Hematologic dyscrasia associated with ticlopidine therapy: evidence for causality

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Abstract

Background: Several rare, potentially fatal types of hematologic dyscrasia, such as agranulocytosis, aplastic anemia, neutropenia, pancytopenia, thrombocytopenia and thrombotic thrombocytopenic purpura (TTP), have been associated with ticlopidine therapy. The extent to which ticlopidine is the causative factor has not been addressed quantitatively.

Methods: We identified 211 published case reports of hematologic dyscrasia associated with ticlopidine therapy from a MEDLINE search. We analyzed the 91 reports that could be evaluated, using the Bayesian Adverse Reaction Diagnostic Instrument to calculate the posterior probability that ticlopidine caused the hematologic dyscrasia based on epidemiologic and clinical trial data (prior odds) and case information (likelihood ratio).

Results: The median posterior probability values (and range) for agranulocytosis, aplastic anemia, neutropenia, pancytopenia, thrombocytopenia and TTP were 0.95 (0.53–0.98), 0.81 (0.57–0.93), 0.86 (0.75–0.96), 0.78 (0.61–0.89), 0.74 (0–0.92) and 1.0 (0.33–1.00) respectively. The posterior probability was 0.75 or greater in 82 (90%) of the case reports.

Interpretation: This systematic analysis provides stronger evidence to implicate ticlopidine as the causative factor in the various types of hematologic dyscrasia in most published case reports.

Ticlopidine, an antiplatelet agent with a mechanism of action distinct from that of ASA, has been shown to be effective for the treatment of cerebrovascular disease (i.e., completed strokes[1] and transient ischemic attacks[2]), coronary artery disease (i.e., unstable angina[3] and after coronary artery bypass grafting[4]) and peripheral vascular disease,[5,6] and after insertion of coronary artery stents (in combination with ASA).[7–9]

Ticlopidine was approved for use in Canada in April 1991. Since it has become widely used, there has been an increase in the number of published reports documenting potentially fatal cases of hematologic dyscrasia associated with ticlopidine therapy, particularly agranulocytosis,[10–20] aplastic anemia,[17,21–39] neutropenia,[10,40–47] pancytopenia,[48–51] thrombocytopenia[52–54] and thrombotic thrombocytopenia purpura (TTP).[47,55–65] As of June 1999 the Canadian Adverse Drug Reaction Monitoring Program had received 138 reports of hematologic dyscrasia associated with ticlopidine therapy, of which 15 resulted in death.

In general, establishing causality of such adverse hematologic drug reactions is challenging. This assessment is usually completed using unaided medical judgement, often leading to a high degree of uncertainty and variability among clinicians.[66–68] Although a spontaneous reporting system (such as the Canadian Adverse Drug Reaction Monitoring Program) effectively detects rare, serious adverse drug reactions, many adverse reactions remain underreported, or the submitted case reports are incomplete or erroneous. Moreover, although these spontaneous reports raise the concern of a potential adverse drug reaction, they do not establish causality between a drug and an adverse reaction.[69]

The Bayesian Adverse Reaction Diagnostic Instrument (BARDI) overcomes many of these limitations and has been proposed as an effective, standardized method for causality assessment.[70–72] Based on conditional probability, this method incorporates both epidemiologic data and case information to differentiate between drug and nondrug causes of an adverse drug reaction.

The objective of this study was to complete a systematic overview and causality assessment, using BARDI, of published case reports documenting various types of hematologic dyscrasia associated with ticlopidine therapy, specifically agranulocytosis, aplastic anemia, neutropenia, pancytopenia, thrombocytopenia and TTP.

Methods

All case reports of hematologic dyscrasia associated with ticlopidine therapy published in English or French between January 1966 and December 1999 were identified from the MEDLINE database. We conducted the search using the following key words: ticlopidine and agranulocytosis, aplastic anemia, neutropenia, pancytopenia, thrombocytopenia and thrombotic thrombocytopenic purpura. We also examined review articles and reference sections to identify any case reports that were not detected through the MEDLINE search. All documented drug and nondrug causes of the various types of hematologic dyscrasia were identified through MEDLINE and standard hematology references.[73,74]

Case reports that failed to provide sufficient information of differential diagnostic value for BARDI analysis were independently excluded by 2 of us (F.L.P.-H. and C.M.A.). Data from case reports that could be evaluated were independently extracted by 2 of us (F.L.P.-H. and C.M.A.), and any discrepancies were resolved through consensus.

We analysed the case reports using BARDI, which has previously been described in detail.[72] A brief description of the instrument follows.

Using a 5-step format, BARDI calculates a posterior probability that ticlopidine caused the hematologic dyscrasia for each individual case report under evaluation.

1. *Identification of case parameters:* The 4 parameters outlining the information used in BARDI analysis are (1) the specific hematologic dyscrasia, (2) the indication for ticlopidine use, (3) all known drug and nondrug causes of the specific hematologic dyscrasia and (4) the time horizon (i.e., period after ticlopidine administration during which one would expect the hematologic dyscrasia to occur if it were in fact caused by ticlopidine). The first 3 parameters were identified from the individual case reports, and the last parameter was determined from epidemiologic data.[75] We analyzed all known drug and nondrug causes of a specific hematologic dyscrasia using a "one-drug-at-a-time" strategy for each case report.[72] In brief, each suspected drug was analyzed against the possibility of nondrug causes, and the results of these separate analyses were then combined to reflect all possible causes of a specific hematologic dyscrasia.

2. *Collection of case information:* The following information of differential diagnostic value between ticlopidine and other potential causes of the various types of hematologic dyscrasia was identified from each case report: patient medical history (history), timing of the hematologic dyscrasia with respect to ticlopidine administration and concomitant drug therapy (timing), characteristics of the dyscrasia (characteristic), recovery time following discontinuation of therapy with ticlopidine and other concomitant drugs (dechallenge), and rechallenge with any of the potential drug causes of the various types of hematologic dyscrasia (rechallenge).

3. *Estimation of the prior odds:* The prior odds is the proportion of patients receiving ticlopidine who, within the time horizon, experience hematologic dyscrasia, divided by the background rate of the same dyscrasia (i.e., in the absence of ticlopidine). The numerator of the prior odds is the ticlopidine-attributable risk, and the denominator is the non-ticlopidine-attributable risk of a specific hematologic dyscrasia. We also calculated the prior odds for all the other potential drug causes identified from the case reports. In general, this information was obtained from placebo-controlled clinical trials.

4. *Estimation of the likelihood ratio:* We calculated a likelihood ratio (LR), expressed as the ratio of suspected drug causes versus nondrug causes, for the history, timing, characteristic, dechallenge and rechallenge for ticlopidine and for other potential drug causes identified from the case reports. The LR(timing) was determined through the use of a "timing distribution," which estimated a probability of the hematologic dyscrasia's occurring for each day during the predefined time horizon following drug administration. This probability takes into consideration the mechanism of the dyscrasia and whether it was detected during drug administration or following its discontinuation.

5. *Evaluation of the posterior odds and posterior probability:* The posterior odds is the product of the prior odds and 5 LRs: posterior odds = prior odds × LR(history) × LR(timing) × LR(characteristic) × LR(dechallenge) × LR(rechallenge). The posterior odds is then expressed as a posterior probability using the following equation: posterior probability = posterior odds/(1 + posterior odds).

We conducted a sensitivity analysis over a range of estimates for prior odds and LRs to test the robustness of the Bayesian model. Both quantitative estimates and estimates based on expert opinion were halved or doubled, as appropriate, to determine the effect on the final posterior odds calculated.

Results

We identified 211 case reports in the literature search, of which 120 (57%) were excluded on the basis that they failed to provide individual case information of differential diagnostic value (e.g., past medical history, concomitant therapy, onset of hematologic dyscrasia). The remaining 91 case reports were deemed to be suitable for evaluation with BARDI. There were 15 reports of agranulocytosis,[10–20] 29 of aplastic anemia,[17,21–39] 14 of neutropenia,[10,40–47] 4 of pancytopenia,[48–51] 3 of thrombocytopenia[52–54] and 26 of TTP.[47,55–65]

Step 1: Identification of case parameters

A summary of the parameters for each of the 6 types of hematologic dyscrasia associated with ticlopidine therapy is given in Table 1. Among the 91 case reports, ticlopidine was used to treat stroke in 31, transient ischemic attacks in

11, coronary artery disease in 14 and peripheral arterial disease in 8, and it was used after coronary stent insertion in 21 cases, and for other indications in 5.

Other possible drug causes for the various types of hematologic dyscrasia included ASA (3 cases),[76] dipyridamole (3 cases),[77,78] allopurinol (2 cases),[79] enalapril (4 cases),[80,81] hydrochlorothiazide (2 cases)[28,77] and, in 1 case each, digoxin[77,78] and furosemide.[28,77] Nondrug causes included renal impairment, in 4 cases.[40,80]

On the basis of an international consensus report, we estimated the time horizon at 4 months for the development of TTP with ticlopidine therapy and at 1 year for each of the 5 other types of hematologic dyscrasia.[75]

Step 2: Collection of case information

The case information for each type of hematologic dyscrasia is summarized in Table 2. Overall, the associated death rate was 24% (22/91), being lowest for thrombocytopenia (0%) and highest for aplastic anemia (38%) and TTP (27%). The median time of onset of the dyscrasia and the recovery time were 35 days (range 7–1825 days) and 15 days (range 2–60 days) respectively.

Step 3: Estimation of the prior odds

Table 3 summarizes the prior odds for the 6 types of

Table 1: Case parameters for the various types of hematologic dyscrasia associated with ticlopidine therapy

Parameter	Agranulocytosis	Aplastic anemia	Neutropenia*	Pancytopenia	Thrombocytopenia*	TTP*
No. of case reports identified	15	29	64	4	4	95
No. of case reports that could be evaluated	15	29	14	4	3	26
Median age of patients (and range), yr	63 (26–87)	69 (51–85)	65 (40–83)	64 (59–78)	71 (67–72)	72 (37–82)
Sex, no.of patients female/male/unknown	9/6/0	19/10/0	3/7/4	3/1/0	0/3/0	9/12/5
Indication for ticlopidine therapy, no. of cases						
Stroke	7	11	5	–	3	5
Transient ischemic attack	1	5	2	1	–	2
Coronary artery disease	3	5	–	3	–	3
After coronary stent insertion	1	3	7	–	–	10
Peripheral arterial disease	1	3	–	–	–	4
Other	2	–	–	–	–	3
Other possible drug causes (no. of cases)	Digoxin (1) Dipyridamole (3) Enalapril (1)	ASA (3) Furosemide (1) HCTZ (1)	Allopurinol (2) Enalapril (3)	HCTZ (1)	–	–
Other possible nondrug causes (no. of cases)	–	Renal failure (1)	Renal failure (3)	–	–	–

Note: TTP = thrombotic thrombocytopenic purpura, HCT = hydrochlorothiazide.
*Excluded case reports failed to provide sufficient information of differential diagnostic value for analysis with the Bayesian Adverse Reaction Diagnostic Instrument.

Table 2: Case information for the various types of hematologic dyscrasia

Information	Agranulocytosis n = 15	Aplastic anemia n = 29	Neutropenia n = 14	Pancytopenia n = 4	Thrombocytopenia n = 3	TTP n = 26
Median onset after initiation of ticlopidine therapy (and range), d	30 (21–112)	46 (16–150)	28 (7–90)	35 (21–90)	30 (30–1825)	28 (14–56)
Outcome, no. of patients died/recovered/unknown	2/13/0	11/16/2	1/12/1	1/3/0	0/3/0	7/19/0
Median time to recovery (and range), d	9 (4–15)	33 (10–60)	9 (2–18)	21 (15–30)	14 (14–49)	14 (4–21)
No. of cases with rechallenge with ticlopidine (and result)	0	0	0	0	0	1 (negative)
No. of cases with rechallenge with HCTZ (and result)	0	0	0	1 (negative)	0	0
No. of cases with rechallenge with ASA (and result)	0	1 (negative)	0	0	0	0

hematologic dyscrasia. In each instance except aplastic anemia, the estimate of the prior odds was higher for ticlopidine than for the other potential drug causes.

Step 4: Estimation of the likelihood ratio

History

The risk of a toxic hematologic effect associated with ticlopidine increases in the presence of renal impairment (since about 30% of the drug is eliminated by the kidneys).[40] This information increased the LR(history) for ticlopidine to 1.5 in the cases of 4 patients with documented renal dysfunction (3 with neutropenia and 1 with aplastic anemia). This was a conservative estimate based on clinical experience and consensus among us and was subjected to sensitivity analysis. The LR(history) for ticlopidine was 1.0 in the remaining 87 patients with normal renal function.

In 2 cases of neutropenia in patients with chronic renal failure, the LR(history) for enalapril was 10.0 (since the incidence of enalapril-induced neutropenia in renal impairment increases from 0.02% to 0.2%).[80] The risk of a toxic hematologic effect associated with allopurinol was also assumed to be increased in the presence of renal impairment (since 30% of this drug is also renally eliminated). This information increased the LR(history) for allopurinol to 1.5 and is the same estimate that was described for ticlopidine.

Timing

The timing distribution for the onset of neutropenia following ticlopidine administration was based on the data reported for 50 patients with ticlopidine-induced neutropenia from the Ticlopidine Aspirin Stroke Study and the Canadian American Ticlopidine Study in Thromboembolic Stroke.[78] This timing distribution was assumed to be similar for agranulocytosis, aplastic anemia, pancytopenia and thrombocytopenia. Because TTP is a multisystem disease, we used a separate timing distribution for the onset of this condition following ticlopidine administration. This timing distribution was based on a sample of 69 published case reports of TTP associated with ticlopidine therapy that were excluded from the BARDI analysis.[62,82]

Overall, the median LR(timing) for ticlopidine compared with that of the other potential drug causes was 2.3 (range 0–9.1) versus 1.0 (range 0–9.1) respectively. In 7 case reports (3 of aplastic anemia, 2 of neutropenia, 1 of agranulocytosis and 1 of pancytopenia), the hematologic dyscrasia was detected 5–17 days after ticlopidine therapy was stopped, which reduced the probability that the drug was the causative agent.

Characteristics

There was no information concerning the characteristics of the event that was of differential diagnostic value in any of the case reports evaluated. Thus, the LR(characteristic) for all the case reports within each category of hematologic dyscrasia was 1.0.

Dechallenge

For neutropenia and agranulocytosis, the distribution for recovery following discontinuation of the drug was based on a general model of recovery for drug-induced neutropenia,[75,84] whereas the distribution for recovery for the other types of hematologic dyscrasia was based on an international consensus report.[75]

With ticlopidine, the LR(dechallenge) was 1.0 for 50 case reports in which the recovery time was unknown or the outcome was death, 1.5 for 21 case reports of agranulocytosis or neutropenia in which recovery occurred within 1 month, and 1.2 for 20 case reports of aplastic anemia, pancytopenia or thrombocytopenia in which recovery occurred within 6 months.

With enalapril, allopurinol, dipyridamole and digoxin, the LR(dechallenge) was 0.01 for 7 case reports of neutropenia and agranulocytosis (since the hematologic dyscrasia resolved without discontinuation of the respective drugs).

Rechallenge

In 3 case reports (ticlopidine, ASA and hydrochloro-

Table 3: Prior odds for the various types of hematologic dyscrasia

Drug	Agranulocytosis	Aplastic anemia	Neutropenia	Pancytopenia	Thrombocytopenia	TTP
Ticlopidine	4.4[78]	2.7[28]	2.2[78]	2.7[28]	1.0*	56.1[82,83]
ASA	–	2.9[76]	–	–	–	–
Allopurinol	–	–	0.536[79]	–	–	–
Digoxin	2.5[77,78]	–	–	–	–	–
Dipyridamole	3.8[77,78]	–	–	–	–	–
Enalapril	0.0161[81]	–	0.0536[80]	–	–	–
Furosemide	–	3.8[28,77]	–	–	–	–
HCTZ	–	0.5[28,77]	–	1.3[28,77]	–	–

*Source: product monograph, Hoffmann–La Roche Limited, Mississauga, Ont.

thiazide in the setting of TTP, aplastic anemia and pancytopenia respectively), rechallenge without recurrence of the dyscrasia was described. This information resulted in a low probability (LR[rechallenge] = 0.01) that the drug caused the dyscrasia. The LR(rechallenge) was 1.0 for the remaining case reports.

Step 5: Evaluation of the posterior odds

The calculated posterior probabilities for all 91 case reports are shown in Fig. 1. The posterior probability for ticlopidine was 0.75 or greater (indicating a probability of at least 75% that ticlopidine caused the dyscrasia) in 82 (90%) of the reports. Overall, the median posterior probability values (and range) for ticlopidine for agranulocytosis, aplastic anemia, neutropenia, pancytopenia, thrombocytopenia and TTP were 0.95 (0.53–0.98), 0.81 (0.57–0.93), 0.86 (0.75–0.96), 0.78 (0.61–0.89), 0.74 (0–0.92) and 1.0 (0.33–1.00) respectively. The median posterior probability values (and ranges) for the other potential drug causes for agranulocytosis, aplastic anemia, neutropenia and pancytopenia were 0.02 (0–0.46), 0.03 (0–0.25), 0 (0–0.054) and 0, respectively.

To illustrate the contribution of case information to the prior odds, the median prior and posterior probabilities for each type of hematologic dyscrasia are given in Table 4. In each instance the median posterior probability was higher than the median prior probability, which indicates that the case information, as reflected in the LRs, points to ticlopidine causation.

Sensitivity analysis

The Bayesian model was robust to wide ranges of changes in all parameters except the numerator and denominator of the prior odds since the results were to a large degree driven by the prior odds. The prior odds estimates were generally based on quantitative data for large patient groups described in the literature and are therefore reasonable estimates of drug-attributable and non-drug-attributable risk. Although the results were sensitive to large variations in the estimates of the prior odds for aplastic anemia (only 10 of the 29 case reports retained a high posterior probability with a decrease of 50% in prior odds) and neutropenia (9 of the 14 case reports retained a high posterior proba-

bility with a decrease of 50%), it is unlikely that the true estimates were substantially different from those used in the model. Thus, in general, the model was robust.

Interpretation

It is estimated that of all the drugs approved for use, about 50% are associated with undetected serious adverse reactions.[85] Although neutropenia, the most common form of hematologic dyscrasia associated with ticlopidine therapy, was first recognized in phase III premarketing clinical trials, it was only through postmarketing surveillance studies and appropriate laboratory monitoring that other rare but serious types of hematologic dyscrasia (such as aplastic anemia, agranulocytosis and TTP) were subsequently detected. As a result of the significant morbidity and mortality associated with this adverse hematologic profile, ticlopidine has been primarily reserved as second-line therapy for symptomatic atherosclerotic disease in patients who are intolerant to, have contraindications to or have not responded to ASA treatment.

As a result of the widespread use of coronary artery stents and the proven benefit of the combination of ticlopidine and ASA for the prevention of subacute stent thrombosis, the use of ticlopidine and the incidence of potentially fatal complications associated with it have increased dramatically.[7–9,86]

Our systematic analysis provides stronger evidence (posterior probability 0.75 or greater) to implicate ticlopidine as the causative factor in 90% (82/91) of published case reports documenting various types of hematologic dyscrasia.
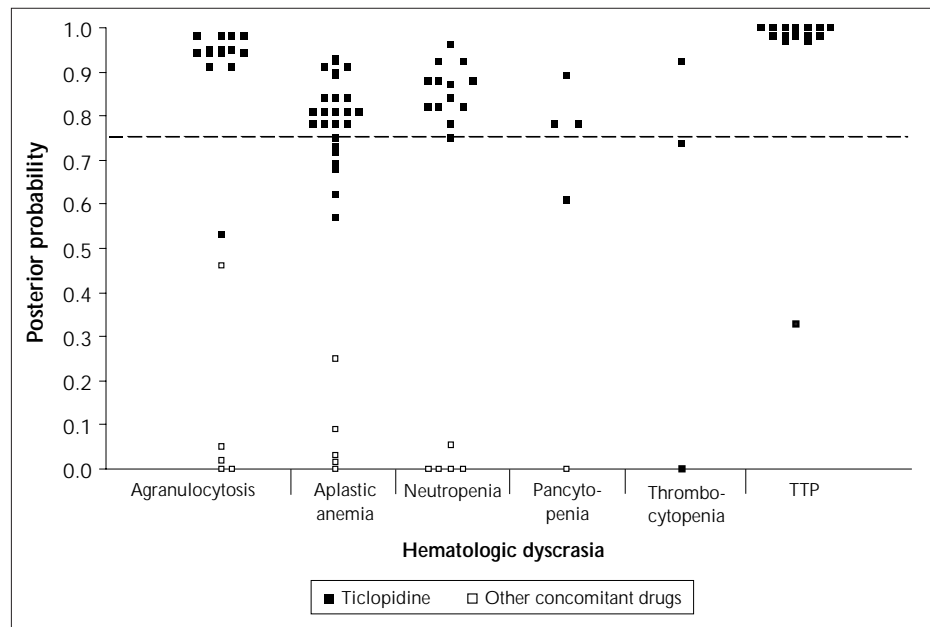

Fig. 1: Posterior probabilities for 91 case reports of hematologic dyscrasia associated with ticlopidine therapy. The posterior probability was 0.75 or greater (indicating a probability of at least 75% that ticlopidine caused the dyscrasia) (dashed line) in 82 (90%) of the case reports. TTP = thrombotic thrombocytopenic purpura.

Table 4: Median prior and posterior probabilities for the various types of hematologic dyscrasia

Variable	Agranulocytosis	Aplastic anemia	Neutropenia	Pancytopenia	Thrombocytopenia	TTP
Median prior probability	0.81	0.73	0.69	0.73	0.50	0.98
Median posterior probability	0.95	0.81	0.86	0.78	0.74	1.00

The restriction of our analysis to published case reports may in part account for this high causality rate, since case reports with a high likelihood of a causal relation may be preferentially submitted and accepted for publication.

Overall, the onset of the hematologic dyscrasia was temporally related to the initiation of ticlopidine therapy, generally occurring within the first 3 months, and the dyscrasia resolved within 3 weeks after discontinuation of therapy. However, in 8% of case reports, the dyscrasia appeared after therapy was stopped. This finding suggests a need for more frequent and longer routine monitoring. The small number of cases that could be evaluated precludes meaningful comparisons of outcomes among the various types of hematologic dyscrasia. Nonetheless, the death rate may be higher with aplastic anemia (38%) and TTP (27%) than with the other forms of dyscrasia.

The pathogenesis of the various types of hematologic dyscrasia associated with ticlopidine therapy is unclear. However, given the differences in their presentation and degree of severity, several mechanisms may be involved.[78] Ticlopidine exerts a dose-dependent direct cytotoxic effect on myeloid precursors in bone marrow cultures, which may be due to local increases in prostaglandin E_1 or genetic predisposition.[16,21,87] As with sulfonamides and various anticonvulsants, the formation of a reactive metabolite with ticlopidine, such as thiophene-S-oxide, may result in toxic hematologic effects in people unable to detoxify such metabolites.[28] Immunologic mechanisms have also been suggested.[14,40,87]

Advantages associated with BARDI include its explicitness, reproducibility and balanced approach in considering numerous possible causes. However, there are several limitations associated with the instrument. Its use requires significant resources to complete an exhaustive literature search as well as a person who is knowledgeable in conditional probability to apply the complex and tedious method. The use of a preprogrammed spreadsheet has been shown to simplify the BARDI process.[88]

The quality of the output of BARDI is directly related to the quality of the input. In our study, detailed information of differential diagnostic value was either lacking or fragmentary in a large number of excluded case reports. This illustrates the degree of uncertainty faced by clinicians when assessing adverse drug reactions.

Despite the routine hematologic monitoring recommended with ticlopidine therapy (which imposes additional cost and inconvenience), the occurrence of the various types of hematologic dyscrasia may be difficult to predict owing to their often sudden onset. Indeed, in most of the case reports that we evaluated, routine monitoring did not predict the dyscrasia, nor did it prevent serious complications.

Recently, the related antiplatelet agent clopidogrel has become available. This drug may be a safer but equally effective alternative to ticlopidine.[89–94] However, rigorous postmarketing surveillance is required to detect any previously undescribed hematologic dyscrasia that may be associated with this newer agent. Of importance, 11 cases of TTP associated with clopidogrel therapy were recently reported.[95]

In conclusion, our study provides stronger evidence that ticlopidine is the causative factor in most cases of serious hematologic dyscrasia that develops during, or shortly after, treatment with this drug. Routine hematologic monitoring during the first 3 months of ticlopidine therapy is important for prompt detection and treatment of such dyscrasia but is unlikely to prevent its occurrence altogether. Clopidogrel may be a safer alternative.

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