Negative oral provocation test with porcine pancreatic enzyme plus cofactors despite confirmed α-Gal syndrome

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We report on a 66-year-old patient who presented in August 2016 after a severe anaphylactic reaction. She was stung by a small dark insect (probably no bee or wasp; unclear if tick bite) in her wrist while gardening in the morning and afterwards developed a common local insect sting reaction. At noon she had eaten "sour" pork kidneys (fine strips soaked in milk, briefly fried and seasoned with salt, pepper and vinegar) for lunch. An hour and a half later, she complained of dizziness, an itchy rash all over her body, followed by swallowing difficulties and shortness of breath. On the way to her family doctor one hour later she collapsed and an emergency medical care was provided including the administration of prednisolone, clemastine and inhaled adrenalin. She was monitored for several hours in a hospital, but was discharged the same day.

In 2009 a pancreas head resection according to Whipple was performed due to a pancreatic carcinoma. Since then, she had long-term medication with Kreon® 25.000 (twice daily) and acetylsalicylic acid (ASA, 100 mg). The patient remembered a few tick bites about 20 years ago. Innards were consumed regularly, but no symptoms had ever occurred before. She tolerated also other mammalian food, e.g. pork meat, salami, ham and milk.

Skin prick testing was performed in 2016 with pork meat, pork kidney, beef meat, beef kidney (each raw and cooked), gelatin, cow milk, cetuximab (500 μg/ml), Gelafundin 4%, Kreon® 10.000 pancreatic powder (Mylan healthcare GmbH, Bad Homburg, Germany), an atopy series (grass, birch, D. pter., cat), part of an idiopathic anaphylaxis series (celery, soy lupine flour, gluten, hydrolyzed wheat protein) and spices. Intracutaneous testing was done with Gelafundin 4% (undiluted), bee and wasp venom.

Testing was positive to pork and beef kidney (raw and cooked), cetuximab, Kreon® and hydrolyzed gelatin (prick), Gelafundin, bee and wasp venom at a concentration of 0.1 mg/ml (i.c.).

Determination of sIgE to α-Gal, bee venom, wasp venom, rApi m1, rApi m2, rApi m5, rApi m10, r Ves v 1, rVes v 5 and CCD, MUXF3 was performed and α-Gal sIgE showed a value of 3.65 kU/L (< 0.10 kU/L). SIgE to all insect venom allergens were negative. Total IgE and tryptase were in the normal range.

In 2016 oral provocation tests with hydrolyzed gelatin (0,5 g, 1 g, 5 g) and pork kidney (3 g, 5 g, 10 g) were performed. Hydrolyzed gelatin was tolerated, but the patient developed generalized erythema, cervical constriction and dyspnea 2 hours after consumption of 10 g pork kidney.

A basophil activation test (BAT) was performed in 2016 with a pork kidney extract (22.7 mg/mL to 0.00022 mg/mL), alpha-Gal-HSA (1000 ng/mL to 0.32 ng/mL) (BAG2-GAL; Bühlmann Laboratories AG, Switzerland) and Kreon® (2227 ng/ml to 0.0227 ng/ml) according to previous reports [1, 2]. All substances activated the basophils.

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In 2018 oral provocation tests with 3 capsules Kreon® 25.000 (first day), ASA (1000 mg) and 3 capsules Kreon® 25.000 (second day), ASA, alcohol (20 ml), physical exercise and Kreon® 25.000 (third day) were performed. No symptoms occurred. SIgE to α-Gal showed a value of 0.77 kU/L (< 0.10 kU/L).

In 2018 the BAT performed one day after the oral provocation test series with Kreon® was positive to alpha-Gal-HSA, negative to Kreon®, to bee and wasp venom. The BAT performed one month later was again positive to Kreon®. (Supplementary Table)

This case shows that Kreon®, an α-Gal-containing porcine pancreas extract can be tolerated in higher than usual doses and despite cofactors in patients with α-Gal syndrome. This is particularly relevant in cases where the drug is necessary to treat exocrine pancreatic insufficiency. Two similar cases have been described [3], but this is the first case in which cofactors, well-known amplifiers of reactions to α-Gal [4], were also tested with the α-Gal-containing drug. After allergy work-up a hymenoptera allergy could be excluded as cause or co-factor of the anaphylaxis.

We will now discuss potential factors for the tolerance of Kreon® despite sensitization. In general it has been shown by provocation tests that the sensitivity to α-Gal can be quite variable: There are patients who only react to pork kidney but routinely tolerate muscle meat even in the presence of cofactors and there are patients e.g. with mastocytosis showing biphasic immediate and delayed severe reactions [5-7]. Higher amounts of α-Gal determinants in the kidney compared with meat may explain these observations. Our patient also tolerated hydrolyzed gelatin. We do not know how much α-Gal is present in Kreon®. In a recently published study [1] and in this patient basophil activation was higher with Kreon® than with pork kidney extract argueing for a relevant amount. It was also shown in inhibition experiments, that the absolute reduction in α-Gal sIgE binding by Kreon® could be reduced by up to 97% (median 83.5%) confirming the specific recognition of α-Gal epitopes in Kreon® [3]. In our patient the eliciting dose of pork kidney was 10 g, the total amount of Kreon® ingested was 0.9 g (with gelcap), which might be below the threshold for eliciting symptoms.

It should also be discussed that α-Gal in the context of protein extracts of Kreon® [1] may not be absorbed gastrointestinally. In vitro studies suggest that only lipid-bound α-Gal is able to cross the intestinal monolayer. In vivo, α-Gal could only be detected in the blood carried by chylomicrons, but not bound to proteins 3 to 6 hours after consumption of beef meat [8].

Tolerance induction to α-Gal in Kreon®, but not to α-Gal in pork kidneys through the long-term intake of Kreon® for pancreatic insufficiency would also be conceivable. The fact that the BAT was negative after three-day high-dose administration of Kreon® argues for a kind of desensitization exclusively to Kreon®, because the basophil activation to alpha-Gal-HSA was not lowered at this time point. A specific desensitization to Kreon® would argue for a contribution of the protein environment to the α-Gal epitope or a diversity of carbohydrates

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near the epitope as suggested previously [9]. Desensitization to the α-Gal containing cetuximab in a rapid protocol resulted in a negativation of α-Gal sIgE [10].

Taken together, it appears there is a clinically relevant difference in vivo between the oral intake of α-Gal-containing pancreatic powder and α-Gal-containing food. Since positive skin tests and BATs probably do not give enough information for clinical relevance and triggering clinical reactions in connection with cofactors cannot be excluded, provocation tests (with cofactors) are essential, if drugs containing α-Gal have to be given for therapeutic reasons. Due to the extensive testing, the patient was recommended to avoid large amounts of red meat and to avoid innards, but to continue taking Kreon®.

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Conflicts of Interests:

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