Population-Based Drug-Induced Agranulocytosis

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Background: Since the publication of a major international case-control study on the risk of agranulocytosis associated with the use of medicines in the 1980s, many new drugs have been introduced in therapeutics.

Methods: Seventeen units of hematology contribute to the case-control surveillance of agranulocytosis and aplastic anemia in Barcelona, Spain. After a follow-up of 78.73 million person-years, 177 community cases of agranulocytosis were compared with 586 sex-, age, and hospital-matched control subjects with regard to previous use of medicines.

Results: The annual incidence of community-acquired agranulocytosis was 3.46:1 million, and it increased with age. The fatality rate was 7.0%, and the mortality rate was 0.24:1 million. The drug most strongly associated with a risk of agranulocytosis was ticlopidine hydrochloride with an odds ratio (OR) of 103.23 (95% confidence interval [CI], 12.73-837.44), followed by calcium dobesilate (OR, 77.84 [95% CI, 4.50-1346.20]), antithyroid drugs (OR, 52.75 [95% CI, 5.82-478.03]), dipyrene (metamizole sodium and metamizole magnesium) (OR, 25.76 [95% CI, 8.39-179.12]), and spironolactone (OR, 19.97 [95% CI, 2.27-175.89]). Other drugs associated with a significant risk were pyrithyldione, cinepazide, aprindine hydrochloride, carbamazepine, sulfonamides, phenytoin and phenytoin sodium, β-lactam antibiotics, erythromycin stearate and erythromycin ethylsuccinate, and diclofenac sodium. Individual attributable incidences for all these drugs, which collectively accounted for 68.6% of cases, were less than 1:1 million per year.

Conclusions: Agranulocytosis is rare but serious. A few drugs account for two thirds of the cases. Our results also provide reassurance regarding the risk associated with a number of newly marketed drugs.

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Granulocytosis is a serious condition, with an estimated incidence of 1.6:1 million to 7.0:1 million inhabitants per year.1,2 Case fatality is around 10%,3,4 but this may depend to a large extent on the availability of prompt antibiotic treatment. Almost all classes of medicines have been implicated in agranulocytosis. Although it has been suggested that more than two thirds of cases are attributable to medicines,4 the evaluation of the etiologic role of these is challenging, because the disease is rare and the prevalence of use of the medicines of interest is generally low. Since the International Agranulocytosis and Aplastic Anemia Study (IAAAS) was carried out in the 1980s,2,5 patterns of pharmaceutical consumption have changed, and many of the medicines marketed in the past 20 years have reached a significant prevalence of use. In the past 2 decades, several epidemiological studies have confirmed some previous findings6-9 or have uncovered drugs with a potential risk.10-12 Experience from clinical trials, anecdotal reports, and series of cases have suggested that certain drugs, namely, antithyroid drugs,13 ticlopidine hydrochloride,14,15 spironolactone,16 and clozapine,17,18 are potential causes.

The metropolitan area of Barcelona, Spain, was one of the regions participating in the 1980-1986 IAAAS. Since the completion of the international study, data collection and analysis continued in our region, with the same methods. We present the results of the case-control epidemiological surveillance of agranulocytosis during 22 years in a population of 4 million inhabitants.

In 1980, a population-based case-control scheme for the surveillance of agranulocytosis and aplastic anemia was established in the metropolitan area of Barcelona, with 17 participating hospital hematology units. The scheme covered a population of 3.3 to 4.1 million inhabitants (described in detail in http:
of at least 100 with a hemoglobin level of at least 10 g/dL and a platelet count
were interviewed by the same monitor. Clinical and laboratory data
cases and their corresponding controls were
during their hospital stay. Detailed infor-
mation, a hematologist confirmed the di-
treatment, or acute infection.
neutropenia are of viral origin). Secondary exclusion criteria were applied to patients who could
not be interviewed during the first 28 days of hospital stay (to
memory bias); those with psychiatric conditions, blind-
and controls were interviewed by trained personnel, with a struc-
tured questionnaire, during their hospital stay. Detailed infor-
mation was obtained on the use of drugs in the 6 months before
admission, by means of an open question on the use of medici-
cines, a list of frequent symptoms often prompting use of medi-
cines, and a list of the top-selling drugs. Since 1998, this list has
been shown to patients with color pictures of the boxes or flasks
of the drugs they take). Because of the diffi-
cuty of establishing acceptable criteria for the selection of ade-
quate controls for in-hospital cases of agranulocytosis with-
out incurring selection bias, in-hospital cases were excluded from the case-control analysis.

Initially, for each case of agranulocytosis or aplastic anemia, we selected no more than 4 controls matched by sex, age, and hospital in the 3 months after admission of the correspond-
ing case, among those of a list of admission diagnoses judged independent of the reasons for use of most of the drugs, such as non–alcohol-related trauma, asymptomatic conditions needing surgical treatment, or acute infection.

The protocol was approved by the ethics committee of the coordinating hospital. After obtaining informed consent, cases and controls were interviewed by trained personnel, with a structured questionnaire, during their hospital stay. Detailed information was obtained on the use of drugs in the 6 months before admission, by means of an open question on the use of medicines, a list of frequent symptoms often prompting use of medicines, and a list of the top-selling drugs. Since 1998, this list has been shown to patients with color pictures of the boxes or flasks of each product. Cases and their corresponding controls were interviewed by the same monitor. Clinical and laboratory data were also recorded. On the basis of the examination of the clinical and laboratory information, a hematologist confirmed the diagnosis and established the index day, ie, the day when the first symptom attributable to agranulocytosis occurred; this review was performed blindly with respect to previous drug exposures. From 1980 to 1986, cases were blindly reviewed by an IAAAS international hematologic committee.2,5

Odds ratios (ORs) were calculated after controlling for confounding by applying a multiple logistic regression model, including potential known confounders and drug terms. The terms finally included in the model were aspirin, dipyrone (metamizole [sodium and magnesium]), proprphazone, acetaminophen, diclofenac sodium, indomethacin, other NSAIDs (nonsteroidal anti-inflammatory drugs), ticlopidine, calcium dobesilate, spironolactone, antithyroid drugs, phenytoin, carbamazepine, sulfonamides (including the combination of trimethoprim and sulfamethoxazole, and sulfasalazine), β-lactam antibiotics, erythromycin (stearate and ethylsuccinate), and a group of drugs with relatively low levels of consumption that are known to cause agranulocytosis (ie, aprindine [hydrochloride], cinzapride, clopidogrel, clarazapine, calcium carbimide [yamamide], gold salts, mianserin [hydrochloride], and pyrithyldione). The pharmaco-
ological terms included in the model were chosen because they were well-established potential causes of agranulocytosis, or because they showed a higher prevalence of use among the cases compared with the controls.

The primary analysis was performed with a conditional multiple logistic regression model. However, with the aim of in-
creasing statistical power for estimation of the risk associated with drugs having a low prevalence of use, a second analysis was done with all the cases for which information on drug exposures was available, and all the controls of both agranulocytosis and aplastic anemia, with an unconditional model that included sex, age, and interviewer as additional terms. Drug exposures were considered in different ways. The main analy-
sis refers to the week before the index day; this definition of exposure was decided after taking into ac-
count that for most of the cases of agranulocytosis, the time elapsed from injury of the bone marrow or of peripheral neutrophils to the appearance of the initial symptoms of infection is usually less than 7 days. The following 2 additional confirmatory analyses were performed: one, with the aim of explor-
ing possible information bias (regarding each drug that was used at least 3 days in the preceding week), and the other, to evalu-
ate protopathic bias (regarding each drug that was used be-
tween 9 and 3 days before the index day) (described in detail at http://www.icf.uab.es/farmavigila/protocols/agranulodrugs.htm).

For drugs showing ORs significantly higher than 1, popu-
lation-attributable risks were calculated from the OR, with the formula AR=[Pc×(OR–1)]/OR, where AR is the attributable risk and Pc is the proportion of exposed cases. We calculated 95% confidence intervals (CIs) as described by Greenland.20 We calculated the overall population-attributable risk by combining all exposures to individual drugs that showed a signific-
ant association as a single term.

For estimation of incidence, the source population was older than 2 years. Incidence rates were calculated by age and sex, and the attributable incidence (number of cases per million and per year) was calculated by multiplying the attributable risk by the incidence of the disease. All patients were followed up to 4 weeks or to hospital discharge, and case-fatality rates were estimated for the 4 weeks after the diagnosis.

RESULTS

Up to June 30, 2001, total follow-up was 78.73 million person-years. Four hundred fifty-four potential cases were
identified for hematologic review. Fifty-eight patients were excluded at this stage, leaving 396 confirmed cases of agranulocytosis (210 women [53%]). Details on the ascertainment of potential cases, and exclusions can be found at http://www.icf.uab.es/farmavigila/protocols/agranulodrugs.htm. Of the 396 confirmed cases, agranulocytosis developed in 123 during hospital admission, and 273 had been admitted to a hospital because of agranulocytosis (community cases).

The annual incidence of the disease was quite stable during the 22-year follow-up (described in detail at http://www.icf.uab.es/farmavigila/protocols/agranulodrugs.htm).
The overall incidence was 5.02:1 million and per year (3.46 for community cases). Among the 396 cases, there were 36 deaths, and the case-fatality rate was thus 9.1% (for community cases, the case-fatality rate was 7.0% [19 deaths among 273 individuals, with a mortality rate of 0.24 per million]). Incidence increased with age, as 55% of community cases were 65 years or older (Figure). The case-fatality rate was 3.57% among those aged 25 to 44 years, 3.48% among those aged 45 to 64 years, and 10.86% among those older than 64 years.

Ninety-six community cases (35%) were excluded (described in detail at http://www.icf.uab.es/farmavigila/protocols/agranulodrugs.htm), thus leaving 177 cases for the case-control analysis.

Five hundred eighty-six controls were interviewed and included in the analysis. Three hundred seventy-nine had trauma, 170 had medical emergencies, and 47 had been admitted for elective surgery. The rates of use of analgesics, nonsteroidal anti-inflammatory drugs, antibiotics, and other drugs of interest did not differ across the various categories of controls (described in detail at http://www.icf.uab.es/farmavigila/protocols/agranulodrugs.htm).

Table 1 shows drug exposures among cases and controls in the week before the index day, and the corresponding ORs and their 95% CIs for the conditional and the unconditional analyses. Estimates of risk for analgesics and nonsteroidal anti-inflammatory drugs did not vary materially with the analysis, but those corresponding to other drugs showed slightly wider differences.

The ORs (and 95% CIs) associated with ticlopidine (103.23 [12.73-837.44]), calcium dobesilate (77.84 [4.50-1346.20]), and antithyroid drugs (52.75 [3.82-478.03]) were high, although the CIs were wide because they were based on only 1 control exposed to each drug. Significant ORs were also found in association with dipyrone (25.76 [8.39-179.12]; 30 cases and 9 controls), spirnalactone (19.97 [2.27-173.89]; 6 cases and 4 controls), carbamazepine (10.96 [1.17-102.64]; 5 cases and 1 control), sulfonamides (8.04 [2.09-30.99]; 11 cases and 5 controls), and β-lactam antibiotics (4.71 [1.74-12.77]; 27 cases and 17 controls). Erythromycin had been taken by 4 cases and no controls (5 cases and 3 controls in the unconditional model; OR, 7.57 [1.12-51.14]), and phenytoin had been taken by 2 cases and 1 control (5 cases and 6 controls in the unconditional analysis; OR, 11.62 [3.11-43.48]).

No association was seen in either analysis between exposure to aspirin, acetaminophen, or propyphenazone and the risk of agranulocytosis.

Table 2 presents the population-attributable risk of the drugs for which a significant OR was found. More than 16% of the cases were attributable to dipyrone, 12.01% to β-lactam antibiotics, 11.19% to ticlopidine, 7.21% to antithyroid drugs, 5.44% to sulfonamides, 5.02% to calcium dobesilate, 4.19% to diclofenac, 3.22% to spirnalactone, 2.57% to carbamazepine, and 16.77% collectively to aprindine, cinapazide, clopidogrel, calcium carbimide, erythromycin, gold salts, maxiserin, pethynoi, or pyrithyldione. In total, these drugs accounted for 68.6% of the cases. The population incidence attributable to each particular drug was less than 0.6:1 million per year (Table 2). Details on numbers of cases and controls exposed to a list of selected drugs that were not found to be associated with a risk of agranulocytosis can be found at http://www.icf.uab.es/farmavigila/protocols/agranulodrugs.htm.

**COMMENT**

The total incidence of agranulocytosis cases was 5.02:1 million inhabitants per year, and the case-fatality rate was 9.1%. The incidence of community-acquired agranulocytosis was 3.46:1 million, and the case-fatality rate was 7%. With such low incidence rates, any moderate increase in the risk of agranulocytosis associated with a particular drug translates into a low number of attributable cases. More than half the cases were 65 years or older. The largest relative increases in risk were seen with pyrithyldione, cinepazide, ticlopidine, calcium dobesilate, and antithyroid drugs. Even for these, however, the estimated attributable incidences were small, of less than 1:1 million. In our milieu, a few drugs—dipyrone, β-lactam antibiotics, ticlopidine, antithyroid drugs, pyrithyldione, aprindine, cinepazide, sulfonamides, calcium dobesilate, diclofenac, spirnalactone, and carbamazepine—accounted for nearly 70% of cases. Our results also provide reassurance about a wide range of drugs in common use.

Three drugs with poor evidence of clinical efficacy, ie, cinepazide, pyrithyldione, and calcium dobesilate, accounted for a significant proportion of cases. This led to regulatory action, with the first two withdrawn from the market and the indications of the last one restricted.

Our data indicate that ticlopidine, consumption of which increased sharply in the 1990s, is associated with a high relative risk of agranulocytosis, and that a substantial proportion of cases are attributable to this drug. The risk of agranulocytosis associated with ticlopidine and clozapine had already been uncovered in clinical trials.

As in previous studies, we found a significant risk associated with the use of dipyrone. In a separate report, we described this association in detail. As in the IAAAS, we found a borderline risk associated with the use of diclofenac. We cannot exclude bias by indication
related to diclofenac use, because the drug is often used as a short-course analgesic in Spain.

Spironolactone was also associated with an increase of risk. The IAAAS had not found an association with agranulocytosis,22 probably because its prevalence of use was much lower than it is now. However, it has been incriminated in several anecdotal reports.15,16

The practical implication of this finding is that spironolactone should be the first suspected cause in case of agranulocytosis in a patient with heart failure not receiving any other suspected drug.

Erythromycin had been taken by 4 cases and no controls; a risk associated with the whole class of macrolides was suggested in the IAAAS,2 4 23 but not in another case-control study with a limited number of patients.8 We believe that the risk associated with its use is very low, if it exists at all.

We found a low relative risk associated with β-lactam antibiotics. Neutropenia associated with short courses of oral β-lactam therapy at lower doses is extremely rare,24 and we cannot entirely exclude bias by indication in this association.

Our results are based on experience systematically gathered by a multicenter collaborative network for 22 years, during which a large case-control database on agranulocytosis and aplastic anemia has been assembled. The cases have been thoroughly ascertainment, and annual incidence rates have been stable throughout the study period. We cannot exclude the possibility that a patient occasionally may have died of agranulocytosis without receiving medical care or without having had a white blood cell count. However, the study population is covered by a high-quality, universal, free health care service, and it is unlikely that patients with overwhelming infection were not admitted to a hospital and have 1 or more blood cell counts. We therefore believe that significant underascertainment is unlikely. Ninety-six (35%) of 273 eligible patients had to be excluded from the case-control study, because the drug is often used as a short-course analgesic in Spain.

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Three approaches were used to minimize information bias due to differential recall between cases and controls. First, the patients were interviewed within 28 days of admission. Second, exposure information was obtained directly from patients with a structured questionnaire, including several carefully worded questions. Third, to avoid information bias, an analysis was performed where only use for 3 or more days during the preceding week (which is presumably less subject to differential recall) was considered. This analysis confirmed the overall findings.

As our results show, agranulocytosis is rare, and two thirds of the cases are caused by a limited number of drugs. Monitoring blood cell counts in patients undergoing long-term treatment with certain drugs (eg, ticlopidine, antithyroid drugs, antiepileptic drugs) during the first few months of treatment may be appropriate to prevent intercurrent infections, because the risk is partly dose related in susceptible patients. However, agranulocytosis induced by other drugs (eg, dipyrone) is often an acute and unpredictable immunological condition, and in this situation surveillance of blood cell counts may be unjustified.

Agranulocytosis is rare and serious. Its epidemiological surveillance by an independent multicenter network allowed identification of previously unknown causes of the disease and evaluation of the risks associated with various known causes. Although almost all drugs have been implicated at least once in the etiology, in our setting, more than two thirds of the cases were attributable to a few products.

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