Which Drugs Cause Thrombocytopenia?

George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, Vondracek T. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med 1998;129:886–90.

Study Overview

Objective. To help clinicians determine which drugs are more likely to cause thrombocytopenia.

Design. Systematic review of English language articles describing drug-induced thrombocytopenia conducted by two independent authors. The articles included in the review were found through a search of the MEDLINE database and alternate search software and through a review of bibliographies of retrieved articles. The list is available at http://moon.ouhsc.edu/jgeorge. Articles describing thrombocytopenia caused by heparin and heparin analogues were excluded because the etiologic relationship of heparin to thrombocytopenia has been established [1]. Of the 581 articles retrieved, 20 were excluded because they did not contain patient case reports. The 561 reviewed articles reported on 774 patients.

Review methods. Two authors used a priori criteria to independently review each patient case report. 259 case reports were excluded because they lacked sufficient clinical data or because of a platelet count of 100,000 cells/μL or more, use of cytotoxic agents that cause marrow suppression, use of nontherapeutic agents (eg, illicit drugs, drug overdose, drugs not currently in use, environmental toxins), drug-induced systemic disease, or disease in children (age 16 years or younger). The drugs in the remaining 515 case reports were categorized by the level of evidence implicating them as the cause of thrombocytopenia. Disagreements between the two reviewers were resolved by a third independent reviewer. If a causal role was supported, the clinical importance of the drug-induced thrombocytopenia was assessed using three levels of severity of bleeding [2]: major (intracranial or retroperitoneal, visible or symptomatic with a decrease of hemoglobin concentration by more than 20 g/L, or the requirement for transfusion of two or more units of erythrocytes); minor (did not meet criteria for major bleeding); or trivial (including petechiae, purpura, brief epistaxis or gingival bleeding, guaiac-positive stool, or microscopic hematuria).

Main outcome measures. A definite or probable causal role for the drug in leading to thrombocytopenia. Episodes of clinically major, minor, and trivial bleeding.

Main results. A definite or probable causal role for a drug was found in 247 patient reports (48%). Among the 98 drugs described in these reports, quinidine was mentioned in 38 case reports, gold in 11, and trimethoprim-sulfamethoxazole in 10. Of the 247 patients described, 23 (9%, 95% confidence interval [CI] = 6% to 14%) had major bleeding, including 2 (0.8%, 95% CI = 0% to 3%) who died of bleeding; 68 patients (28%, 95% CI = 22% to 34%) had minor bleeding; and 96 patients (39%, 95% CI = 33% to 45%) had trivial bleeding. Sixty patients (24%, 95% CI = 19% to 30%) had no bleeding symptoms. Major bleeding was not associated with age or sex. Both patients who died had quinine-induced thrombocytopenia.

Conclusion

Many articles reporting drug-induced thrombocytopenia do not provide adequate evidence to support a definite or probable causal relationship between the drug and thrombocytopenia. Future patient case reports should use standard criteria to explicitly establish the etiologic role of the drug.

Commentary

The 9% rate of major bleeding associated with drug-induced thrombocytopenia suggests that the problem is clinically important; however, in practice the rate may be lower. Although reports of drug-induced thrombocytopenia are common, most do not present evidence that shows that a drug is either a definite or a probable cause of thrombocytopenia. More poulation-based studies are needed to show an association between specific causal agents and actual incidence and prevalence rates of thrombocytopenia.

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Applications for Clinical Practice

Because many patients are taking several drugs when thrombocytopenia is first discovered, clinicians need to better understand the likelihood of a causal role for each drug. Toward this end, the authors' systematic review provides physicians with carefully collected case report data. Unfortunately, the articles reviewed do not permit strong conclusions to be drawn regarding which drugs may be implicated in causing thrombocytopenia.

References

1. Warkentin TE, Chong BH, Greinacher A. Heparin-induced thrombocytopenia: towards consensus. Thromb Haemost 1998;79:1–7.
2. Graafsma YP, Prins MH, Lensing AW, de Haan RJ, Huisman MV, Buller HR. Bleeding classification in clinical trials: observer variability and clinical relevance. Thromb Haemost 1997;78:1189–92.