Medicinal mishaps

Carbamazepine toxicity

Prepared by Mahesan Anpalahan, Consultant Physician, Western Hospital, Melbourne

Case

A man in his forties was referred by his general practitioner for investigation of high fever associated with leucopenia, neutropenia, lymphopenia, thrombocytopenia and abnormal liver function. He had been off colour for two weeks with intermittent fevers, headaches and severe constitutional symptoms. According to the patient and his doctor’s letter he had previously been well, did not smoke, consumed alcohol in moderation and was not receiving any long-term medications. He had not been overseas recently and did not have risk factors for hepatitis or HIV infections. He said his only medication was a recent prescription for cyproheptadine for poor appetite.

On examination, the patient was unwell, with a temperature of 39.8°C and there were a few petechiae on the trunk. The rest of the physical examination was unremarkable.

The patient was managed symptomatically and investigations excluded bacterial and viral infections, and haematological malignancies. Initial investigations revealed the following abnormal results:

- white blood cells 2.3 x 10^9/L (neutrophils 0.4 x 10^9/L, lymphocytes 0.5 x 10^9/L)
- platelets 28 x 10^9/L
- gamma-glutamyl transferase 789 IU/L
- alanine aminotransferase 334 IU/L
- aspartate aminotransferase 121 IU/L
- alkaline phosphatase 334 IU/L
- bilirubin 24 micromol/L
- platelets 28 x 10^9/L

Three days after admission during a ward round it was noticed that he had been prescribed carbamazepine 400 mg daily and his bloodwork showed he had received one dose. His wife had informed the medical team about this medication two days after admission. The patient was then prescribed carbamazepine as it was felt that he was missing out on one of his usual medications.

Further enquiry revealed that the patient was prescribed carbamazepine 18 days before admission by his psychiatrist for a mood disorder. He was initially advised to take 200 mg daily and the dose was increased to 400 mg five days before admission. Before starting carbamazepine his blood tests had been normal apart from mild thrombocytopenia (platelets 121 x 10^9/L) and a low normal total white blood cell count (4.1 x 10^9/L).

With this new information it was realised that carbamazepine could have been the cause of the patient’s illness. The carbamazepine was stopped and the fever settled after day four. The haematological and liver function abnormalities resolved completely over the following weeks. The bone marrow showed normal cellularity with granulomatous changes.

Comment

Febrile illness, leucopenia, neutropenia, lymphopenia, thrombocytopenia and liver function abnormalities are recognised features of carbamazepine toxicity. However, manifestation of all of these in one patient is rare. The temporal relationship, the doses of the drug used and the clinical syndrome would probably suggest that our patient had an idiosyncratic reaction. The normal cellularity of the bone marrow suggests a peripheral, probably immune-mediated, mechanism for the cytopenia.

Conclusion

This case illustrates how unwittingly breached basic medical principles may adversely affect patients. Had the full drug history been available to the treating team or if the team had been efficient in obtaining this vital information at the time of admission, the delay in diagnosis and many unnecessary investigations would have been avoided. There are many reasons why drug histories are not available, and the way a hospital

Self-test questions

The following statements are either true or false (answers on page 75)

9. Patients should start acamprosate the day before they commence detoxification.
10. Patients taking disulfiram need regular tests of liver function.
This case once again emphasises that traditional dictum that relevance to the patient’s condition is considered.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer’s approved product information, a drug information centre or some other appropriate source.

Sulesomab

LeukoScan (Australian Radioisotopes)
3 mL vials containing 0.31 mg powder for reconstitution
Approved indication: diagnosis of osteomyelitis
Prompt treatment of osteomyelitis may prevent bone necrosis. Early diagnosis is therefore important, but the infection may not show up on a plain X-ray. A technetium (\(^{99m}\)Tc) bone scan will detect most cases, but sometimes cannot distinguish infection from other causes of inflammation. Using sulesomab may overcome this problem.

Sulesomab is a monoclonal antibody which binds to antigens on the surface of neutrophils. If it is labelled with \(^{99m}\)Tc it will reveal areas where there is intense inflammation. In vitro studies suggest that labelled sulesomab binds more avidly to activated granulocytes.

After the sulesomab and the \(^{99m}\)Tc are mixed they are given by intravenous injection. Imaging can take place between one and eight hours after the injection. Most of the dose is renally excreted, with 41% of the radioactivity appearing in the urine within 24 hours of the dose.

Sulesomab has been studied in 122 patients with diabetes who were thought to have osteomyelitis secondary to foot ulcers. The performance of the scan was assessed by bone biopsy. The scan detected 74 of the 81 patients with osteomyelitis and excluded it in 23 of the 41 patients who did not have osteomyelitis. Sulesomab therefore has a sensitivity of 91% and a specificity of 56%. The sensitivity compares favourably with the technique of using radiolabelled white blood cells, which has a sensitivity of 79%. Sulesomab imaging has slightly greater accuracy (81% versus 75%) and the results are likely to influence the patients’ management.1

Leucocyte numbers fall after the injection, but usually recover within 10 days. Other reported adverse effects include eosinophilia and rashes. The production of sulesomab involves mice, but no anti-mouse antibody reactions occurred in the trial.

Sulesomab is safer and easier to use than radiolabelled white blood cells, so it is being studied in other conditions, such as inflammatory bowel disease, where the detection of inflammation is important.

REFERENCE

Tegaserod

Zelmac (Novartis)
6 mg tablets
Approved indication: irritable bowel syndrome in women
Australian Medicines Handbook Section 12.2.1
The cause of irritable bowel syndrome is uncertain. As there are several possible mechanisms a variety of drugs have been used in treatment. There has been interest in drugs acting on 5-HT receptors because of the effects of serotonin in the gastrointestinal tract.

Tegaserod is a partial agonist of the 5-HT\(_4\) receptor. It stimulates the peristaltic reflex and accelerates gastrointestinal transit. Tegaserod may therefore have a role in patients with irritable bowel syndrome who are predominantly troubled by constipation.

A double-blind trial randomised 881 patients with constipation-predominant irritable bowel syndrome to take tegaserod or a placebo for 12 weeks. Tegaserod produced statistically significant subjective improvements in bowel movements and abdominal discomfort. There was a non-significant improvement in bloating.1

Patients take tegaserod twice a day before meals. Its bioavailability is only 10% and this is reduced by food. Most of the dose is excreted unchanged in the faeces, but a metabolite is produced which is excreted in the urine. Liver impairment increases the plasma concentrations of tegaserod.

Adverse reactions to tegaserod most frequently involve the gastrointestinal tract. The effect of the drug will result in approximately 9% of patients developing diarrhoea. Other adverse events occur with a frequency similar to that of placebo.

There is a large placebo response in patients with irritable bowel syndrome. In the largest study of tegaserod 43.5% of patients responded, but so did 38.8% of the patients given a placebo. The therapeutic advantage of tegaserod appears to decline with time so it should be discontinued if there has been no response after one month of treatment. In patients who respond, the maximum duration of treatment should be 12 weeks. As the number of men in the clinical trials was limited, tegaserod is only approved for women with constipation-predominant irritable bowel syndrome.