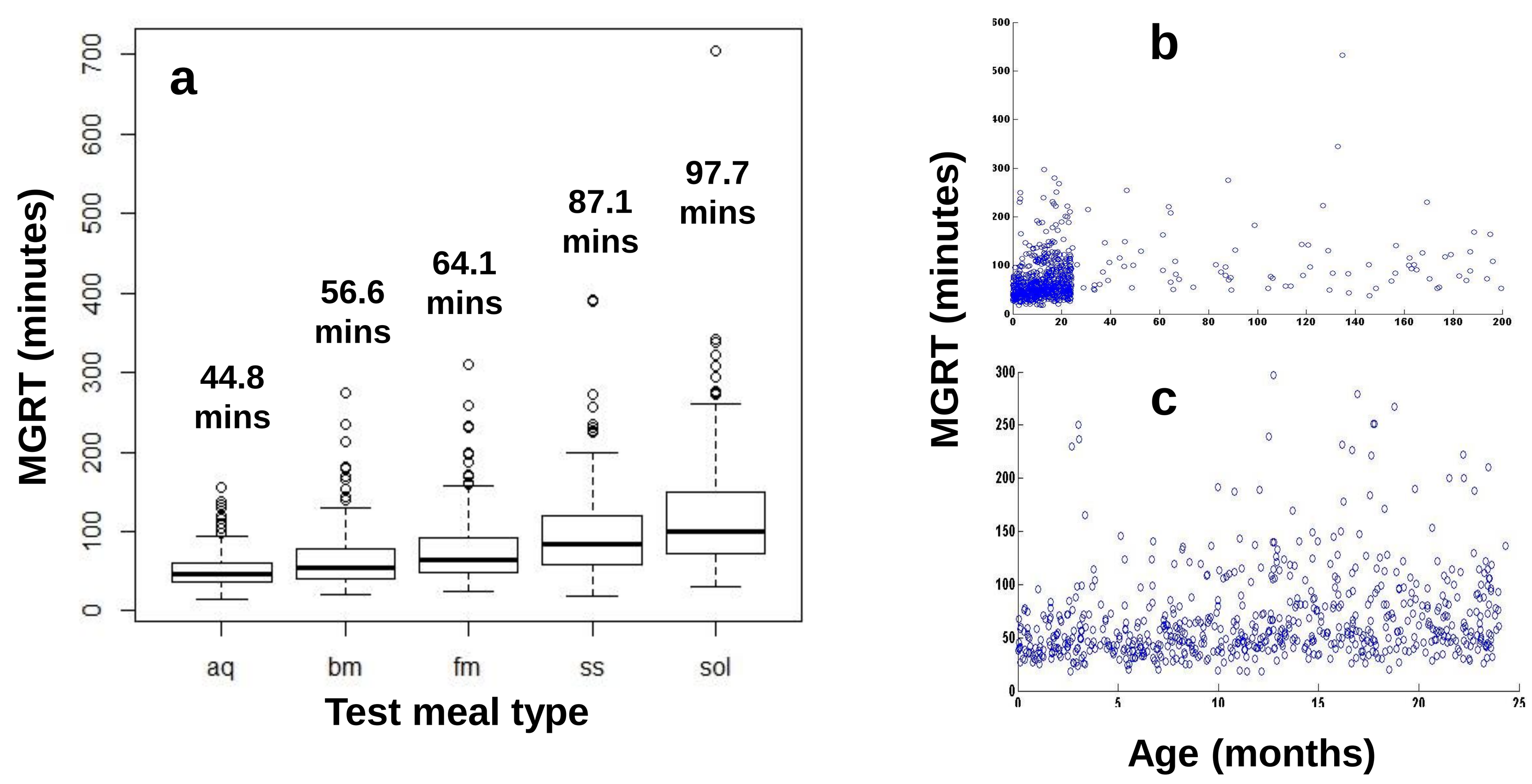

Figure 3. Simulation results a) Mean gastric residence times by meal type b) Mean gastric residence times *vs.* age c) Expanded view, 0 – 25 months

Discussion

These findings challenge the assertion that gastric emptying time is different in neonates, including premature neonates, as compared with older children and adults, and reinforce the significance of food type in modulating gastric emptying time. However, age and food type are confounded in the analysis and further prospective studies across a wide age range are required.

References

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TAIN TREATMENT OF ADRENAL INSUFFICIENCY IN NEONATES AND INFANTS