A Population-Based Case-Cohort Study of Drug-Associated Agranulocytosis

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Background: Agranulocytosis is a life-threatening disorder, often caused by drugs. Incidences or risks of drug-induced agranulocytosis are not well known, since it is rare.

Methods: To determine the risk of drug-associated agranulocytosis as a reason for admission to Dutch hospitals, we performed a population-based case-cohort study. Hospital discharge data came from the Dutch Centre for Health Care Information, Utrecht, which contains data on all general and university hospitals in the Netherlands. The reference cohort consisted of all persons in the catchment area of the Pharmaco Morbidity Record Linkage System (PHARMO RLS) in the Netherlands, composing a population of approximately 220,000 to 484,000 persons from 1987 through 1990. All admissions during that period with agranulocytosis or related diagnoses were included in the study (n = 923). The potential causes of agranulocytosis were assessed in all cases classified as probable or possible agranulocytosis.

Results: Discharge summaries were received of 753 admissions, of which 678 contained enough information for analysis. Of the 678, 108 were classified as “agranulocytosis probable” or as “agranulocytosis possible.” In 75 of these 108 cases, agranulocytosis had been the reason for admission. Fifteen patients had used methimazole within 10 days before developing agranulocytosis; 2, carbimazole; 9, sulfasalazine; 8, sulfamethoxazole-trimethoprim; 4, clomipramine hydrochloride; and 2, dipyrone with analgesics, yielding adjusted relative risks of agranulocytosis of 114.8 (for thyroid inhibitors combined) (95% confidence interval [CI], 60.5-218.6), 74.6 (95% CI, 36.3-167.8), 25.1 (95% CI, 11.2-55.0), 20.0 (95% CI, 6.1-57.6), and 26.4 (95% CI, 4.4-11.1), respectively.

Conclusions: The highest relative risks were found for thyroid inhibitors, sulfamethoxazole-trimethoprim, sulfasalazine, clomipramine, and dipyrone combined with analgesics.

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MATERIALS AND METHODS

SETTING

Data on morbidity were obtained from the Dutch Centre for Health Care Information, Utrecht, which holds a standardized computerized register of hospital diagnoses. Admission data are filed continuously from all general and university hospitals in the Netherlands. Whenever a patient is discharged from a hospital, data on sex, date of birth, dates of admission and discharge, 1 principal diagnosis (mandatory), and up to 9 additional diagnoses (optional) are recorded. All diagnoses are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification. At the time of initiation of this study, the most recent years on file available were 1987 through 1990. In this study, we analyzed all records containing potential cases of agranulocytosis, ie, admissions with the codes 288.0 (agranulocytosis), 288.1 (functional disorders of polymorphonuclear neutrophils), 288.2 (genetic anomalies of leukocytes), and 288.9 (unspecified diseases of white blood cells) as principal diagnoses.

Data on dispensed drugs were obtained from the Pharmaco Morbidity Record Linkage System (PHARMO RLS), a registry of community pharmacy data, with a complete coverage of filled prescriptions in its catchment area of approximately 220,000 persons in 1987, 331,000 persons in 1988, 419,000 persons in 1989, and 484,000 persons in 1990. All data on prescription-only drugs dispensed by all pharmacies in the catchment area are registered, as well as sex and date of birth of the patients these are dispensed to. In the Dutch health care system, all patients are designated to 1 pharmacy for filling their prescriptions. The vital statistics concerning age (overall and stratified) and sex were similar to those of the total Dutch population. It has been demonstrated that these data are good estimators of drug exposure in the Dutch population.

STUDY DESIGN

In this study, a population-based case-cohort design was used, in which drug use in cases was compared with drug use in a reference cohort. In the case-cohort design, the reference cohort may contain 1 or more cases. Cases were patients admitted to a hospital with a validated diagnosis of agranulocytosis. The reference cohort consisted of all people in the catchment area of all pharmacies included in the PHARMO RLS.

CASE DEFINITION

Agranulocytosis was defined as severe neutropenia (neutrophil count, ≤0.5 × 10^9/L) in an individual 2 years of age or older who used to have normal hematologic values, and who had symptoms compatible with agranulocytosis, notably fever and infections. In addition, cases had to comply with all of the following criteria: (1) hemoglobin level of 6.5 mmol/L or more or hematocrit of 0.32 or more if normochromic (men and women); (2) platelet count of 100 × 10^9/L or more; and (3) bone marrow aspirate or biopsy that confirmed the diagnosis, or if there was none, recovery of the absolute number of neutrophilic granulocytes within 30 days to greater than 1.5 × 10^9/L unless the patient died.

EXPOSURE DEFINITION

For every case, an index day was defined as the first day of the onset of fever (temperature ≥38°C), chills, or a sore throat. Furthermore, if the symptoms disappeared 5 days before admission or earlier, these were not taken into account. For every case, a risk time window was defined as the 10-day period preceding the index day. In all cases of a reaction classified as “agranulocytosis probable” or “agranulocytosis possible,” the reporting consultant was asked for permission to contact the general practitioner and the pharmacist of the patient to assess the use of drugs in the 3 months before admission. These data were used as exposure data, in combination with the data from the patient record. If not available, data on exposure to request for information for 753 admissions (81.6%). In approximately 50% of the cases, all relevant information was received (ie, at least a copy of the discharge summary, and the laboratory and bone marrow results). In the remainder, the hospitals were asked for additional information, resulting in data on 678 admissions, of which 66 concerned patients who had been admitted more than once. Another 86 cases were excluded because of insufficient data (eg, no description of symptoms or leukocyte counts) and 114 were excluded because the patient was younger than 2 years or had no symptoms on admission (ie, agranulocytosis was discovered by coincidence).

The remaining 478 admissions were classified as follows: agranulocytosis probable (n = 72), agranulocytosis possible (n = 36), agranulocytosis unlikely (n = 363), and agranulocytosis unclassifiable (n = 7) (Figure 2). Of the 108 admissions classified as agranulocytosis probable or agranulocytosis possible, 78 concerned adverse reactions that had their onset outside the hospital and that were the direct reason for admission. The remaining 30 consisted of reactions that occurred either in the outpatient clinic or inside the clinic during admission.

Of the admissions coded as diagnosis 288.0 (agranulocytosis), 333 (74.5% of classified admissions) were classified as agranulocytosis unlikely (Figure 2). Most of these patients had been admitted with pancytopenia or a combination of leukocytopenia with anemia or thrombocytopenia caused by chemotherapy.

Only the events that occurred outside the hospital and led to admission and that were classified as agranulocytosis probable or agranulocytosis possible were used in the further analysis, as cases occurring in the hospital could not be related to the exposure data acquired from community pharmacies. This group consisted of 78 cases. Of these, 6 patients died (8%), and in an additional 6 patients the event was severe in view of development of sepsis or septic shock. Fever was present in an additional 66 patients, often with chills.

Blood cultures were performed in 65 patients, of which 39 were positive. Bone marrow was examined in 47 patients, and in 44 it confirmed the diagnosis of agranulocytosis.
drugs were collected from the patients’ hospital records only. For every drug, the exposure period was calculated by divid-
ing the total number of dispensed tablets or capsules by the prescribed daily number of tablets or capsules. To correct for undercompliance and carryover effects, this period was multi-
tplied by a factor of 1.1, with a maximum of 14 days. Cases were consid-
ered exposed to all drugs for which the exposure period fell (partly) within the 10-day risk time window. If the drug was discontinued before the index day, the last day of use of the particular drug had to be within 10 days before the index day. Since the data from the reference cohort include only data from community pharmacies and not from hospi-
tal pharmacies, patients who developed agranulocytosis dur-
ing hospital admission (and thus probably caused by drugs supplied by a hospital pharmacy) were excluded from the study.

For every member of the reference cohort aged 2 years or older, a random 10-day period was chosen in each year separately. People in the reference cohort were considered exposed to all drugs of which the exposure period fell within this 10-day period. For every drug, the exposure period was calculated as defined above. The average number of users in each year of the study period was calculated in each age and sex stratum, standardized to the population size in the PHARMO RLS catchment area in 1990 (n = 471 812).

PROCEDURES

In 1992, a request for information was sent to all hospitals where patients had been discharged in the years 1987 through 1990 with 1 of the principal diagnoses mentioned above. All phys-
icians involved in the treatment of these patients received a request for a copy of the discharge summary, laboratory re-

results, and, if available, descriptions of bone marrow material, after removal of the patient identification.

If the data received were too scanty, further information was requested. All patient data were analyzed, with-
out prior knowledge of the suspected cause of agranulo-
cytosis, as follows.

Every admission was analyzed according to a predefined algorithm and classified as “agranulocytosis probable,”
“agranulocytosis possible,” “agranulocytosis unlikely,” or “agranulocytosis unclassifiable” (Figure 1). A Hematol-
ogy Review Committee assessed the clinical details of those admissions, without knowledge of the suspected cause, where the diagnosis was not straightforward. Also, other diseases that have been associated with leukopenia, such as preceding sepsis, systemic lupus erythematosus, Felty syndrome, and leukemia were excluded. If 2 members differed in their opinion on the classification of an admission, it was dis-
cussed in a joint meeting of the committee. Then, final clas-
sification was based on consensus (same classification by all 3 members) or on majority of votes in case of a minor discrep-
ancy (eg, agranulocytosis possible vs agranulocytosis un-
likely). If no agreement was obtained, the admission was clas-
sified as agranulocytosis unclassifiable. Furthermore, a random 10%-sample of the remainder of admissions was re-
analyzed by 1 of the members of the Hematology Review Committee (R.G.) to check the validity of the first analysis.

An admission because of agranulocytosis was classified as severe if the patient developed sepsis or septic shock caused by the agranulocytosis.

DATA ANALYSIS

The relative risk of developing agranulocytosis when being exposed to a certain drug (group) compared with not being exposed was estimated by dividing the ratio of cases exposed (c1) and not exposed (c0) to drug (group) X by the ratio of cohort members exposed (b1) and not exposed (b0) to this drug (group): relative risk = (c1/c0)/(b1/b0).

Point estimates were calculated with their 95% con-
fidence intervals for case-cohort studies.23,24

The etiologic fractions and excess risks were calculated according to standard procedures.25 All causes that were significantly associated with agranulocytosis in the univariate analysis were subsequently adjusted for age, sex, and concomitant drug use in a stratified analysis24 where concomitant use of drugs that have been associ-
ated with agranulocytosis was included as a dichoto-

mous variable.

In 3 patients the results were inconclusive. Once the cause of agranulocytosis was discontinued, the neutrophil count recovered within 30 days in 43 patients, it did not recover within this period in 8 patients, there were no data in 22 patients, and 5 other patients died before recovery of their neutrophil count.

Five patients were admitted twice, 2 of these on sepa-
rate occasions. Three patients, however, were trans-
ferred from one hospital to another for the same diag-
nosis. These 3 admissions were therefore excluded.

After exclusion, 75 cases remained, 30 men (me-
dian age, 48.5 years; 25th-75th percentile, 32-67 years) and 45 women (median age, 61 years; 25th-75th percentile, 42-73 years).

The incidence of agranulocytosis was estimated at 1.7 per million inhabitants in 1987, 2.2 per million in 1988, 2.5 per million in 1989, and 1.6 per million in 1990.

In the cases classified as agranulocytosis probable or agranulocytosis possible, in which the event had been the reason for admission, the main drugs used before the index day were methimazole (n = 15), digoxin (n = 12), prednisone (n = 10), sulfasalazine (n = 9), sulfamethoxa-

zole-trimethoprim (n = 8), acetaminophen including combi-

nations (n = 8), furosemide (n = 6), hydrochlorothia-

zide with potassium-sparing drugs (n = 6), levotyroxine sodium (n = 5), ibuprofen (n = 5), acenocoumarol (n = 5), propranolol hydrochloride (n = 5), and oxazepam (n = 5). The prevalence of use in the reference cohort is also given in the Table for drug groups and for the individual drugs most frequently used before agranulocytosis. The relative risks of hospital admissions because of agranulocytosis, adjusted for age, sex, and concomitant drug use, are also shown in the Table, as are the etiologic fraction and excess risk for drugs for which the adjusted relative risk was significantly elevated.

This study was performed to examine the drug-related hospital admissions because of agranulocytosis in the Netherlands, with a population-based case-cohort de-

sign. Excluded admissions mostly pertained to diag-

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noses closely related to agranulocytosis. These admissions were all excluded from our study, since they mostly concerned hospital-acquired pancytopenia, aplastic anemia, or a combination of agranulocytosis with anemia or thrombocytopenia, which were not our topic of interest. Moreover, only admissions of patients with community-acquired agranulocytosis could be used for the relative risk and incidence estimations, as in-hospital exposure data were not available. A large group of patients developed agranulocytosis to chemotherapy, an adverse reaction that has already been studied extensively.

In this study, we were not able to assess an incidence rate of mild leukopenia, as not all such patients would have been admitted. It is likely, however, that few cases of agranulocytosis (which is mostly symptomatic) have been missed and that our study gives a fairly accurate estimation of the incidence of community-acquired symptomatic agranulocytosis. Although psychiatric hospitals were not included, symptomatic cases of agranulocytosis are almost always referred to a general hospital. It should be noted that patients could have been admitted with agranulocytosis and coded otherwise in the registry of the Dutch Centre for Health Care Information. To assess false-negative misclassification, we added 3 diagnosis codes that could have included cases of agranulocytosis, and found only 1 possible case. Thyroid inhibitors had the highest relative risk and excess risk of drug-associated agranulocytosis, but also sulfamethoxazole-trimethoprim, sulfasalazine, clomipramine, hydrochloride, and dipyrone combined with analgesics were associated with high risk estimates.

For this study we used a case-cohort design. Because of the low incidence of agranulocytosis, we did not consider a cohort study a useful approach. Case-control studies are suitable for studying rare diseases, but we had several reasons for not using a case-control design. First, recall bias would have been likely. As agranulocytosis is an impressive event that patients are not likely to forget, it would not have been easy to find controls subject to the same recall of exposure as cases. Second, as drugs are a well-known cause of agranulocytosis, physicians might inquire more insistent about drug use in the index group than in the control group. Third, although agranulocytosis is considered to be rare, the low population exposure prevalence of some drugs (eg, thyroid inhibitors) could consequently have meant that none of the controls would have been exposed to those drugs.

Theoretically, selection bias might occur if agranulocytosis to one drug is more severe than agranulocytosis to other drugs, or if patients with agranulocytosis to a particular drug are admitted more readily. However, there are no reasons to believe that agranulocytosis to orally administered methimazole or sulfasalazine has a worse prognosis than agranulocytosis to other orally administered drugs. Hence, this will mean that the proportion of community-acquired cases of agranulocytosis that leads to admission is more or less the same for these drugs. Information bias might result if physicians who anticipate an increased risk of agranulocytosis perform more blood tests. This could occur, for instance, in patients taking thyroid inhibitors, as these are a well-known cause of agranulocytosis. Therefore, we excluded all cases that were asymptomatic and discovered only because of a routine blood test. Information bias by differential recall of drug use by patients (recall bias) was not a problem because the information came from automated pharmacies and had been gathered before disease onset. In patients in whom drug use could be checked in pharmacy data or general practitioner’s records, 85% of drugs mentioned in the hospital data could be confirmed. Although it was possible to obtain the filling data on most cases, it was virtually impossible to get these data during a longer episode than the risk period. Therefore, dose- and duration-related risk estimates could not be obtained. Confounding is unlikely, as apart from drugs there are few independent risk factors.

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for agranulocytosis, and we adjusted for age, sex, and concurrent drug use.

In the IAAAS, the overall incidence of community-acquired agranulocytosis was estimated at 3.4 per million inhabitants per year, which is slightly higher than the 1.6 to 2.5 per million inhabitants per year found in our study. The IAAAS has been heavily debated, since bias was thought to play a role. One of the difficulties was that the rate ratio regarding dipyrone varied between regions from 0.8 to 23.7. Insofar as we are aware, our study is the first that includes all admitted community-acquired cases of admitted agranulocytosis from a whole country. Our results were comparable with those of the IAAAS with regard to the elevated risks found for thyroid inhibitors and dipyrone, although the absolute number of cases involving dipyrone was small. For thyroid inhibitors, a relative risk of 102 was found in the IAAAS (excess risk, 4.9 per million during 10 days of exposure) found in the current study. Also, in the IAAAS, the risk for methimazole seems to be higher than that for carbimazole. Since carbimazole is converted to methimazole in vivo, this higher risk is difficult to explain. With regard to anti-infective agents, an elevated relative risk was found for sulfamethoxazole-trimethoprim (12; excess risk, 1.6 per million with 2 weeks of exposure) and the macrolides (excess risk, 7.1 per million). Several drugs with an elevated relative risk in our study have been associated with agranulocytosis in the medical literature, including diuretics (eg, chlorothalidone), antithyroid drugs (carbimazole, methimazole, and propylthiouracil), penicillins, indomethacin, acetaminophen, dipyrone, benzodiazepines, antidepressants (eg, amitriptyline), sulfasalazine, sulfamethoxazole-trimethoprim, carbazapine, and phenothiazines. For several other drugs, eg, coumarins, digoxin, and prednisone, this was not the case, although in the IAAAS an elevated relative risk was also found for digoxin and prednisone, for which the authors had no explanation. Since agranulocytosis disappeared in our patients despite continuation of these drugs, the association with these 2 drugs is probably not causal. Clozapine, which has been studied extensively because of its ability to cause agranulocytosis, was not registered in the Netherlands during the study period.

In conclusion, we found a slightly lower cumulative yearly incidence of community-acquired agranulocytosis in the Netherlands than was found in the multicenter IAAAS. In our study, thyroid inhibitors, sulfamethoxazole-trimethoprim, sulfasalazine, clomipramine, and dipyrone combined with analgesics were associated with the highest risks of agranulocytosis.

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### Table: Drug-Associated Agranulocytosis: Drug Groups and Individual Drugs Used Before Index Day in 1987 to 1990 (N = 75)*

<table>
<thead>
<tr>
<th>Drug Groups</th>
<th>No. of Cases</th>
<th>No. of Users in PHARMO RLS</th>
<th>Adjusted Relative Risk (95% CI)</th>
<th>Etiologic Fraction</th>
<th>Excess Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid inhibitors</td>
<td>17</td>
<td>752</td>
<td>114.8 (60.5-218.6)†</td>
<td>0.23</td>
<td>4.85</td>
</tr>
<tr>
<td>Diuretics</td>
<td>17</td>
<td>22 095</td>
<td>2.3 (1.2-4.3)†</td>
<td>0.13</td>
<td>0.06</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>15</td>
<td>29 824</td>
<td>1.5 (0.8-2.9)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>12</td>
<td>5011</td>
<td>8.2 (4.2-16.0)†</td>
<td>0.14</td>
<td>0.34</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>12</td>
<td>20 220</td>
<td>2.5 (1.3-4.9)†</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>Acetaminophen, including combinations</td>
<td>8</td>
<td>14 003</td>
<td>2.4 (1.1-5.2)†</td>
<td>0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>Acetylcysteine or bromhexine hydrochloride or carbocysteine</td>
<td>7</td>
<td>7745</td>
<td>3.9 (1.6-8.8)†</td>
<td>0.07</td>
<td>0.15</td>
</tr>
<tr>
<td>Coumarins</td>
<td>7</td>
<td>6547</td>
<td>2.7 (1.1-6.5)</td>
<td>0.06</td>
<td>0.09</td>
</tr>
<tr>
<td>Penicillins</td>
<td>6</td>
<td>10 697</td>
<td>3.1 (1.3-7.9)†</td>
<td>0.05</td>
<td>0.11</td>
</tr>
<tr>
<td>Saliycylates</td>
<td>5</td>
<td>4748</td>
<td>3.6 (1.3-9.3)†</td>
<td>0.05</td>
<td>0.14</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>5</td>
<td>5444</td>
<td>1.9 (0.7-5.1)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Nitrates</td>
<td>5</td>
<td>5499</td>
<td>1.9 (0.6-4.9)</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individual Drugs</th>
<th>No. of Users in PHARMO RLS</th>
<th>Adjusted Relative Risk (95% CI)</th>
<th>Etiologic Fraction</th>
<th>Excess Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methimazole</td>
<td>15</td>
<td>315</td>
<td>230.9 (120.4-453.5)†</td>
<td>0.20</td>
</tr>
<tr>
<td>Digoxin</td>
<td>12</td>
<td>5108</td>
<td>5.9 (2.8-12.6)†</td>
<td>0.13</td>
</tr>
<tr>
<td>Prednisone</td>
<td>10</td>
<td>1587</td>
<td>19.9 (10.1-43.7)†</td>
<td>0.13</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>9</td>
<td>523</td>
<td>74.6 (36.3-167.6)†</td>
<td>0.12</td>
</tr>
<tr>
<td>Sulfamethoxazole-trimethoprim</td>
<td>8</td>
<td>1952</td>
<td>25.1 (11.2-55.0)†</td>
<td>0.10</td>
</tr>
<tr>
<td>Clomipramine hydrochloride</td>
<td>4</td>
<td>714</td>
<td>20.0 (6.1-67.6)†</td>
<td>0.05</td>
</tr>
<tr>
<td>Dipyrone with analgesics</td>
<td>2</td>
<td>325</td>
<td>26.4 (4.4-111.1)†</td>
<td>0.03</td>
</tr>
<tr>
<td>Carbimazole</td>
<td>2</td>
<td>376</td>
<td>16.7 (2.6-97.9)†</td>
<td>0.03</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>2</td>
<td>1590</td>
<td>5.9 (1.0-24.4)</td>
<td>ND</td>
</tr>
<tr>
<td>Amitriptyline hydrochloride</td>
<td>2</td>
<td>1266</td>
<td>4.0 (0.7-16.9)</td>
<td>ND</td>
</tr>
<tr>
<td>Promethazine hydrochloride</td>
<td>2</td>
<td>3024</td>
<td>3.6 (0.6-15.1)</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Number of users is standardized to the population in 1990. The risk of agranulocytosis is expressed as relative risk with 95% confidence interval (CI) (adjusted for age, sex, and concomitant drug use), etiologic fraction, and excess risk per 1 million persons during 10 days of exposure. PHARMO RLS indicates Pharmacor Morbidity Record Linkage System; NSAIDs, nonsteroidal anti-inflammatory drugs; and ND, not done.

† Significantly elevated.
REFERENCES


