1.1. Folic acid and anaphylactic reactions

Introduction

Folic acid (vitamin B11) is essential to numerous bodily functions ranging from nucleotide biosynthesis to the remethylation of homocysteine. It is especially important during periods of rapid cell division and growth. Both children and adults require folic acid to produce healthy red blood cells and prevent anemia. Folic acid has been registered in the Netherlands since March 1994. It is indicated for *treatment of megaloblastic anemia caused by folic acid deficiency and for treatment / prevention of folic acid deficiency due to disturbed absorbance, chronic alcoholism or long term use of anti-epileptics. Folic acid is used by women intending to become pregnant and in the early months of pregnancy to reduce the risk of neural tube defects.*
The SmPC of folic acid, 0.5 mg or 5 mg, mentions hypersensitivity reactions / allergic reactions like fever and rash as uncommon adverse drug reactions. Anaphylactic reactions are not mentioned [1,2].

Reports

On November 5, 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports of anaphylactic reactions associated with the use of folic acid, all in a dose of 5 mg per day (see Table 1). All four cases were rated as serious according to the CIOMS criteria and occurred after intake of the first tablet.
The anaphylactic symptoms varied. Patient A experienced generalized pruritus, burning sensation, dizziness, dyspnoea, tearing eyes and chest pain, within 10 minutes after first intake. She recovered upon intravenous noradrenaline treatment in the ambulance. For patient B only 'anaphylactic reaction' was reported, without further information. Patient C developed dyspnoea, severe pruritus, erythema and nausea within 10 minutes, treatment and outcome were unknown. Patient D suffered from severe erythema, dyspnoea and chest pain, one hour after intake of folic acid. Fifteen minutes later he became pale, with low blood pressure and rash. He recovered upon treatment in the ambulance. Patient D also had symptoms during use of folic acid in the past: rash, pruritus, dyspnoea and high blood pressure.

Tabel 1. Reports of anaphylactic reactions associated with the use of folic acid.

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 37406 F, 41 to 50	folic acid tablet 5mg pyridoxin tablet 100mg For hyperhomocys-teinemia	acetylsalicylic acid disp tablet, nifedipin tablet, isosorbidedinitrate, nitroglycerine oromucosal spray, lisinopril tablet, clopidogrel tabl	anaphylactic reaction	10 minutes after first intake discontinued recovered
B 74015 M, 21 to 30	folic acid tablet 5mg For folic acid deficiency		anaphylactic reaction	2 hours after first intake discontinued unknown

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
C 82192 F, 51 to 60	folic acid tablet 5mg Rescue factor after use of methotrexate	methotrexate tablet, tramadol capsule, omeprazol capsule	anaphylactic shock	10 minutes after first intake discontinued unknown
D 90207 M, 41 to 50	folic acid tablet 5mg For folic acid deficiency		anaphylactic reaction	55 minutes after first intake discontinued recovered

Other sources of information

Literature

Eleven cases with immediate-type allergy caused by folic acid have been reported in literature [3, 5-7]. Ten of these cases involved anaphylaxis and only one showed chronic, intermittent urticaria with angio-edema, suggesting that this condition tends to show severe symptoms. The symptoms were induced by folic acid containing tablets, including multivitamin tablets and supplements. In four cases multivitamin tablets were used, with a known dose of <0.5 mg folic acid in two cases / an unknown dose in the other two cases. In the remaining seven cases a higher dose of folic acid was used: 1 mg (one case), 5 mg (three cases), 20 mg (one case) and 50 mg (one case) plus one with unknown dose [3].

Databases

On November 5 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained four reports of anaphylactic reactions associated with the use of folic acid. The reporting odds ratio supports a causal relationship between folic acid and anaphylactic reactions (ROR = 9.1: 95% CI 3.3 – 25.2).
The WHO database of the Uppsala Monitoring Centre contained 15 reports of anaphylactoid reactions in association with folic acid which was not reported disproportionally.

On December 23rd 2009, the Eudravigilance database contained 21 reports of anaphylactic reactions or anaphylactic shock associated with use of folic acid. In all but four reports, folic acid was the sole medication used. Patients experiencing an anaphylactic reaction were predominantly female (n=18), two were male for one patient gender was not specified. According to reporters, in none of the cases, the reaction led to the death of the patient, disability or life threatening aspects. In six cases hospital admission was the reason for considering the reaction to be serious, in the remaining cases this was due to other reasons. It must be noticed that five of the reported cases originated from New Zealand, a country with 4.3 million inhabitants.

Prescription data

Low dose folic acid can be obtained without prescription. For 5 mg tablets a prescription is needed. The number of users of the 5 mg folic acid tablets is show in table 2.

Table 2. Number of folic acid (dosage 5 mg) users in the Netherlands between 2005 and 2008 [4]

Drug	2005	2006	2007	2008
Folic acid	108,760	111,730	111,530	117,720

Mechanism

Folic acid induced anaphylaxis is assumed to be an immediate-type allergy, because IgE antibodies to folic acid is detected in the patient's serum [3,5]. Folic acid is thought to be able to act as a hapten in immunogenic reactions, corresponding with its low molecular weight (441d), well below the 1000d threshold usually required for an agent to be recognized as a complete antigen or allergen. The ability of folic acid solutions to elicit positive immediate skin test reactions suggest that folic acid must be capable of rapidly combining with self-proteins or polypeptides in the skin to form a complete allergen [5].
Due to the short latency period in two of the four cases it could be possible that the reaction is not IgE mediated however.
Folic acid is abundant in leafy vegetables, such as spinach and beans. Dietary folic acid is composed of folic acid and 5 to 8 glutamate residues, and is slowly broken down into the monoglutamate form of folic acid in the small intestine. This step by step absorption may prevent transient increases in the concentration of the intact form of folic acid in the circulation, while taking synthetic folic acid could allow the intestine to easily absorb folic acid, resulting in a rapid increase and development of allergic symptoms [3,5].
All Dutch cases all concern the use of 5 mg folic acid tablets, while the cases in literature are ascribed to doses of folic acid varying from 0.38 mg to 50 mg.
The fact that Lareb only received reports of the 5 mg tablets could reflect that the reaction is dose-related or could be due to under-reporting for the 0.5 mg tablets.
There are no indications for a link between folic acid deficiency itself and anaphylaxis. It cannot be ruled out that the excipients in the tablets played a role in the reaction.

Conclusion

The Lareb reports support a possible relation between folic acid (5 mg) and anaphylactic reactions. Literature reports support this association. Given the seriousness of this adverse drug reaction and the fact that folic acid (in a lower dose) is available without prescription, the SmPC should contain a clear warning.

References

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This signal has been raised on February 2010. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).