Adverse drug reaction of the month

Ticlopidine-induced severe neutropenia

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Ticlopidine is a recently introduced antiplatelet agent that has been shown to be effective in the prevention of thrombosis in cerebral and coronary atherosclerotic disease.^{1–7} Thus, in the Canadian American Ticlopidine Study (CATS), ticlopidine reduced the overall risk of vascular death, nonfatal stroke, or nonfatal myocardial infarction by 30% compared with placebo in patients with a recent completed stroke.² In addition, in the Ticlopidine Aspirin Stroke Study (TASS), ticlopidine reduced the overall risk of nonfatal or fatal stroke by 21% compared with aspirin in patients with reversible cerebrovascular ischaemic events or patients with minor stroke.^{1,6}

Despite its proven clinical efficacy, more than 50% of the patients who received the drug, in the two largest clinical trials of ticlopidine (TASS¹ and CATS²) experienced various adverse effects, the most serious of which was reversible neutropenia and pancytopenia^{1,2} (2.3% (35/1518) and 2.1% (11/525) in TASS and CATS, respectively). Severe neutropenia (absolute neutrophil count (ANC) $<0.45 \times 10^9/l$) was reported in 17/2048 patients compiled from TASS and CATS, but was claimed to be of minor clinical significance, as there were no fatalities directly related to the neutropenia, and all reversed when the drug was discontinued.⁴

The aim of the present report is to emphasize this potential severe and fatal outcome of ticlopidine administration.

Patients and methods

During 1994–96, four patients who had been treated with ticlopidine were admitted to the Department of Medicine C at The Chaim Sheba Medical Center, Tel Hashomer (a 38-bed general internal medicine department) with severe neutropenia (ANC $<0.45 \times 10^9/l$). The details of their clinical course form the basis of the present report.

Case 1

An 87-year-old Ashkenazi-Jewish woman was referred in April 1995 for a febrile disease and weakness. She had been treated for two months with ticlopidine, 250 mg bid, because of a recent stroke and aspirin intolerance. Other medications included nifedipine, captopril, isorbide-dinitrate, famotidine, perphenazine, furosemide and brotizolam. Complete blood count (CBC) revealed: leucocytes (WBC) $1.0 \times 10^9/l$, ANC $0.1 \times 10^9/l$, haemoglobin 11.8 g/dl, and platelets $265 \times 10^9/l$, compared with WBC $11.9 \times 10^9/l$, ANC $7.39 \times 10^9/l$, haemoglobin 14.8 g/dl and platelets $272 \times 10^9/l$

before initiation of ticlopidine. Ticlopidine was stopped and she was treated with broad-spectrum antibiotics, as well as with granulocyte-colony-stimulating factor (G-CSF). She remained neutropenic and died on the 14th day of hospitalisation.

Case 2

A 69-year-old Ashkenazi-Jewish woman was referred in March 1994 with a four-day history of fever (39°C), sore throat and dysphagia. Ticlopidine 250 mg bid daily had been started one month before admission following a recent stroke. CBC on admission revealed: WBC $0.4 \times 10^9/l$, ANC $0.04 \times 10^9/l$, haemoglobin 11.8 g/dl and platelets $267 \times 10^9/l$. A diagnosis of acute epiglottitis was made, ticlopidine was stopped and piperacillin, ceftazidime and gentamycin were administered. However, the patient remained neutropenic and died on the 4th day of hospitalisation.

Case 3

An 86-year-old Ashkenazi-Jewish woman was referred in February 1995 because of abdominal cramps, diarrhoea of two weeks duration and fever. Ticlopidine 250 mg daily had been started six weeks before admission after two episodes of stroke. CBC on admission revealed WBC $1.0 \times 10^9/l$, ANC $0.112 \times 10^9/l$, haemoglobin 10.4 g/dl and platelets $146 \times 10^9/l$. A CBC taken one month before admission had shown WBC $10.6 \times 10^9/l$, ANC $7.2 \times 10^9/l$, haemoglobin 11.6 g/dl and platelets $314 \times 10^9/l$. Ticlopidine was stopped and G-CSF was started. G-CSF was continued until a rise in WBC was observed ($4.6 \times 10^9/l$, ANC $2.6 \times 10^9/l$), 26 days after ticlopidine had been stopped. A CBC performed four weeks later, revealed a normal WBC, ANC, and platelet count ($235 \times 10^9/l$), but the haemoglobin was still low (9.9 g/dl).

Case 4

A 75-year-old North-African Jewish man was referred because of fever (38.5°C). Ticlopidine, 250 mg bid, had been started seven weeks before admission, after a recurrent stroke which occurred despite aspirin therapy. CBC on admission revealed total WBC $0.07 \times 10^9/l$, haemoglobin 13.6 g/dl, and platelets $203 \times 10^9/l$. Ticlopidine was stopped and broad-spectrum antibiotics were administered, but the fever persisted. On the 14th day of hospitalisation, an abdominal computed tomography scan revealed typhlitis (cectitis). Four days later the WBC counts began to rise ($2.9 \times 10^9/l$ and ANC $1.6 \times 10^9/l$), and after an additional six days they returned to normal.

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Discussion

Herein we present four patients who developed severe neutropenia during ticlopidine treatment. Three of them had also received other medications, of which captopril, famotidine, perphenazine, furosemide and glibenclamide have been reported to be associated with similar haematologic disturbances.⁸ Although their role in the induction of neutropenia in the present cases should be considered, it could not be assessed.

Ticlopidine-induced myelotoxicity has been known for more than 10 years, although it has been regarded as a rare adverse effect,¹⁻⁷ with an incidence of 0.8%.⁴ However, in contrast to the present report, with a fatality rate of 2/4 (50%), the neutropenia was associated with neither mortality nor severe morbidity.^{1,2} We found a further six (27%) ticlopidine-associated fatalities in the literature out of 23 published cases. G-CSF or granulocyte-monocyte colony-stimulating factor (GM-CSF), had been administered to six patients and three of these died. Three of our four patients were treated with G-CSF, of whom

one died. Thus, although G-CSF shows some promise in the treatment of life-threatening ticlopidine-induced neutropenia, its efficacy should be further evaluated.⁹

Because of the adverse potential reaction of this valuable antiplatelet drug, its use is restricted to patients with a recent stroke, transient ischaemic attacks or unstable angina, provided that they cannot use aspirin. It might also be prescribed to patients taking aspirin who nevertheless have ischaemic events.⁴

In the near future it is probable that the significance of ticlopidine-induced severe neutropenia will decrease with the potential introduction of clopidogrel, a new derivative similar to ticlopidine, which has been reported to have enhanced efficacy compared to aspirin in preventing vascular events, without the neutropenia associated with ticlopidine.¹⁰ Further studies should provide the appropriate recommendations to the use of ticlopidine or its new derivative in various ischaemic vascular diseases.

Keywords: ticlopidine; neutropenia

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