Strategies for Enhancing Oral Drug Bioavailability: Inter-Individual Variability and Manual Control of Gastric pH in Fasting Cynomolgus Monkeys

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Introduction

Cynomolgus monkeys are widely used in preclinical studies to evaluate oral drug bioavailability. Some literature reports that their fasting gastric pH typically ranges from 1.0 to 2.0, which is comparable to human gastric acidity[1]. However, our preliminary data reveal significant inter-individual variability, with fasting gastric pH ranging from 1.5 to 7.0. This variability may impact the assessment of oral drug bioavailability, especially for pH-sensitive drugs[2]

This poster presents our investigation of baseline gastric pH values in fasting cynomolgus monkeys. Furthermore, we examine the effects of pretreatment with Pentagastrin or histamine on gastric pH, and compare these effects with direct acidification using hydrochloric acid (HCl). Our findings aim to offer methodological insights for managing gastric pH variability, thereby enhancing the reliability of oral drug bioavailability assessments in preclinical studies.

Methods

A total of 26 cynomolgus monkeys were included in this study. All experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of WuXi AppTec. Gastric fluid was collected via nasogastric intubation, and pH was measured using pH paper. For baseline assessment, daily fasting pH measurements were obtained from 8 monkeys at consistent time points over three consecutive days. To evaluate gastric pH modulation, the remaining 18 monkeys were equally divided into 3 groups(Table 1). pH monitored lasted for 1 hour[3,4] . In group 4, after measuring the intragastric pH values of 6 cynomolgus monkeys at the pre-time point, only the two animals with gastric pH values above 5 were treated and subsequently tested.

Table 1. Experimental Design for Manual Regulation of Gastric pH in Cynomolgus Monkeys

Group	Animals Used	Pre-treatment	Dosage (μg/kg-mL/animal)	Time Point (min)
1	8	6	-	Once daily for 3 days
2	6	Pentagastrin (IM)	100	0, 10, 20, 30, 40, 50, 60
3	6	Histamine (SC)	100	15, 30, 45, 60
4	2	HCl Water (PO)	15	0, 5, 15, 30, 60

Results

The fasting gastric pH of the 8 Cynomolgus monkeys was 4.73 ± 1.76 ranged from 1.5 to 7.0 (Table 2).

We found no significant change in gastric pH within one hour following Pentagastrin (100 μg/kg, IM) administration in 6 monkeys, with a mean pH of 4.92 ± 2.05 (range 1.5 to 7.0) at 50 minutes (Figure 1) [3], or Histamine (100 μg/kg, SC) administration in 6 monkeys, with a mean pH of 4.67 ± 2.49 (range 1.0 to 7.0) at 30 minutes (Figure 1) [4]. In contrast, oral administration of hydrochloric acid (15 mL, 0.1M) in 2 monkeys (selected from 6 monkeys with initial gastric acid pH above 5) successfully reduced intragastric pH to 2.0 within 5-15 minutes (Figure 1). The effect lasted approximately 30 minutes.

Experimental results revealed significant inter-individual variability in response to Pentagastrin and histamine treatments. Neither treatment consistently reduced gastric pH below 2.0 in cynomolgus monkeys. In stark contrast, oral administration of acidified water (0.1M HCl) rapidly and effectively lowered gastric pH to <2.0, achieving the target range for controlled gastric pH conditions(Table 3).

Table 2. Individual and Mean Gastric pH Values in the Control Group of Fasted Monkeys

Animal Number	Day1	Day2	Day3	Mean(SD)
Monkey 1	2.5	2.5	3	2.67 (0.289)
Monkey 2	4	4.5	4	4.17 (0.289)
Monkey 3	3.5	3.5	3	3.33 (0.29)
Monkey 4	7	7	7	7.00 (0.00)
Monkey 5	3.5	7	6	5.50 (1.80)
Monkey 6	7	5	7	6.33 (1.15)
Monkey 7	1.5	7	4.5	4.33 (2.75)
Monkey 8	3	6	4.5	4.50 (1.50)
Mean(SD)	4.00 (2.00)	5.31(1.73)	4.88(1.62)	4.73 (1.76)

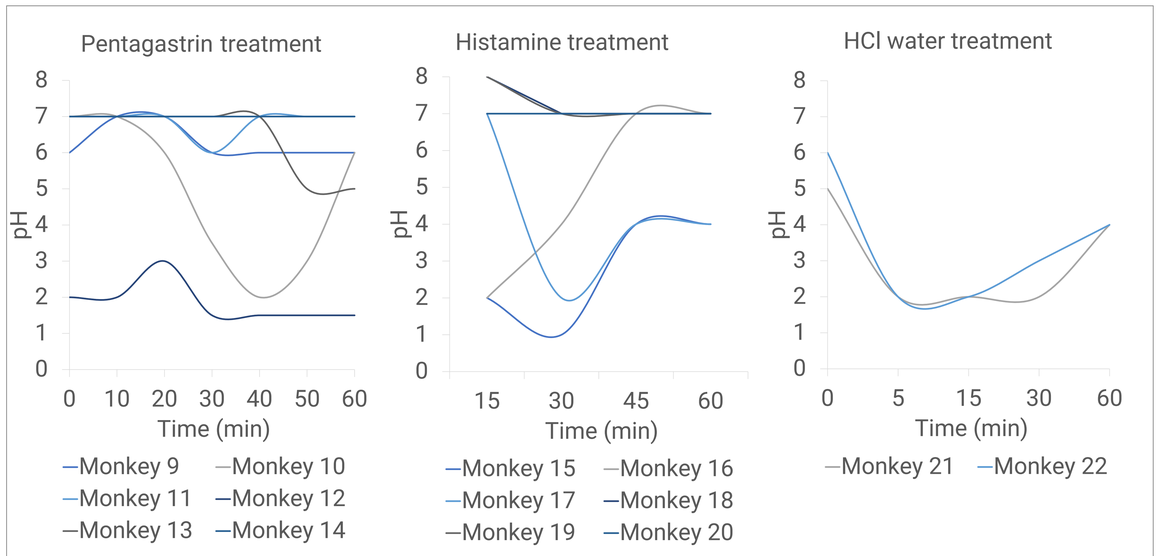

Figure 1. Monkey Gastric pH after Pentagastrin, Histamine, and Hydrochloric Acid Water Treatments

Table 3. Mean Gastric pH Values in Cynomolgus Monkeys with and without Pretreatment

Group	Animals Used	Pre-treatment	Dosage (μg/kg-mL/animal)	Lowest Mean Gastric pH	Range
1	8	6	-	4.73 ± 1.76	1.5 to 7.0
2	6	Pentagastrin (IM)	100	4.92 ± 2.05	1.5 to 7.0
3	6	Histamine (SC)	100	4.67 ± 2.49	1.0 to 7.0
4	2	HCl Water (PO)	15	2	2

Conclusions

Fasting cynomolgus monkeys exhibit significant gastric pH fluctuations, highlighting the importance of considering individual variability in oral drug bioavailability assessments. Notably, oral administration of 0.1M hydrochloric acid (HCl) reliably reduce gastric pH, achieving pH levels (<2.0) that closely mimic the fasting human gastric environment.

References

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