Acute Thrombocytopenic Purpura in Relation to the Use of Drugs

By David W. Kaufman, Judith P. Kelly, Catherine B. Johannes, Allan Sandler, David Harmon, Paul D. Stolley, and Samuel Shapiro

The relation of acute thrombocytopenic purpura (TP) to the use of drugs was investigated in a case-control study conducted in eastern Massachusetts, Rhode Island, and the Philadelphia region: 62 cases over the age of 16 years with acute onset and with a rapid recovery were compared with 2,625 hospital controls. After control for confounding by multiple logistic regression, use of the following drugs in the week before the onset of symptoms was significantly associated: trimethoprim/sulfamethoxazole (relative risk [RR] estimate, 1.24), quinidine/quinine (101), dipyridamole (14), sulfonyleurases (4.8), and salicylates (2.8). The overall annual incidence of acute TP was estimated to be 18 cases per million population. The excess risks for the associated drugs were estimated to be 38 cases per million users of trimethoprim/sulfamethoxazole per week, 26 per million for quinidine/quinine, 3.9 per million for dipyridamole, 1.2 per million for sulfonyleuraxes, and 0.4 per million for salicylates. Associations with sulfonamides, quinidine/quinine, sulfonyleuraxes, and salicylates have been previously reported, but the present study has provided the first quantitative measures of the risk. The association with dipyridamole was unexpected. In general, despite large RRs, the incidence rates attributable to the drugs at issue (excess risks) were low, suggesting that TP is not an important consideration in the use of the various drugs.

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From the Slone Epidemiology Unit, School of Public Health, Boston University School of Medicine, Brookline, MA; the Department of Hematology/Oncology, Massachusetts General Hospital, Boston, MA; and the University of Maryland School of Medicine, Department of Epidemiology and Preventive Medicine, Baltimore, MD. Submitted July 21, 1992; accepted July 12, 1993.

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Address reprint requests to David W. Kaufman, ScD, Slone Epidemiology Unit, 1371 Beacon St, Brookline, MA 02146.

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mainder, 255 were confirmed as TP by the panel of hematologists. The day of clinical onset (index day) was determined for the interviewed cases without knowledge of drug use; it was deemed to be the day on which the first manifestation of bleeding occurred, as reported by the patient. The analyses were confined to the 143 confirmed cases for whom the index day could be determined and for whom the index day was not more than 21 days before admission (because detailed information concerning possible drug use covering a full week was not available for them). These cases were classified as acute, chronic, or indeterminate by a hematologist (D.H.). Because of the possibility that the etiology differs between acute and chronic TP, it would not have been appropriate to include both types of cases in a combined analysis, and the present report refers only to acute TP, defined as follows: (1) there was full and rapid recovery (platelets ≥150,000/μL) without corticosteroid therapy or splenectomy, 7 cases; (2) steroids were tapered rapidly and completely within 2 months as the platelets recovered fully, and there was no relapse off-therapy after at least 2 more months of follow-up, 32 cases; and (3) steroids were tapered rapidly, and there was an acute recovery pattern but with less precise documentation of the final date when treatment was discontinued (thus it was somewhat less certain that there were a full 2 months of normal counts off-therapy), 23 cases. The median age of the 62 acute cases was 49 years, 65% were women, and the median onset was 2 days before admission.

Of the remaining cases, 12 were classified as chronic and 69 as indeterminate (the recovery pattern could not be determined).

Controls. These were selected from other hospital patients of the same sex and age as the cases, according to a list of acceptable admission diagnoses judged to be independent of the antecedent use of the drugs of interest. Patients with diagnoses that could be related to drug use, such as thrombophlebitis (associated with oral contraceptive use), or with chronic conditions such as arthritis (associated with the use of nonsteroidal antiinflammatory drugs, gold, etc) were not eligible. The acceptable diagnoses included trauma, acute infections, and various other conditions, such as hernia. Controls were subject to the same exclusion criteria as the cases. Of the initially selected controls, 10% refused to participate. All interviewed controls, regardless of whether they were originally selected for comparison with acute or other cases of TP or with cases of urogenital problems or aplastic anemia, were considered potentially eligible for inclusion in the present analysis; there were 2,872 subjects.

As with the cases, an index day was specified for each control. For those controls with trauma, it was the day the injury occurred; for those with infections or other acute conditions, it was the day on which the first symptom occurred; and for those admitted electively for long-standing conditions (such as hernia), it was the day of admission. Also as with the cases, those whose index day was more than 21 days before admission were excluded (5) along with those for whom the index day could not be determined (242). This left 2,625 controls; 1,232 (47%) were admitted for trauma, 804 (31%) for acute infections, and 589 (22%) for other conditions. The median age was 42 years, and 49% were women. Table 1 shows rates of use of various drugs in the week before the index day among the 3 diagnostic categories, directly standardized to the overall age, sex, and geographic distribution of the controls. The rates varied for some drugs (eg, digoxin and dipyridamole), but there was no consistent pattern of variation according to diagnosis.

Data analysis. The relative risk (RR) was estimated for use of a drug in the week before the index day compared with no use during that period (use that ended more than 1 week before was not likely to be etiologically relevant). All drugs used by at least 5 cases were evaluated; these included quinidine/quinine, digoxin, beta-blockers, dipyridamole, furosemide, thiazide diuretics, sulfonyluracil, salicylates, and paracetamol.

To control confounding by the concomitant use of more than one possibly causal drug, as well as by other factors, multiple logistic regression was used. Apart from drugs, the following factors were included in the multivariate model: age (<30, 30 to 49, 50 to 69, and ≥70 years); sex; body mass index (weight/height* ≤20, >20 to 24, ≥25 to 29, and ≥30); geographic region (Massachusetts/Rhode Island and Philadelphia); alcohol consumption (none, <1 time a month, 1 to 3 times a month, 1 to 3 times a week, and ≥4 times a week); history of bruising, allergy, blood transfusions, acute hepatitis, infectious mononucleosis, blood diseases, joint diseases, or infections in the month before hospital admission; and occupational exposure to insecticides or solvents. All variables were dichotomous unless otherwise specified; no interaction terms were included in the model, and the confidence intervals (CI) were not adjusted for simultaneous inference. To further control confounding, individual drugs with fewer than 5 exposed cases were combined into heterogeneous groups for which terms were included in the model. These were antihypertensives other than beta-blockers, diuretics other than furosemide and thiazides, cardiovascular drugs other than quinidine or digoxin, nonsteroidal antiinflammatory drugs other than aspirin, a combined category of other drugs suspected of increasing the risk of TP, and a combined category of all other drugs not already specified.

For each drug significantly associated with TP, we also estimated the incidence attributable to exposure (excess risk). This was done in two steps. First, the overall incidence of acute TP was estimated indirectly as follows: we obtained from the Massachusetts Health Data Consortium (MHDC) the number of patients over the age of 16 who were discharged from Massachusetts hospitals during October 1987 through September 1988 with diagnoses of thrombocytopenia (ICD-9 codes 287.3 through 287.5) and resided in a defined region of the eastern part of the state; there were 4,699 such patients. We then conducted a survey in 25 hospitals that participated in the present study to determine the proportion of patients with the same ICD-9 diagnosis codes who met the study criteria as cases of TP. This proportion (13.5%) was applied to the MHDC total to yield the numerator, 148 cases. The denominator population was derived from 1980 US Census data for the defined area; it was 3.6 million. Thus, the annual incidence of all TP (acute, chronic, and indeterminate combined) was estimated to be 41 cases per million population; because 43% of the classified cases in this study were acute, the incidence of acute TP was estimated to be 18 per million. For Rhode Island and Philadelphia, the incidence was assumed to be the same as in Massachusetts.
Median durations of consecutive days of use among cases and controls are shown in Table 3 for all associated drugs. For quinidine and dipyridamole, the medians were strikingly lower among the cases (45 and 77 days, respectively), with a more than 15-fold difference compared with the controls. There was a lesser difference for sulfonamides (566 v 1,021 days), and the median among both cases and controls was relatively long. For sulfonamides and salicylates, the medians were relatively short among both cases and controls.

The highest excess risk estimate was for trimethoprim/sulfamethoxazole, 38 acute cases per million users per week. Also relatively high were the estimates for quinidine and quinine, 26 per million for users of either drug and 35 per million per week for users of quinidine specifically. Excess risks for the remaining associated drugs were estimated to be 3.9 per million for dipyridamole, 1.2 per million for sulfonamides, and 0.4 per million for salicylates.

**DISCUSSION**

The present results confirm previously reported associations between the use of quinidine/quinine, sulfonamides, sulfonamides, and salicylates and an increased risk of TP. Quantitative estimates of the magnitude of the risk of acute TP among persons aged at least 17 years have been provided for the first time, with relative increases ranging between twofold and 125-fold. However, in absolute terms, the risks were small. The highest excess risk estimate was 38 cases per million users in a week for trimethoprim/sulfamethoxazole; for quinidine/quinine, the estimate was 26, and for all other associated drugs, the estimates were less than 10 cases per million users. An unexpected association was observed for dipyridamole, with a 14-fold relative increase in risk. Again, however, the excess risk estimate was small, less than 5 cases per million users in a week. No association was observed with the use of thiazide diuretics. This is surprising, because there have been case reports of thiazide-induced TP, and this group of compounds is chemically related to sulfonamides.

It should be noted that some of the associated drugs are sometimes used for extended durations, and if the excess risk remains constant, it could eventually reach substantial levels. The short median duration of use of quinidine and dipyridamole observed among cases compared with controls suggests that, for these drugs, the risk may actually

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cases</th>
<th>Controls</th>
<th>Multivariate RR Estimate (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine/quinine</td>
<td>14</td>
<td>13</td>
<td>101 (31-324)</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>8</td>
<td>22</td>
<td>14 (3.5-54)</td>
</tr>
<tr>
<td>Beta-blockers†</td>
<td>10</td>
<td>190</td>
<td>1.3 (0.5-3.8)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>6</td>
<td>74</td>
<td>2.8 (0.8-10)</td>
</tr>
<tr>
<td>Thiazide†</td>
<td>6</td>
<td>194</td>
<td>0.4 (0.1-1.7)</td>
</tr>
<tr>
<td>Sulfonamides§</td>
<td>6</td>
<td>22</td>
<td>40 (10-162)</td>
</tr>
<tr>
<td>Sulfonylureas‖</td>
<td>5</td>
<td>51</td>
<td>4.8 (1.5-16)</td>
</tr>
<tr>
<td>Salicylates†</td>
<td>23</td>
<td>466</td>
<td>2.6 (1.3-5.0)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>10</td>
<td>454</td>
<td>0.7 (0.3-1.5)</td>
</tr>
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</table>

* Relative to no use during the week before the index day.
† Includes propranolol (4 cases, 52 controls); atenolol (4, 35); metoprolol (2, 40); timolol (0, 28); nadolol (0, 21); betaxolol (0, 10), and labetalol (0, 4).
‡ Includes hydrochlorothiazide (5 cases, 170 controls); methylcloethiazide (1, 10); chlorothiazide (0, 8); bendroflumethiazide (0, 2); trichloromethiazide (0, 2); hydroflumethiazide (0, 1); and metolozaine (0, 1).
§ Includes trimethoprim/sulfamethoxazole (6 cases, 12 controls); sulfasalazine (0, 6); sulfadiazine (0, 2); acetamide (0, 1); and sulfisoxazole (0, 1).
‖ Includes glyburide (2 cases, 21 controls); tolazamide (2, 9); glipizide (1, 6); chlorpropamide (0, 11); tolbutamide (0, 4); and acetohexamide (0, 1).
†† Includes aspirin (23 cases, 428 controls); subsalicylate bismuth (0, 15); aspirin + subsalicylate bismuth (0, 7); diflumestal (0, 3); aspirin + salicylamine (0, 2); magnesium choline trisalicylate (0, 2); salicylic acid (0, 2); salicylamide (0, 2); magnesium salicylate (0, 1); sodium salicylate (0, 1); salisalate (0, 1); sweet birch oil (0, 1); and aspirin + magnesium choline trisalicylate (0, 1).

The second step in the calculation of the excess risk attributable to each drug was to estimate incidence rates in the exposed and nonexposed populations; these were derived from the RR, the etiologic fraction, between twofold and 125-fold. However, in absolute terms, the risks were small. The highest excess risk estimate was for trimethoprim/sulfamethoxazole, 38 acute cases per million users per week. Also relatively high were the estimates for quinidine and quinine, 26 per million for users of either drug and 35 per million per week for users of quinidine specifically. Excess risks for the remaining associated drugs were estimated to be 3.9 per million for dipyridamole, 1.2 per million for sulfonamides, and 0.4 per million for salicylates.

**DISCUSSION**

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It should be noted that some of the associated drugs are sometimes used for extended durations, and if the excess risk remains constant, it could eventually reach substantial levels. The short median duration of use of quinidine and dipyridamole observed among cases compared with controls suggests that, for these drugs, the risk may actually
decline with increasing duration. For the remaining drugs, the durations were either relatively long (sulfonylureas) or relatively short (sulfonamides and salicylates) in both the cases and the controls.

Virtually all of that which is known about the drug etiology of TP has been derived from case reports and laboratory studies. Early experimental investigations established that an immune mechanism is involved. They showed the presence, at a time coinciding with the clinical thrombocytopenia, of drug-dependent, antiplatelet antibodies, which destroyed circulating platelets only in the presence of the drug in question.24,25 Such investigations have subsequently been used to confirm the etiology in patients with TP in whom a specific drug has been suspected on clinical grounds6 and to elucidate mechanisms.26 However, laboratory research has not established the full range of drugs that may cause TP, and it cannot provide estimates of the incidence of the disease in exposed populations.

There are numerous case reports implicating quinidine,6,8,30 quinine,6,8-10,31-33 sulfonamides,11-14,26 and sulfonylureas.2,3 Various other drugs (eg, heparin13,16,34 and gold salts13,35) have also been implicated; they were too uncommonly used in the present study to allow for estimation of the risk (in the case of heparin, because the study did not cover drug use in the hospital). Salicylates have also been implicated but only rarely.36 There are limitations to case reports because they are susceptible to bias and because the absence of accurate numerators and denominators makes it impossible to determine incidence.

One Swedish study attempted to estimate the incidence of TP based on case reports.8 Oral diuretics were the most commonly implicated, and the denominator was estimated from sales data; the estimated risk was 1 case per 15,000 users. The interpretability of this estimate is limited because no time interval was specified, the case definition was not rigorous (and included all types of TP), and no allowance was made for the concomitant use of other drugs.

The association with dipyridamole in this study was unexpected, and it must be independently confirmed in further investigations. If it should persist, it shows how an association may escape detection in the absence of formal epidemiologic evaluation. Dipyridamole is commonly used together with other agents known to cause TP, such as antiarrhythmics. The latter drugs would be more likely to be reported when there is concomitant exposure.

The possibility that the present findings could be biased must be considered. The identification and enrollment of cases was performed by study personnel and did not rely on voluntary reporting by hospital staff; which could well have been incomplete and selectively related to drug use or prior beliefs about drug risks. Nevertheless, it is possible that some cases escaped detection. In addition, some 34% of the identified cases were not enrolled; it is possible that they may have differed in terms of their drug use from the included cases. By contrast, only 10% of identified controls were not included. Selection would have had to be strongly and differentially related to drug use among the cases and controls to materially affect the large RRs that were observed for most of the associated drugs. However, the more modest associations (eg, with salicylates) could more plausibly have been affected by selection bias. A further restriction of the cases was to those classified as acute. This necessarily relied, to some extent, on clinical judgement; however, that judgement was made without knowledge of patients’ prior drug use and was, thus, free of selection bias.

Information bias is possible because medical personnel would undoubtedly have questioned the cases about medication use before the study interview. Controls would not have been subjected to the same prior questioning. Information bias was minimized through the use of a highly structured questionnaire, including systematic questions about indications for drug use followed by a list of trade names. To further maximize recall, subjects were interviewed as soon as possible after admission. The possibility of memory loss was also reduced for most associated drugs because they were taken for extended periods for serious illnesses. Information bias is more likely for salicylates, which are often casually used. With regard to confounding, numerous factors, particularly the concomitant use of other drugs, were taken into account. Nevertheless, it remains possible that there was confounding by unidentified factors.

In the present study the excess risk estimates provide a measure of the relevance of the associations in both individual and public health terms. They were calculated using the overall incidence of all TP (acute, chronic, and indeterminate), which was estimated to be 41 per million per year in those aged at least 17 years. This estimate is similar to the few other published figures, all from Scandinavia (55 to 59 per million for all ages).14,37 We then calculated the incidence of acute TP by simple proportion. However, the resulting estimate of 18 per million was almost certainly too low, because the speed of recovery could not be determined for 48 percent of the classified cases, some of which were almost certainly acute. Hence, the excess risks presented here are minimum estimates. If the extreme assumption is made that all indeterminate cases were in fact acute, the incidence would be 38 per million; thus, the excess risks would be, at most, about twice as high as those reported here.

We have not evaluated the drug-related risk of chronic TP because there were insufficient cases. Our study was also restricted to cases that were admitted to hospital with evidence of bleeding, and the results may, therefore, not be generalizable to less severe TP.

In summary, this study has confirmed several associations between drugs and acute TP, and it has provided quantitative estimates of the risk. The drug most strongly associated was trimethoprim/sulfamethoxazole. However, even for this compound, the excess risk was relatively low, 38 cases per million users per week. An unexpected finding was an increased risk among users of dipyridamole. The excess risk was low, and the association remains to be confirmed.

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REFERENCES


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