Idiosyncratic metronidazole-induced neutropaenia in an older adult

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Introduction

Metronidazole is a widely used and effective agent against anaerobic infections with a benign side-effect profile. Metronidazole-induced neutropaenia is an exceedingly rare complication with an incidence rate of less than 1:10 000 patients. Older adults have been observed to have 80% higher area under the curve of the oxidised metabolite than younger controls and are therefore at risk of toxicity with therapeutic dosing. This article presents a case of idiosyncratic metronidazole-induced neutropaenia in an older adult with recurrent *Clostridium difficile* infection, where the degree of neutrophil suppression and slow recovery of marrow function were notable. The phenomenon appears reversible if recognised promptly with cessation of the drug and initiation of supportive measures.

Case report

An 84-year-old woman presented with a 2-week history of diarrhoea. She had been discharged from another institution 5 weeks ago after being successfully treated for *Clostridium difficile* infection, for which she had received oral vancomycin 125 mg 6-hourly for 10 days. Past medical history was insignificant.

Physical examination was normal. Laboratory investigations revealed a white cell count of 8.73x10^9/litre (normal range 4.0–11.0x10^9/litre) with a neutrophil count of 4.27x10^9/litre (normal range 2.0–7.0x10^9/litre). The remaining haematological and metabolic profiles were normal. Blood and urine cultures were sterile. Stool samples were positive for *C. difficile* using polymerase chain reaction.

The patient was prescribed oral metronidazole 400 mg 8-hourly for a planned duration of 14 days. Stool frequency reduced over 7 days, suggesting resolution of *C. difficile* infection. Daily blood counts showed progressive neutropaenia from day 1 of treatment and by day 10 the neutrophil count had dropped to 0.75x10^9/litre (**Figure 1**). Other haematopoietic stem cell lines measured as part of the full blood count remained preserved. Blood film revealed absolute neutropaenia with no abnormal cells.

The patient had no previous exposure to metronidazole based on electronic records from primary care, and no drug allergies or sensitivities were documented. Suspicious of drug-induced neutropaenia, the Naranjo algorithm was applied which showed a probable adverse effect (6/10) (**Table 1**) in favour of metronidazole, so this was discontinued on day 8 and switched to oral vancomycin 125 mg 6-hourly for a further 6 days. In view of worsening neutropaenia, on day 16 (0.55x10^9/litre) 30 million units of filgrastim were administered subcutaneously daily for 3 days. This resulted in significant neutrophilia (>23x10^9/litre) within 72 hours, thereby confirming bone marrow integrity and supporting a diagnosis of (drug-induced) myelosuppression rather than failure. After cessation of filgrastim, over the next 48 hours, the neutrophil count dropped to 1.57x10^9/litre, reached the normal level on day 29 (>2.5x10^9/litre) and plateaued at around 3.0x10^9/litre over the next week when the patient was discharged (**Figure 1**).

Extended viral screen, levels of serum folate, vitamin B_{12}, trace elements, iron indices, thyroid function, glycosylated haemoglobin, markers for haemolysis, immunoglobulin/protein electrophoresis and autoimmune screen were normal. Markers of hepatic and renal function remained normal. Computed tomography of the chest, abdomen and pelvis did not show any malignancies.

The patient was managed with infection barrier measures and did not develop infections. She was safely discharged after 30 days. On follow up at 60 days, the neutrophil count was 3.0x10^9/litre and the patient remained well.

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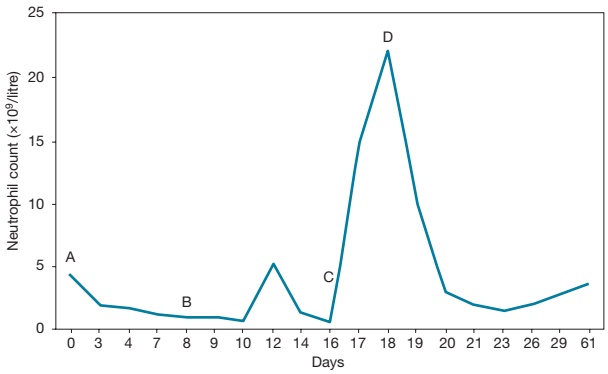

Figure 1. The trend in the patient's neutrophil count (x10^9/litre) (normal range 2.0–7.0x10^9/litre. A = day of initiating oral metronidazole 400 mg three times a day, B = day of discontinuing metronidazole therapy; C = day of initiating filgrastim 30 million units subcutaneously once daily; D = day of discontinuing filgrastim therapy.

Table 1. Assessing the adverse drug probability of metronidazole-induced neutropaenia using the Naranjo scale

Question	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	+1
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
Did the adverse event reappear when the drug was readministered	+2	-1	0	0
Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	+2
Did the reaction reappear when a placebo was given?	-1	+1	0	0
Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	0
				Total score: 6/10

The adverse drug reaction is assigned to a probability category from the total score as follows: definite >8; probable 5–8; possible 1–4; doubtful <1. Modified from Naranjo et al (1981)

Discussion

Neutropaenia is defined as a neutrophil count of <2.5x10^9/litre with severe neutropenia at levels <1.0x10^9/litre, where patients become immunocompromised and are at high risk of sepsis. Neutropaenia occurs in 1–5 cases per million population per year and 70% of cases are attributed to medication adversities. Risk factors include advanced age, female sex, and chronic systemic and autoimmune diseases.

Metronidazole is a bactericidal nitroimidazole which is a potent inhibitor of the cytochrome P450 enzyme isoforms that influence the pathways by which metronidazole is converted to its main active metabolite before excretion, accounting for most drug–drug interactions that it has been implicated in. Polymorphisms of these enzyme isomers lead to unanticipated drug poisoning.

Oxidative metabolism of metronidazole leads to a covalently bonded drug–neutrophil cell membrane antigen against which antibodies develop with consequent neutrophil depletion. Patients aged >70 years have 80% higher area under the curve of the oxidised metabolite 2-hydroxymetronidazole than controls aged <40 years, with no difference in area under the curve of metronidazole. The risk of metronidazole toxicity is amplified in older adults

because of concurrent metabolic abnormalities which shift metabolism towards oxidation leading to the accumulation of active metabolites, and as a result of sarcopenia.

There are several cases reporting less severe neutropaenia associated with metronidazole therapy. However, to the authors' knowledge, this is the fourth report of idiosyncratic metronidazole-induced neutropaenia with levels <1x10^9/litre (McKendrick and Geddes, 1979; Smith, 1980; Gutiérrez García et al, 2012). Neutropaenia is listed as a 'very rare side effect' (<1 case per 10 000 population) by manufacturers. As in previous reports, this patient received <20 g of metronidazole with neutropaenia occurring approximately 7 days following initiation of therapy. Lefebvre and Hesseltine (1965) documented white cell differentials of 386 patients being treated with metronidazole for *Trichomonas vaginalis* infection and reported a 1% incidence of transient neutropaenia which was not clinically important, and which spontaneously resolved after 14 days of treatment. Taylor (1965), in a letter of reply, supported these findings in a series of 605 patients where 12 patients developed a similar pattern of insignificant neutropaenia. Serial bone marrow examinations in four patients did not show suppression, but rather increased haematopoietic activity which was reflected in the blood films. She hypothesised that rather than bone marrow suppression, accelerated disappearance of these elements from the blood temporarily exceeded bone marrow release. Any linear relationship between the duration or dose of metronidazole treatment and the onset or degree of neutropaenia has not been characterised.

In McKendrick and Geddes' (1979) case, the patient was receiving azathioprine that may have potentiated the neutropaenic process. In the present case there were no drugs given concomitantly or disease processes that could have contributed to the neutropaenia.

Conclusions

Metronidazole is effective against anaerobic infections with a favourable side-effect profile during therapeutic use. In the absence of previous exposure to metronidazole, the proposed mechanism of neutropaenia in this patient is bone marrow suppression rather than a cell membrane antigen process associated with peripheral destruction. Also, the rapid rate of neutrophil reduction favours bone marrow suppression rather than a pre-existing autoantibody. The authors suspect that underlying *C. difficile* infection may have weakened this patient's immunity and compounded the bone marrow suppressive effect of metronidazole. Unique to this case are the degree of neutrophil suppression and the slow recovery of marrow function with a reversed neutrophil/lymphocyte ratio for >21 days. Unlike previous reports, the authors were able to positively demonstrate bone marrow function using granulocyte colony-stimulating factor which supported a diagnosis of drug-induced agranulocytosis. A high index of suspicion should therefore be exercised among older patients who are at risk of metronidazole toxicity even at therapeutic doses.

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Learning points

- Metronidazole-induced severe neutropenia is very rare and may result from a bone marrow suppressive effect.
- Patients aged >70 years have 80% higher area under the curve of the oxidised active metabolites compared to patients <40 years.
- Older adults are therefore at risk of toxicity with therapeutic dosing and this risk is heightened by concurrent metabolic abnormalities and low body weight.
- Although bone marrow suppression can be protracted, it should be reversible on cessation of the drug.

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