Low Drug Attributability of Aplastic Anemia in Thailand

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From 1989 to 1994, a population-based, case-control study of aplastic anemia was conducted in Thailand, including the regions of Bangkok, Khonkaen in the northeast, and Songkla in the south. An annual incidence in Bangkok of 3.7 cases per million population, about twice as high as in Western countries, has been reported. To evaluate the etiologic role of drugs, 253 subjects were compared with 1,174 hospital controls. With multivariate adjustment for confounding, a significant association was identified for exposure 2 to 6 months before admission to thiazide diuretics (relative risk estimate 7.7; 1.5 to 40). There were crude associations with sulfonamides (relative risk estimate 7.9; P = 0.004) and mebendazole (6.3; P = 0.03) (there were insufficient data for multivariate adjustment). Excess risks for the three drugs were in the range of 9 to 12 cases per million users. There was no significant association with chloramphenicol, although the multivariate relative-risk estimate was elevated (2.7; 0.7 to 10). Other drugs that have been reported to increase the risk of aplastic anemia, such as nonsteroidal anti-inflammatory drugs and anticonvulsants, were not commonly used. There were no associations with commonly used drugs, including benzodiazepines, antihistamines, oral contraceptives, and herbal preparations. For all associated drugs, the overall etiologic fraction (the proportion of cases attributable to an exposure) was 5%, compared with 25% in Europe and Israel. Drugs are uncommon causes of aplastic anemia in Thailand, and their use does not explain the relatively high incidence of the disease in that country.

PLASTIC ANEMIA is thought to have multiple causes, with exposure to drugs and other chemicals being the most prominent. At the end of the 19th century, Santesson described benzene-induced marrow failure in Swedish bicycle tire workers,1 and in the early 20th century a strong link was established between dipyrone and the related dyscrasias, agranulocytosis.2 Subsequent case reports have documented an association between a large variety of pharmaceutical agents and aplastic anemia.3-5 In published case series, drugs have been the most commonly identified causes of aplastic anemia,1 chloramphenicol has been mentioned especially frequently. Drug-associated aplastic anemia has important implications for the prescribing practice of physicians, drug development, governmental regulation and the wording of warning labels, and expensive tort actions.

For decades, aplastic anemia has appeared to be more common in Asia than in the West.5,7 In a population-based study, we recently documented the incidence of the disease in Bangkok as approximately twice that in Europe and Israel.8 There is little evidence for ethnic variability in the rates of aplastic anemia, and one of the suggested explanations for the higher incidence in the Far East has been drug use.9,10 For example, chloramphenicol is believed to be widely used in developing countries as compared with its infrequent use in the West. A recent publication suggested that the use of pyrazolone derivatives might be partly responsible for the higher incidence.11 In general drugs are more freely available in Asia, usually without prescription, and may be components of folk or herbal remedies.

In 1989 we instituted a population-based case-control study of aplastic anemia, with the specific intent of addressing drug and chemical exposures. The study was conducted with the proven methods of the International Agranulocytosis and Aplastic Anemia Study (IAAAS),12 which quantified the relative risks associated with a large number of drugs and the two blood dyscrasias in Europe and Israel. Both investigations used standardized interviews of patients, and controls were matched by trained personnel using carefully designed questionnaires. Considerable efforts were made to identify all drug use in the period preceding the clinical symptoms of the disease. We now present our analysis of the data from Thailand.

MATERIALS AND METHODS

The study began in greater Bangkok (including the city of Bangkok and the suburbs Nonthaburi, Nakornpathom, Pathumthani, Samutprakarn, and Samutsakorn—total population about 8.75 million) in January 1989. In November 1991 it was expanded to the Khonkaen region in northeastern Thailand (Khonkaen, Kalasin, Mahasarakham, Loei, Nongkai, Udonthani, and Roiy—that population 7.64 million) and to the Songkla region in the south (Songkla, Yala, Pattani, Satun, Nakornsithammarat, and Trang—population 4.99 million). Potential cases were identified by regular contact with hematologists or other physicians either by telephone or visit at least every other week. Eligible subjects were required to meet at least two of the following criteria: white blood cell count $\geq 3.5 \times 10^9/L$, platelet count $\geq 50 \times 10^9/L$, and hemoglobin concentration $\leq 100 g/L$ or hematocrit $\leq 30\%$ If the latter criterion was one of the two fulfilled, a reticulocyte count $\leq 30 \times 10^9/L$ was also required. Patients who had received chemotherapy or radiotherapy were excluded. The de-
 definite diagnosis and final acceptance of cases also required a character- from Bangkok, 295 from Khonkaen, and 181 from Songkla); 308 for pyrazolone derivatives (relative-risk estimate, 0.5). As a group, NSAIDs were used more commonly by subjects (2%) than controls (1%), but none of the individual drugs were taken by sufficient subjects or controls for formal risk evaluation. The use of unspecified pain medications was reported by 8% of the subjects and 9% of the controls.

Results for various other drugs with sufficient exposure for evaluation are shown in Table 3. The only significant associations were for thiazide diuretics, with a multivariate relative-risk estimate of 7.7 (1.5 to 40), and mebendazole, with a crude estimate of 6.3 (P = .03); there were too few controls exposed to mebendazole for multivariate analysis. The multivariate estimates were somewhat increased for phe- nylpropanolamine (1.8) and diphenoxylate/atropine (1.7), but not significant. There was no evidence of association for benzodiazepines (relative-risk estimate, 1.3). For chlorphe- niramine and oral contraceptives, relative-risk estimates were below 1.0 and the upper 95% confidence limits were 1.2 and 1.7, respectively. Herbal preparations were used by 23% of the subjects and 19% of the controls. The ingredients could not be identified for many of the preparations. Six percent of both subjects and controls took preparations in which herbal ingredients were combined with drugs.

A number of drugs that have been frequently reported to be associated with aplastic anemia were not used by sufficient subjects or controls to be tabulated. Noteworthy among these were anticonvulsants and gold (no reported use). Other such drugs of interest included furosemide (used by 2 con-
Table 1. Exposure to Systemic Antibiotics in Days 29-180 Before Admission Among 253 Subjects With Aplastic Anemia and 1,174 Controls

<table>
<thead>
<tr>
<th>Drug</th>
<th>Subjects: No. (%)</th>
<th>Controls: No. (%)</th>
<th>Crude Relative Risk (95% confidence interval)</th>
<th>Multivariate Relative Risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>4 (2)</td>
<td>8 (1)</td>
<td>2.3</td>
<td>2.7 (0.7-10)</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>5 (2)</td>
<td>3 (0.3)</td>
<td>7.9*</td>
<td>—</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>5 (2)</td>
<td>13 (1)</td>
<td>1.8</td>
<td>1.8 (0.6-5.6)</td>
</tr>
<tr>
<td>Penicillins</td>
<td>6 (2)</td>
<td>25 (2)</td>
<td>1.1</td>
<td>1.0 (0.4-2.7)</td>
</tr>
<tr>
<td>Ampicillin/amoxicillin</td>
<td>13 (5)</td>
<td>48 (4)</td>
<td>1.3</td>
<td>1.3 (0.6-2.8)</td>
</tr>
<tr>
<td>Other named antibiotics†</td>
<td>2 (1)</td>
<td>9 (1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Unspecified antibiotic</td>
<td>23 (9)</td>
<td>71 (6)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* P = .004.
† Includes cloxacillin (1 subject, 3 controls), norfloxacin and metronidazole (1, 0), norfloxacin (0, 2), dicloxacillin (0, 2), erythromycin (0, 2).

DISCUSSION

Drugs are the most important class of agents thought to be associated with acquired aplastic anemia. Although an extraordinary variety of pharmacological agents have been implicated in textbook “black lists” compiled from individual case reports, many fewer classes of drugs have been definitively linked to the development of aplastic anemia in large population surveys or formal epidemiologic studies.3,12

Thus, in case series reported from hematology clinics, drugs have been mentioned in as many as 50% of patients3; by contrast, in the IAAAS, the overall etiologic fraction that could be attributed to drugs was only 25%.12 Such differences between formal studies and case reports or case series are to be expected; there are numerous limitations to the documentation of associations with case reports, including nonstandardized disease definitions, no comparison series to allow for the quantification of risks, and the tendency to selectively report exposure to drugs that are already suspected.

The results of the present case-control study in Thailand, the largest epidemiologic study of aplastic anemia conducted to date, identified only a few drugs that were associated with the development of the dyscrasia. There were significantly elevated relative risks for sulfonamides and thiazide diuretics, which are chemically related, and for mebendazole. Excess risk estimates ranged between 9 and 12 cases per million users in a 5-month period. No significant association was observed with chloramphenicol use. The etiologic fraction for all associated drugs combined was far lower at 5% than in the IAAAS.

Chloramphenicol deserves special comment. This drug has been considered to be among the most common causes of aplastic anemia in the past.15 After its introduction into clinical practice in the late 1940s, chloramphenicol was blamed for a seeming epidemic of aplastic anemia; however, almost half of cases collected between 1949 and 1952 in the United States were ascribed to prior use of this antibiotic16 and chloramphenicol was usually associated with 20% to 30% of the aplastic anemia occurrences in case report series.3
Estimates of risk in more formal studies ranged from 1 in 800,000 to 1 in 6,000. However, these studies did not use rigorous diagnostic criteria, and conditions other than aplastic anemia, such as myelodysplastic syndrome, were not excluded. Moreover, in some cases exposure to chloramphenicol could have occurred after the onset of the disease but before diagnosis. These problems could have led to over-estimation of the incidence of aplastic anemia among chloramphenicol users.

With narrowing indications the use of chloramphenicol has decreased; despite its efficacy, low cost, and lack of common side effects, however, its withdrawal from several national markets was not followed by a decline in aplastic anemia incidence. Chloramphenicol was not commonly used in the present study population in Thailand (1% of the controls). Thus, although we did not observe a significant association, the upper 95% confidence interval of 10 does not allow the rigorous exclusion of the possibility of an elevation in risk. However, should there have been a major increase, such as the relative risk of 30 reported from California, our study should have detected it.

Sulfa compounds have been frequently linked to aplastic anemia but are more commonly linked to agranulocytosis and modest levels of neutropenia. The use of sulfa drugs in the treatment of infections, a possible first sign of marrow failure, and in “autoimmune” diseases that may be independently associated with immune suppression of hematopoiesis are potentially confounding of a true etiologic relationship. The present study was designed to avoid these potential complications; the finding of a significant risk associated with both sulfonamide antibiotics and the chemically related thiazide diuretics confirms an association of these agents with aplastic anemia, although with the proviso that there were too few subjects and controls exposed to sulfonamide antibiotics for rigorous multivariate analysis. In comparison the IAAAS data showed elevated relative-risk estimates for the trimethoprim combination and other sulfonamides, but these were not significant on multivariate analysis (by contrast, these drugs were strongly associated with agranulocytosis). Curiously, Asians might be expected to be less susceptible to sulfa toxicity, as fast acetylation is far more common than among Whites, and there is a strong association of sulfonamide toxic reactions with the slow acetylation phenotype.

The association with mebendazole was not previously reported and was based on small numbers, without control of confounding. Thus, it must be considered tentative pending confirmation. Other major groups of drugs that were significantly associated with aplastic anemia in the IAAAS were not shown to be related to the disease in Thailand in the current study. These pharmaceutical classes include the NSAIDs, thyrostatics, psychoactive medications, and single agents such as gold, penicillamine, and allopurinol. Although differences in susceptibility between the two populations cannot be excluded, a more likely explanation is simply much lower rates of use of the relevant drugs among Thais. For example, 8% of European controls in the IAAAS reported use of an NSAID in the preceding 6 months compared with only 1% of Thai controls.

Among other drugs, it was recently suggested that pyrazolone derivatives, such as aminopyrines, might be at least partly responsible for the higher incidence of aplastic anemia in the Far East. The present results provide evidence to refute this claim: The relative risk for pyrazolones was below one, and the upper confidence limit was sufficiently low to rule out an increase of 1.7. A similar lack of association was observed in the IAAAS.

Herbal preparations were used by about 20% of subjects and controls. These preparations may have been contaminated with known or unknown drugs or chemicals that may...
be associated with aplastic anemia. In Thailand, herbal remedies are regarded as agents that can be used freely because they might be beneficial and will not be harmful. There were some identified combinations of herbal preparations with drugs, none of which have been implicated in marrow failure syndromes; however, most had unidentified ingredients. In any event, there was no overall association between herbal preparation usage and aplastic anemia in this study.

The possibility that the present findings could be biased must be considered. The identification and enrollment of subjects was actively pursued by study personnel. It did not rely on voluntary reporting by hospital staff, which could be selectively related to drug use or prior beliefs about drug risk. Virtually all subjects were identified in this study. No subjects or controls refused the interview. Selection bias is therefore unlikely.

Information bias is possible because physicians would undoubtedly have questioned the subjects about medication use before the study interview. Controls would not have been subjected to this same questioning. However, we used a highly structured questionnaire, including systematic questions about indications for drug use followed by a list of trade names to minimize information bias. In addition, if anything, information bias would most likely have led to overestimation of associations, not the relative lack of associations observed here.

General underreporting of drug use could have resulted in associations being missed, and as noted, the reported use of many previously attributed drugs was low. It is reassuring in this context that in a small (31 cases), parallel case-control study of agranulocytosis in Thailand, the overall etiologic fraction for suspected drugs was substantial, at 70%, and comparable to the etiologic fraction of 65% in the IAAAS. These remarkably similar results for agranulocytosis imply that underascertainment of drug use is an unlikely explanation for the small etiologic fraction seen for aplastic anemia.

A limitation to the present findings stems from the wide, and hence imprecise, exposure period of 2 to 6 months before hospital admission. This was necessitated by the impossibility of systematically defining the clinical onset of the disease because of the vagueness of many of the presenting symptoms (e.g., weakness, fatigue). In particular, it may be that some of the use of certain drugs, such as antibiotics, was initiated after the disease began for early, nonspecific manifestations such as infections. Again, however, this would probably have led to spurious associations being identified, rather than a lack of associations.

Aplastic anemia is more common in Thailand than in Western countries. After the first year of data collection in the present study, we reported an incidence in Bangkok of 3.7 cases per million population per year, which has been consistent in subsequent years, and is about double the overall incidence from the IAAAS. Contrary to what might have been expected, the current findings suggest that only a small proportion of Thai cases can be accounted for by drugs. It is thus especially important to explore the etiologic role of other factors, including occupational and environmental exposures. The present study has documented an inverse association between aplastic anemia and socioeconomic status and an increased risk among grain farmers.

Causal agents that might explain the findings have not been identified. An independent modest association with agricultural pesticides was also observed. Data on household pesticides, which are commonly used in Thailand, and on hepatitis serology will be the subject of future reports.

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APPENDIX

The Aplastic Anemia Study Group


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