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Investigation of lipid digestion by fungal and porcine lipase supplements for severe pancreatic insufficiency using the *in vitro* dynamic TIM model

Tânia Martins Garcia[a]*, Ioannis Vrasidas[a], Alexander Iphöfer[b], Bartosz Lipowicz[b]

[a]The TIM Company, Thijsseweg 11, Delft, The Netherlands

[b] REPHA GmbH, Alt-Godshorn 87, Langenhagen, Germany

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*Corresponding author.
Tel.: +31 6 1851 0061
E-mail:
tania.garcia@theTIMcompany.com

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SUMMARY

Exocrine pancreatic insufficiency (EPI) is caused by insufficient secretion or limited activity of pancreatic enzymes, especially lipase. Chronic pancreatitis (CP) is the most common EPI disease. CP patients suffer from gastrointestinal symptoms such as diarrhea, abdominal pain, and decreased uptake of nutrients as a consequence of inadequate food digestion. To improve their nutritional status, pancreatic enzyme supplements can be orally administered, known as pancreatic enzyme replacement therapy (PERT). PERT is commonly based on oral porcine preparations, despite their pH sensitivity which results in a limited timeframe for optimal activity. Instead, fungal enzymes could be used to prolong enzyme activity duration, since they are active over a wide pH range. The performance of fungal enzymes was compared to porcine enzymes by measuring total fatty acids under severe pancreatic insufficiency conditions in the tiny-TIM*sg* dynamic *in vitro* gastrointestinal model. Administration of 14.000 fungal lipase units (Nortase) led to similar lipid digestion compared to 20.000 porcine lipase units (Kreon and Pangrol). Additionally, opening the Nortase capsules had no negative effect on fungal lipase activity. This work demonstrates that fungal lipases, administered as capsules or powder, can be used as an alternative treatment for EPI patients.

INTRODUCTION

PERT enhances fat digestion and absorption, leading to a decrease in gastrointestinal (GI) symptoms and improved quality of life in EPI patients (Iglesia-Garcia 2017). The porcine lipases used in PERT show optimal activity between pH 5 to 7 and are, thus, formulated as capsules to protect them from gastric acid inactivation. As a result, porcine enzyme activity is restricted to the small intestine. However, as EPI worsens, duodenal pH falls below pH 5. This poses a great challenge for therapy using porcine enzymes. In contrast, fungal enzymes are active between pH 3 and 9 and can start their postprandial enzymatic activity directly in the full stomach, thus prolonging the timeframe for digestion.

Investigation of the efficiency of oral enzyme supplements in human interventional trials is challenging. *In vitro* models that can closely simulate the dynamic luminal conditions of the GI tract represent an alternative approach. This work aimed to compare the lipolytic capacity of encapsulated fungal (Nortase) and porcine (Kreon and Pangrol) enzymes. The impact of opening the Nortase capsules and administering its powder content on the lipase

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activity was also investigated to simulate administration in CP patients unable to swallow whole capsules (e.g. preterm infants and intensive care patients).

MATERIALS AND METHODS

Enzyme supplements were administered into the gastric compartment of the tiny-TIM*sg* together with a FDA-recommended High Fat Meal (HFM) (**Fig. 1**). To simulate CP conditions, no gastric lipase was secreted, the concentration of small intestinal pancreatic enzymes was reduced to 5% of healthy levels, and small intestinal pH was kept at 5.0-5.5, instead of the healthy pH 6.5. The efficacy of the administered pancreatic enzymes was determined by measuring the amount of bioaccessible total fatty acids (FA) that would be available for absorption *in vivo*. As negative control, the fat digestion was measured during simulation of CP without supplementation (baseline lipid digestion).

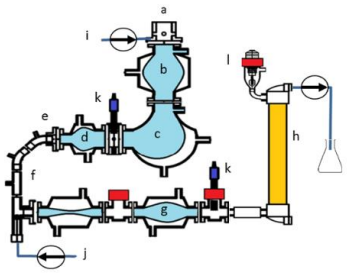

Fig. 1. *tiny-TIMsg in vitro model of the stomach (b, d, c) and small intestine (g). Bioaccessible FA are collected using a semipermeable membrane (h).*

RESULTS AND DISCUSSION

Pancreatic enzyme administration significantly increased the total FA bioaccessibility compared to the CP control (**Fig. 2**). Besides, fungal enzymes (Nortase) and porcine enzymes (Kreon and Pangrol) led to similar total FA bioaccessibility profiles over time (**Fig. 2**). This is likely due to the wider pH range in which the fungal lipases can be active compared to the porcine lipases.

Nortase administration as powder significantly increased the total FA bioaccessibility compared to the CP control (**Fig. 3**), indicating no disadvantage in opening the capsules and applying the enzyme powder.

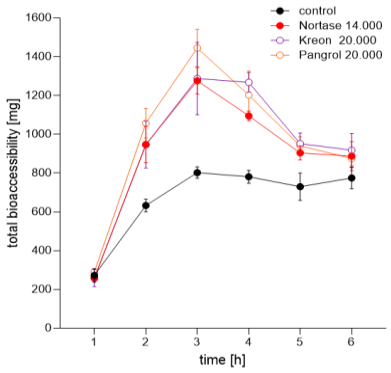

Fig. 2. *Total bioaccessibility of FA overtime [mg] upon administration of Nortase, Kreon, and Pangrol capsules, in comparison with CP control. Means ± SD (N=3 runs).*

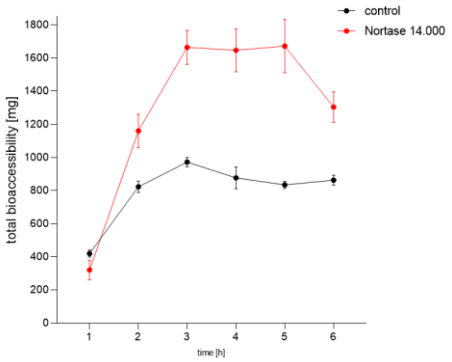

Fig. 3. *Total bioaccessibility of FA overtime [mg] upon administration of Nortase powder, in comparison with CP control. Means ± SD (N=3 runs).*

CONCLUSIONS

This work shows that lower amounts of Nortase fungal lipases result in similar lipid digestion compared to higher amounts of Kreon and Pangrol porcine lipases and that opening the Nortase capsules has no negative effect on fungal lipase activity.

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