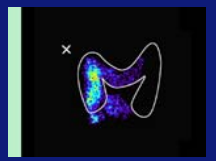
Quantifying the Impact of a Drug on Gastric Emptying: Measuring the Pharmacodynamic Effect in Clinical Trials

A Rankin, M Paterson, A Connor

Pharmaceutical Profiles, Mere Way, Ruddington Fields, Ruddington, Nottingham, NG11 6JS, UK

Tel: +44 (0) 115 974 9000
Email: enquiry@pharmprofiles.com
www.pharmprofiles.com



Introduction

Many drug classes are known to alter the rate of gastric emptying (GE). Whilst there is no specific regulatory guidance requiring the impact of drugs on GE to be measured, it is important to fully understand the mode of action and the relationship between the pharmacokinetic (PK) profile and the pharmacodynamic response.

The effect on GE may be a beneficial and hence a targeted effect or it may be detrimental. In either case, the impact of altering the rate of GE on the PK profile of other drugs likely to be administered to a particular patient population should not be under-estimated.

Therefore, the accurate quantification of the rate of GE is critical to supporting proof of concept, label claims and predicting the impact on co-administered drugs.

Methods

Three methods suitable for measuring GE in clinical trials were compared:

- Scintigraphic imaging
- Paracetamol (acetaminophen) absorption
- ^{13}C-octanoic acid breath test

A review of the methods, as reported in the literature and based on our experience, was performed to identify the relative merits of each technique.

Scintigraphic imaging

The use of scintigraphic imaging for the quantification of GE was first introduced in 1966[1] and has been further refined since then.

Methods and facilities:
A short half-life gamma emitting radionuclide is incorporated into the solid and / or liquid phase of a meal[2]. A gamma camera is used to acquire scintigraphic images at regular intervals for a defined period. Quantification of the amount of radioactivity within the stomach is then performed, including standard data corrections for radioactive decay and tissue attenuation. A facility with appropriate approvals to handle and administer radioactivity to volunteers, plus access to a gamma camera is required (i.e. a specialist unit or hospital nuclear medicine department).

Data generated:
The complete profile of GE is determined and clearly defined, standard parameters are calculated for the direct assessment of GE. Key parameters include:

- Time to initial GE (lag phase)
- % remaining in the stomach over time (GE profile)
- Gastric half emptying time ($t_{50\%}$)

Solid and liquid phase GE can be measured concurrently and detailed analysis of intra-gastric distribution can be performed[3]. The processes of solid and liquid phase GE are regulated by distinct mechanisms. Further, the distribution of stomach contents is known to impact on gastrointestinal (GI) symptoms such as feelings of satiety.

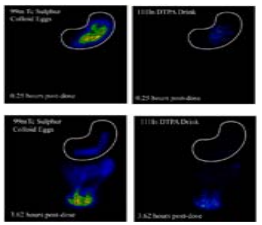


Figure 1: Representative scintigraphic images illustrating assessment of GE.

Paracetamol absorption

In 1973 Nimmo and colleagues reported the impact of altering the rate of GE on paracetamol absorption[4]. A correlation between paracetamol PK and GE $t_{50\%}$, as measured scintigraphically, was noted leading to the use of paracetamol absorption as a surrogate measure of GE.

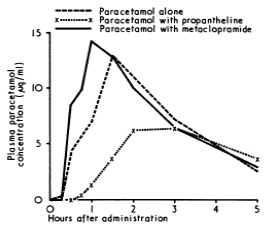


Figure 2:
The effect of propantheline and metoclopramide on paracetamol absorption[4]

Methods and facilities:
Paracetamol is administered, as a solution (common) or a solid dosage form (less common). Following dosing, blood samples are taken at regular intervals for a defined period and are submitted for bioanalysis using standard methods. This study type can be performed in most clinical units.

Data generated:
Standard pharmacokinetic parameters are used as an indirect measure to approximate the rate of GE. Different groups use different parameters, including C_{max}, t_{max}, AUC and concentration at a fixed time.

^{13}C-octanoic acid breath test

This is a novel method that was first proposed in 1993[5] and is still being refined[6]. Following ingestion, ^{13}C-octanoic acid is rapidly absorbed from the duodenum and oxidised in the liver to $^{13}CO_2$. The $^{13}CO_2$ is immediately exhaled in the breath. As a result, the rate limiting process for $^{13}CO_2$ excretion is GE.

Methods and facilities:
The solid phase of a meal is labelled with ^{13}C-octanoic acid, a stable isotope. Breath samples are then taken for a defined period and are analysed for ^{13}C concentration. This can be performed at most clinical units. However, access to isotope ratio mass spectrometry is required for analysis of the samples.

Data generated:
The % ^{13}C excreted per hour is determined. Complex mathematical corrections and modelling are then performed to account for absorption, metabolism and excretion of the label[7]. Key parameters include:

- Time to initial GE (lag phase)
- Gastric half emptying time ($t_{50\%}$)
- Gastric emptying coefficient

Comparison of approaches

Paracetamol absorption vs. scintigraphic imaging:
Unlike scintigraphic assessments, the data generated from paracetamol assessments do not provide the full GE profile. Further, they represent the liquid phase of GE only and events within the stomach e.g. intra-gastric distribution cannot be elucidated. Willems and colleagues performed a literature survey in 2001 to compare the measurement of GE *via* paracetamol absorption with the results from scintigraphic imaging[8]. Data from 13 published studies were reviewed and approximately 40% (5/13) revealed only a moderate or poor correlation. The authors concluded that in general, paracetamol correlates well with liquid phase GE, but the accuracy of the technique is dependent on the methods of analysis.

^{13}C octanoic acid breath test vs. scintigraphic imaging:
The data reflects the solid phase of GE only since the ^{13}C is added to the solid phase of the meal. A profile for GE is obtained, but as for paracetamol absorption, the events within the stomach cannot be determined.

A number of research groups, including the original team proposing this method, have compared the results to scintigraphic data[e.g. 9-13]. Mixed outcomes have been obtained, ranging from excellent correlation to poor correlation and some questions regarding sensitivity. In general, the data would suggest that there is a correlation between ^{13}C excretion and solid phase GE, but accuracy may be dependent on the parameters compared and the applicability of the mathematical corrections.

Summary

A comparison of the three approaches is provided in Table 1.

Scintigraphic Imaging	Paracetamol Absorption	^{13}C-octanoic acid breath test
Non-invasive	Non-invasive	Non-invasive
Direct measurement	Surrogate marker	Surrogate marker
Clearly defined meaningful parameters	Standard PK parameters	Mathematical corrections and modelling required
Accurate	Approximation	Approximation
Concurrent solid and liquid phase emptying	Liquid phase emptying	Solid phase emptying
Intra-gastric distribution data	No intra-gastric parameters	No intra-gastric parameters
Nuclear medicine department or specialist unit	Any clinical site	Any clinical site plus specialist analytical laboratory
Radiation exposure (low dose)	No radiation exposure	No radiation exposure

Table 1: Comparison of three approaches to quantify the rate of gastric emptying

Conclusions

Scintigraphic imaging provides accurate detailed and clinically relevant data. It is the gold standard for the assessment of GE and the only direct and non-invasive measure that provides the complete GE profile, including intra-gastric distribution, for the assessment of both solid and liquid phase GE.

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