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The effect of antacids and multivitamins on raltegravir

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INTRODUCTION

- Integrase inhibitors are increasingly being used as first line therapy in the treatment of HIV.
- All integrase inhibitors are known to bind to divalent cations.
- Previous studies have shown the raltegravir (RAL) interaction with antacids is distinctly different from other integrase inhibitors.[1]
- RAL absorption is influenced by antacids and gastrointestinal pH.
- It is unclear which mechanism has the predominant effect on pharmacokinetic (PK) variability.

OBJECTIVES OF THE RalpH STUDY

- To assess the pharmacokinetic interactions of single dose RAL with antacids and multivitamins.
- To determine the role of intestinal pH in these interactions.

METHODS

- ***Study Design:*** Single centre, open label, randomised, 3 arm, 5 phased controlled healthy volunteer study.
- Eligibility Criteria: Age ≥ 18 years and < 60 years; written informed consent; no significant acute or chronic illness; negative screen for HIV, hepatitis B & C; no proton pump inhibitors, multivitamins and/or antacids.
- Regulatory (EudraCT 2013-000278-31) and ethical (NRES 13/SC/0257) approval were gained. ClinicalTrials.gov registration NCT01784302.
- ***Study Treatment:*** Healthy volunteers received single dose RAL (Isentress 400 mg film coated tablets), followed by RAL plus Maalox Plus (30 ml; MP), sodium bicarbonate (1 g; SB), multivitamin (Forceval 1 capsule; Vit) or Maalox Plus (30 ml; MP2 2 h prior to dosing) without food, for 4 study days.
- ***Sampling:*** Intensive PK sampling was undertaken over the dosing period on study days at pre-dose (0 h), 1, 2, 3, 4, 6, 8, 10 and 12 h post-dose.
- RAL plasma concentrations were quantified by a fully validated HPLC-MS/MS method with a lower and upper limit of quantification of 5 and 5000 ng/L, respectively.
- ***pH Measurements:*** Heidelberg pH diagnostic system was used to collect ambulatory gastrointestinal pH on study days at pre-dose (0 h), 1, 2, 3, 4, 6, 8, 10 and 12 h post-dose. Participants swallowed a capsule that transmitted pH data transcutaneously to a transceiver linked to a computer via telemetry (http://www.phcapsule.com/).
- ***Safety & Tolerability:*** Evaluated clinically by vital signs, laboratory investigations, questionnaire and clinical review.
- Adverse events (AEs) graded using Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (2004). Causality was assigned using Liverpool assessment tool.
- ***Data Analysis:*** RAL PK parameters (area under the concentration-time curve over 12 h, AUC_{0-12}; maximum concentration, C_{MAX}; concentration 12 h post-dose, C_{12}; time to maximum concentration, T_{MAX}) were calculated by non-compartmental methods using WinNonLin™.
- To assess differences between phases, geometric mean ratios (GMR) and 90% CI were calculated using log-transformed data then expressed as linear values. Changes were considered significant if CI did not cross 1.

Table 1. Single dose RAL PK parameters

RAL PK	RAL n = 14	RAL + Vit n = 10		RAL + SB n = 11		RAL + MP n = 11		RAL + MP2 n = 10	
	GM (% CV)	GM (% CV)	GMR * (90 % CI)	GM (% CV)	GMR * (90 % CI)	GM (% CV)	GMR * (90 % CI)	GM (% CV)	GMR * (90 % CI)
C_{MAX} ng/mL	1586 (96)	1312 (109)	0.88 (0.32 – 2.38)	3255 (66)	2.07 (1.00 – 4.30)	1628 (91)	0.95 (0.53 – 1.69)	1276 (105)	0.85 (0.45 – 1.63)
C_{12} ng/mL	27.92 (71)	23.93 (68)	0.9 (0.60 – 1.35)	39.82 (90)	1.35 (0.95 – 1.91)	19.55 (67)	0.73 (0.52 – 1.03)	16.78 (82)	0.63 (0.49 – 0.81)
AUC_{0-12} ng.h/mL	5150 (85)	4037 (94)	0.83 (0.33 – 2.08)	9964 (61)	1.96 (1.04 – 3.72)	4518 (83)	0.83 (0.48 – 1.43)	3768 (101)	0.78 (0.45 – 1.35)
T_{MAX} (h)	2.46 (33)	2.11 (49)	0.85 (0.68 – 1.05)	2.15 (35)	0.83 (0.66 – 1.04)	1.42 (44)	0.58 (0.43 – 0.78)	2.32 (45)	0.93 (0.68 – 1.28)

* against RAL single dose

Figure 1. Geometric mean raltegravir concentrations with 90 % CI from all arms (pooled data).

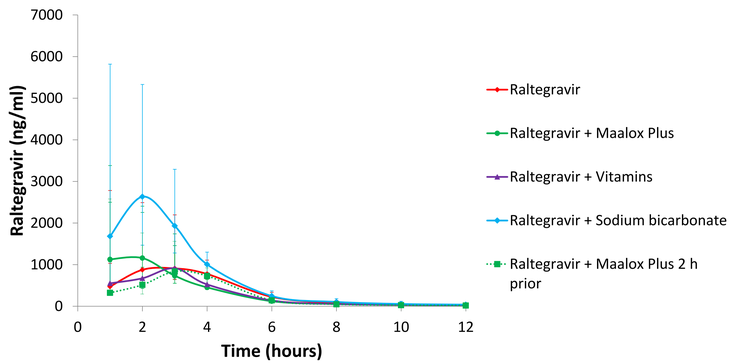
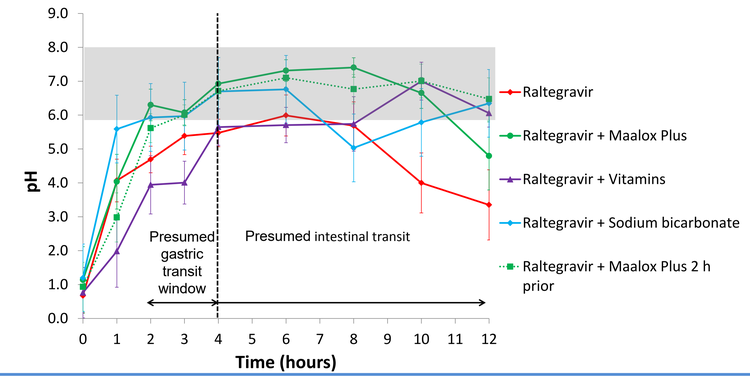


Figure 2. Geometric mean pH (+/- standard error) measurements for all arms (pooled data). pH recorded as capsule moved down the GI tract. Shaded area represents the optimal pH for raltegravir solubility.[2]



RESULTS

- ***Participants:*** Fifteen healthy volunteers (11 female, 13 Caucasian, 1 Black, 1 Asian) were randomised. One withdrew consent and four did not fully complete due to adverse events (3) and inability to attend further follow-up (1). Mean age, weight and BMI (range) were 32 years (23 - 56), 76 kg (53 - 107) and 26 kg/m^2 (20 - 36).
- ***PK:*** RAL concentrations and PK parameters for the 12 h dosing interval alone and in combination with Maalox Plus, sodium bicarbonate, vitamins are presented (Table 1; Figure 1).
- RAL AUC_{0-12} and C_{MAX} were significantly higher when dosed with sodium bicarbonate.
- RAL T_{MAX} was significantly lower when dosed with Maalox Plus at the same time.
- ***pH:*** Figure 2 shows the mean pH measurements from all arms observed for the RAL dosing period (12 h).
- ***Safety & Tolerability:*** All combinations of RAL with antacids and multivitamins were generally well tolerated.
- One participant was withdrawn by the investigator due to a Grade 2 creatinine kinase elevation, probably related to raltegravir. Two participant withdrawals occurred following transient Grade 2 eGFR reductions possibly related to study drug.
- There was one serious adverse event, hospitalisation for a urinary tract infection, which was deemed to be unrelated to study drug.

CONCLUSIONS

- Assuming a gastric retention time of 2-4 h, 3 arms (sodium bicarbonate, Maalox Plus +/- 2 h) achieved the optimal gastric pH (6-8) for RAL solubility[2] whereas this was only achieved later (more distally) in the RAL alone or RAL + vitamins arms.
- A significant increase in absorption of RAL was only observed in the presence of sodium bicarbonate (an antacid lacking divalent cations). This is likely to relate to the unopposed 'boosting' effect of a raised pH upon absorption and the known pH-dependent solubility of RAL.
- Although Maalox Plus dosed simultaneously or 2 h apart achieved similar pH no significant increase in RAL absorption was observed. It is possible that any 'boosting' effect of pH was counteracted by the presence of divalent cations. This suggests that not all antacids influence the PK of RAL in the same way
- Surprisingly, vitamins did not significantly affect the PK of RAL even though multivitamins and iron containing supplements are known to reduce the bioavailabilty of other integrase inhibitors.
- Further study into the effect of multivitamins on raltegravir is warranted.

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