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Platelet Measurements versus Discharge Diagnoses for Identification of Patients with Potential Drug-Induced Thrombocytopenia

A Cross-Sectional Study in the Netherlands

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Abstract

Background: In pharmacoepidemiological studies on the risk of drug-induced blood dyscrasias, including drug-induced thrombocytopenia (DIT), hospital discharge diagnoses have been used to identify potential cases. One of the possible limitations of discharge diagnoses is that due to incomplete registration not all potential cases are identified, which may limit statistical power. Clinical laboratory data have been suggested as a data type that is potentially more sensitive for identifying potential cases of adverse drug reactions than discharge diagnoses.

Objective: To compare the number of patients with potential DIT that could be identified by using platelet measurements with the number of patients with potential DIT that could be identified by using discharge diagnoses for thrombocytopenia within a population of hospitalized patients.

Methods: The study population of this cross-sectional study comprised all patients admitted to the University Medical Center Utrecht in 2004 and 2005, as captured within the Utrecht Patient Oriented Database (UPOD). The ratio of the number of patients with potential DIT based on platelet measurements (≥1 platelet count below 100×10^9/L without alternative diagnoses for DIT) to the number of patients with potential DIT based on discharge diagnoses for thrombocytopenia (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes 287.3–287.5 without alternative diagnoses for DIT) was determined.

Results: Within the study period there were 56 411 hospitalizations. 2817 patients (5.0%) had ≥1 platelet count below 100×10^9/L. In 96.3% of these

patients, alternative diagnoses for DIT were present, resulting in 103 (0.2%) patients with potential DIT based on platelet measurements. There were 74 patients (0.1%) with a discharge diagnosis for thrombocytopenia. In 81.1% of these patients, alternative diagnoses for DIT were present, resulting in 14 (0.02%) patients with potential DIT based on discharge diagnoses. This resulted in a ratio of the number of patients with potential DIT based on platelet measurements to the number of patients with potential DIT based on discharge diagnoses for thrombocytopenia of seven.

Conclusion: This study showed that the use of platelet measurements is a more sensitive approach to the identification of patients with potential DIT than the use of discharge diagnoses for thrombocytopenia.

Background

Drug-induced blood dyscrasias such as agranulocytosis, aplastic anaemia and thrombocytopenia are among the most frequently reported fatal adverse drug reactions,[1] and have been a major reason for drug withdrawal from the market during the past 50 years.[2] Several epidemiological studies have been conducted following up important signals on drug-induced haematological toxicity,[3-8] of which the IAAAS (International Agranulocytosis and Aplastic Anemia Study) is probably the best known example.[9] We have previously investigated the risk for drug-induced thrombocytopenia (DIT) following exposure to non-cytotoxic drugs that are most often reported to cause thrombocytopenia in the general population.[7]

The majority of the observational studies on drug-induced blood dyscrasias have been conducted within large population-based administrative databases, using coded (e.g. International Classification of Diseases [ICD], 9th Revision, Clinical Modification [ICD-9-CM][10]) hospital discharge diagnoses as identifiers for patients with a potential drug-induced blood dyscrasia.[3-8] However, the validity of using discharge diagnoses for case-finding of drug-induced blood dyscrasias could be threatened by the nature of the registration of discharge diagnoses. Firstly, the registration of discharge diagnoses is primarily driven by reimbursement purposes and not by clinical care needs, and therefore discharge diagnoses are not necessarily registered for all present conditions,[11] thereby potentially limiting sensitivity. Secondly, coding mistakes by administrative personnel could occur,[11] potentially limiting both sensitivity and specificity. These two limitations could lead to incomplete case-finding, thereby introducing the potential for selection bias as well as limiting statistical power.

An alternative approach for identifying patients with potential drug-induced blood dyscrasias for pharmacoepidemiological research is the use of clinical laboratory data (i.e. blood cell counts) as an identifier. Clinical laboratory data are gathered for patient care purposes, measured using validated instruments and procedures, and the results of the measurements are increasingly automatically (i.e. without human data entry) stored in hospital information systems, including the electronic medical record. Laboratory data are therefore expected to be less prone to selective registration and coding mistakes than discharge diagnoses. In contrast to discharge diagnoses, which have been used successfully in pharmacoepidemiological research since the beginning of the 1990s,[12] clinical laboratory data have become widely available for this type of research only recently.[13] The objective of the current study was to compare the number of patients with potential DIT that could be identified within a population of hospitalized patients by using platelet measurements with the number of patients with potential DIT that could be identified by using discharge diagnoses for thrombocytopenia.

Methods

Design, Data Source, Setting and Study Population

This retrospective cross-sectional study with prospectively collected data was conducted using the Utrecht Patient Oriented Database (UPOD). UPOD is a platform for clinical epidemiological research, the structure and content of which have been described in more detail elsewhere.[13] In brief, UPOD is an infrastructure of relational databases comprising data on patient characteristics, hospital discharge diagnoses, medical procedures, medication orders and laboratory tests for all patients treated at the University Medical Center Utrecht (UMC Utrecht, Utrecht, the Netherlands) since 2004. The UMC Utrecht is a 1042-bed academic teaching hospital in the centre of the Netherlands, with approximately 28 000 clinical and 15 000 day-care hospitalizations and 334 000 outpatient visits annually.[13] UPOD data acquisition and data management is in accordance with current Dutch privacy and ethical regulations.

The study population included all patients who were clinically admitted to the UMC Utrecht during the 2-year period between 1 January 2004 and 31 December 2005. Patients could be hospitalized more than once during the study period.

Drug-Induced Thrombocytopenia (DIT)

DIT is defined as thrombocytopenia due to a decreased platelet production, an increased platelet destruction or an increased platelet consumption, following an immune response to a drug or a direct toxic effect of a drug on the megakaryocytopoiesis in the bone marrow.[14] The diagnosis of DIT in clinical practice is usually the outcome of exclusion of all other possible explanations for a thrombocytopenia. DIT is commonly defined as a platelet count below 100×10^9/L without alternative diagnoses.[14-16]

Potential DIT

In this study, two different approaches for the identification of patients with potential DIT – defined as patients with thrombocytopenia without alternative diagnoses for DIT – were compared. The first approach was based on using platelet measurements as the identifier for patients with potential DIT, and the second approach was based on using discharge diagnoses for thrombocytopenia. Patients with potential DIT based on platelet measurements were defined as patients with at least one platelet count below 100×10^9/L during hospitalization, without the presence of alternative diagnoses for DIT.[15] Patients with potential DIT based on discharge diagnosis of thrombocytopenia were defined as patients with an in-patient discharge diagnosis of primary (ICD-9-CM code 287.3), secondary (287.4) or unspecified thrombocytopenia (287.5), without the presence of alternative diagnoses for DIT. The discharge diagnosis for secondary thrombocytopenia (ICD-9-CM code 287.4) codes for DIT, among other types of secondary thrombocytopenia. However, in this study, all three discharge diagnoses that code for thrombocytopenia according the ICD-9-CM classification (table I) were taken into account in defining potential DIT based on discharge diagnoses for thrombocytopenia. This was done to anticipate potential misclassification of patients with DIT as primary or unspecified thrombocytopenia.

Table I. Thrombocytopenia coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)[10]

Code	Description
287.3	Primary thrombocytopenia
	287.30: primary thrombocytopenia unspecified
	287.31: idiopathic thrombocytopenic purpura (ITP), tidal platelet dysgenesis
	287.32: Evans's syndrome
	287.33: congenital and hereditary thrombocytopenia, thrombocytopenia with absent radii (TAR)
	287.39: other primary thrombocytopenia
287.4	Secondary thrombocytopenia
	post-transfusion purpura
	thrombocytopenia due to dilution, drugs, extracorporeal circulation of blood, massive blood transfusion, platelet alloimmunization
287.5	Thrombocytopenia, unspecified

Alternative diagnoses for DIT were defined as diseases or therapeutic procedures that could explain the thrombocytopenia. The presence of alternative diagnoses for DIT was investigated using automated data on discharge diagnoses (coded according to the ICD-9-CM),[10] medical procedures (coded according to the Classification of Procedures by Medical Specialists, published by the Dutch CBV Foundation)[17] and haematological laboratory parameters, as captured within UPOD.[13] Alternative explanations for DIT were based on causes of thrombocytopenia reported in different textbooks on haematology.[18-21] Treatment with chemotherapy was taken into account as an alternative diagnosis, since the study concerned potential immune-mediated DIT and not DIT due to myelotoxicity that is caused by chemotherapy. The alternative diagnoses for DIT were grouped into (i) underlying hematologic disease, (ii) congenital causes not included in ICD-9-CM code 287.33, (iii) acquired immune causes, and (iv) acquired non-immune causes (table II; see also appendix I in the supplementary material ['ArticlePlus'] at http://drugsafety.adisonline.com).

Outcomes

The ratio of the number of patients with potential DIT based on platelet measurements to the number of patients with potential DIT based on discharge diagnoses for thrombocytopenia was determined. In addition, it was investigated whether patients that were identified as patients with potential DIT based on platelet measurements were also identified as patients with potential DIT based on discharge diagnoses for thrombocytopenia, and vice versa.

Data Handling

Data selection, transformation and analysis was performed using SAS Software, version 9.0 of the SAS System for Windows (© 2004, SAS Institute Inc., Cary, NC, USA) under Windows XP.

Results

Within the study period there were 56 411 clinical hospitalizations for 41 112 unique patients. In 27 984 patients (49.6%) at least one

Table II. Categories and most prevalent alternative diagnoses for drug-induced thrombocytopenia (DIT) in patients with thrombocytopenia according to platelet measurements and discharge diagnoses for thrombocytopenia (see Appendix I of the supplementary material for further details)

Alternative diagnosis	≥1 platelet count $<100\times10^9$/L [n (%)] (n = 2817)	Discharge diagnoses of thrombocytopenia [n (%)] (n = 74)
Hospitalizations with ≥1 alternative diagnoses	2714 (96.3)	60 (81.1)
Underlying haematological disease	2310 (82.0)	45 (60.8)
anaemia based on haemoglobin measurement	2034 (72.2)	36 (48.6)
blood transfusion (proxy for haematological instability)	1791 (63.6)	30 (40.5)
leukopenia based on white blood cell measurement	903 (32.1)	15 (20.3)
neutropenia based on neutrophil measurement	827 (29.4)	12 (16.2)
Congenital causes not included in ICD-9-CM code 287.33	10 (0.3)	0 (0.0)
Acquired immune causes	125 (4.4)	5 (6.8)
Acquired nonimmune causes	2612 (92.7)	50 (67.6)
bleeding	298 (10.6)	7 (9.5)
cardiac surgery with cardiopulmonary bypass	477 (16.9)	7 (9.5)
chemotherapy	372 (13.2)	4 (5.4)
haematological malignancy	628 (22.3)	6 (8.1)
pregnancy (proxy for gestational [incidental] thrombocytopenia)	415 (14.7)	6 (8.1)
surgery	1515 (53.8)	17 (23.0)

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification.

Table III. Potential drug-induced thrombocytopenia based on discharge diagnosis of thrombocytopenia

Discharge diagnosis for thrombocytopenia	Hospitalizations with a discharge diagnosis of thrombocytopenia (n)	Hospitalization with a discharge diagnosis of thrombocytopenia without alternative diagnoses [n (%)]
Any	74	14 (18.9)
Primary	29	9 (31.0)
Secondary	11	1 (9.1)
Unspecified	34	4 (11.8)

platelet count was measured at any time during hospitalization. In 2817 (5.0%) patients there was at least one platelet count below 100×10^9/L during hospitalization. In 2714 (96.3%) of these patients there was at least one alternative diagnosis for DIT present during hospitalization (table II and Appendix I of the supplementary material), resulting in 103 (0.2%) patients with potential DIT based on platelet measurements. A discharge diagnosis for thrombocytopenia was registered for 74 (0.1%) patients, mostly concerning unspecified thrombocytopenia, followed by primary and secondary thrombocytopenia (table III). In 60 of these patients (81.1%) there was at least one alternative diagnosis for DIT present during hospitalization (table II and Appendix I of the supplementary material), resulting in 14 (0.02%) patients with potential DIT based on a discharge diagnosis for thrombocytopenia. Comparison of the number of patients with potential DIT based on platelet measurements and on discharge diagnoses for thrombocytopenia resulted in a ratio of seven (103 vs 14).

In both patients with at least one platelet count below 100×10^9/L and patients with a discharge diagnosis for thrombocytopenia, underlying haematological diseases (severe anaemia, severe leukopenia/neutropenia, blood transfusion) and acquired nonimmune causes (surgery [mostly cardiac], pregnancy and haematological malignancy) were the most prevalent alternative diagnoses for DIT present (table II and Appendix I of the supplementary material).

There were 12 patients who were identified as having potential DIT using both platelet measurements and discharge diagnoses for thrombocytopenia (figure 1). This corresponds with 11.6% of the patients with potential DIT based on platelet measurements and 85.7% of the patients with potential DIT based on discharge diagnoses for thrombocytopenia. For one patient with potential DIT based on discharge diagnoses for thrombocytopenia that was not identified with platelet measurements, no platelet measurements were performed; for another patient with potential DIT based on discharge diagnoses for thrombocytopenia that was not identified with platelet measurements, the platelet count did not drop below 100×10^9/L during admission (figure 1).

Discussion

In this study the use of platelet measurements was found to result in the identification of seven times more patients with potential DIT than the use of discharge diagnoses for thrombocytopenia, suggesting that platelet measurements are

		Patients with potential DIT based on platelet measurement		
		Yes	**No**	**Total**
Patients with potential DIT based on discharge diagnoses for thrombocytopenia	**Yes**	12	2[1]	14
	No	91	12 913	13 004
	Total	103	12 915	13 018[2]

Fig. 1. Patients identified as having potential drug-induced thrombocytopenia (DIT) based on platelet measurements compared with patients identified as having potential DIT based on discharge diagnoses for thrombocytopenia. **1** In one patient no platelet count was performed, in the other patient the platelet count did not drop below 100×10^9/L during admission. **2** There were 13 018 patients without alternative diagnoses for DIT.

a more sensitive identifier for DIT than ICD-coded discharge diagnoses for thrombocytopenia. In this study the identification of patients with potential and not actual DIT was investigated, because such case-finding would be the first step in an epidemiological investigation of DIT. Patients with potential DIT are cases that need further detailed medical chart review to determine whether DIT actually occurred. Studying methods for case-finding is important because a more complete identification of patients with potential DIT could lead to a more complete identification of patients with actual DIT, and therefore to more statistical power and less bias in pharmacoepidemiological studies on DIT. A potential increase in statistical power is relevant, since our recent population-based study on the relative risk for DIT, using a source population of >2 million patients during 13 years, and discharge diagnoses for thrombocytopenia as case identifier, lacked sufficient power to evaluate the risk of DIT in patients using drugs with lower exposure frequency.[7]

The strength of this study lies in the use of complete and validated automated data available within UPOD.[13] However, this study is potentially limited because UPOD comprises data from only one hospital. Because differences in characteristics of patient populations may exist, as well as differences between hospitals regarding the process of registration of discharge diagnoses or in the practice of requesting platelet measurements, we have to be careful in extrapolating our findings to other settings.

In this study, potential DIT based on platelet measurements was defined by a commonly used definition of DIT: a platelet count below 100×10^9/L without alternative diagnoses.[15,16] When a lower cutoff for the platelet count was used, the ratio of the number of patients with potential DIT based on platelet measurements to the number of patients with potential DIT based on discharge diagnoses for thrombocytopenia decreased. For example, considering a platelet count of 50×10^9/L as the cutoff value in defining potential DIT would have resulted in 28 patients with potential DIT based on platelet measurements and, consequently, in a ratio of 2.0 between both case-finding approaches (i.e. 28 vs 14 patients with potential DIT based on discharge diagnoses for thrombocytopenia). This suggests that a discharge diagnosis for thrombocytopenia is more likely to be registered in a case of severe thrombocytopenia. Comparable findings were made for the registration of a discharge diagnosis for hyponatraemia in patients with low serum sodium levels.[22]

In addition to the sensitivity of discharge diagnoses and platelet measurements for identifying patients with DIT, it is also important to consider the specificity of these identifiers for this purpose. Both platelet measurements and discharge diagnoses for thrombocytopenia can be considered as nonspecific identifiers for DIT, since there are many causes of thrombocytopenia, and no specific ICD code for DIT exists (table I). The finding that alternative explanations for DIT were present in 96.3% of the patients with a platelet count below 100×10^9/L and in 81.1% of the patients with a discharge diagnoses for thrombocytopenia illustrates the nonspecificity of both identifiers for DIT. In case-finding potential DIT with either identifier it is necessary to deal with the nonspecificity in order to limit an elaborative and time-consuming process of medical chart review. A way of dealing with the nonspecificity is excluding patients with all other causes for thrombocytopenia, as we did in the current study and in our previous study on the risk for DIT using discharge diagnoses for thrombocytopenia as the case identifier.[7] A potential limitation of this approach is that patients who experienced DIT in the presence of an alternative diagnosis for DIT are excluded, which reduces sensitivity.

From the current study it cannot be concluded whether the use of platelet measurements will result in the identification of more patients with actual DIT than the use of discharge diagnosis for thrombocytopenia. Future studies should look into the validation of these case-finding strategies by using detailed medical chart review. Such studies should also focus on the drugs associated with these validated cases, taking into account diagnostic criteria for DIT such as exposure to drugs reported to cause thrombocytopenia, the

time of onset of the thrombocytopenia in relation to the start of drug exposure, and improvement of the platelet count after drug withdrawal.

It has been reported that approximately 60–65% of adverse drug reactions can be detected with a laboratory test;[23-25] for example, drug-induced blood dyscrasias such as anaemia, neutropenia and thrombocytopenia, and drug-induced hyponatraemia or hyperkalaemia. Laboratory data can be considered as an identifier for patients potentially experiencing these adverse drug reactions. The relative sensitivity of platelet measurements compared with discharge diagnoses for thrombocytopenia found in the current study is illustrative for the potential value of using laboratory measurements for case-finding for pharmacoepidemiological research.[13] Two other population-based studies compared the presence of severe neutropenia and hyponatraemia based on discharge diagnoses with the presence of these conditions based on laboratory measurements, and found that discharge diagnoses could lead to an incomplete identification of patients.[22,26] Although we have to be cautious in generalizing the results from the current study, it is to be expected that the availability of clinical laboratory data within database systems fit for pharmacoepidemiological research will increase the possibilities for conducting drug safety studies.

Conclusion

This study compared the identification of patients with potential DIT based on platelet measurements and based on discharge diagnoses. The use of platelet measurements was found to be a more sensitive approach to the identification of patients with potential DIT than using discharge diagnoses for thrombocytopenia. The results of this study illustrate the potential value of clinical laboratory data for case-finding for pharmacoepidemiological research.

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