Drug-induced thrombocytopenia: a systematic review of published case reports

Authors' objectives
To determine the strength of clinical evidence for individual drugs as a cause of thrombocytopenia.

Searching
MEDLINE (1966 to 31 December 1997) was searched using the search terms thrombocytopenia and chemically induced. Limits were set for human only and English language only. Reference Update, Research Information Systems, Inc and Carlsbad, California were searched from 1989 to 1997. The bibliographies of retrieved references were cross-checked to identify additional reports.

Study selection
Study designs of evaluations included in the review
No restrictions were placed on design of included studies. However, included studies had to have either level I or level II evidence (see "On What Criteria Was the Validity of Included Studies").

All studies included were case reports.

Specific interventions included in the review
One hundred and fifty two different drugs that were being taken for a variety of reasons. Articles reporting thrombocytopenia associated with heparin and heparin analogues were not included because the etiological relation of heparin to thrombocytopenia is well established.

Participants included in the review
Participants had a platelet count of less than 100,000 cells/μl and were over 16 years of age. Patients were excluded if they had used a known cytotoxic agent that causes marrow suppression, or if they were exposed to a nontherapeutic agent or used an agent in a nontherapeutic manner (for example, environmental toxins, illicit drugs, drug overdose, and drugs not currently in use). Patients were also excluded who had drug-induced disease that included thrombocytopenia, but predominantly involved other abnormalities, such as aplastic anemia or the thrombotic thrombocytopenic purpura-hemolytic uremic syndrome.

Outcomes assessed in the review
Outcomes were three levels of severity of bleeding:

1. Major bleeding (defined as intracranial or retroperitoneal bleeding) or overt bleeding (defined as visible or symptomatic bleeding) with a decrease of hemoglobin concentration by more than 2 g/dL (20 g/L) or the requirement for transfusion of two or more units of erythrocytes.

2. Minor bleeding, defined as overt bleeding that did not meet the criteria for major bleeding (melena, gross hematuria, epistaxis or gingival bleeding that is prolonged for more than 30 minutes or requires medical intervention; excessive menstrual bleeding or vaginal bleeding other than menses).

3. Trivial bleeding, which included petechiae, purpura, brief epistaxis or gingival bleeding, guaiac-positive stool, or microscopic hematuria.

How were decisions on the relevance of primary studies made?
Level (I) or (II) evidence was one of the criteria for inclusion. Two authors independently reviewed each patient case report to establish the level of evidence for a causal role of the drug in thrombocytopenia. Disagreement between the two reviewers was resolved by adjudication by a third independent reviewer.

It was not stated how decisions on the other criteria for inclusion/exclusion were made.
Assessment of study quality
Studies were rated according to four criterion:

1. Therapy with the candidate drug preceded thrombocytopenia and recovery from thrombocytopenia was complete and sustained after therapy with the drug was discontinued.

2. The candidate drug was the only drug used before the onset of thrombocytopenia or other drugs were continued or reintroduced after discontinuation of therapy with the candidate drug with a sustained normal platelet count.

3. Other causes for thrombocytopenia were excluded.

4. Re-exposure to the candidate drug resulted in recurrent thrombocytopenia.

Studies meeting criteria 1 to 4 were given level (I) evidence; studies meeting criteria one to three were given level (II) evidence; studies meeting criteria one only were given level (III) evidence; and studies in which criteria one was not met were given level (IV) evidence. Two authors independently reviewed each patient case report to establish the level of evidence for a causal role of the drug in thrombocytopenia. Disagreement between the two reviewers was resolved by adjudication by a third independent reviewer.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The percentages of patients with level I or II evidence who had major, minor or trivial bleeding were calculated, along with the associated 95% confidence intervals.

How were differences between studies investigated?
Tests for heterogeneity were not presented.

Results of the review
There were 515 patient reports involved.

For the 515 patient case reports, 87 case reports were rated level 1 (definite), 160 were rated level II (probable), 172 were rated level III (possible), and 96 were rated IV (unlikely). The initial two reviewers agreed on 452 (88%) of the 515 case reports. Adjudication was required for 63 (12%) of the patient case reports; in all cases, the third reviewer agreed with one of the two primary reviewers. Forty-eight drugs had level I evidence, and 50 other drugs had level II evidence.

In 247 (48%) patient case reports with level I or II evidence, 23 patients (9%; 95% CI: 6%, 14%) had major bleeding, including 2 patients (0.8%; 95% CI: 0%, 3%) who died of bleeding. Sixty-eight patients (28%; 95% CI: 22%, 34%) had minor bleeding and 96 patients (39%; 95% CI: 33%, 45%) had trivial bleeding. Sixty patients (24%; 95% CI: 19%, 30%) had no bleeding symptoms. Both patients who died had quinine-induced thrombocytopenia. Among the 98 drugs described in these 247 reports, quinidine was mentioned in 38 case reports, gold in 11, and trimethoprim-sulfamethoxazole in 10.

When the sex (74% woman) and mean age (54 years) of the 23 patients who experienced major bleeding were compared with the sex (57 woman) and mean age (53 years) of patients without major bleeding, the difference was not significant (p>0.1).

Authors' conclusions
The evidence supported a definite (level I evidence) or probable (level II evidence) causal role for drug-induced thrombocytopenia in 247 patient case reports (48%). Future patient case reports should incorporate standard criteria to clearly establish the etiological role of the drug.
CRD commentary
The review focuses on a well-defined question. The inclusion and exclusion criteria were appropriate, and the level of evidence of included studies was assessed.

The search could have been extended to include other databases such as EMBASE and an attempt to identify unpublished literature. Publication bias can not be ruled out. Another limitation of the search is that it only included papers published in English.

There were too many case reports (515) included in the systematic review to provide details of all of them. However, the authors note that the full list of articles reviewed is available at: http://www.ouhsc.edu/platelets/index.html.

The conclusions follow from the results, but both should be interpreted with caution, because only case reports were included, and studies evaluating different types of drugs were combined.

Implications of the review for practice and research
Practice: No implications for practice were stated.

Research: Future case reports should contain more detail, for example information on whether other drugs were used or continued, and whether other causes of thrombocytopenia were excluded.

Bibliographic details

PubMedID
9867731

Original Paper URL
http://www.annals.org/cgi/content/full/129/11_Part_1/886

Other publications of related interest
This additional published commentary may also be of interest. Rizvi MA, Kojouri K, Geirge JN. Drug-induced thrombocytopenia: an updated systematic review. Annals of Internal Medicine 2001;134(4):346.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.