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Adverse Haematological Effects of Ticlopidine

Prevention, Recognition and Management

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Abstract

Ticlopidine is an antiplatelet agent that is used to reduce the occurrence of atherothrombotic arterial events. There have been major multicentre placebo-controlled trials evaluating its use in stroke, peripheral arterial disease and unstable angina. In rare cases, adverse haematological effects have been seen with ticlopidine.

Ticlopidine has been associated with neutropenia in some of the major trials and in subsequent case reports it has been associated with aplastic anaemia, thrombocytopenia and thrombotic thrombocytopenic purpura, which have been fatal in some instances. Ticlopidine should be used only in patients with an established indication for its use. Patients should be educated about the potential adverse effects and complications associated with ticlopidine, including possible death. Finally, there should be careful attention to haematological monitoring to screen for and promptly detect any adverse effects.

Ticlopidine hydrochloride is a thienopyridine derivative that first emerged in the late 1970s for use as an antiplatelet agent. It is used to reduce the occurrence of atherothrombotic arterial events, such as ischaemic stroke. It also has been studied for use in peripheral arterial disease, unstable angina and, more recently, following coronary artery stenting. Its mechanism of action is different from that of other available antiplatelet agents. In addition, it has different adverse effects associated with it.

1. Indications

In the treatment of cerebrovascular disease, ticlopidine is indicated to reduce the risk of atherothrombotic stroke (fatal or nonfatal) in patients who have experienced transient ischaemic attacks and in patients who have had an ischaemic stroke. In the US, its use is reserved for patients who are intolerant to aspirin (acetylsalicylic acid) therapy because of either allergy or adverse effects, or for patients who continue to have recurrent ischaemic cerebrovascular events in spite of aspirin therapy. The basis for the use of ticlopidine for prevention of stroke comes from 2 large, multicentre, randomised, double-blind trials.

The Canadian-American Ticlopidine Study (CATS) enrolled 1053 patients (62% of whom were men) who were admitted to the study between 1 week and 4 months after a moderate to severe thromboembolic stroke.[1] Patients with cardiac embolic strokes, haemorrhages or cerebral infarctions, that occurred as a complication of carotid endarterectomy or angioplasty, were excluded from the study. Ticlopidine 250mg twice daily was compared with placebo. The data were examined by an on-treatment analysis and by an intention-to-treat analysis. Primary outcome clusters included recurrent nonfatal stroke, myocardial infarction and vascular death. Secondary outcomes included nonfatal and fatal stroke. Patients were followed for a mean period of 2 years. The relative risk reduction for the clusters of stroke, myocardial infarction or vascular death with ticlopidine was 30.2% [95% confidence interval (CI) 7.5 to 48.3; $p = 0.006$]. Correspondingly, stroke and stroke death was reduced 33.5% ($p = 0.008$).

The Ticlopidine Aspirin Stroke Study (TASS) evaluated 3069 patients (65% of whom were men) who had experienced transient ischaemic attacks (TIA) or a minor stroke in the preceding 3 months.[2] These patients received either ticlopidine 250mg twice daily or aspirin 650mg twice daily. Patients were followed for a mean of 3.3 years. Ticlopidine reduced the risk of fatal or nonfatal stroke by 46% over aspirin in the first year ($p = 0.0002$). Fatal or nonfatal stroke was reduced by 21% at 3 years (95% CI 4 to 38; $p = 0.024$). The relative risk reduction in the event rate of nonfatal stroke or death was 12% (95% CI –2 to 26; $p < 0.05$).

Ticlopidine also has been studied in patients with peripheral arterial disease in the Swedish Ticlopidine Multicentre Study (STIMS).[3] In this study, 687 patients were randomly assigned in a double-blind fashion to receive either ticlopidine 250mg twice daily or placebo. Over a 5-year period, patients were followed for outcomes of myocardial infarction, stroke and TIA. There was a reduction of 11.4% for this outcome cluster ($p = 0.24$) and a 29.1% reduction in overall mortality in the ticlopidine group compared with placebo ($p = 0.015$).

The Studio della Ticlopidina nell'angina Instabile (STAI) trial studied the use of ticlopidine in patients with unstable angina.[4] In this study, 652 patients were randomly assigned to receive conventional therapy (β-blockers, calcium antagonists, or nitrates) or ticlopidine 250mg twice daily plus conventional therapy. A risk reduction of 53.2% (95% CI 0.24 to 0.79; $p = 0.006$) was seen for nonfatal or fatal myocardial infarction and a 46.8% reduction (95% CI 0.23 to 1.24; $p = 0.006$) was observed for fatal myocardial infarction and vascular death.

The Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial evaluated 517 patients after coronary artery stent placement.[5] Treatment with aspirin 100mg twice daily given with ticlopidine 250mg twice daily was compared with anticoagulant therapy with intravenous heparin, phen-

procoumon (a coumarin derivative) plus aspirin. Over a treatment period of 4 weeks after placement of coronary artery stents, there was an 82% lower risk of myocardial infarction and a 78% lower need for repeat intervention in patients treated with aspirin and ticlopidine. There was a lesser incidence of occlusion of the stented vessel; 0.8% versus 5.4% for aspirin and ticlopidine compared with anticoagulant treatment, respectively (relative risk 0.14; 95% CI 0.02 to 0.62; p = 0.004). There were no haemorrhagic complications in the aspirin-ticlopidine group compared with an incidence of 6.5% in the anticoagulant group. An 87% reduction in the risk of peripheral vascular disease was seen in the aspirin-ticlopidine group (relative risk 0.13; 95% CI 0.01 to 0.53; p = 0.001).

The Antiplatelet Trialists' Collaboration's meta-analysis of 142 trials, involving more than 73 000 high-risk patients in various disease categories, showed clearly that antiplatelet drugs reduced the incidence of the outcome cluster stroke, myocardial infarction or vascular death, the relative odds reduction being 27%.[6] In placebo-controlled trials with aspirin or with ticlopidine, the odds reductions were 25% and 33%, respectively. In trials with direct comparisons of aspirin and ticlopidine, there was a relative odds reduction of 10% in favour of ticlopidine.

Ticlopidine has been used for patients with peripheral vascular disease. A recent study showed that ticlopidine improved long term patency of saphenous vein bypass grafts in the legs when compared with placebo.[7]

The African-American Antiplatelet Stroke Prevention Study (AAASPS) is underway to compare ticlopidine 500 mg/day with aspirin 650 mg/day in the secondary prevention of noncardioembolic infarcts in African-Americans.

2. Mechanism of Action

Ticlopidine inhibits the adenosine diphosphate (ADP)–induced pathway of platelet aggregation by altering the platelet membrane response to fibrinogen–associated thrombogenic stimuli.[8,9] Unlike aspirin, ticlopidine does not interfere with the prostacyclin-thromboxane pathway. Studies have reported a decrease in platelet deposition in atheromatous plaques in patients with cerebrovascular disease and decreased fibrinogen levels and blood viscosity in patients with peripheral vascular disease.[8] Ticlopidine also prolongs the bleeding time as a result of its effect on platelets.[10]

The inhibition of platelet aggregation with ticlopidine is both dose and time-dependent. The onset of action is within 24 to 48 hours of administration, is maximum at 3 to 5 days and lasts for the lifetime of the platelet.[8]

3. Dosage and Administration

The recommended dosage of ticlopidine for use in cerebrovascular disease in Europe and North America and that which was used in a majority of the clinical trials is 250mg twice daily given orally. Trials conducted in Japan generally have used lower dosages (200 to 300 mg/day) for most conditions.[8] In the controlled trials, ticlopidine was given with food to minimise adverse gastrointestinal adverse effects. No dosage reduction is required for elderly patients.

Contraindications for the use of ticlopidine include an active peptic ulcer, blood dyscrasias, hypersensitivity, severe liver impairment, neutropenia and thrombocytopenia. Drug interactions have been observed with corticosteroids, anticoagulants, theophylline, thrombolytic agents, other antiplatelet agents, probenecid, nitrofurantoin, antacids, aminoglycosides, cellulose-containing laxatives, nifedipine/verapamil, phenytoin, sulfonamides, methotrexate and aminosalicylate.

4. Pharmacokinetic Profile

Following oral administration of ticlopidine, more than 80% of the drug is absorbed, with peak plasma concentrations occurring approximately 2 hours after a single 250mg dose.[8] Steady-state peak and trough plasma concentrations are obtained after administration of ticlopidine 250mg twice daily for 14 days.[10] Ticlopidine reversibly binds to plasma proteins. Metabolism occurs in the liver. Excretion is primarily in the urine and to a

lesser extent in the faeces. The clearance of ticlopidine decreases with age, but dosage adjustment is not usually required. In addition, there is an extended half-life of the drug after administration of multiple doses.[11] In patients with hepatic dysfunction, ticlopidine plasma concentrations ticlopidine are slightly increased. In patients with renal dysfunction, there is decreased clearance, but no significant difference in ADP-induced platelet aggregation. Bleeding times are prolonged in patients with moderate renal impairment and logically also in those with severe renal impairment, although the latter group apparently has not been studied.

5. Non-Haematological Adverse Effects

The most frequent non-haematological adverse effects associated with ticlopidine in the major studies that reported such events are outlined in table I. The most common adverse effects are diarrhoea and rash. Other gastrointestinal abnormalities such as gastrointestinal pain, gastrointestinal haemorrhage and peptic ulcers were rather infrequent, especially in comparison to aspirin.[2]

6. Haematological Adverse Effects

Haematological toxicity has been associated with ticlopidine in a small percentage of patients. Potential adverse haematological experiences have included neutropenia, agranulocytosis, aplastic anaemia, pancytopenia, thrombotic thrombocytopenic purpura (TTP) and thrombocytopenia. It is reported that through to 1994, there were 645 cases of combined aplastic anaemia, bone marrow suppression, pancytopenia and agranulocytosis worldwide that were related to ticlopidine, of which 102 (16%) were fatal.[12] There are no available data regarding the total number of persons exposed to the drug during this period. In the US, through to March 1995, the US Food and Drug Administration received reports of 13 cases of aplastic anaemia, 87 of agranulocytosis, 18 of pancytopenia, 45 of neutropenia, 25 of TTP and 21 of thrombocytopenia.[13] Again, there are no data regarding the number of persons treated with ticlopidine during that period. 36 of the 188 patients died (19%). Median duration to the onset of symptoms ranged from 30 to 45 days in this group.

While these adverse reactions are relatively uncommon, they are potentially serious and fatal. Proportionately greater frequencies of women aged 75 years and older developed haematological disorders in comparison to all ticlopidine users.[13,14] While women aged 75 years or more accounted for 19% of patients prescribed ticlopidine, 31% of patients developing haematological adverse effects were women in this age group.[13,14] The experience with these adverse reactions will now be reviewed and preventive measures and treatment of complications will be discussed.

6.1 Neutropenia

Neutropenia can occur with ticlopidine (table II). In fact, the initial clinical trials of ticlopidine in the UK were suspended because of neutropenia. The mechanism of ticlopidine-induced neutropenia is reportedly caused by reversible inhibition by ticlopidine of myeloid colony growth.[15] Inhibition of myelopoiesis in patients with impaired medullary reserve and inhibition of mito-

Table I. Number of patients (%) experiencing non-haematological adverse experiences in CATS, TASS and STIMS[1-3]

Adverse experience	STIMS		CATS		TASS	
	ticlopidine (n = 346)	placebo (n = 341)	ticlopidine (n = 525)	placebo (n = 528)	ticlopidine (n = 1518)	aspirin (n = 1527)
Any	NA	NA	283 (54)	181 (34)	945 (62)	813 (53)
Diarrhoea	75 (21.7)	30 (8.8)	113 (21.5)	53 (10)	310 (20)	150 (9.8)
Rash	12 (3.5)	6 (1.8)	78 (14.9)	43 (8.1)	180 (11.9)	80 (5.2)
Other GI effects	57 (16.5)	35 (10.3)	NA	NA	142 (9.4)	245 (16)

CATS = Canadian-American Ticlopidine Study**; GI** = gastrointestinal; **NA** = not applicable; **STIMS** = Swedish Ticlopidine Multicentre Study; **TASS** = Ticlopidine Aspirin Stroke Study.

Table II. Reported incidence of neutropenia in major randomised controlled studies of ticlopidine

Study	No. of pts receiving ticlopidine	Total no. of pts with neutropenia (%)	No. of pts with severe neutropenia (%)
CATS[1]	525	11 (2)	4 (1)
TASS[2]	1518	35 (1.4)	13 (0.9)
STIMS[3]	346	3 (0.9)	0
STAI[4]	314	0	0

CATS = Canadian-American Ticlopidine Study; **STAI** = Studio della Ticlopidina nell'Angina Instabile; **STIMS** = Swedish Ticlopidine Multicentre Study; **TASS** = Ticlopidine Aspirin Stroke Study.

chondrial oxidative phosphorylation have also been described.[16,17]

On the basis of the combined data from the CATS and TASS studies, there is a 2.4% incidence of neutropenia and a 0.85% incidence of severe neutropenia and agranulocytosis.[1,2,18] The incidence of neutropenia has varied in the major trials involving ticlopidine (table II). In CATS, among a total of 525 patients receiving ticlopidine, 11 patients (2%) developed neutropenia [absolute neutrophil count (ANC) $<1.2 \times 10^9$/L] of which 4 cases were severe (ANC $<0.45 \times 10^9$/L). The neutropenia developed within the first 3 months. Upon discontinuing ticlopidine, the neutropenia reversed within days. There were no reported clinical complications or deaths as a result of the neutropenia.

In TASS, 1518 patients received ticlopidine.[2] The parameters defining neutropenia were the same as for CATS. 35 patients (2.3%) developed neutropenia, of which 13 (0.9%) were severe. The severe neutropenias developed between 1 and 3 months after ticlopidine therapy was initiated. The neutropenia resolved within 3 weeks of discontinuing ticlopidine. However, 1 death was attributable to treatment of complications arising from the neutropenia. This patient died of renal failure caused by aminoglycoside therapy that was given for a systemic infection.

In STIMS, there were 346 patients who received ticlopidine.[3] Blood monitoring was performed at 1 month after starting ticlopidine and every 3 months thereafter for the duration of the study. Three patients with neutropenia were identified in the formal analysis. The parameters for defining these cases of neutropenia are not given. The authors state that in 2 of these patients the neutropenia was considered unlikely to be related to ticlopidine. In 1 patient, white blood cell counts normalised with continued therapy and in the other the neutropenia persisted upon withdrawal and was unchanged upon rechallenge with ticlopidine. The third patient was asymptomatic and the neutropenia occurred 2.5 years after treatment was initiated and the patient's neutrophil count remained low for several years after withdrawal from therapy. Upon subsequent analysis of the laboratory data, there were 8 unreported cases of white blood cell counts of $<3.5 \times 10^9$/L on at least one occasion. The lowest recorded value was 2.2×10^9/L. There were no clinical complications and ticlopidine was not withdrawn.

In the STAI trial, a total of 314 patients were treated with ticlopidine.[4] Complete blood counts were done at 1, 2, 3 and 6 months after initiation of ticlopidine. There were no clinically significant changes in the white blood cell counts.

In the ISAR trial, no cases of neutropenia were observed.[5] However, complete blood counts were not monitored in most patients after discharge from the hospital after the first 10 days of treatment. As the authors point out, cases of neutropenia could have been missed. However, Haushofer et al.[19] reported a different experience in this population in a small series of patients after coronary artery stenting. In 51 patients treated with ticlopidine 250mg twice daily and aspirin 100mg per day, complete blood counts were obtained at baseline, days 1 to 7, day 14, day 28 and day 35. Five patients developed neutropenia defined as a white blood cell count $<2.2 \times 10^9$/L. The neutropenia occurred between days 14 and 35. One patient proceeded to agranulocytosis with fever and required initiation of filgrastim, a granulocyte colony stimulating factor. The patient's neutrophil count returned to normal in 2 to 3 weeks after discontinuation of ticlopidine. Based on this experience, the authors recommended regular monitoring of blood counts, even during short (4 week) courses of therapy and

Table III. Review of case reports of aplastic anaemia associated with ticlopidine

Case report	Age/gender	Time after initiation of therapy	Time to recovery	Bone marrow findings	Other complications	Treatment
Garnier et al.[27]	74/M	2 mo	60 days	Hypoplastic cellularity and histological pattern of aplastic anaemia	None	ATB, RBC and platelet transfusions
Troussard:[28] case 1	73/F	3 mo	10 mo	Histological pattern of aplastic anaemia	Streptococcal bacteremia	Platelet transfusion, androgeno-therapy
Troussard:[28] case 2	66/F	5 mo	14 mo	Absence of granulocyte and megakaryocytic series with marked erythroid hypoplasia	None	ATB, platelet transfusion, methenolone
Elias et al.[21]	64/F	3.5 wks	1 mo	Severely aplastic	Rash	ATB
Khelif et al.:[29] case 1	61/M	2 mo	5 wks	Hypocellular, nearly empty marrow spaces with a few lymphocytes and plasmocytes	Pneumonia, herpetic stomatitis, otitis with facial palsy	ATB, GM-CSF
Khelif et al.:[29] case 2	79/M	6 wks	Died on day 7	(i) Severe myeloid hypoplasia with moderate medullary fibrosis and an increase in lymphoplasmocyte lineage; (ii) Postmortem examination showed severe myeloid hypoplasia with persistent plasma cell infiltration	Bilateral amygdalitis, inflamed left cervical lymph node, and pneumonia	ATB, GM-CSF
Martin-Nunez, et al.[30]	66/F	43 days	Died on day 4	Severe aplastic anaemia with very hypoplastic cellularity and absence of cells of granulocyte, erythroid and megakaryocytic lineages with mainly lymphocytes, macrophages and plasma cells	*Escherichia coli* sepsis, multi-organ failure	ATB
Lesesve et al.:[31] case 1	62/M	16 wks	1 mo	'Regenerative features'	None	None
Lesesve et al.:[31] case 2	51/M	10 wks	7 wks	Absence of granulocyte and megakaryocyte series with a marked erythroid hypoplasia	Purpura	ATB, platelet transfusions
Lesesve et al.:[31] case 3	69/M	54 days	Incomplete at 88 days	(i) Aplastic marrow with only lymphoid lineage cells (on admission); (ii) hypoplastic bone marrow (on day 43)		ATB, platelet transfusions, G-CSF, corticosteroids
Mallet and Mallet[32]	84/F	6 wks	Died on day 76	Severe hypoplasia with agranulocytosis	None	ATB, antifungal drugs; RBC and platelet transfusions, G-CSF
Rodriguez et al.[33]	69/M	2 mo	Died on day 24	(i) Slight hypocellularity with absence of granulocyte line (on admission); (ii) slight cellularity consisting only of lymphocytes, plasma cells and macrophages (on day 17)	GI bleeding, sepsis	ATB, G-CSF, corticosteroids

Table III. Contd

Case report	Age/gender	Time after initiation of therapy	Time to recovery	Bone marrow findings	Other complications	Treatment
Arribalzaga et al.[34]	78/F	6 wks	WBC recovered in 2 days. Hb and platelets remained low. Died 5 mo later due to GI bleeding	Severe aplastic anaemia	Sepsis, GI bleeding	ATB, RBC and platelet transfusions, G-CSF, high dose immunoglobulins, recombinant epoietin (erythropoietin)
Dunn:[35] case 1	66/F	6 wks	Improving at day 24	Mostly acellular marrow with plasma cells and lymphocytic infiltration	UTI	ATB, filgrastim[a]
Dunn:[35] case 2	67/M	6 wks	Improving at day 30	Markedly hypocellular marrow with absent myeloid and erythroid series	Pneumonia and bacteremia	ATB, platelet transfusions, and filgrastim
Shapiro and Walk[36]	80/F	5 wks	>6 wks	Cellularity <5% and rare normal cellular precursors	None	RBC transfusion, filgrastim, epoietin-α

a Filgrastim is a granulocyte colony-stimulating factor.

ATB = antibacterial(s); **F =** female; **GI =** gastrointestinal; **G-CSF =** granulocyte-colony stimulating-factor; **GM-CSF =** granulocyte-macrophage colony-stimulating factor; **Hb =** haemoglobin; **M =** male; **RBC =** red blood cell; **UTI =** urinary tract infection; **WBC** = white blood cell.

1 week after discontinuation of ticlopidine therapy.[19]

There have been a small number of reports in the literature of other instances of neutropenia or agranulocytosis.[20-26] Some of these report development of delayed neutropenia.[20-22] While some cases of neutropenia have developed 2 to 5 days after discontinuing ticlopidine, one case has been reported where the neutropenia occurred 18 days after it was discontinued.[20,22] This phenomenon is probably related to the fact that ticlopidine undergoes nonlinear pharmacokinetics that results in a decreased clearance after repeated administration. The elimination half-life of the drug has been observed to be over 90 hours after 21 days of administration of ticlopidine 250mg twice daily.[11]

In summary, neutropenia occurs in approximately 2.4% of patients treated with ticlopidine, with 0.85% of these having severe neutropenia or agranulocytosis. The number of cases of agranulocytosis is slightly less than the 1 to 2% incidence with clozapine. The incidence of neutropenia is comparable to the 2% incidence of persistent leucopenia with carbamazepine.

There are certain guidelines and recommendations that should be followed in order to minimise the occurrence of neutropenia or to detect it rapidly if it does occur. First, ticlopidine therapy should not be initiated without an established indication for its use. Secondly, if ticlopidine is chosen as the best medication to use, patients should be educated about the potential adverse effects and complications, including possible death. Finally, there should be careful attention to haematological monitoring. Ticlopidine-induced neutropenia, as well as other haematological adverse effects, can be detected promptly by following the recommendation to monitor a complete blood cell count at baseline and every 2 weeks for the first 3 months of therapy. More frequent monitoring should be undertaken if ANC is less than 30% of the baseline value. Ticlopidine should be discontinued if the ANC is $<1.2 \times 10^9$/L. Haematological monitoring should also be done when patients take ticlopidine for short courses. It is also recommended to obtain a complete blood count and differential 2 weeks after discontinuation of ticlopidine if the drug is stopped within the first 90 days of therapy. At any time when there are signs or symptoms of infec-

tion, a complete blood count with differential should be obtained. More frequent monitoring is indicated when the white blood cell count has changed significantly or remains abnormal. If ticlopidine is stopped and then restarted at a later date, the monitoring needs to be reinitiated every 2 weeks for 3 months.

6.2 Aplastic Anaemia

Aplastic anaemia has been reported in rare instances with ticlopidine (table III).[21,27-36] While the frequency of ticlopidine-related marrow aplasia is low, some authors have suggested that this complication is underestimated.[31] While some authors have reported that ticlopidine–induced aplastic anaemia generally has a favourable outcome, there have been cases of delayed medullary regeneration and death in a worrisome number of patients.[31] Aplastic anaemia is characterised by pancytopenia with the bone marrow showing profound hypocellularity with absence of precursor cells and fatty replacement.

Aplastic anaemia has occurred as early as 3.5 weeks and as long as 5 months after initiation of ticlopidine in case reports.[21,27-36] Time to recovery from aplastic anaemia has been as short as 1 month and as long as more than 1 year. There have been fatal outcomes because of sepsis or other complications, such as bleeding. In 1 case, the patient never recovered from aplastic anaemia and died on day 76 of the illness.[32]

The exact mechanism by which ticlopidine causes aplastic anaemia is not clear. Ticlopidine-induced aplastic anaemia may be an idiosyncratic effect or it may be caused by direct toxicity from the drug. The effect of ticlopidine on *in vitro* myeloid [colony-forming unit granulocyte-macrophage (CFU-GM)] growth has been studied.[21,37] It is reported that ticlopidine inhibits CFU-GM growth, suggesting that ticlopidine is directly toxic to bone marrow cells, mainly the myeloid line. Some authors have favoured a direct toxic effect because the haematological toxicity may appear after more than 3 months, because there may be involvement of more than 1 haematopoietic cell line and because the toxic effect is usually transient.[21] The reason for the rarity of this adverse effect is not clear.

Development of this complication is serious and often leads to the necessity of prolonged and expensive supportive care to prevent the complications of sepsis and bleeding. Intravenous broad-spectrum antibacterials and antifungal agents are often administered. Patients often require transfusions of packed red blood cells and platelets. Other supportive therapies that have been given include androgenotherapy,[27] corticosteroids,[31-33] granulocyte colony-stimulating factors (G-CSF) or granulocyte-macrophage colony-stimulating factors (GM-CSF) and epoietin (erythropoietin).[34,36] The results of use of G-CSF or GM-CSF for ticlopidine-induced aplastic anaemia or neutropenia have been varied.[29,31-36] These agents are haematopoietic growth factors that have been used extensively for neutropenia related to the use of chemotherapy. The efficacy of their use in drug-induced neutropenia or aplastic anaemia caused by ticlopidine is not known. There have been no instances described where patients underwent bone marrow transplantation or antithymocyte globulin (ATG) therapy.

There have been some cases where either agranulocytosis or thrombocytopenia precedes the development of aplastic anaemia.[29,33] The timing of this complication can be well after the recommended 3 months of haematological monitoring. Therefore, the haematological monitoring can be inadequate in detecting all cases of this complication.

6.3 Thrombocytopenia and Thrombotic Thrombocytopenic Purpura

Thrombocytopenia and TTP have rarely been described with ticlopidine. There were no reports of thrombocytopenia or TTP in the major trials, although there were reports of purpura in 4% in the ticlopidine group in TASS.[2] Isolated thrombocytopenia with ticlopidine has been reported from 4 weeks to 5 years after initiation of the drug.[38] Patients have been asymptomatic or have had extremity haematomas, epistaxis and petechiae. One

case involved a person with epistaxis and petechiae who had been receiving ticlopidine 200 mg/day for 5 years.[39] The patient's platelet count had dropped to 32.0×10^9/L (normal usually $\geq 150 \times 10^9$/L). The patient's platelet count rose to 85×10^9/L, 2 weeks after withdrawal of ticlopidine and complete recovery occurred in 7 weeks. The level of platelet-associated immunoglobulin (Ig) G was extremely high just after withdrawal of ticlopidine and was normal 7 weeks later. It was postulated that this was an immunologically-mediated process. Some authors have suggested periodic determination of the platelet count during long term therapy with ticlopidine.[38]

There have been less than a dozen cases of TTP associated with ticlopidine reported in the English literature;[39-44] these occurred between 3 and 8 weeks after initiation of ticlopidine. TTP is a multisystem disease characterised by fever, thrombocytopenia, microangiopathic haemolytic anaemia, renal dysfunction and fluctuating neurological signs. One patient presented with a cerebral haemorrhage and TTP 3 weeks after starting ticlopidine therapy.[39] The all cause mortality rate described with TTP is often as high as 40%. Several authors have reported deaths caused by ticlopidine-induced TTP.[41,43,44] The aetiology of TTP is unknown, as is the mechanism by which ticlopidine causes this syndrome. It has been postulated that an immunoallergic mechanism may be involved as antibodies to platelets have been detected in the serum of a patient with ticlopidine-induced TTP.[44] Treatment with plasma exchange has significantly improved survival with TTP.[45] The successful use of plasma exchange for ticlopidine-induced TTP has been described.[40]

7. Conclusion

Ticlopidine is a drug that has very specific indications, including reduction of the risk of atherothrombotic stroke in persons with transient ischaemic attacks or completed ischaemic stroke when they are intolerant to aspirin therapy or in persons who continue to have recurrent ischaemic cerebrovascular events in spite of aspirin therapy. Ticlopidine has also been used in patients with unstable angina, in patients with peripheral arterial disease for the prevention of myocardial infarction, TIA and stroke and in combination with aspirin after coronary artery stenting. Ticlopidine has been associated with cases of neutropenia, aplastic anaemia, thrombocytopenia and TTP which have been fatal in some instances. The guidelines to monitor patients by performing complete blood counts and white blood cell differentials every 2 weeks for the first 3 months of therapy should be adhered to strictly. Rarely, patients will develop adverse haematological effects after the first 3 months. Patients should be educated about the potential for these life-threatening and sometimes fatal adverse events.

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