

Drug-Induced Thrombocytopenia

An Updated Systematic Review, 2012

Using methodology initially established in 1998,^[1] we have systematically reviewed all English-language reports on drug-induced thrombocytopenia, publishing updates every 2 years. Our previous literature search was on 20 October 2010.^[2] The goal of these continuing updates is to provide an accessible website database as a resource for standardized analysis of all published reports of drug-induced thrombocytopenia (www.ouhsc.edu/platelets). The database describes the methodology of our review process and defines the levels of evidence and exclusion criteria. For each published report, the level of evidence for a causal role of each drug, the patient demographics and clinical outcomes are described. A link to the publication is also provided. In addition to the data on published reports, the website also contains (i) a database for drugs that were confirmed as causes of drug-induced thrombocytopenia by documentation of drug-dependent, platelet-reactive antibodies by the Blood Center of Wisconsin; (ii) a database for complementary and alternative medicines, herbal remedies, nutritional supplements, and foods and beverages that have been associated with thrombocytopenia; and (iii) a database of drugs causally associated with thrombocytopenia by data mining of the US FDA Adverse Event Reporting System (AERS) database.^[3]

This letter presents the results of our current literature search. On 23 January 2012 we identified articles published since October 2010 using our previously described literature search strategy.^[1] Articles were selected for review based on the title and abstract. Reviewing the bibliographies of the selected articles, additional articles published prior to October 2010 were also identified that had not been previously reviewed. We retrieved 57 articles for review. Using our evaluation criteria,^[1] each article was reviewed independently by both authors to assess the level of evidence for

a causal role of the drug for thrombocytopenia; disagreements were resolved by discussion. After reading the articles, ten were excluded from further analysis because they contained no patient data.^[1] Of the remaining 47 articles, 33 reported data on 36 individual patients who had thrombocytopenia associated with 25 different drugs. Five articles described level 1 (definite) evidence for five drugs in seven patients; one article described level 1 (definite) evidence for a combination of two drugs in one patient. Eight articles described level 2 (probable) evidence for eight drugs in nine patients; eight articles described level 3 (possible) evidence for eight drugs in eight patients; eight articles described level 4 (unlikely) evidence for eight drugs in eight patients. Three patient reports describing three drugs were not evaluable because of our previously defined criteria;^[1] in two reports the platelet count was not less than 100 000/ μ L; in one report the drug caused marrow suppression. Fourteen articles reported group data, describing thrombocytopenia associated with 11 drugs. Eight articles were not evaluable because of our previously defined criteria;^[1] three had insufficient patient data; in five reports the drugs caused marrow suppression. The remaining six articles reported data on five drugs: one article had level 1 (definite) evidence, four had level 3 (possible) evidence, and one had level 4 (unlikely) evidence.

Three reports of individual patients described level 1 (definite) evidence for three drugs that had

Table 1. Drugs identified as causing thrombocytopenia in the 2012 literature search that had not been documented in previous reviews

Drug ^a	Number of reports with level 1 evidence
Alfuzocin ^[4]	1
Iloprost ^[5]	1
Phenobarbital/lamotrigine combination ^[6]	1

a These three drugs had no previously reported evidence supporting a causal relation to thrombocytopenia (www.ouhsc.edu/platelets). Definite evidence (level 1) required re-exposure to the drug causing a repeated episode of thrombocytopenia. In this 2012 review there were no other drugs that qualified for evidence supporting a causal relation of the drug to thrombocytopenia by one report with definite evidence, two reports with level 2 (probable) evidence or by evidence from group data that had not been previously identified.

not been previously reported to have a causal relation to thrombocytopenia supported by either one report with level 1 (definite) or two reports with level 2 (probable) evidence (table I). Two reports described thrombocytopenia associated with alfuzosin,^[4] and iloprost.^[5] One report described a patient who became thrombocytopenic with phenobarbital and lamotrigine; thrombocytopenia recurred when the patient was rechallenged with the combination of these two drugs but thrombocytopenia did not occur with the individual drugs.^[6] Lamotrigine has been previously causally associated with thrombocytopenia by the documentation of drug-dependent, platelet-reactive antibodies. Phenobarbital has been previously suspected of causing thrombocytopenia but a test for drug-dependent, platelet-reactive antibodies was negative. Lamotrigine, phenobarbital and alfuzosin have been causally associated with thrombocytopenia by data mining of the FDA AERS database.^[3]

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