

Anaphylactic reaction to folic acid verified by provocational testing

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Folic acid (pteroylmonoglutamic acid; Fig. 1A) – the synthetic and unconjugated form of folate B vitamins in foods – is widely used in vitamin supplements. It is essential for DNA synthesis and other metabolic processes. The recommended daily intake of folic acid is

400 µg; deficiency may lead to impaired growth, neural tube defects and megaloblastic anemia amongst others. Due to its importance and frequent lack in the diet food manufacturers are more and more required to add folic acid to enriched grain products such as breakfast cereals, bread, pasta and rice (1).

Although a few cases (2–4) of presumed folic acid allergy have already been published the proof of an allergy to folic acid in double-blind placebo-controlled oral challenge with folic acid as single substance has so far been lacking. We present the first case of an anaphylactic reaction to folic acid itself proven by oral provocational testing.

A 44-year-old Caucasian woman had suffered from an anaphylactic reaction with tachycardia, generalized skin eruption and dyspnea 10 min after intake of a multivitamin tablet. Four similar reactions had occurred within 20 min after intake of various multivitamin products from different sources, such as multivitamin juices, tablets and sweets in the last 5 years.

As ingredients common to all suspected multivitamin agents vitamin B6, B12 and folic acid were found. The patient was otherwise healthy and did not take any medication; there was no personal or family history of atopy or other allergic diseases.

Skin prick tests revealed positive reactions to only one of the suspected multivitamin tablets vaso-loges® (Dr Loges und Co. GmbH, Winsen, Germany; consisting of vitamin B6, B12, folic acid, gelatine, titandioxide, ferrum oxide, magnesium stearate) as well as Dreisafol® (GRY-Pharma GmbH, Kirchzarten, Germany; consisting of folic acid, magnesium stearate, cellulose, lactose and silicium dioxide). Three healthy control subjects showed no reactions when tested with vaso-loges® and Dreisafol®. Other multivitamin agents, vitamin B6 and B12 showed no reaction.

Additive substances (titandioxide 100 mg, magnesium stearate 5 g, colors (E127, E131, E132, E151, E172) 5 mg and gelatine 10 g) were also negative on oral challenge (5). Vaso-loges® did not show reactions when labially and lingually challenged. However, after oral provocation with 1/4 tablet vaso-loges®

(one whole tablet contains 440 µg folic acid, 4.4 mg vitamin B6 and 8.8 µg vitamin B12) the patient developed a generalized urticarial eruption and mild laryngeal dyspnea. Symptoms resolved gradually upon treatment with intravenous H1 – Antagonist dimetindene (4 ml) and prednisolone (250 mg) together with fenoterol aerosol (two puffs).

After a resting period of more than 4 weeks the patient was challenged with vitamin B6 and B12 which was well tolerated. After negative labial and lingual challenge also Dreisafol® was orally challenged. At the dose of 500 µg folic acid (=1/10 tablet) the patient reacted with a generalized urticarial eruption, conjunctival injection, dyspnea, tachycardia and blood pressure decrease (90/50 mmHg; Fig. 1B). Upon treatment with dimetindene, prednisolone and hydroxyethyl starch solution intravenously and fenoterol as aerosol the patient recovered quickly, without any symptoms in the overnight inpatient observation.

As a consequence of the strong reactions after oral challenge the patient was advised to avoid synthetically produced folic acid and enriched

Folic acid is an essential vitamin needed for DNA synthesis and metabolic processes. We present the first verified clinical anaphylactic reaction to folic acid.

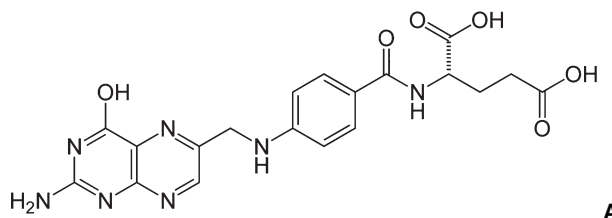


Figure 1. (A) Chemical structure of folic acid. (B) Anaphylactic reaction with an urticarial exanthema, dyspnea and blood pressure decrease 10 min after oral provocation with 500 µg folic acid.

products and was prescribed an emergency medication kit consisting of dimetindene, prednisolone and an epinephrine autoinjector (Anapen®; Lincoln Medical Ltd, Salisbury, UK) (6).

She was further advised to keep a diet rich in natural folates – which according to the patient's history are tolerated – to provide adequate nutrition.

Naturally occurring folate vitamins (pteroylpolyglutamates) are composed of folic acid and polyglutamate moieties which are cleaved in the gastrointestinal lumen before absorption of the reduced form of folic acid – tetrahydrofolic acid.

This is the first case of an anaphylactic reaction to folic acid demonstrated by direct provocation testing.

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Severe delayed erythema multiforme to vancomycin in a woman on regular hemodialysis

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Key words: adverse drug reaction; drug allergy; erythema multiforme; skin rash; vancomycin.

A 47-year-old woman, without history of allergy, presented to our emergency department with a progressive generalized itching skin eruption for 3 days. She was a Buddhist nun and had been on vegetarian diet for more than 10 years. She had been diagnosed as a hepatitis B carrier for decades and hypertension was also noted for 7 years, which was controlled by irbesartan and amlodipine in recent 4 years. She did not take any other medicines. For end-stage IgA nephropathy, she had been on regular hemodialysis via the native arteriovenous fistula (AVF) in her left forearm

A case of severe delayed erythema multiforme to vancomycin without other systemic symptoms.

for 5 years. However, redness with mild local heat of the AVF was noticed at a local hemodialysis center about 2 months ago. For a suspicious infection of the AVF, intravenous vancomycin 750 mg was administered weekly there for 4 weeks. Because of limited effect, the dose of vancomycin was titrated to 500 mg three times a week for another 2 weeks. The redness of the AVF was partially resolved, but it got worse with progressive itching skin eruption over the whole body since 3 days before this hospitalization. She was referred to our hospital because the skin eruption was resistant to oral and intravenous antihistamine therapy. On physical examination, diffuse pink-red plaques and target lesions (Fig. 1) on the trunk and four limbs with sparing of palmoplantar surface and scalp were noted. The patient claimed that the plaques resulted from confluent target lesions. The skin rashes were painless, but severely pruritic. There was no fever, blister, mucosal erosion, nor enlarged lymph node. The laboratory studies including bacterial cultures, viral serology tests and serum level of vancomycin were unremarkable. Delayed erythema multiforme to vancomycin was highly suspected. Vancomycin was thus discontinued on admission. Oral prednisolone 10 mg t.i.d. (for 1 week) and antihistamines



Figure 1. Multiple pink-red plaques (resulted from confluent target lesions) and diffuse target lesions on left forearm, in which an engorged native arteriovenous fistula was created.