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The role of the stomach in drug absorption as observed via absorption rate analysis

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ABSTRACT

Absorption rate analysis (ARA) was introduced in 2011 as a no-cost investigative tool for elucidating the details of drug absorption recorded in individual plasma time–concentration profiles. The method continues to be refined since its introduction, so that a new article offering more advanced applications of the method is appropriate. The stomach has been observed to exert considerable influence on the drug absorption process beyond the usual issues of drug solubility and stability in the gastric environment. This article is intended to demonstrate how readers can use ARA to reveal common factors affecting drug absorption. A newly introduced technique is to make observations concerning individual subjects, then assemble those individual observations to reveal factors not observable on an individual basis. This technique considerably increases the utility of ARA for revealing potential barriers to drug absorption.

1. Introduction

In a previous article (Roush, 2011), absorption rate analysis (ARA) was introduced as a powerful, no-cost investigative tool for extracting a detailed description of the drug absorption process as drug product passes through the gastro-intestinal tract. Initially, the method's main use was for elucidating the cause of unexpected results in pharmacokinetic studies. Over time, the primary focus of investigations has shifted from answering "what went wrong?" to how to use the method to develop more effective formulations. Appropriate formulation decisions are made with greater confidence when pharmaceutical scientists are forearmed with knowledge of where drug dissolves and absorbs, as well as unexpected risks or opportunities that may be encountered during a drug development program.

ARA is intended as a practical tool to be used prior to and in parallel with drug formulation development. This article is meant to provide additional guidance concerning the method's application during the early stages of product development, illustrate the way some common physiological interactions are expressed in pharmacokinetic data and comment on how use of the method can add significant value to a drug development program.

As of this writing, ARA has been used to characterize the drug absorption process for approximately 60 separate phase I clinical studies. During these investigations, it has been observed that the activity of the stomach frequently has the largest influence on the rate and extent of drug absorption. The stomach's role in drug absorption has been recognized for many decades (Hunt, 1963; Prescott, 1974; Heading et al., 1973)and a review of previous research on the topic is beyond the scope of this article. The present work is meant to illustrate how to discern factors influencing absorption using pharmacokinetic data that is already in hand.

2. Methods

Individual plasma time–concentration data has been deconvolved and absorption rate profiles were obtained as described in the article introducing absorption rate analysis (Roush, 2011). All data presented in this article were collected during human phase I clinical trials which were carried out in accordance with the Code of Ethics of the World Medical Association for experiments involving humans.

Deconvolution of plasma time–concentration data is a two step process. The unit impulse response (UIR) for each drug discussed in the article was calculated using the WinNonLin IVIVC toolkit, version 2.1. For oral drug studies, the regimen with the highest bioavailability was chosen as the reference dose. All calculated values for fraction absorbed and absorption rate are relative to the mean unit impulse response determined for the population that received the reference dose. Ideally, an oral reference regimen would be a low dose solution or suspension but some flexibility is required in making the choice, depending on the regimens that

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were actually tested. After determining the UIR, deconvolution of the data set was performed using the deconvolution tool provided in Phoenix WinNonLin, version 6.3. Absorption rate profiles are generated automatically during deconvolution, since the error minimization routine employed by WinNonLin software estimates the absorption rate required between successive time points to approximate the observed time-concentration profile that is being deconvolved.

Four specific sites of absorption have been identified, based on comparison of absorption rate profiles with gamma scintigraphy images (Roush, 2011). These are the duodenum, ileum, ascending colon and late colon, which includes both transverse and descending colon, usually unresolved from each other. Absorption in the ascending colon is easiest to identify for drugs capable of absorbing in that site. Duodenum absorption is also readily identified, since it occurs first. Resolution of duodenum and ileum absorption peaks depends largely on the gastric emptying process. Depending on the degree of absorption peak resolution, it is sometimes challenging to attribute the amount of absorption that occurred in the ileum. As a general rule, the ileum absorption peak will occur at about 3 h from the beginning of duodenum absorption.

Since the present article deals with the influence of gastric activity on drug absorption, a practical definition of the gastric emptying time period is required. The reader will appreciate that absorption rate peaks have a strong resemblance to peaks observed in chromatography. For convenience, the standard definition for peak width in chromatography has been adopted. Also, residence time in the proximal small intestine (duodenum) is a function of the gastric emptying time period. For practical purposes, duodenum residence time may be assumed to be identical to the gastric emptying period. Therefore, the gastric emptying time period is defined as the width of the duodenum absorption peak at 5% of peak height (see Fig. 1). This definition is the starting point for more advanced data interpretation techniques that will be illustrated further in the text of the article. It should be understood that any mention of mean absorption rate further in the text of this article implies that an individual's gastric emptying time period has been measured and values shown are the mean absorption rate during gastric emptying.

3. Results and discussion

In many instances, the rate of drug absorption is limited by the rate of gastric emptying. However, that recognition leaves the pharmaceutical scientist with an incomplete concept of the range of possible effects. How gastric emptying rate affects absorption may be further divided into instances where intestinal transporters play a role in drug absorption and where they do not.

3.1. Drug absorption is restricted to the duodenum

It frequently occurs that a drug's gastric solubility is poor and its absorption is restricted to the duodenum. Assuming that intestinal transporters are not involved in the absorption process, slow gastric emptying naturally promotes additional absorption. The two individuals represented in Fig. 1 were given an identical dose of a drug that only absorbs in the duodenum. Subject 2114 experienced gastric emptying over a period of 1.3 h while subject 5103 had gastric emptying over 3.8 h. As a result, the drug administered to subject 5103 had more time to dissolve in the stomach and more contact time with the site of absorption. Consequently, subject 5103 absorbed nearly 4 times as much of the drug as subject 2114. This may have significant implications when clinical studies are conducted in patients, rather than healthy volunteers. It is well known that diabetes, as well as some other disease states contribute to gastro paresis (Stacher, 2001), and when this condition exists, drug exposure can be significantly higher than with normal gastric emptying.

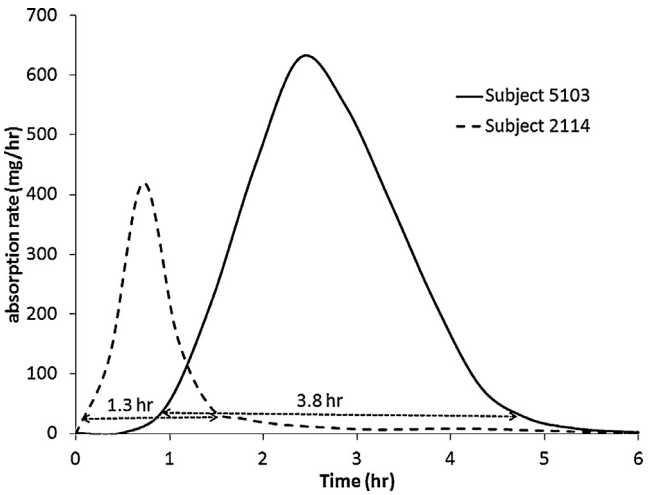

Fig. 1. Two subjects received the same dose of a drug that absorbs only in the duodenum. Subject 5103 experienced a longer gastric emptying period than subject 2114. Prolonged gastric emptying permits the drug more time to dissolve as well as longer contact with the duodenum. The gastric emptying time period is measured at 5% of the peak height for duodenum absorption.

3.2. Gastric emptying rate is variable and intestinal transporters play a role in drug absorption

The effect of gastric emptying rate is more complicated when intestinal transporters are involved in the absorption process. Active uptake transporters and efflux transporters operate by moving drug in opposite directions across intestinal enterocytes. However, the impact of a change in gastric emptying rate is expressed in similar ways in absorption rate profiles. Active uptake transporters move drug very rapidly into systemic circulation, but only if dissolved drug is presented very rapidly to the intestinal lumen. If gastric emptying slows even a little, the effect on rate and extent of absorption can be quite large. The individual illustrated by Fig. 2 participated in a bioequivalence study in which a three drug combination was compared to the same three drugs dosed as

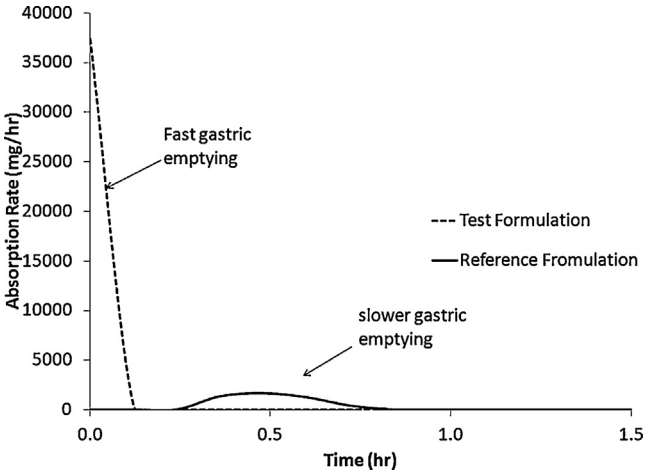

Fig. 2. This individual received a rapidly dissolving drug that is absorbed via active uptake transporters. The gastric emptying period for the test formulation was 8 min, versus gastric emptying over 25 min for the reference formulation.