Improving the prediction of oral bioavailability using fresh human intestinal tissue

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Abstract

Here we present data obtained using fresh human small intestinal mucosa tissue mounted in Ussing chambers to showcase its utility as a predictive model of drug intestinal absorption and metabolism. When comparing the permeability data sets, a sigmoidal relationship was observed between in vitro permeability coefficients (Papp) and the reported clinical Fa values for the same test compounds. Both metabolic (phase 1 and phase 2 enzyme systems) and transporter activities were also shown to be preserved in the test system. Using chambers and fresh human gastrointestinal tissue therefore offer the opportunity to model human absorption whilst taking into account physiologically relevant intestinal metabolism and transporter effects. Ussing chambers also allow the opportunity to directly compare and understand regional and/or preclinical species differences in intestinal absorption and metabolism.

Introduction

Orally administered drugs continue to be the most common route of drug therapy. It is also increasingly recognised that intestinal biology not only influences absorption but is also an important site of metabolism that influences oral bioavailability. Before a drug progresses to the clinic an estimation of the fraction reaching the systemic circulation is required to optimise the first in man dose. At present, these predictions routinely rely on inputs from animal in vivo or cell based assay models. While the implementation and utilisation of models such as Caco-2 have greatly increased prediction performance over the years, the predictions are recognised to be superior for IV profiles over the more relevant PO profiles for the same set of drugs1. This suggests a need to better model the intestinal absorption and metabolism of oral drugs in humans. Here we present data obtained using fresh human small intestinal mucosa tissue mounted in Ussing Chambers.

Methods

Fresh human intestinal tissue, residual from resection surgery, was obtained from the ReproCELL clinical network. On arrival, the mucosa was dissected free from surrounding tissue and mounted in Ussing chambers. Samples were collected from each chamber at various time-points and analysed by LC-MS/MS. Voltage and current electrodes: electrical parameters were measured to monitor ion flow and barrier integrity. Tissue formed a barrier between right and left chambers. Addition of test substance to apical or basolateral surface of mucosa. Target concentration was 10μM in donor chamber at time zero. Heated, gassed physiological saline solution (pH 7.4, 37°C).

Results

Conclusions

- Using chambers and fresh human gastrointestinal tissue provide the opportunity to model human intestinal absorption whilst taking into account physiologically relevant metabolic and transporter effects.
- Using chambers also provide the opportunity to directly compare and understand regional and/or preclinical species differences in intestinal absorption and metabolism.
- The data presented here supports and expands upon the findings of other researchers2,3.

References