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Drug-Induced Thrombocytopenia
A Population Study

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Abstract

Background: Drug-induced immune thrombocytopenia, excluding heparin-induced thrombocytopenia, is a rare adverse drug reaction for which the evidence about frequency, relative risk and risk factors mainly originates from case reports and case studies. This study aims to quantify the risk for thrombocytopenia following exposure to drugs that are most often reported to cause thrombocytopenia in the general population.

Methods: A retrospective, case-control study was conducted within the PHARMO record linkage system. Cases were defined as patients hospitalised for thrombocytopenia in the period 1 January 1990 to 31 December 2002. For each case, up to four controls were matched based on age, sex and geographical area. Exposure on the index date to anticonvulsants, β-lactam antibacterials, cinchona alkaloids, disease modifying antirheumatic drugs (DMARDs), diuretics, NSAIDs, sulfonamide antibacterials and tuberculostatics was assessed and categorised into mutually exclusive groups of current, recent, past and non-use. The risk was quantified with multivariate conditional logistic regression analysis.

Results: The study population comprised 705 cases and 2658 controls. Current use of β-lactam antibacterials was associated with an increased risk for thrombocytopenia (adjusted odds ratio 7.4, 95% CI 1.8, 29.6). Increased risk estimates, although not significant, were found for current exposure to DMARDs and the sulfonamide antibacterial cotrimoxazole (trimethoprim/sulfamethoxazole). No increased risk was found for anticonvulsants, cinchona alkaloids, diuretics, NSAIDs or tuberculostatics.

Conclusion: More evidence for an increased risk for thrombocytopenia in current use of β-lactam antibacterials in the general population was provided. The expected increase in risk could not be confirmed for the other drugs investigated, which is possibly a result of the limited statistical power. Future studies including more patients and with laboratory data should confirm our findings before drawing definite conclusions.

Background

If not recognised in time, thrombocytopenia is a potential life-threatening disorder.[1] Thrombocytopenia is commonly defined as a fall in platelet count to $<100 \times 10^9$ platelets/L of blood or a drop in platelet count of >50% compared with baseline.[1] Although it may initially be asymptomatic, thrombocytopenia is often diagnosed by the occurrence of bruising, petechiae, ecchymosis and epistaxis.[1] When the thrombocytopenia persists, bleeding from mucous membranes and severe purpura can occur.[1]

Drugs can cause thrombocytopenia, either through a direct toxic effect on the thrombopoietic mechanism in the bone marrow resulting in decreased platelet production or through immune-mediated mechanisms resulting in increased platelet destruction.[2,3] Thrombocytopenia, together with other blood dyscrasias, is a frequent adverse effect of treatment with chemotherapeutics that cause bone-marrow toxicity by direct interference with cell formation.[3] Another relatively well studied type of immune-mediated drug-induced thrombocytopenia is heparin-induced thrombocytopenia, which is reported to occur in up to 2.6% of hospitalised patients exposed to unfractionated heparin and in 0.2–0.8% of patients exposed to low-molecular weight heparins.[4,5]

A review of the literature on drug-induced immune thrombocytopenia, which was published in *Drug Safety* last year, concluded that other drugs that are most frequently reported as possible causes of thrombocytopenia are anticonvulsants, β-lactam antibacterials, cinchona alkaloid derivates, disease modifying antirheumatic drugs (DMARDs), diuretics, sulfonamide antibacterials, NSAIDs and tuberculostatics.[2] However, the current evidence about the frequency and possible risk factors for thrombocytopenia induced by these drugs was found to be limited and mainly to originate from case reports and studies with spontaneous-reporting databases.[6-12]

These limited data revealed that the overall incidence of drug-induced thrombocytopenia in the general population is considered to be approximately 10 cases per 1 million inhabitants per year. However, this estimate might be much higher for specific populations such as hospitalised patients.[2] Although case reports and studies with spontaneous-reporting databases provide detailed information on the aetiology of adverse drug reactions, it is not possible to quantify the strength of the association between drug exposure and the adverse reaction and to identify risk factors in the absence of a control group. Therefore, studies with a controlled design, e.g. a case-control study, are preferred when studying the risk of rare adverse drug reactions, such as thrombocytopenia.[13] To our knowledge, only one case-control study has been performed to provide quantitative risk estimates for the association between drug exposure and hospitalisation for acute thrombocytopenic purpura, in which increased risks were reported for several drugs, for example the sulfonamide antibacterial cotrimoxazole (trimethoprim/sulfamethoxazole) and quinine/quinidine.[14]

To quantify the risk for thrombocytopenia following exposure to drugs that are most frequently reported as a possible cause for thrombocytopenia, a case-control study was conducted in a well defined population of community-dwelling patients.

Methods

Data Collection

Data were obtained from the PHARMO record linkage system, a database that since 1985 has linked dispensing records of prescription drugs from a representative sample of Dutch community pharmacies to hospital discharge data from individual patients,[15] and currently contains data for >2 million residents. Since the majority of patients in The Netherlands are registered in a single community pharmacy, the patient's drug exposure history is virtually complete with regard to prescription drugs.[16]

The computerised drug-dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen and the estimated duration of use. The duration was estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification.

The hospital-discharge records were obtained from the Dutch National Medical Registry (LMR database, Prismant), which covers all hospital-discharge records from The Netherlands since the 1960s in a standardised format. These records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases (9th Edition), Clinical Modification (ICD-9-CM).[17]

Patients

The source population comprised all subjects that were registered in the PHARMO database during the study period that started on 1 January 1990 and ended on 31 December 2002. All patients who were hospitalised at least once for thrombocytopenia during the study period were identified. Although drug-induced thrombocytopenia is considered as a secondary cause of thrombocytopenia according to the ICD-9-CM classification, all three defined categories of thrombocytopenia, i.e. primary (ICD-9-CM code 287.3), secondary (287.4) and non-specified thrombocytopenia (287.5), were considered.[17] The index date was defined as the date of admission to the hospital. Patients with a history of <180 days in the PHARMO database prior to the index date were excluded from the study. If patients were hospitalised more than once for thrombocytopenia, the first hospitalisation in time was selected.

This study aimed to quantify the risk for drug-induced thrombocytopenia following drug exposure in the general population. Therefore, cases that were likely to be related to other causes were excluded. To prevent the inclusion of patients who were treated with chemotherapy, cases with a discharge diagnosis for agranulocytosis (ICD-9-CM code 288.0) at the index date were excluded. Additionally, cases with a discharge diagnosis for thrombocytopenia-related medical conditions at the index date were excluded. The following conditions were excluded: cancer (014.0–023.9); aplastic anaemia (284.8–9); vitamin B_{12} deficiency (281.1); folate deficiency (281.2); alcohol abuse (305.0); splenomegaly (289.4–5); systemic lupus erythematosus (695.4, 710.0); HIV infection (044.9, 795.8); measles (055.9); mononucleosis infectiosa (075.0–9); malaria (084.1, 4.6); thrombotic thrombocytopenia purpura (446.6); and haemolytic uremic syndrome

(283.1). The remaining cases were included in the study population.

For each case, up to four control patients were randomly selected from the source population and matched to cases based on sex, age (5-year intervals) and geographical area. Controls were assigned the same index date as the cases. Controls were only eligible for inclusion if they had ≥180 days of history in the PHARMO database prior to the index date of the matched case. The same exclusion criteria were used for cases and controls.

Exposure Definition

From the drug-dispensing histories, all prescriptions for the following drugs, which were *a priori* considered as the drug classes that are most frequently reported in the literature to cause thrombocytopenia[2] and were available on the Dutch market during the study period, were selected: anticonvulsants; β-lactam antibacterials; cinchona alkaloids; DMARDs; diuretics; NSAIDs; the sulfonamide antibacterial cotrimoxazole; and tuberculostatics.

Exposure at the index date was assessed and categorised into mutually exclusive groups of current, recent, past and non-use. Current use was defined as exposure to the drug in the period of 4 weeks before or at the index date, recent use was defined as exposure in the period of 3 months through 4 weeks before the index date, past use was defined as exposure in the period of 6 months through 3 months before the index date and non-use was defined as having dispensed a prescription >6 months before the index date or not having dispensed a prescription at all. The drug exposure window was defined as the period between the dispensing date and the theoretical end date, which was calculated by adding the estimated duration of use to the start date.

Potential Confounding Factors

By restricting the selection of cases to patients hospitalised for thrombocytopenia without discharge diagnoses for agranulocytosis and other thrombocytopenia-related conditions at the index date, potential confounding by these risk factors was eliminated. However, it was investigated if potential confounding was introduced by the presence of thrombocytopenia-related morbidity in the period of 6 months before the index date. Hospitalisations for the following conditions were considered: malignant disease, aplastic anaemia, vitamin B_{12} deficiency, folate deficiency, alcohol abuse, splenomegaly, systemic lupus erythematosus, HIV infection, measles, mononucleosis infectiosa, malaria, thrombotic thrombocytopenia purpura and haemolytic uremic syndrome. Additionally, the use of unfractionated heparin or low-molecular weight heparins, antineoplastic and immunosuppressive drugs, dispensed by the community pharmacy in the 6-month period prior to the index date was considered as a potential confounder.

Data Analysis

The association between drug exposure and thrombocytopenia was estimated with conditional logistic regression and expressed as relative risk by calculating odds ratios (ORs) with 95% confidence intervals. Power calculations with $\alpha = 0.05$, suggested that the study would give an 80% chance of detecting a significant OR >2.7 based on 705 cases and assuming, on average, a proportional drug exposure in the control group of 1 in 100 patients.[18]

Initially, crude ORs were calculated with univariate conditional logistic regression. Additionally, multivariate conditional logistic regression was used to adjust crude odds ratios for concurrent exposure to other drugs most frequently reported to cause drug-induced thrombocytopenia, and for potential confounders. Potential confounders were included

Table I. Characteristics of the study population

Characteristics	Cases (n = 705)	Controls (n = 2658)
Demographics		
female [n (%)]	461 (65.4)	1753 (66.0)
mean age [y (SD)]	48.7 (24.1)	47.9 (23.8)
Discharge diagnosis [n (%)]		
primary thrombocytopenia	162 (23.0)	NA
secondary thrombocytopenia	79 (11.2)	NA
unspecified thrombocytopenia	464 (65.8)	NA
Potential confounders[a,b] [n (%)]		
cancer	55 (7.8)	10 (0.4)
aplastic anaemia	10 (1.4)	0
SLE	0	1 (0)
TTP	1 (0.1)	0
use of UFH or LMWH	1 (1)	0
use of antineoplastic drugs	3 (0.4)	0

a Presence of thrombocytopenia-related morbidity in the period of 6 months before the index date.

b No cases and controls were identified for the other potential confounders that were investigated (i.e. vitamin B_{12} deficiency, folate deficiency, alcohol abuse, splenomegaly, SLE, HIV infection, measles, mononucleosis infectiosa, malaria, HUS and exposure to immunosuppressants drugs).

HUS = haemolytic uremic syndrome; **LMWH** = low-molecular weight heparin; **NA** = not applicable; **SLE** = systemic lupus erythematosus; **TTP** = thrombotic thrombocytopenia purpura; **UFH** = unfractionated heparin.

in the final model when they changed the point estimate by >10%.[19]

In case a significant adjusted risk estimate was found, sensitivity analyses were performed regarding four different definitions of current exposure to the drug: (i) within 7 days of the index date; (ii) within 14 days of the index date; (iii) within 28 days of the index date; and (iv) within 42 days of the index date.

Results

In the source population, 1213 patients with at least one hospitalisation for thrombocytopenia were identified during the study period. Of those patients, 233 were excluded because they had a history of <180 days in the PHARMO database prior to the index. Additionally, 179 cases were excluded because they had a diagnosis for agranulocytosis at the index date, and another 96 cases were excluded because they had a diagnosis for aplastic anaemia, cancer, haemolytic uremic syndrome, malaria or systemic lupus erythematosus at the index date.

After matching, the final study population comprised 705 cases and 2658 controls. The characteristics of the study population are presented in table I. The majority of the cases (65.8%) were classified as hospitalised for unspecified thrombocytopenia. Hospitalisation for cancer during the period of 6 months before the index date was the only potential confounder found to be associated with an increased risk for thrombocytopenia (crude OR 22.5, 95% CI 11.1, 45.5).

Current use of β-lactam antibacterials (crude OR 7.8, 95% CI 1.9, 31.1) was associated with an increased risk for thrombocytopenia (table II). After adjusting for potential confounding by concurrent exposure to one of the other drugs most frequently reported to cause thrombocytopenia and a hospitalisation for cancer in the period of 6 months before the index date, the current use of β-lactam antibacterials was associated with a >7-fold increase (adjusted OR 7.4, 95% CI 1.8, 29.6) in the risk for thrombocytopenia. No increase in the risk for thrombocytopenia was found for past and recent use of β-lactam antibacterials. The specific β-lactam antibacterials used by the six cases identified as currently exposed were amoxicillin (n = 4), pheneticillin (n = 1) and cefaclor (n = 1). Sensitivity analysis concerning different exposure windows revealed that the risk for thrombocytopenia in exposure to β-lactam antibacterials increased with narrowing the exposure window (table III).

An increased point estimate for the risk for thrombocytopenia was found for current exposure to DMARDs (adjusted OR 4.3, 95% CI 0.3, 69.3) and cotrimoxazole (adjusted OR 3.7, 95% CI 0.5, 24.3),

Table II. Risk for thrombocytopenia following drug exposure

Drug exposure[a]	Cases (%)	Controls (%)	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Anticonvulsants				
non-use	701 (99.4)	2646 (99.5)	1.0 (referent)	1.0 (referent)
past use	1 (0.1)	0 (0.0)	NA	NA
recent use	1 (0.1)	2 (0.1)	2.0 (0.2, 22.1)	2.0 (0.2, 22.2)
current use	2 (0.3)	10 (0.4)	0.7 (0.2, 3.3)	0.8 (0.2, 3.5)
β-Lactam antibacterials				
non-use	688 (97.6)	2626 (98.8)	1.0 (referent)	1.0 (referent)
past use	6 (0.9)	15 (0.6)	1.5 (0.5, 3.8)	1.0 (0.3, 3.1)
recent use	5 (0.7)	14 (0.5)	1.4 (0.5, 3.9)	1.1 (0.3, 3.6)
current use	6 (0.9)	3 (0.1)	7.8 (1.9, 31.1)	7.4 (1.8, 29.6)
Cinchona alkaloids				
non-use	699 (99.1)	2650 (99.7)	1.0 (referent)	1.0 (referent)
past use	2 (0.3)	2 (0.1)	4.0 (0.6, 28.4)	3.0 (0.4, 25.6)
recent use	2 (0.3)	1 (0.0)	8.0 (0.7, 88.2)	9.1 (0.8, 102.2)
current use	2 (0.3)	5 (0.2)	1.3 (0.2, 6.9)	1.3 (0.2, 8.0)
Diuretics				
non-use	675 (95.7)	2603 (97.9)	1.0 (referent)	1.0 (referent)
past use	6 (0.9)	7 (0.3)	3.4 (1.1, 10.8)	3.0 (0.9, 10.0)
recent use	4 (0.6)	5 (0.2)	3.2 (0.9, 12.0)	2.5 (0.6, 10.1)
current use	20 (2.8)	43 (1.6)	1.8 (1.0, 3.2)	1.7 (0.9, 3.0)
DMARDs				
non-use	703 (99.7)	2655 (99.9)	1.0 (referent)	1.0 (referent)
past use	0 (0)	1 (0)	NA	NA
recent use	1 (0.1)	1 (0)	4.0 (0.2, 63.9)	2.3 (0.1, 52.3)
current use	1 (0.1)	1 (0)	4.0 (0.2, 63.9)	4.3 (0.3, 69.3)
NSAIDs				
non-use	675 (95.7)	2553 (96.1)	1.0 (referent)	1.0 (referent)
past use	9 (1.3)	33 (1.2)	1.0 (0.5, 2.1)	1.0 (0.5, 2.3)
recent use	9 (1.3)	34 (1.3)	1.0 (0.5, 2.1)	1.0 (0.5, 2.3)
current use	12 (1.7)	38 (1.4)	1.2 (0.6, 2.4)	1.3 (0.6, 2.6)
Tuberculostatics				
non-use	705 (100)	2657 (100)	1.0 (referent)	1.0 (referent)
past use	0 (0)	0 (0)	NA	NA
recent use	0 (0)	0 (0)	NA	NA
current use	0 (0)	1 (0)	NA	NA
Cotrimoxazole (trimethoprim/sulfamethoxazole)				
non-use	701 (99.4)	2647 (99.6)	1.0 (referent)	1.0 (referent)
past use	1 (0.1)	5 (0.2)	0.8 (0.1, 6.8)	0.8 (0.1, 7.3)
recent use	0 (0)	4 (0.2)	NA	NA
current use	3 (0.4)	2 (0.1)	5.7 (0.9, 34.0)	3.7 (0.5, 24.3)

a Current use was defined as exposure to the drug in the period of 4 weeks before or at the index date, recent use was defined as exposure in the period of 3 months through 4 weeks before the index date, past use was defined as exposure in the period of 6 months through 3 months before the index date and non-use was defined as having dispensed a prescription >6 months before the index date or not having dispensed a prescription at all.

b Adjusted for hospitalisation for cancer in the period of 6 months before the index date and concurrent exposure to the other drugs investigated in this study.

NA = not applicable; **OR** = odds ratio.

although both did not reach statistical significance (table II). No increased risk for thrombocytopenia was found for current exposure to anticonvulsants, cinchona alkaloids, NSAIDs and tuberculostatics. Past use of diuretics was found to be associated with an increased risk for thrombocytopenia in univariate analysis. However, after adjusting for potential confounding the risk estimate became non-significant (table II).

Discussion

The results of this study, one of the few large epidemiological studies designed to quantify the association between drug exposure and thrombocytopenia, indicate that the current use of β-lactam antibacterials is associated with a 7-fold increased risk for thrombocytopenia in the general population. β-Lactam antibacterials have been reported to cause thrombocytopenia by immune-mediated mechanisms[2,20] and by bone-marrow suppression.[21,22] Furthermore, β-lactam antibacterials were found to be associated with an increased risk for blood dyscrasias in a cohort study using data from the British General Practice Research Database.[23] However, the authors suggested that confounding by indication has to be considered when an association is found between the use of antibacterials and blood dyscrasias, because the antibacterial drug might be prescribed to treat an infection that could be considered as early manifestation of a blood dyscrasia related to the underlying disease.[23,24] In the current study, we cannot rule out confounding by indication; however, by excluding patients with thrombocytopenia that also had agranulocytosis and/or thrombocytopenia-related medical conditions at the index date, we believe it is not likely that confounding by indication can explain our results.

From the results of this study the expected increased risk for thrombocytopenia could not be confirmed for the other drug classes investigated. This is in contrast with findings of a previous case-control study that reported an increased risk for hospitalisation for acute thrombocytopenic purpura and the use of cotrimoxazole (multivariate relative risk 124; 95% CI 19, 821) and quinine/quinidine (multivariate relative risk 101; 95% CI 31, 324).[14]

The lack of statistical power resulting from the low number of cases is a possible explanation for the current findings, such as in the case of cotrimoxazole. Considering the study design, a matched retrospective case-control study, the *a priori* defined criteria for significance ($\alpha = 0.05$) and power (80%, $\beta = 0.2$), the increased point estimate of 5.4 that was found for current exposure to cotrimoxazole could only have been statistically confirmed for this number of exposed controls (2 of 2658) if >2350 cases were identified, i.e. three times more then were included in the study.[18] Therefore, future studies including more patients are necessary to confirm our findings.

The extensive information on drug exposure, potential confounders and patient characteristics that is

Table III. Sensitivity analysis current exposure to β-lactam antibacterials

Exposure window in days to the index date	Cases [n (%)]	Controls [n (%)]	Crude OR[a] (95% CI)	Adjusted OR[a,b] (95% CI)
7	3 (0.4)	0 (0.0)	NA	NA
14	4 (0.6)	1 (0.0)	15.2 (1.7, 136.0)	14.2 (1.6, 127.8)
28	6 (0.8)	3 (0.1)	7.8 (1.9, 31.1)	7.4 (1.8, 29.6)
42	7 (1.0)	6 (0.2)	4.6 (1.6, 13.6)	3.8 (1.2, 11.7)

a Non-use taken as reference category.

b Adjusted for hospitalisation for cancer in the period of 6 months before the index date and concurrent exposure to the other drugs investigated in this study.

NA = not applicable; **OR** = odds ratio.

available within the PHARMO database is the strength of this study. Nevertheless, the study design and the available resources introduce potential limitations. It is quite possible that patients who developed drug-induced thrombocytopenia, who were identified by including those with thrombocytopenia who required hospitalisation, were only the tip of the iceberg, leaving patients who recovered after termination of therapy and patients who died unidentified.[25]

Incomplete and inaccurate coding of discharge diagnosis could have introduced misclassification of outcome.[25] Inaccurate coding might be reflected by the finding that two-thirds of the identified hospitalisations for thrombocytopenia were classified as unspecified. Since no data were available on medication administered during hospitalisation, we might have included patients who developed thrombocytopenia related to drug exposure (e.g. chemotherapy, immunosuppressants, unfractionated heparin or low-molecular weight heparins) administered during hospitalisation. On the other hand, by excluding patients with a diagnosis for agranulocytosis or thrombocytopenia-related medical conditions at the index date and by adjusting for confounding, this bias, if existing, seems relatively small. Nevertheless, additional studies including cases that are validated by retrieving all detailed information on all aetiologic causes of thrombocytopenia from the original patient records remain necessary before drawing final conclusions. Some misclassification of exposure may have occurred, since pharmacy records, which provide information that the drug was dispensed but not if the patient actually took it, were used for identification of drug exposure. However, this misclassification is expected to be limited[16] and was assumed to be evenly distributed over cases and controls. Furthermore, non-differential misclassification may systematically lead to underestimation of the investigated effects.[26] Finally, it cannot be ruled out that potential residual confounding can explain part of the associations found.

Database systems comprising administrative healthcare data have proven to be useful for detection, verification and quantification of the risk for adverse drug reactions in the general population.[27] Considering the design of the current study we believe the results contribute to the knowledge on drug-induced thrombocytopenia. Nevertheless, we have discussed sample size and the use of hospitalisation data that limit the risk estimation and the identification of risk factors for drug-induced thrombocytopenia. Potentially, the use of laboratory data, i.e. platelet count, in future pharmacoepidemiological studies aimed at quantifying the risk for drug-induced thrombocytopenia and identification of potential risk factors, will overcome these issues partially. Furthermore, the use of laboratory data will enable us to study the severity and potentially the time of onset of the thrombocytopenia in more detail. In the current study, it was unclear what platelet count threshold was used in diagnosing the patient with thrombocytopenia. We would expect the platelet count in all cases to be $\leq 100 \times 10^9$ platelets/L; however, we could not verify this because of the lack of laboratory data.

Conclusion

This study provided more evidence on the increased risk for thrombocytopenia in current exposure to β-lactam antibacterials in the general population. The expected increased risk for thrombocytopenia could not be confirmed and quantified for the other drugs investigated. Therefore, future studies including more patients are necessary to confirm our findings. The potential for large retrospective studies within administrative databases investigating adverse drug reactions, such as drug-induced thrombocytopenia, might be enhanced if cases were sampled from routine laboratory data that were gathered during daily practice.

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References

1. Handin RI, Lux SE, Stossel TP. Blood principles and practice of hematology. 2nd ed. Philadelphia (PA): Lippincott Williams and Wilkins, 2003
2. van den Bemt PMLA, Meyboom RH, Egberts ACG. Drug-induced immune thrombocytopenia. Drug Saf 2004; 27 (15): 1243-52
3. Carey PJ. Drug-induced myelosuppression: diagnosis and management. Drug Saf 2003; 26 (10): 691-706
4. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005; 106 (8): 2710-5
5. Prandoni P, Siragusa S, Girolami B, et al. The incidence of heparin-induced thrombocytopenia in medical patients treated with low-molecular-weight heparin: a prospective cohort study. Blood 2005; 106 (9): 3049-54
6. Li X, Hunt L, Vesely SK. Drug-induced thrombocytopenia: an updated systematic review. Ann Intern Med 2005; 142 (6): 474-5
7. George JN, Raskob GE, Shah SR, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med 1998; 129 (11): 886-90
8. Rizvi MA, Kojouri K, George JN. Drug-induced thrombocytopenia: an updated systematic review. Ann Intern Med 2001; 134 (4): 346
9. Hibbard AB, Medina PJ, Vesely SK. Reports of drug-induced thrombocytopenia. Ann Intern Med 2003; 138 (3): 239
10. Pedersen-Bjergaard U, Andersen M, Hansen PB. Thrombocytopenia induced by noncytotoxic drugs in Denmark 1968-91. J Intern Med 1996; 239 (6): 509-15
11. Danielson DA, Douglas SW, Herzog P, et al. Drug-induced blood disorders. JAMA 1984; 252 (23): 3257-60
12. Bottiger LE, Westerholm B. Thrombocytopenia: II. Drug-induced thrombocytopenia. Acta Med Scand 1972; 191 (6): 541-8
13. Strom BL. Pharmacoepidemiology. 3rd ed. Chichester, UK: John Wiley & Sons Ltd, 2000
14. Kaufman DW, Kelly JP, Johannes CB, et al. Acute thrombocytopenic purpura in relation to the use of drugs. Blood 1993; 82 (9): 2714-8
15. Herings RMC. PHARMO: a record linkage system for postmarketing surveillance of prescription drugs in the Netherlands. Utrecht: Utrecht University, 1993
16. Lau HS, de Boer A, Beuning KS, et al. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997; 50 (5): 619-25
17. CDC National Center for Health Statistics. International Classification of Diseases, 9th Revision. Clinical Modification (ICD-9-CM) [online]. Available from URL: http://www.cdc.gov/nchs/about/otheract/icd9/abticd9.html [Accessed 2006 Jun 27]
18. Dupont WD, Plummer WD. Power and sample size calculations for studies involving linear regression. Control Clin Trials 1998; 19 (6): 589-601
19. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989; 79 (3): 340-9
20. Patnode NM, Gandhi PJ. Drug-induced thrombocytopenia in the coronary care unit. J Thromb Thrombolysis 2000; 10 (2): 155-67
21. Kumar A, Choudhuri G, Aggarwal R. Piperacillin induced bone marrow suppression: a case report. BMC Clin Pharmacol 2003; 3 (1): 2
22. Reichardt P, Handrick W, Linke A, et al. Leukocytopenia, thrombocytopenia and fever related to piperacillin/tazobactam treatment: a retrospective analysis in 38 children with cystic fibrosis. Infection 1999; 27 (6): 355-6
23. Huerta C, Garcia Rodriguez LA. Risk of clinical blood dyscrasia in a cohort of antibiotic users. Pharmacotherapy 2002; 22 (5): 630-6
24. Rawson NS, Harding SR, Malcolm E, et al. Hospitalizations for aplastic anemia and agranulocytosis in Saskatchewan: incidence and associations with antecedent prescription drug use. J Clin Epidemiol 1998; 51 (12): 1343-55
25. Movig KL, Leufkens HG, Lenderink AW, et al. Validity of hospital discharge International Classification of Diseases (ICD) codes for identifying patients with hyponatremia. J Clin Epidemiol 2003; 56 (6): 530-5
26. Hofler M. The effect of misclassification on the estimation of association: a review. Int J Methods Psychiatr Res 2005; 14 (2): 92-101
27. Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ 2004; 329 (7456): 44-7

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