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Animal versus human oral drug bioavailability: Do they correlate?

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ABSTRACT

Oral bioavailability is a key consideration in development of drug products, and the use of preclinical species in predicting bioavailability in human has long been debated. In order to clarify whether any correlation between human and animal bioavailability exist, an extensive analysis of the published literature data was conducted. Due to the complex nature of bioavailability calculations inclusion criteria were applied to ensure integrity of the data. A database of 184 compounds was assembled. Linear regression for the reported compounds indicated no strong or predictive correlations to human data for all species, individually and combined.

The lack of correlation in this extended dataset highlights that animal bioavailability is not quantitatively predictive of bioavailability in human. Although qualitative (high/low bioavailability) indications might be possible, models taking into account species-specific factors that may affect bioavailability are recommended for developing quantitative prediction.

1. Introduction

The understanding of the absorption of oral dosage forms is a key consideration in drug development. Oral routes are preferred for being less invasive and more physiological and due to ease of administration and patient compliance. However, compared to the direct entry of the drug to systemic circulation that is achieved through intravenous dosing, additional elements affecting the availability of the drug following oral administration must be considered. These may include potential for degradation in stomach or gut lumen, metabolism in the gut wall and liver, permeability through the gut wall and incomplete release of the drug from the formulation. The molecular structure of the drug and constituents of the dosage form can determine many of these processes and they define how much of a drug reaches the systemic circulation. With all of these factors in mind, the OrBiTo project is aiming to deliver rational methods and a framework for predicting how orally-administered drugs will perform (OrBiTo, 2012). In doing so, it is important to recognise some of the current practices related to estimation of the oral drug bioavailability in humans and their validity.

Understanding oral bioavailability is not just a drug development issue but it has regulatory implications as defined by the many agencies such as FDA in their guidance for industry (FDA, 2003). These usually distinguish between the rate and extent which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. Since measurement at the site of action is not practical, bioavailability calculation for extravascular administration acts as a surrogate to determine the amount of drug reaching site of action relative to those from intravascular administration (Sietsema, 1989).

Subtle differences in the methods of calculating bioavailability exist which may give rise to variable results for a given drug or drug formulation. Without an understanding of these assumptions, comparison of various bioavailability measures would not be prudent. In the current drug development paradigm, administration of drugs in various preclinical species prior to human clinical studies is common for variety of reasons. It is often assumed that data on drug absorption from animals could provide reasonable estimates of bioavailability in humans. However, whilst similarity of permeability and fraction absorbed to gut wall between animals and human is established (Chiou and Barve, 1998; Chiou et al., 2000; Chiou and Buehler, 2002; Cao et al., 2006) there are considerable interspecies differences in first-pass gut and liver metabolism. These differences can prevent concluding a level of overall bioavailability in humans based on the

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animal data. Comparisons and correlations of human and animal bioavailability have previously been reported in the literature, and although these seem to indicate that animal values are not predictive of human bioavailability, they have mainly been limited to small sets of measurements, or comparisons within one species. In some instances queries have been raised regarding the treatment, analysis and sources of the data forming the reports. Furthermore, it is not clear whether formulations have been matched when comparing human with animal bioavailability; e.g., oral doses may have been given via solution or suspension to animals while human studies make use of solid formulations which might result in formulation-linked bioavailability differences rather than solely a species difference. There may also be differences in study design such as use of the same or different study groups for oral and iv administration which may cloud the comparisons. These issues should not be overlooked when making comparisons.

We report an extensive analysis of the published data conducted as part of OrBiTo project to clarify the relationships between human and animal bioavailability, paying specific attention to those issues described above. It is expected that this report contributes to providing an answer to the question that whether a correlation exists between the bioavailability in animals and humans and whether such animal data can be used for predicting human bioavailability; quantitatively or qualitatively.

2. Methods

2.1. Calculation of bioavailability

The overall bioavailability is often considered as a composite function of fraction released and absorbed into gut wall (F_{abs}), fraction escaping first-pass gut wall metabolism (F_G) and fraction escaping first-pass hepatic metabolism (F_H):

$$F = F_{abs} \times F_G \times F_H \quad (1)$$

Calculation of oral bioavailability (F), and the definition of the fraction absorbed F_{abs} (which is one of its three components), is not unified. Pang and Rostami have recently commented on these (2011). Whilst one may consider the total oral drug bioavailability based on deducting the fraction "unabsorbed" ($1 - F$) via analysis of feces, in many cases the dose normalised relative area under the curve (AUC) after oral and iv administration is used as a measure of oral bioavailability.

There are implications in certain situations for using each of the above methods however in general they should produce the same results. Disparities might occur when there are significant elements of entero-hepatic recirculation or high first-pass metabolism in lung. When the F_{abs} is defined as the fraction of given dose that passes through the gut wall, the integration of all the mass transfer (alongside the GI tract) over the time period that absorption is happening may include the drug that originates from entero-hepatic circulation. This leads to an apparent F_{abs} can become higher than 1 when traditional comparison of AUC after iv and oral administration is used to assess bioavailability (hence F could be greater than 1).

Considering the differences between definitions used to determine F, it was essential to pay attention to methodologies used for calculating oral bioavailability before making comparisons between various species.

2.2. Sources for human and animal bioavailability values

A number of reports have previously compared human and animal bioavailability values for series of compounds. One of the commonly known comprehensive reports carried out by Grass and Sinko (2002), utilising the dataset published by Sietsema (1989). There has been no attempt to expand the data within the 2002 report with any additional data published since then or refine some ambiguities in the original report. Anecdotal evidence indicated that the number of data points in the published comparisons (within a scatter graph) were not consistent with the number of compounds that appeared in the original dataset. The reasons for this were not immediately clear from the description given in the report. To assess the number of data points and their consistency with original source, the scatter plot of human vs. animal bioavailability in Grass and Sinko (2002) was digitised using GetData *Graph Digitizer v2.22* (Get Data Graph Digitizer, 2012), and the extracted data compared to that published in the original study by Sietsema (1989). In addition, the relationships between human and animal bioavailability, reported in this original database (Sietsema, 1989) were reviewed. References sources were obtained where available and checked against criteria developed for "inclusion" which ensured the values and the species were relevant to current study. Some studies were marked as 'Rodent' which were considered too broad in light of currently utilised preclinical species. Hence, all data relating to species other than mouse, rat, dog and non-human primates were discarded.

Additional compounds were identified using the human bioavailability database published by Varma et al. (2010). Some information on were obtained from other human vs. animal literature reports (Chiou and Buehler, 2002; Cao et al., 2006; Akabane et al., 2010). Where original data and references were not provided in the publication, the authors were contacted and invited to clarify the sources of information.

Finally, systematic literature searches being carried out using PubMed and Google Scholar for the bioavailability values in human and their corresponding animal data. Original references were obtained and inspected in all cases.

2.3. Inclusion and exclusion criteria

Inclusion criteria (Table 1) were applied to ensure integrity of the data and consistency between various researchers conducting the reviews. Mean bioavailability values were extracted directly from the publications. If iv and oral data had not been obtained from the same individuals and they were from different studies, bioavailability measures were considered unreliable due to potential effects of inter-subject variability. Where more than one dose was reported, the bioavailability for the lowest dose was selected in order to minimise the potential impact of saturation effects. Information on formulations were recorded. The details of strain and sex of animals utilised were noted for each reference, along with parameters relating to the compound type and use. Additional information were noted if considered beneficial to the aims and objectives of the current investigation (e.g. number of subjects where more than one reference was found) and recorded in a 'comments section' of database. Studies relating to controlled release formulations were discarded.

Table 1
Inclusion criteria for studies.

1. Oral and intravenous data should be established in the same group
2. Species should fall under category of Mouse, Rat, Dog or Non-Human Primate
3. AUC should be calculated to infinity or absorption phase should be complete
4. Original study data (no review articles) must be included when possible