EVALUATING BARRIERS TO BIOAVAILABILITY IN VIVO: VALIDATION OF A
TECHNIQUE FOR ASSESSING NEW THERAPEUTIC AGENTS.
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ABSTRACT
Most orally administered therapeutic agents must reach the systemic
circulation to be delivered to the site of action. There are a number of
barriers potentially preventing complete oral absorption of orally
administered compounds into the systemic circulation including gastric
instability, poor membrane permeability, site-dependent absorption, and
hepatic first pass extraction. A method for determining the contributions
of these barriers to oral bioavailability has been successfully
demonstrated on 5 reference compounds. Aminocillin, antipyrine,
atenolol, propranolol and testosterone were administered intravenously,
via the intraportal vein (IPV), intraduodenally (ID) and colonically to
male Sprague-Dawley rats. The bioavailability was determined for each
compound for four route of administration and the barriers to oral
bioavailability evaluated. Testosterone had a BA of less than 10% in all
administered compounds into the systemic circulation including gastric
absorption, and high first pass hepatic extraction.

INTRODUCTION
Bioavailability (BA) is a measurement of the extent (amount) of a
therapeutically active drug that reaches the systemic circulation intact
following an administration via an extravascular route. Thus bioavailability
is an important biological determinant of therapeutic efficacy.
The majority of drugs are administered orally and delivered to the site of
action via the systemic circulation. A drug administered orally typically
must travel from the stomach to the intestines, be absorbed across the
intestinal mucosa into the general circulation through the liver and
finally to the systemic circulation. There are a number of factors which
contribute to low oral bioavailability including: poor solubility in the
gastrointestinal tract, chemical instability in gastrointestinal fluids, poor
permeability across the membranes of the gut wall, site-dependent
absorption, and high first pass hepatic extraction.

Since it is essential to understand the cause of incomplete oral
bioavailability to be able to optimize bioavailability, determining the
barriers to systemic absorption will aid in the development of orally
bioavailable drug candidates.

METHODS
In this study, we compared the bioavailabilities of various test
compounds in rats following administration via the:

- jujurulin (intravenous)
- portal vein
- duodenum
- colon

This is illustrated in Figure 1. Rats were surgically prepared with a
jujurulin cannula for blood sample collection and a second cannula for
drug administration. Rats were not anaesthetised during the experiment. Test compounds
were dosed in capsules. Blood samples were taken at specific
times, plasma was separated and analysed. The area under the
plasma concentration versus time curve (AUC) in (sec) was then
determined for each route of administration.

Dosing Vehicle: C100.5 mg/mL of each compound:
- 10% DMSO
- 40% PEG 400
- 50% Water

Plasma Sample Analysis: 60 min following dosing

Pharmacokinetic analysis: WinNonlin v. 3.1

Analytical
A method for analysis of this five-compound cassette was
developed. Figure 2 shows a typical chromatogram.

Figure 1: BARRIER TO BIOAVAILABILITY SCHEMATIC

Figure 2: Chromatogram of a 200 mg/mL Standard

Test Compounds
Antipyrine was selected as a well-absorbed reference
compound. Atenolol was selected as an incompletely
absorbed, non-metabolized reference compound. Propranolol
and testosterone represent compounds known to undergo
significant pre-systemic metabolism. And amoxicillin was studied as a compound known to have site-
dependent absorption because of the involvement of active
transporters predominantly localized in the upper small
intestine.

Pharmacokinetic Profiles
Plasma concentration vs. time profiles for propranolol
and atenolol are shown in Figures 5 and 6. Antipyrine,
testosterone, and amoxicillin curves are not shown, but
had no unusual features.

Table 1: Summary of Pharmacokinetic Parameters

CONCLUSIONS
This model is demonstrated to be useful for identifying the causes of oral
bioavailability. It separately evaluates intestinal absorption, hepatic extraction, and site-dependent
absorption. Concentration-dependence of saturable processes can also be examined.