

Q: What is the best way to determine if thrombocytopenia in a patient on multiple medications is drug-induced?

NAVNEET S. MAJHAIL, MD

Department of Internal Medicine, The Cleveland Clinic

ALAN E. LICHTIN, MD

Department of Hematology and Oncology, The Cleveland Clinic

A: The diagnosis of drug-induced thrombocytopenia can be made only by demonstrating resolution of thrombocytopenia once a suspected drug is stopped. The dilemma in patients taking multiple drugs is how to accomplish this without unnecessarily stopping needed drugs that are not causing a problem.

Non-drug causes must be considered before a making a diagnosis of drug-induced thrombocytopenia (TABLE 1). Equally important is to distinguish between drug-induced thrombocytopenia and idiopathic thrombocytopenic purpura (ITP), since the latter is essentially a diagnosis of exclusion.¹

TABLE 2 presents an algorithmic approach to a patient with suspected drug-induced thrombocytopenia, in which the drug most likely to cause the thrombocytopenia is discontinued in a systematic manner.

■ CRITERIA FOR DRUG-INDUCED THROMBOCYTOPENIA

Criteria have been suggested for the diagnosis of drug-induced thrombocytopenia.²⁻⁴ Thrombocytopenia is defined as a platelet count of less than $100 \times 10^9/L$. More than a 50% drop in the platelet count from baseline should also arouse the suspicion of an adverse drug-induced event. However, a cause-and-effect relation between a drug and thrombocytopenia can be established only if all the following criteria are fulfilled:

- Therapy with the suspected drug preceded the thrombocytopenia

**Not available for online publication.
See print version of the
*Cleveland Clinic Journal of Medicine***

**Not available for online publication.
See print version of the
*Cleveland Clinic Journal of Medicine***

TABLE 3

Mechanisms of drug-induced thrombocytopenia

Decreased platelet production

Generalized bone marrow suppression (cytotoxic agents)

Selective suppression of megakaryocyte production (chlorothiazides, ethanol, tolbutamide)

Accelerated platelet destruction

Non-immunologic (ristocetin, protamine sulfate, bleomycin)

Immunologic (acetaminophen, gold salts, heparin, methicillin, penicillin, quinidine, quinine, rifampin)

Unknown mechanisms (amiodarone, cimetidine, chlorpromazine, digoxin, diazoxide, isoniazid, minoxidil, nitroglycerine, procainamide)

Identifying the offending drug early avoids severe complications

- Recovery from thrombocytopenia was complete and sustained after the drug was stopped
- The suspected drug was the only drug used before the onset of thrombocytopenia
- Other drugs were continued or reintroduced after discontinuation of therapy with the suspected drug, with a sustained normal platelet count
- Other causes of thrombocytopenia were excluded
- Re-exposure to the suspected drug resulted in recurrent thrombocytopenia.³

Laboratory assays. Current laboratory assays for drug-dependent antiplatelet antibodies are not very useful for diagnosing drug-induced thrombocytopenia. Limited availability, the long wait for results, and issues of standardization, sensitivity, and specificity limit their widespread use.

MECHANISMS OF DRUG-INDUCED THROMBOCYTOPENIA

TABLE 3 summarizes the various mechanisms of drug-induced thrombocytopenia.

Adverse drug reactions are generally classified into two categories. Type A reactions are common, predictable, related to the pharmacologic actions of the drug, and may occur in any patient. Type B reactions are uncom-

mon, unpredictable, usually not related to the pharmacologic actions of the drug, and occur only in particularly susceptible patients.^{5,6}

With the exception of cytotoxic agents, which lead to a dose-related suppression of thrombopoiesis, most drug-induced thrombocytopenia occurs through antibody-mediated idiosyncratic (type B) mechanisms. Immune-mediated thrombocytopenia may involve direct interaction of the drug with a specific platelet receptor (platelet surface glycoproteins Ib-IX or IIb/IIIa, platelet endothelial cell adhesion molecule-1 [PECAM 1], etc), or the drug in conjunction with an antibody may attach to the platelet surface. The drug may also combine with plasma proteins to form haptens that may interact with an antibody in the plasma or on the platelet surface.⁷

DIAGNOSTIC APPROACH

In a patient with suspected drug-induced thrombocytopenia, the initial approach should begin with a close review of the patient's drug history. Any history of previous drug-induced reactions should be sought. The time of onset of thrombocytopenia and its temporal relation to the initiation and discontinuation of the suspected agent should be noted. Except for gold-induced immune thrombocytopenia, which may continue for months due to persistence of the antigen in the reticuloendothelial system, recovery can be expected within 2 to 4 weeks after the drug is stopped.

The dose and duration of therapy with the suspected drug are also important. Drugs that suppress bone marrow tend to cause dose-dependent suppression of platelet counts.

Initial laboratory evaluation

The initial laboratory evaluation of a patient suspected of having drug-induced thrombocytopenia should include a complete blood cell count and peripheral blood smear examination. In vitro drug-specific antibody testing, though desirable, is often not useful for the reasons already mentioned above.

Examination of the bone marrow may be required occasionally. However, in most situations, the diagnosis of drug-induced thrombocytopenia is usually based on clinical judgment.



**Not available for online publication.
See print version of the
*Cleveland Clinic Journal of Medicine***

**Quinidine
and the
sulfonamides
are among
the most
common drugs
that cause
thrombocytopenia**

Keep pseudothrombocytopenia in mind

Pseudothrombocytopenia, defined as a clumping of platelets in vitro without clinical significance, must be kept in mind when evaluating patients with thrombocytopenia. More than one third of low platelet counts observed in patients undergoing coronary interventions and being treated with abciximab are due to pseudothrombocytopenia.⁸ It has been postulated that EDTA alters the conformation of platelet surface glycoprotein IIb such that a

neoepitope (antigenic determinant) is exposed and recognized by autologous antibodies. Evaluation of the automated platelet count and peripheral smear in blood anticoagulated in citrate can distinguish pseudothrombocytopenia from true thrombocytopenia. The distinction is critical because thrombotic or hemorrhagic risk is not increased with pseudothrombocytopenia, antithrombotic and antiplatelet therapy can be continued, and invasive procedures can be performed.



Evidence varies for different drugs

Many patients are on several drugs when thrombocytopenia is discovered and need to stop one or more of the drugs. It is important to know the probability of each drug causing thrombocytopenia in such situations so that necessary therapy is not interrupted. George et al³ and Rizvi et al⁹ have systematically reviewed the literature and attempted to distinguish drugs for which evidence shows a definite or probable causal relation vs those for which evidence is weaker (TABLE 4). The full and updated list of articles reviewed and the database established by this review are available online at: <http://moon.ouhsc.edu/jgeorge> and <http://www.acponline.org>.

Quinidine and sulfonamides are among the most common drugs associated with drug-induced thrombocytopenia. As the etiologic relation of thrombocytopenia with cytotoxic agents and heparin/heparin analogues is well established, they were excluded from the review.

■ REFERENCES

1. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996; 88:3–40.
2. Standardization of definitions and criteria of causality assessment of adverse drug reactions: drug-induced cytopenia (Report of consensus meeting of Council for International Organizations of Medical Sciences). *Int J Clin Pharmacol Ther Toxicol* 1991; 29:75–81.
3. George JN, Raskob GE, Shah SR, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998; 129:886–890.
4. Pedersen-Bjergaard U, Andersen M, Hansen PB. Drug-induced thrombocytopenia: clinical data on 309 cases and the effect of corticosteroid therapy. *Eur J Clin Pharmacol* 1997; 52:183–189.
5. Gruchalla RS. Clinical assessment of drug-induced disease. *Lancet* 2000; 356:1505–1511.
6. deShazo RD, Kemp SF. Allergic reactions to drugs and biologic agents. *JAMA* 1997; 278:1895–1906.
7. Aster RH. Drug-induced immune thrombocytopenia: an overview of pathogenesis. *Semin Hematol* 1999; 36(suppl 1):2–6.
8. Sane DC, Damaraju LV, Topol EJ, et al. Occurrence and clinical significance of pseudothrombocytopenia during abciximab therapy. *J Am Coll Cardiol* 2000; 36:75–83.
9. Rizvi MA, Kojouri K, George JN. Drug-induced thrombocytopenia: an updated systematic review. [letter]. *Ann Intern Med* 2001; 134:346.

ADDRESS: Alan E. Lichtin, MD, Department of Hematology and Oncology, R35, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail lichtia@ccf.org.