Anaphylactic shock secondary to intravenous administration of folinic acid: a first report

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Background: Folates, components of the B-complex vitamins, have numerous pharmacological effects. In oncology combining folates with 5-fluorouracil (5-FU) enhances the cytotoxic effects of chemotherapy in colon cancer patients. Folic acid has been rarely involved in adverse allergic reactions. To the best of our knowledge no anaphylactic reaction secondary to folinic acid (FA) administration has ever been reported before.

Patients and methods: An 80-year-old patient had adjuvant chemotherapy for colon cancer including FA and 5-FU and irinotecan as a second line agent after multiple metastases.

Results: Following FA administration anaphylactic shock occurred. Diagnosis was made according to the French method of adverse reactions monitoring.

Conclusion: Anaphylactic shock may be an adverse reaction of FA in patients receiving chemotherapy for colon cancer.

Key words: adverse reaction, anaphylactic shock, chemotherapy, colon cancer, folinic acid

Introduction

Five-fluorouracil (5-FU)-based adjuvant therapy is recommended for patients with resected stage III colon cancer [1]. Levamisole or folates (folic acid or FA) can be added to enhance the 5-FU efficacy. Adverse reactions to chemotherapeutic agents are common but rarely include anaphylactic shock. We report a case of such toxicity related to the administration of folinic acid (FA). To the best of our knowledge, similar events have never been reported before.

Case report

An 80-year-old patient was admitted for adjuvant chemotherapy after left colon resection for Dukes’ C stage adenocarcinoma. Past medical history included sideroblastic anemia and mild asthma. Bolus infusion of 5-FU (400 mg/m²/day) and FA (200 mg/m²/day) for 5 days every 4 weeks were administered from September 1999 to February 2000. Tolerance was excellent and no side effects were reported.

In April 2000, increased carcinoembryonic antigen levels led to the diagnosis of multiple hepatic and pulmonary metastases. Second line chemotherapy included bolus infusion of irinotecan (180 mg/m²) and 5-FU (400 mg/m³) over 90 min, and FA (200 mg/m²) over 120 min for day 1 followed by continuous infusion of 5-FU (2400 mg/m²) over 2 days. Anti-emetic and anticholinergic prophylaxis included ondansteron and atropin, respectively. During the first course of chemotherapy the patient presented a nettle rash following the administration of odansteron and FA. Odanasteron, incriminated as the initiating factor, was withdrawn and replaced by metoclopramide and prednisone as anti-emetic agents for the next course. During the second course and just after the administration of FA, metoclopramide and prednisone the patient experienced another rash and profound hypotension requiring intravenous epinephrine. FA was withdrawn. The following FA-free courses were uneventful.

An imputation method of assessing the relationships between an adverse reaction and a drug has been developed in France [2]. This method is based on the evaluation of three parameters including the chronological imputability (C), the semiological imputability (S) and the intrinsic imputability (I). According to the French imputation tables [2] the reaction was scored C3/S3/I14. The final decision table considered the drug–effect relation to be very likely, which corresponds to the highest score on the scale.
Discussion

Folates, members of the B-complex vitamins, function as a single carbon donor in the synthesis of serine from glycine, in the synthesis of nucleotides from purine precursors, indirectly in the synthesis of transfer RNA and as a methyl donor to create methylcobalamin, which is used in the re-methylation of homocysteine to methionine [3]. Folic acid is reduced by the liver to metabolically active 5-methyltetrahydrofolate. FA (5-formyltetrahydrofolate) bypasses the reduction steps required for folic acid. Folates have numerous pharmacological effects either therapeutic as in hyperhomocysteinemia [4], gout [5], vitiligo [6], macrocytic anemia [7] and gingivitis [8], or preventive as in neural tube defects during pregnancy [9], cervical dysplasia [10] and inflammatory bowel disease [11]. Reports also indicate that many neuropsychiatric diseases may be secondary to folate deficiency [3].

In oncology, thymidylate synthase is the cellular target of the 5-FU–FA mechanism of cytotoxic action [12]. Fluorodeoxyuridylate, one of the 5-FU metabolites, binds to thymidylate synthase in the presence of FA leading to its inhibition via a covalent ternary complex. FA, at high doses, increases 5-FU toxicity by stabilizing the ternary complex [13, 14]. The association of 5-FU–FA has demonstrated its clinical efficacy in colorectal cancer, both in adjuvant and metastatic settings. Folates are regarded as not toxic for humans [3]. However, they may mask vitamin B12 deficiency or interfere with zinc absorption [3]. Besides these minor and rare effects, anaphylactic reactions due to ingestion or injection of folic acid have been reported previously [15, 16]. However, to the best of our knowledge, this case represents the first report of anaphylactic shock involving FA.

Conclusion

FA may be a rare cause of anaphylactic shock in cancer patients receiving 5-FU–FA chemotherapy.

References