Establishing the Colonic Mean Residence Time for Different Physical Drug Entities in Caucasians: A Meta-Analysis

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Background

Predicting the rate and extent of drug absorption is a critical aspect of drug development. Physiologically-based pharmacokinetic (PBPK) models are routinely utilized for drug absorption predictions[1], hence, a realistic representation of the gastrointestinal physiological parameters, including small intestinal and **colonic mean residence time (MRT)** for a specific population **with variability** is required in order to predict drug absorption with more confidence[2].

A meta-analysis based upon data from 30 individuals of colonic MRT for single dosage unit forms by magnetic marker monitoring data was recently described[3]. However, an exhaustive search of the literature measuring **colonic MRT in Caucasians and for various drug physical entities** has not been undertaken or published so far.

Aim

A **literature meta-analysis** was performed to establish the total and ascending colonic MRT (mean, coefficient of variation (CV)) in adult Caucasians.

Data were collated for several physical entities of the drug; **fluid and dissolved drug; fine particles; pellets** and **monoliths** for incorporation into the North European Caucasian population library of the Simcyp Simulator, Version 16 (Simcyp, a Certara company, Sheffield, UK).

Methods

A search for Caucasian colonic transit times for fluids; fine particles; pellets and monoliths were performed through a keyword search using electronic databases such as PubMed; Google Scholar and university databases (*e.g.* DIVA). Where available, total and ascending colonic MRTs were incorporated into the final meta-analysis. It is important to clarify that 'transit time' is a general term that encompasses; total colonic transit, MRT and transit half life (t½). Where a t½ is reported this is transformed to an MRT using the natural log function - LN(2), where

Equation 1 - $$\mathbf{MRT} = \frac{t½}{LN(2)}$$

Where individual data was not reported data were extracted *via* GetData graph digitizer. Weighted mean, geometric mean, and CV were calculated. Data were tested for heterogeneity.

For monoliths a variety of studies using single dosage technologies were used. Pellet studies typically employed radio-opaque markers of different shapes, while fine particle MRT was determined using radio-labelled activated charcoal. An orally-dosed non-absorbable radiolabelled solution permitted fluidic MRT to be measured.

Where studies reported separate MRTs for males and females, a gender-specific meta-analysis was performed.

In brief, inclusion criteria for the final database included;

- Healthy adult Caucasian volunteers (18-81 years)
- Colonic transit distinguished by anatomical or physiological markers
- Original research sources sought in preference to reviews

In instances where there were missing data and to enable an appropriate value to be incorporated in to the Caucasian population library of the Simcyp Simulator, version 16, scaling approaches using relationships to other entities where data was available were undertaken.

Results

- Data from **67 references** were logged in the database
- **38 references** encompassing **46 studies** fulfilled the **inclusion criteria**
- Total colonic MRT data from **1160 individuals** were collated for the final meta-analysis

Gap Analysis - There were no suitable data available for meta-analysis of total colonic MRT for fine particles as these studies typically spanned only 48 h duration, which is insufficient to determine a total colonic MRT. Like-wise there was no suitable data reported for ascending colon MRT for monoliths and fluids.

References

1. Kostewicz *et al*., 2014, EJPS, 57, 300-321;
2. Sjogren *et al*., 2014, EJPS, 57, 99-151;
3. Henin *et al*., 2016, Pharm Res, 33, 751-762;
4. Proano *et al.,* 1991, Am J Physiol, 23, G13-16.

As the size of the entity increases, the duration of total colonic MRT shortens (Figure 1), thus **monoliths possess shorter mean residence times than other entities**.

Females consistently possess longer total colonic MRT than males.

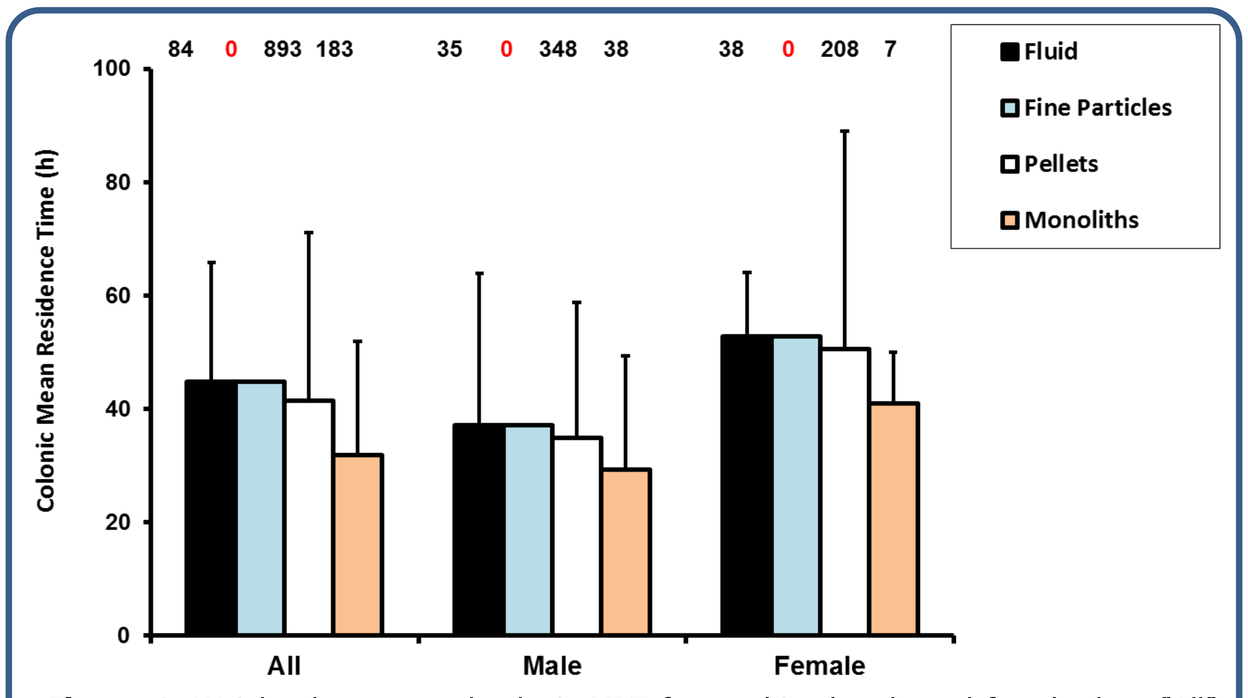

Figure 1. Weighted mean total colonic MRT for combined male and female data ('All') and separated by gender specifically for fluid (black), fine particles (light blue), pellets (white) and monoliths (orange). Error bars denote SD and the values above the bars represent the number of individuals in the analysis.

There was no suitable data available to characterise fine particle total colonic MRT. Based on the assumption that fine particles migrate with luminal fluid, the fluid-based MRTs were used as a surrogate for each gender.

There were fewer individuals (n=614) suitable for determination of weighted mean ascending colon MRT than for total colonic MRT (Figure 2).

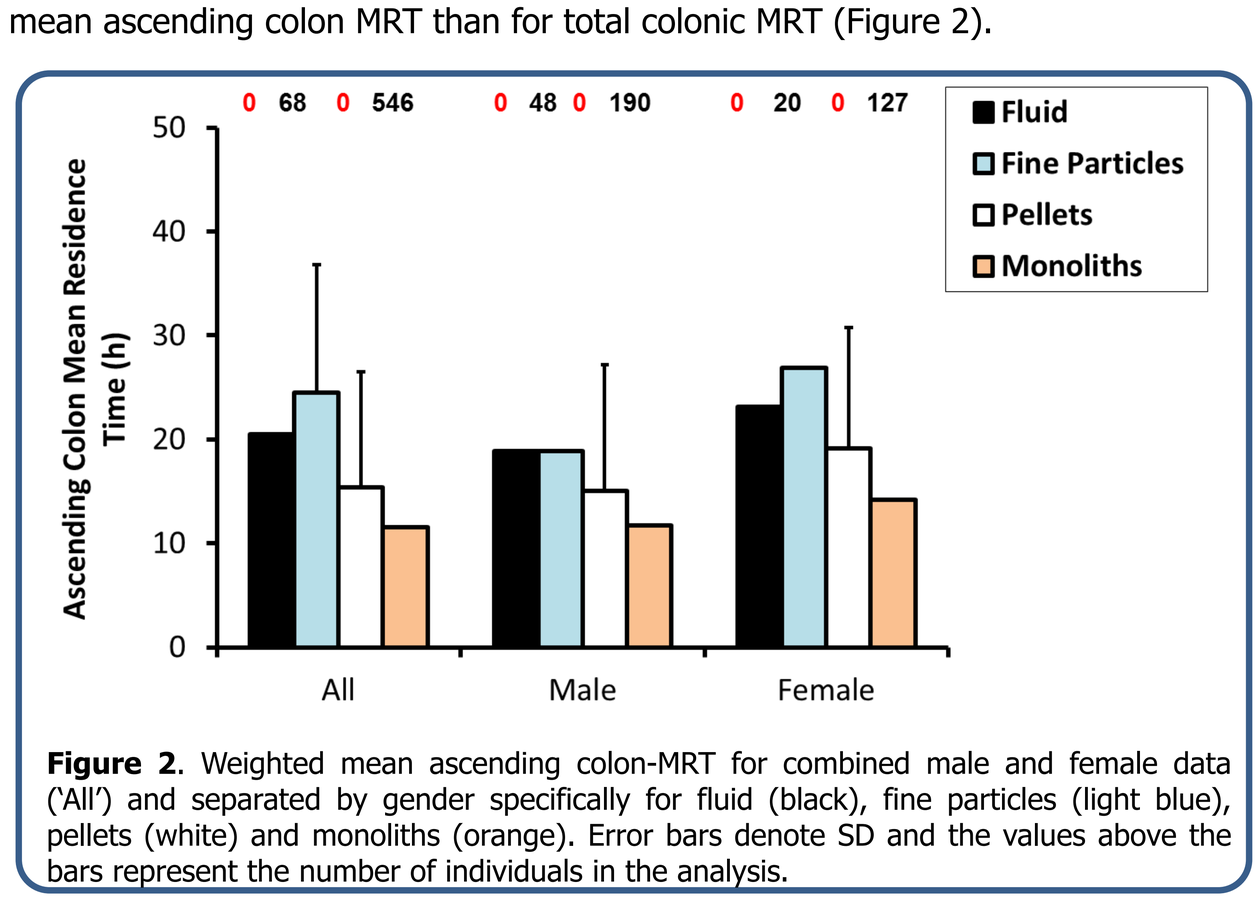

Figure 2. Weighted mean ascending colon-MRT for combined male and female data ('All') and separated by gender specifically for fluid (black), fine particles (light blue), pellets (white) and monoliths (orange). Error bars denote SD and the values above the bars represent the number of individuals in the analysis.

Where suitable data was directly available for individuals (*i.e.,* fine particles and pellets) **the larger entity pellets possessed faster ascending colon MRT compared to fine particles** (**Figure 2**)**.**

Also in this sub-set, **females consistently possess longer total colon-MRT than males**.

There was no suitable data available to characterise fluid or monolith ascending colon MRT. Values for fluid and monolith ascending colon MRT were assigned based on fluid total colonic MRT values corrected for percentage time spent (36%) in ascending colon for pellets, and a correction for entity-specific colon-MRT bias (1.26-fold)[4] was used for fluid corrections.

Conclusions

- To our knowledge this study provides the most exhaustive meta-analysis to obtain Caucasian total and ascending colonic MRT values with variability to date.
- The data reveal that females consistently possess longer total and ascending colonic MRTs than males.
- There is an inverse relationship between the physical drug entities size and the total and ascending colonic MRT
- This system data should enable more robust prediction of colonic drug absorption using PBPK modelling and simulation.