**Review**

**Guide for judicious use of the paracetamol absorption technique in a study of gastric emptying rate of liquids**

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**Abstract:** The paracetamol absorption technique, a widely used method for evaluating the gastric emptying rate of liquids, appears to be performed inappropriately, resulting from a lack of consideration of pharmacokinetics in paracetamol absorption. This review suggests that appropriate study designs and logical choice of the parameters for the rate of paracetamol absorption are the cornerstone of reliable investigation of gastric emptying using the paracetamol method.

**Key words:** gastric emptying rate, paracetamol (acetaminophen), pharmacokinetics, rate of absorption

**Introduction**

Since disorders in the gastric emptying rate (GER) of solids directly contribute to common gastrointestinal symptoms, the GER of solids appears to receive more attention than the GER of liquids. However, knowledge of pathophysiological factors in liquid GER has important clinical implications. For instance, a delay in GER of liquids can alter the effects of orally administered premedication in a patient undergoing elective surgery, may lead to pulmonary aspiration injury in an intensive care unit patient, and is often responsible for intolerance to enteral feeding in a head-injured patient. Hence, further investigations are being conducted of GER in the liquid phase. For clinical and experimental purposes, various methods are available for GER measurements.

Paracetamol (acetaminophen) in solution is rapidly absorbed from the small intestine, with little absorption from the stomach. Based on the assumption that the rate of paracetamol absorption exclusively represents GER, it has been widely used as a pharmacological marker of liquid GER. The popularity of the paracetamol method is probably due to its safety, simplicity, reproducibility, and good acceptance by patients. Nonetheless, the validity of the paracetamol method is not necessarily admitted. We believe that, due to a lack of pharmacokinetic considerations in users, the full potential of the paracetamol method is not reached despite its utility. Here, we review pharmacokinetic aspects of the paracetamol method and discuss these, with the aim being to make it more suitable for GER studies.

**Validity of paracetamol method**

The reliability of the paracetamol method is still being debated. Some investigators have found a significant correlation between the parameters for the rate of paracetamol absorption and scintigraphically measured gastric half-emptying time, the “gold standard” for GER measurement, but others have failed to find such correlation. Based on the absence of “significant” correlation, the validity of the paracetamol method has been challenged. It should be noted that authors who were against the paracetamol method studied only healthy volunteers in whom disorders in GER were not anticipated and, consequently, the range of half-emptying time would be relatively narrow. A “significant” correlation is unlikely to be found between quantities within limited ranges. On the other hand, in research favoring the paracetamol method, the range of half-emptying time was expanded by enrolling patients with a possible disorder in GER or by pharmacological interventions. As a result, a significant correlation would be disclosed. Based on these findings, we believe that real correlation exists between the rate of paracetamol absorption and the scintigraphy-based measurement of GER, although the strength of the cor-
relation may depend on the range of scintigraphic half-emptying time.

**Pharmacokinetics of oral paracetamol**

The validity of the compartmental theory has been established in pharmacokinetic analysis. Although, in general, orally given paracetamol behaves according to the multi-compartment model, the one-compartment model is also utilized in describing the kinetics of oral paracetamol. To clarify and simplify the discussion hereafter, single exponential terms are assumed for absorption and disposition. Accordingly, the time course of plasma (or serum) concentrations of paracetamol after an oral dose \( [C(t)] \) is expressed as:

\[
C(t) = F \times \left( D/Vd \right) \times \left[ ka / (ka - kel) \right] \times \left[ \exp(-kel \times t) - \exp(-ka \times t) \right]
\]

where \( F \) = the fraction of dose reaching the systemic circulation, \( D \) = oral dose, \( Vd \) = apparent volume of distribution, \( ka \) = the rate constant of absorption, and \( kel \) = the rate constant of elimination. Unless specified otherwise, the time \( t \) is expressed in h. Of note is that \( ka \) reflects the rate at which paracetamol enters the systemic circulation, and it is therefore a hybrid. Hence, \( ka \) depends on the rates of all contributing steps, but it is primarily determined by the slowest process. Since GER is three times as slow as the rate of paracetamol absorption from the small intestine, it is regarded as the rate-limiting step, indicating that \( ka \) is the representative of GER. Oral paracetamol is handled by the body as shown in Fig. 2. In brief, paracetamol in solution instantly reaches the stomach, and is delivered to the small intestine in an exponential manner. Before its appearance in the systemic circulation, a variable portion of paracetamol is lost through first-pass metabolism by the liver (\( F \)). Subsequently, paracetamol is distributed to the body tissue (\( Vd \)) and simultaneously undergoes an elimination (\( kel \)) (Fig. 2).

**Choice of appropriate parameter for rate of paracetamol absorption**

The accuracy of the paracetamol method greatly depends on the absorptive index used. Nonetheless, the most suitable index for the rate of paracetamol absorption remains inconclusive. Various pharmacokinetic parameters have conventionally been used as the rate metrics in the paracetamol method, such as the plasma concentration at 0.75h \( [C(0.75)] \), the maximum concentration (\( Cmax \)), the time to its occurrence (\( tmax \)), and the area under the time-concentration curve from 0 to \( t \) \( [AUC(t)] \) (\( t = 0.75, 1.0, 1.25, 1.5, \) and 2.0 etc.). More recently, novel metrics have been proposed, including the \( AUC(t)/AUC(2.0) \) ratio \( (t = 0.5 \) or 1.0 etc.), and the \( C(2t)/C(t) \) ratio \( (t = 0.25, \) or 0.5 etc.). Further, the Wagner and Nelson method has successfully been introduced to the paracetamol method. The \( Cmax/AUC(\infty) \) ratio is also considered to be a useful index for the rate of drug absorption, but it has not yet been applied to the paracetamol method. These parameters are mathematically expressed in Table 1. It should be recalled that the ideal rate metrics for the paracetamol method should represent \( ka \) as exclusively as possible. Advantages and limitations of each parameter are discussed below.

**Parameters influenced by \( ka \) \( D, F, Vd, \) and \( kel \)**

Numerical expressions of \( C(0.75) \), \( Cmax \), and \( AUC(t) \) reveal that they are confounded by the extent of absorption (\( D \) and \( F \)), \( Vd \), and the rate of elimination (\( kel \)). Because \( F \) and \( Vd \) cannot be estimated accurately in conducting the paracetamol method, their influences on the reliability of the rate parameters are not completely excluded. It was reported that \( F \) ranged from 0.9 after an oral dose of 1.0g to 0.68 after an oral dose of 0.5g. This suggests that administration of a smaller dose may widen inter-individual variation in \( F \). Since paracetamol is distributed throughout most body tissue and fluids, except for fat and cerebrospinal fluid, at the same intensity, \( Vd \) is thought to increase in proportion.