Transit and pH in Fasted Beagle Dogs with the IntelliCap System

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ABSTRACT SUMMARY

The pH profiles and transit in fasted male beagle dogs were studied using the IntelliCap drug delivery and monitoring system. The IntelliCap capsule measures pH and temperature while passing the gastro-intestinal tract. Data curves are analyzed retrospectively to determine the gastric residence, small bowel, and total transit times. The values from several studies with a variety of experimental designs are collected and analyzed. Selected examples of atypical curves are also illustrated.

INTRODUCTION

The beagle dog is a commonly selected pre-clinical model for pharmacokinetics (PK) studies. The actual individual gastro-intestinal (GI) transit times and local pH values can have a significant impact on the obtained PK data. Thus a knowledge and understanding of the averages and variability can be critical to the experimental design and interpretation of the results.¹,²

Solubility and absorption are key properties of compounds for oral administration. Solubility of most compounds is pH dependent and is a key factor for absorption. Absorption in the GI tract is highly dependent on location. Thus the transit times can have a significant impact on exposure. This is especially true for modified or extended release products. As both pH and transit times are typically not known during an individual test, published averages are relied on. Published traces often show “textbook” examples to illustrate the average. However the potential for variation and characteristics of outlier behavior are important to understand and interpret data correctly.

Medimetrics has developed the IntelliCap® system as a tool for the in-vivo study of oral drugs when delivered in the GI tract.³,⁴ The IntelliCap capsule comprises a drug reservoir and an electronic body. The electronic body houses a pH and temperature sensor, along with a microprocessor, wireless transceiver, and actuator for drug dispensing. The pH and temperature profiles are used to determine regional transit. This can be used to target drug delivery to specific regions in the GI tract. The system is flexible in operation and has been used in a variety of studies and at several locations. This has resulted in a detailed view on the transit and pH profiles in beagle dogs. In addition to the “typical” profile/transit behavior, several examples of atypical behavior are explored. The experience gained with the system enables a realistic view on the expected variability of transit and pH in a research setting.

EXPERIMENTAL METHODS

This is a retrospective analysis of the pH and transit of fasted male beagle dogs. Data from different studies with the IntelliCap system is examined. The IntelliCap capsule is a swallowed electronic capsule containing a pH sensor and a temperature sensor. Capsule size is 11 mm diameter by 26.7 mm long. When loaded with a water payload the capsule specific density is 1.5.

Subjects are fasted overnight and administered the capsule in the morning by deep throat deposition followed by a rinse of water to assist swallowing. The capsule measures pH and temperature throughout GI transit every 10 to 30 seconds, depending on the design of the experiment.

Time of administration and excretion are determined from the temperature profile. These points determine total transit time. Emptying from the stomach past the pylorus into the small bowel is determined by a rapid rise in pH. After entering the small bowel there is a steady rise in pH. The pH then drops quickly by about 1.0 or greater. This drop indicates transit past the ileocecal valve. Gastric residence is the time from administration to passage of the pylorus. Small bowel transit is time from pylorus passage to time of arrival in the cecum. The use of pH as landmarks for GI transit is consistent to that reported for the SmartPill system in clinical studies.⁵ A “typical” pH profile for beagle dog illustrating the main transit regions is shown in Figure 1. It is sometimes difficult to determine pylorus passage. This is particularly true in dog as the pH can be high and/or fluctuate in the stomach. To help determine capsule location, a flush of cold water may be given. If the capsule measures a drop in temperature, it still resides in the stomach. If a drop in temperature is not recorded, the capsule has passed into the small bowel.

Figure 1: Typical pH profile in beagle dog outlining transit in the major gut regions.
Traces of pH and temperature after complete GI transit are analyzed for the landmarks described above and transit times determined. Data from several studies are collected. Median and standard deviation are calculated along with discrete probability density in time bins. Further several examples of interest are presented.

RESULTS AND DISCUSSION

The median and standard deviation of transit times collected from 22 studies are given in Table 1. A plot of the probability density for gastric residence and small bowel transit is in Figure 2. Probability is calculated for occurrence between previous and indicated time point.

<table>
<thead>
<tr>
<th></th>
<th>Gastric Residence</th>
<th>Small Bowel Transit</th>
<th>Total Transit Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1:12</td>
<td>1:54</td>
<td>18:31</td>
</tr>
<tr>
<td>St Dev</td>
<td>6:29</td>
<td>0:46</td>
<td>9:59</td>
</tr>
<tr>
<td>N</td>
<td>188</td>
<td>186</td>
<td>197</td>
</tr>
</tbody>
</table>

Table 1: Composite values for transit over several studies (time as hour:min).

There is significant variability in gastric residence. An example of both short gastric residence and high stomach pH is shown in Figure 3. It is not uncommon to observe high pH in untreated dogs (no pentagastrin). Further when pH is high it is not uncommon to observe rapid stomach clearance. This combination suggests that when gastric pH is high, the pylorus is not closed and may allow the capsule to quickly pass through. All the studies examined here are fasted studies. If food is returned while capsule is still in the stomach, gastric residence time is greatly increased. In comparison to the gastric residence, the small bowel transit shows a much smaller variation. Still atypical cases do occur. An example of very fast small bowel transit is shown in Figure 4. Notice also there are extended periods of high pH in the stomach.

CONCLUSION

There is significant variability in the pH profiles and transit times in the GI tract. Past research has explored these properties and the resulting average values are typically assumed when interpreting results of pharmacokinetic studies. While averages are useful, the occurrence of atypical behavior can skew results and lead to incorrect conclusions.

The IntelliCap system is a new tool for the in-vivo study of oral drugs. The examination of pH and transit in subjects over a wide range of conditions has led to a good picture on expected behavior. While the average behavior is consistent with previously published results, understanding atypical behavior is very important. Further, the ability to measure pH and transit in every subject during a PK test is extremely valuable in interpreting results and generating a consistent picture in the face of inevitable variation.

REFERENCES