Beyond Cancer and Chemotherapy:
A Drug-Drug interaction

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Abstract: We are reporting an important interaction between fluorouracil and phenytoin that resulted in phenytoin toxicity in an elderly man with colorectal cancer. He presented with worsening confusion, slurred speech and poor gait resulting in many falls at home. After stopping the phenytoin his symptom resolved rapidly confirming the toxic effect of phenytoin. This level of phenytoin has not yet been reported in the patients on concurrent phenytoin and fluorouracil in the literature. This case report highlights the need for cautious monitoring of the antiepileptics and act promptly to avoid the serious toxicities particularly in elderly patients.

Key word: FOLFOX – fluorouracil, leucovorin, Oxaliplatin;

Case

A 73 year old man with a history of secondary epilepsy, on phenytoin 400 mg for last 28 years, diagnosed with metastatic colorectal cancer in early 2015. He was commenced on FOLFOX and Bevacizumab in April 2015. He was admitted in our hospital with complaints of drowsiness, slurred speech and worsening gait disturbance resulting multiple falls.

His past medical history includes: subarachnoid hemorrhage – 28 years ago resulting seizures, hypertension and gastroesophageal reflux disease. He was on phenytoin, ACE-inhibitor and proton pump blocker. His phenytoin levels were frequently checked and was stable prior to commencement of the chemotherapy. After commencement of his chemotherapy his phenytoin level was noted to be elevated on various occasions from 100umol/L to 135umol/L (normal 40-80 umol/L). During the course of the cancer treatment he reported drowsiness and difficulty walking. His symptoms were fluctuating and prior to the next dose of chemotherapy, he used to be deemed fit enough to receive the next dose. Later on, he was noted to have mild peripheral neuropathy which was thought to be as a result of Oxaliplatin and therefore, it was ceased from the regimen with mild improvement.

He had presented to the hospital two weeks prior to this admission with worsening of gait and it was attributable to his limb ataxia and later, he was given a four wheel walker as a walking aid.

Two weeks later, he re-presented to hospital with further falls and worsening drowsiness. On examination, he was drowsy and delirious. His neurological examination was notable for dysarthria, and marked bilateral limb ataxia with proprioceptive deficits in both lower limbs limited to feet. The Romberg sign was positive. Other systemic examination was normal. His routine blood tests were unremarkable and a CT head only showed some age related changes.

His phenytoin level was 190 umol/L. He was diagnosed with phenytoin toxicity and therefore, was ceased with significant improvement in symptoms in 2 days. He was discharged home on day 4 and was commended on levetiracetam 500 mg twice daily for the epilepsy control. On further follow up, he was doing well and walking unaided.

Discussion

The phenytoin toxicity has long been recognised in the epilepsy patients and its interactions with many drugs have been well noted and described in literature. Here, we report a case of phenytoin and 5 FU interaction which appears less recognised in the field of oncology and therefore, often missed. The concomitant use of fluorouracil (5FU) and phenytoin potentially can result in phenytoin toxicities (1).

This drug-drug interaction is believed to be via CYP 450 2C9. Phenytoin is metabolized by CYP2C9 and inhibition of this isoenzyme by 5FU is likely the main cause of the interaction. In a case report it has been proposed that this interaction causes decreased clearance and increase serum concentrations and hence the toxicity. However the exact pathways of interaction has not been fully elucidated yet (2).
Conclusion

We emphasise the need for wider understanding and education about this drug-drug interaction which has not only incapacitating effect on the patients, but it has huge psychosocial cost if not recognised (3). This case also emphasises the need for regular monitoring of phenytoin and dose changes may be necessary in most of the cases (4). This problem can also be managed by changing anti-epileptics if required. This case also raises the need for patient education, particularly when they are on phenytoin. The patient can prompt the clinician for interaction monitoring and act upon it accordingly.

References

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Conflict

There are no conflicts to disclose.

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