EVALUATION OF AN INTESTINAL ACCESS PORT DOG MODEL FOR STUDYING GASTROINTESTINAL SITE OF DRUG ABSORPTION

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INTRODUCTION

Drugs can be delivered to the systemic blood by many routes; however, the most desirable route for drug administration in humans is the oral route. The ability of a drug to reach the systemic circulation after oral administration can be determined by physicochemical, biochemical, and physiological factors. Physiological factors include, gastrointestinal pH, gastric emptying time, and gastrointestinal transit time (1). Slower gastric emptying might increase the absorption of poorly absorbed, but it might decrease the extent of absorption of soluble drugs.

Animals have been commonly used as experimental models to study various aspects of gastrointestinal drug absorption and pharmacokinetics. As animal models, dogs have numerous advantages. The gastrointestinal tract of the dog permits the administration of standardized dosage forms without altering movement patterns. In addition, the gastrointestinal tract of the dog resembles that of the human in motility patterns, bile composition, pancreatic enzymes, pancreatic secretion, gut diinaasia, peptic secretion, and glandular mucosa of the stomach. However, accurate assessment of gastrointestinal drug absorption in dogs could be difficult. For example, it may be difficult to achieve reproducible intragastric drug administration with oral gavage, especially in some animals. In addition, following intragastric administration compounds might undergo chemical degradation or precipitation in the acidic gastric pH (2). With these considerations in mind, a dog model was developed to study gastrointestinal regional drug absorption.

METHODOLOGY

A. Dog Model

A colony of Beagle dogs were surgically prepared with intestinal access ports (IAP). Each dog had two IAPs on one in the duodenum and one in the colon (Figure 1). The procedure used to prepare the dogs has been previously described (4). After an appropriate healing and recovery time, the correct location and condition of the ports was verified by contrast radiography.

B. Model Compounds

Four compounds were used to validate the model: antipyrine, atenolol, propranolol, and amoxicillin. Of these, only propranolol is extensively metabolized, the other compounds are not.

- Antipyrine is rapidly and completely absorbed (5). Its absorption occurs through the cell membrane and thus is not expected to show large regional dependence.
- Atenolol is moderately (50%) absorbed (5). Atenolol crosses the intestinal epithelial layer mostly between the cells (i.e. paracellular pathway). Atenolol absorption is expected to show some regional dependence as a result of a) the decrease in surface area after distal administration and b) the greater tightness of the intercellular junctions of the colonic mucosa compared with those of the duodenal mucosa.
- Propranolol is rapidly and completely absorbed (5). Its absorption occurs via passive transcellular transport permeability. The rate and mechanism involved in propranolol absorption is likely to result in limited site-dependent absorption.
- Amoxicillin is approximately 80% absorbed (5). The intestinal absorption of amoxicillin is mediated primarily by PEPT1, an intestinal peptide transporter. Because PEPT1 is located in the small intestine but not in the colon, the gastrointestinal absorption of amoxicillin is expected to exhibit a marked regional dependence.

RESULTS

Antipyrine

Antipyrine showed no appreciable decrease in systemic area under the curve (AUC) with increasingly distal administration (Figure 1). This trend is not unexpected because antipyrine is well absorbed along the gastrointestinal tract. Thus, a marginal decrease in AUC probably reflects only differences in the surface area distal from the site of dosing.

Amoxicillin

The amoxicillin AUC after oral and intraduodenal dosing were comparable; however, the AUC after intracolonic (IC) dosing showed a clear decrease (Figure 2). The lower AUC after IC dosing probably is the result of two factors: the available absorptive surface decreases from the site of dosing and the tighter intercellular junctions in the colon compared to the small intestine.

Propranolol

Propranolol showed generally low and variable AUC across the different sites of dosing, consistent with extensive hepatic first-pass metabolism and marked inter-animal variability in drug metabolizing activity (Figure 3). Despite low AUC values there was a trend towards a decrease in systemic absorption after IC dosing compared with either intragastric (IG) or intraduodenal (ID) dosing.

Amoxicillin

The AUC of amoxicillin showed a clear and progressive decrease with increasingly distal site of dosing (Figure 4). This is consistent with the gradual decrease in expression of PEPT1 along the small intestine and absence of PEPT1 in the colon.

Table 1. Experimental access ports implanted in the dogs

<table>
<thead>
<tr>
<th>Dogs</th>
<th>Dosage</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D</td>
<td>3mg</td>
<td>twice a week x 2 weeks</td>
</tr>
<tr>
<td>IV</td>
<td>0.5mg, 5mg, 2mg, 5mg, 1mg</td>
<td>twice a week x 2 weeks</td>
</tr>
<tr>
<td>ID, IC</td>
<td>5mg, 5mg, 5mg, 1mg, 5mg, 2mg</td>
<td>twice a week x 2 weeks</td>
</tr>
</tbody>
</table>

Figure 1. Regional-dependence of systemic drug absorption of propranolol following IV, ID, ID and IC administration to intestinal portal dogs.

Figure 2. Regional-dependence of systemic drug absorption of antipyrine following IV, ID, ID and IC administration to intestinal portal dogs.

Figure 3. Regional-dependence of systemic drug absorption of amoxicillin following IV, ID, ID and IC administration to intestinal portal dogs.

CONCLUSION

• The systemic absorption of antipyrine showed no clear segmental-dependence.
• The systemic absorption of amoxicillin showed a slight decrease upon distal dosing, probably reflecting the distal surface area.
• Propranolol, despite the role of metabolism, exhibited a lower AUC after IC compared with IG and ID.
• The absorption of amoxicillin compound showed a marked decrease after distal dosing, consistent with the mechanism of absorption of this compound.
• The IAP dog model appears to be a valuable tool to understand intestinal drug absorption.

The IAP dog model could aid in the selection of formulation development strategies with greater probability of success.

REFERENCE