REVIEW ARTICLE

Drug Safety 2004; 27 (15): 1243-1252
0114-5916/04/0015-1243/$31.00/0

Drug-Induced Immune Thrombocytopenia

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Abstract

Thrombocytopenia can have several causes, including the use of certain drugs. The mechanism behind drug-induced thrombocytopenia is either a decrease in platelet production (bone marrow toxicity) or an increased destruction (immune-mediated thrombocytopenia). In addition, pseudothrombocytopenia, an *in vitro* effect, has to be distinguished from true drug-induced thrombocytopenia. This article reviews literature on drug-induced immune thrombocytopenia, with the exception of thrombo-haemorrhagic disorders such as thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia and thrombosis.

A literature search in PubMed combined with a check of the reference lists of all the retrieved articles resulted in 108 articles relevant to the subject. The drug classes that are most often associated with drug-induced immune thrombocytopenia are cinchona alkaloid derivatives (quinine, quinidine), sulfonamides, NSAIDs, anticonvulsants, disease modifying antirheumatic drugs and diuretics. Several other drugs are occasionally described in case reports of thrombocytopenia; an updated review of these case reports can be found on the internet. A

small number of epidemiological studies, differing largely in the methodology used, describe incidences in the magnitude of 10 cases per 1 000 000 inhabitants per year. No clear risk factors could be identified from these studies. The underlying mechanism of drug-induced immune thrombocytopenia is not completely clarified, but at least three different types of antibodies appear to play a role (hapten-dependent antibodies, drug-induced, platelet-reactive auto-antibodies and drug-dependent antibodies). Targets for drug-dependent antibodies are glycoproteins on the cell membrane of the platelets, such as glycoprotein (GP) Ib/IX and GPIIb/IIIa.

Diagnosis of drug-induced immune thrombocytopenia may consist of identifying clinical symptoms (bruising, petechiae, bleeding), a careful evaluation of the causal relationship of the suspected causative drug, general laboratory investigation, such as total blood count and peripheral blood smear (to rule out pseudothrombocytopenia), and platelet serology tests. The sensitivity of these tests is dependent on factors such as the concentration of the drug in the test and the potential sensitisation of the patient by metabolites instead of the parent drug.

Drug-induced immune thrombocytopenia can be treated by withholding the causative drug and, in severe cases associated with bleeding, by platelet transfusion.

Although drug-induced thrombocytopenia is a relatively rare adverse drug reaction, its consequences may be severe. Therefore it is important to extend our knowledge on this subject. Future research should focus on the identification of potential risk factors, as well as the exact mechanism underlying drug-induced thrombocytopenia.

After the introduction of new drugs to the market, rare adverse effects can be detected that were not revealed in clinical trials with those drugs. Such rare adverse drug reactions (ADRs) include effects on the blood cells, for example agranulocytosis, aplastic anaemia and thrombocytopenia. These reactions, especially agranulocytosis, have played a substantial role in several drug withdrawals.[1] Agranulocytosis has been the subject of a number of studies, such as the IAAAS (International Agranulocytosis and Aplastic Anemia Study).[2] Thrombocytopenia, on the other hand, has not been studied to the same extent as agranulocytosis. However, in view of the serious consequences of this condition, thrombocytopenia is an important ADR that merits further study.

Thrombocytopenia is usually defined as a platelet count of $<100 \times 10^9$/L or >50% drop in the platelet count from baseline. Severe thrombocytopenia, defined as platelet counts of $<50 \times 10^9$/L, involves an increased risk of bleeding during invasive procedures. Platelet counts of $<10 \times 10^9$/L may have serious bleeding consequences and may even result in patient mortality.[3-5] Thrombocytopenia can have numerous causes, for example infection, sepsis, diffuse intravascular coagulation, microangiopathic processes (haemolytic uremic syndrome and thrombotic thrombocytopenic purpura) and the use of certain drugs.[3,6] Thrombocytopenia with no clear cause and with normal bone marrow is called idiopathic thrombocytopenic purpura (also known as primary immune thrombocytopenic purpura),[5] of which two distinct disorders exist: an acute form occurring mainly in young children and a chronic form affecting adults.[5] This latter form sometimes resembles drug-induced immune thrombocytopenia and should therefore be included in the differential diagnosis of drug-induced thrombocytopenia.[5] However, the reverse is much more common; patients with drug-induced immune thrombocytopenia

are often diagnosed with idiopathic thrombocytopenic purpura.[7] On the other hand, acute idiopathic thrombocytopenic purpura in children closely resembles drug-induced thrombocytopenia in its sudden onset and spontaneous recovery. As children rarely use drugs, diagnosis is not usually a problem.

Drugs can cause thrombocytopenia by two main mechanisms:

- Decreased platelet production. For example cytotoxic drugs induce bone marrow toxicity, which results in decreased blood cell production (red and white blood cells and platelets). Drugs with an influence on folic acid metabolism can also cause thrombocytopenia by this mechanism.
- Increased destruction of platelets (whether immune-mediated or not).[3]

Apart from these two main mechanisms, a phenomenon called pseudothrombocytopenia has to be taken into account when looking into the cause of low platelet numbers. Pseudothrombocytopenia is caused by the clumping of platelets *in vitro*, resulting in low platelet counts. However, the number and function of platelets *in vivo* is normal. This effect arises from the cold reacting IgM or IgG antibodies that bind to platelets causing clumping at room temperature. It is probably caused by the use of the anticoagulant ethylene diamine tetra-acetic acid (EDTA) instead of citrate.[8] However, pseudothrombocytopenia may also occur in anticoagulants such as heparin and citrate.[9,10]

The same symptoms that are caused by thrombocytopenia may occur in patients with thrombocytopathy. The platelet counts are normal but the function of thrombocytes is impaired. This effect is caused, for example, by aspirin (acetylsalicylic acid), NSAIDs and selective serotonin reuptake inhibitors.

This review will focus on the immune-mediated type of drug-induced thrombocytopenia, with the exclusion of heparin-induced thrombocytopenia and thrombosis (HITT). HITT is excluded because of the distinct features of this syndrome (potentially accompanied by thrombosis[11]). Although focusing on immune-mediated drug-induced thrombocytopenia, the review will also include drug-induced thrombocytopenia cases in which the mechanism is still unclear (and may be non-immune-mediated).

1. Literature Search

A literature search was performed using PubMed in January 2003, with the search strategies 'thrombocytopenia [MeSH] and drug-induced', 'adverse effect and thrombocytopenia', 'thrombocytopenia [MeSH] and drug toxicity [MeSH]' and 'drug-induced and drug-dependent'. No limit was set on the publication date. Articles in English and Dutch were included. Articles on cytotoxic drugs, heparin or heparin analogues and articles not concerning the topic of interest were excluded. The search resulted in 67 articles. Checking the reference lists of the retrieved articles resulted in another 41 papers. Having found a systematic review of case reports,[12] no additional case reports were retrieved.

In table I these 108 articles are categorised by type of publication.

2. Implicated Drugs

The most frequently implicated drugs in immune thrombocytopenia are described in a systematic review of case reports by George et al.[12] and

Table I. Articles retrieved in the literature search and categorised by type of publication

Type of publication	Number of articles retrieved in search	References
Epidemiological studies (including systematic review of case reports)	11	12-22
Articles on specific drug classes	35	23-57
Articles on mechanism of thrombocytopenia	13	58-70
Articles on pseudothrombocytopenia and laboratory tests	5	8-10,71,72
General review articles	19	3-6,73-87
Case reports	25	7,88-111

Table II. Epidemiological studies on drug-induced thrombocytopenia (DIT)

Study	Duration (years)	Method	Incidences of DIT	Most frequently implicated drugs or drug classes
Pedersen et al.[13,14,16]	24	Retrospective study of 309 spontaneous case reports from the Danish reporting system for adverse drug reactions; cytotoxic drugs excluded (including discharge diagnoses from a number of Danish hospitals)	0.96 per 100 000 inhabitants per year	NSAIDs, anticonvulsants, sulfonamides, gold salts, cinchona alkaloids
Böttiger et al.[17-19]	5	Retrospective study of 126 spontaneous case reports from the Swedish reporting system for adverse drug reactions; cytotoxic drugs included (including discharge diagnoses from a number of Swedish hospitals)	0.1–11 per 1 000 000 inhabitants per year (for age group 0–4 years to age group >70 years)[a]	Diuretics, cinchona alkaloids, NSAIDs, sulfonamides
Danielson et al.[20]	10	Discharge diagnoses (drug-induced blood disorders, including 15 diagnoses of thrombocytopenia) from hospitals within the Group Health Cooperative of Puget Sound, USA; cytotoxic drugs excluded	Only given for all blood disorders combined	Cinchona alkaloids, sulfonamides, heparin
Kaufman et al.[21]	8 in Massachusetts and Rhode Island; 2 in Philadelphia region	Case control study – cases identified by contacting relevant personnel in hospitals; cytotoxic drugs excluded (n = 62). Controls were selected from other hospital patients (trauma, acute infections, hernia and some other diagnoses) [n = 2625]	Acute thrombocytopenia 18 per 1 000 000 inhabitants per year (excess risk estimate for cotrimoxazole [trimethoprim-sulfamethoxazole] 38 cases per 1 000 000 users per week)	Cinchona alkaloids, dipyridamole, sulfonamides, sulphonylureas, salicylates

a Female sex was identified as a possible risk factor (not statistically significant).

others.[15,22] After the exclusion of articles reporting on cytotoxic drugs, heparin and heparin analogues, 515 case reports involving 152 drugs were included in that review. The causality in these case reports was classified as definite, probable, possible and unlikely, using a predetermined set of criteria. The drugs that were most often implicated in definite or probable reports were quinine/quinidine, rifampicin (rifampin) and cotrimoxazole (trimethoprim-sulfamethoxazole).[12] In 2001 and 2003, updates of this review were published, adding indinavir, atorvastatin, pentoxifylline, mesalazine (mesalamine), ticlopidine, octreotide, naproxen, sulfalene, abciximab, eptifibatide, chlorpropamide and acetazolamide as definite or probable causal agents.[15,22] The most recent update can be found on the internet.[112]

Apart from this systematic review, a number of epidemiological studies have been performed on the subject of drug-induced thrombocytopenia (table II). The studies differ largely in methodology used, in inclusion and exclusion criteria (e.g. cytotoxic drugs) and in duration. Nevertheless, the reported incidences of drug-induced immune thrombocytopenia all are in the same order of magnitude (around 10 cases per 1 000 000 inhabitants per year). In comparison, the incidence of agranulocytosis in the IAAAS study was 4.4 per 1 000 000 inhabitants per year.[2] Both the incidence of thrombocytopenia and the incidence of agranulocytosis are expressed per million inhabitants and thus concern an unselected population. The incidence in selected populations (e.g. the users of high-risk drugs) may be substantially higher. The annual incidence in diuretic users, for example, was 1 per 15 000 users in a Swedish study conducted by Böttiger and Westerholm.[17] In all epidemiological studies the same (classes of) drugs are mentioned as being the most frequently implicated: NSAIDs, anticonvulsants, sulfonamides, diuretics, cinchona alkaloid derivatives, penicillamine and gold salts. When looking at the number of reports per million defined daily doses (in order to correct for the frequency of drug usage) Pedersen-Bjergaard et al. found that gold

salts, valproic acid, penicillamine and quinidine were associated most often with thrombocytopenia.[14] Danielson et al. found 11 cases of quinine- or quinidine-induced thrombocytopenia per 5089 users of these drugs and three cases attributed to a sulfa containing drug per 46 000 users.[20] Finally, Kaufman et al. found 38 cases of thrombocytopenia per 1 000 000 cotrimoxazole users per week, 26 cases per 1 000 000 users of either quinine and quinidine and 35 cases per 1 000 000 per week for users of quinidine specifically.[21]

Apart from these general epidemiological studies, several epidemiological studies investigated the association between specific drug classes and thrombocytopenia, in particular antirheumatic drugs (gold salts, penicillamine, sulfasalazine, NSAIDs),[23-27,29,30,32,33,36,37,40] glycoprotein (GP) IIb/IIIa receptor inhibitors,[35,41,43,46-48] anticonvulsants[49-57] and antibacterials such as cotrimoxazole and penicillin,[28,34,38,39,42] all of which are also mentioned in the systematic review of case reports.[12,15,22,112]

None of the epidemiological studies identified any additional risk factors for drug-induced immune thrombocytopenia. Although one of the studies mentioned female gender as a potential risk factor, this was not statistically significant in association with the occurrence of thrombocytopenia.[17]

Table III summarises all the available evidence for the different drug classes that are associated with thrombocytopenia in the literature.

3. Mechanism

At least three different mechanisms for the development of immune-mediated, drug-induced thrombocytopenia have been proposed.[70,73]

3.1 Type I – Hapten-Dependent Antibodies

Although infrequent, penicillins and cephalosporins can cause thrombocytopenia.[39,42] These betalactam antibiotics – or haptens – bind covalently to autologous proteins (in this case a cell membrane protein of the thrombocyte) to form allergens.[73,74] Antibodies are subsequently formed, directed against this hapten-protein complex and ultimately result in cell destruction.[74] Betalactam antibacterials may also cause thrombocytopenia by a different mechanism, which possibly resembles the quinine type.[111]

3.2 Type II – Drug-Induced, Platelet-Reactive Auto-Antibodies

Platelet-specific auto-antibodies appear to be involved in the thrombocytopenia caused by gold and procainamide[74] and occasionally by quinine and quinidine.[58] These auto-antibodies are induced by

Table III. Summary of evidence regarding thrombocytopenia as a potential adverse drug reaction in different drug classes (those drug classes that are mentioned most often in the literature)

Drug class	Evidence from case reports	Evidence from specific studies[a]	Evidence from epidemiological studies
Antimicrobials			
sulfonamides	+	+	+
betalactam	+	+	±
trimethoprim	+	−	±
tuberculostatics	+	−	−
cinchona alkaloids	+	+	+
NSAIDs	+	+	+
Disease modifying antirheumatic drugs and immunosuppressants	+	+	+
Anticonvulsants	+	+	+
Diuretics	+	−	+

a Specific studies are studies looking into the relation of thrombocytopenia with a specific drug class.

+ indicates association found in most studies; ± indicates association found in some studies; − indicates no association found.

these drugs but bind to platelet membrane targets without a requirement for added drugs.

3.3 Type III – Drug-Dependent Antibodies

The drug-dependant antibody mechanism has been recognised for some time and seems to be the most common type, but the exact way in which drugs cause the formation of antibodies that eventually result in platelet destruction is still not clear. How a drug promotes the binding of these antibodies, once they are formed, to platelet membrane glycoproteins is poorly understood.[73] The most likely explanations are:

- The drug binds noncovalently to the target glycoprotein complex of the cell membrane of the thrombocyte. These combinatorial epitopes or 'compound epitopes' are subsequently recognised by antibodies.
- The drug binds to a site on the cell membrane distinct from the site of the glycoprotein complex and thus induces a conformational change in the glycoprotein. Antibodies recognise this changed glycoprotein.[73]

The favoured glycoproteins (as targets for antibodies) are the GPIb/IX/V and GPIIb/IIIa glycoprotein complexes.[60,66,69,73,79] Platelet endothelial cell adhesion molecule-1 (PECAM-1)[62] and GPIX[63,64] were also found to be target glycoproteins. The same specific sequences (or sequences very close to each other) of GPIX serve as epitope for quinine-[69] and rifampicin-dependent[63] antibodies. Gentilini et al. showed that this is also the case for ranitidine.[64] Therefore, this sequence of GPIX may be localised to the epitopes of other drug-induced antibodies.[63] The exact amino acid sequence of GPIX has not been elucidated yet. Identifying this sequence may result in the discovery of genetic polymorphisms that predispose individuals to the development of drug-induced thrombocytopenia.[79]

In the literature, the immune complex or 'innocent bystander' mechanism has also been proposed as a potential mechanism,[70] but evidence for this hypothesis is still lacking; the immune complexes with affinity to platelets have never been demonstrated. Furthermore, the binding of antibody to platelets is not initiated by the Fc domain of the antibody as would be the case with immune complexes.

4. Diagnosis

4.1 Clinical Signs

As a rule, an increased bleeding tendency (varying from petechiae to severe bleeding) becomes apparent when the number of platelets reaches a very low level ($<50 \times 10^9$/L), unless there is a concomitant impairment of platelet function (e.g. NSAID use) or when anticoagulants are taken. In addition, it should always be kept in mind that bleeding may be symptomatic of underlying pathology.[6] Thrombocytopenia can also be a chance finding on routine laboratory testing. Especially in this case, pseudothrombocytopenia must be ruled out.

The distinction between drug-induced thrombocytopenia and other forms of thrombocytopenia is often difficult to make, especially when patients suffer from multiple diseases. Furthermore, drugs seem to play a role in certain cases of thrombotic thrombocytopenic purpura and haemolytic uremic syndrome.[3,75,84] By considering the onset of thrombocytopenia in relation to the start of the suspected drug, a potential causative agent may be identified. Drugs that have been linked to thrombocytopenia in the literature should be considered as potential causes (see section 2). A dechallenge with a positive result (i.e. the symptoms disappear after stopping the drug) and the ruling out of other (medical) causes contribute to the establishment of a causal relationship. A rechallenge test may further strengthen the causal relationship, but this is only indicated if the result is of major importance for the patient and must be carried out under strict medical observation as the risks may be great.[3]

4.2 General Laboratory Investigation

Although drug-induced thrombocytopenia is only rarely accompanied by neutropenia and/or anaemia, a complete blood count should be obtained. The bone marrow aspirate is generally compatible with a peripheral platelet destructive process with

normal or increased numbers of megakaryocytes.[71] However, a bone marrow aspirate is generally unnecessary.[4]

As mentioned earlier, pseudothrombocytopenia should be ruled out; it can be diagnosed by detection of a difference between platelet count in two anticoagulants, by platelet clumping on a blood smear made from anticoagulated blood or by obtaining a normal platelet count on a blood smear made from nonanticoagulated blood.[8]

4.3 Platelet Serology Tests

In idiopathic thrombocytopenic purpura, positive direct and indirect antiglobulin tests are often found. In drug-induced immune thrombocytopenia, additional attempts may be made to detect drug-related antibodies against platelets. When, after the drug has been withdrawn, patient or donor platelets are incubated with the drug and then washed, platelet bound antibodies can sometimes be detected. Likewise, reconvalescent serum of the patient can be incubated with a drug and used for testing. However, these tests are often still experimental and more experience is needed with regard to their sensitivity and specificity and to the concentrations of drugs or metabolites needed.[71,72]

In performing these tests, one should consider the possibility that a patient is sensitised to the metabolite of the drug instead of the original compound. This has been described for paracetamol (acetaminophen),[90] naproxen[90] and sulfamethoxazole.[6] Sensitivity of the tests also depends on the concentration of the drug, which should be well controlled in both the assay and the wash solution. The concentrations needed for the test depend on the drug tested.[71]

5. Management

When drug-induced thrombocytopenia is suspected, the potentially causative drug should be stopped. Drug-induced thrombocytopenia is reversible, with a median recovery within 1 week,[12] even though drug-induced autoimmunity may be more persistent. If the stopping of a drug does not result in a rise in the platelet count within 2–6 weeks, other potentially causative drugs should also be withheld.[4,113] In certain instances, recovery may take a longer period of time, as in the case of drugs with a long elimination half-life. Corticosteroid therapy has no proven benefit in drug-induced thrombocytopenia.[6,14] Nevertheless, in severe cases, corticosteroids (e.g. prednisone 1–2 mg/kg/day for 2–4 weeks) may be administered as the diagnosis may be difficult to distinguish from idiopathic thrombocytopenic purpura in which corticosteroids are of proven benefit.[5,6,75] For the same reason, intravenous immunoglobulin (1 g/kg/day on 2 consecutive days) may be given.[5,76,108]

Platelet infusion should only be considered in cases of severe thrombocytopenia that is associated with bleeding. In immune thrombocytopenia the survival time of infused platelets is reduced to a few hours. Nevertheless, this may help to control bleeding.[6]

6. Conclusion

Thrombocytopenia is a multicausal pathological condition. Drugs are just one of the possible causes of the condition. In the literature, drug-induced immune thrombocytopenia is most often linked to NSAIDs, sulfonamides, cinchona alkaloids and diuretics. The limited number of epidemiological studies on this subject reveal that the incidence of drug-induced immune thrombocytopenia is around 10 cases per 1 000 000 inhabitants per year. This incidence is measured in the general population; within specific populations (e.g. hospitalised patients) the incidences may be substantially higher. No clear risk factors are described in these studies. The exact mechanism underlying this ADR is still not completely known, but three major types of antibodies are likely to play a role: hapten-dependent antibodies, drug-induced, platelet-reactive auto-antibodies and drug-dependent antibodies. Serologic tests have been developed to identify these antibodies. Diagnostic tests may include these serologic tests but should at least be directed at establishing a causal relationship with the drug. Management consists of withholding the causative drug and – in

severe cases associated with bleeding – platelet infusions.

Although drug-induced thrombocytopenia is a relatively rare ADR, its consequences may be severe. Therefore, it is important to extend our knowledge on this subject. Future research should focus on the identification of potential risk factors, unravelling of the underlying mechanisms and development of reliable tests for identifying the offending drugs.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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