



Phenytoin toxicity in a patient receiving 5-fluorouracil-based chemotherapy for metastatic colorectal cancer

KEY WORDS

Phenytoin toxicity, FOLFIRI, chemotherapy, colorectal cancer, 5-fluorouracil

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In addition to chemotherapeutics, cancer patients often take a variety of medications for reasons related and unrelated to their underlying cancer. Some of these medications have the potential to interact with their chemotherapy, potentially leading to symptomatic drug toxicity. In particular, antiepileptic medications can interact with several chemotherapy agents¹. The antiepileptic class of compounds is generally associated with steep dose-toxicity curves and narrow therapeutic ranges^{2,3}. For cancer patients receiving chemotherapy, interactions between antiepileptic medications and chemotherapy drugs can result in serious clinical consequences for the patient.

A commonly prescribed chemotherapy regimen for patients with metastatic colorectal cancer is FOLFIRI, which consists of 3 chemotherapy drugs: 5-fluorouracil (5FU), leucovorin, and irinotecan. Here, we describe a patient with metastatic colorectal cancer who developed phenytoin toxicity after treatment with 5FU.

A 64-year-old woman initially presented to her family physician with pelvic discomfort and, on ultrasonography, was found to have a pelvic mass. She underwent laparotomy for a presumed gynecologic malignancy and was found intraoperatively to have a mass in the transverse colon, with omental caking. Debulking surgery was carried out, and pathology was consistent with poorly differentiated adenocarcinoma of the colon with metastases to the ovary and omentum.

With respect to other medical problems, this patient had been diagnosed with epilepsy in childhood and had remained seizure-free since 1994 on oral phenytoin 200 mg three times daily. Her other oral

medications included venlafaxine XR 112.5 mg once daily; combined etidronate and calcium carbonate, 1 tablet daily; and docusate sodium 100 mg twice daily.

After recovery from surgery, the patient was initiated on FOLFIRI chemotherapy for residual intra-abdominal metastatic colorectal cancer. Her baseline serum phenytoin level was measured at 17 $\mu\text{mol/L}$ (normal range: 40–80 $\mu\text{mol/L}$) just before chemotherapy started, and her phenytoin dose was not altered.

At 26 days after the initiation of FOLFIRI chemotherapy, the patient noticed severe dizziness, drowsiness, and difficulty in maintaining her balance. She was unable to walk in a straight line without assistance. A neurologic examination revealed significant ataxia, hyperreflexia, and inability to walk heel-to-toe. The serum phenytoin level was repeated at this time and found to be significantly elevated at 139 $\mu\text{mol/L}$. The patient was diagnosed with phenytoin toxicity and was advised to discontinue phenytoin for 1 week. Serum phenytoin levels returned to normal, and the clinical symptoms of toxicity subsequently resolved.

Eventually, a recurring pattern in each cycle several days after administration of the FOLFIRI chemotherapy was noted: serum phenytoin levels became elevated, with mild symptoms of phenytoin toxicity. Despite this complication, the patient received a total of 7 cycles of FOLFIRI chemotherapy, and computed tomography imaging of the abdomen and pelvis showed a significant reduction in tumour bulk.

To determine the likelihood of a true interaction between 5FU and phenytoin, we calculated a Drug Interaction Probability score. The Drug Interaction Probability Scale was developed to provide a guide for evaluating drug interaction causation in a specific patient⁴. In our patient, the Drug Interaction Probability score for phenytoin and 5FU was found to be +9, consistent with a high probability of an interaction resulting in clinical symptoms and signs of phenytoin toxicity.

This case adds to a growing body of literature (5–9) and highlights the potential risk of drug–drug interactions between 5FU-based chemotherapy and phenytoin.

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CONFLICT OF INTEREST DISCLOSURES

The authors have no conflicts of interest to declare.

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