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, 124), quinidine/quinine (101), dipyridamole (14), sulfonylureas (4.8), and salicylates (2.6). 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 sulfonylureas, and 0.4 per million for salicylates. Associations with sulfonamides, quinidine/quinine, sulfonylureas, 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.

THROMBOCYTOPENIC purpura (TP) can occur in association with systemic diseases, such as collagen disorders, or with primary bone marrow disorders, such as leukemia,[1,2] and it is a well-recognized complication of cancer chemotherapy.[1] It can also complicate viral infections.[1] Among the remaining so-called "idiopathic" cases, drugs are thought to play a prominent etiologic role, often as a consequence of immune-mediated platelet destruction.[3-6] Perhaps the best known association is with quinidine and related compounds such as quinine;[6-10] other commonly identified drugs include sulfonamides,[3,11-13] oral diuretics,[6,14] heparin,[3,15,16] and gold salts.[3,17] What is known about the drug etiology has been derived almost entirely from case reports and laboratory-based studies. There is only one study with quantitative estimates of the risk among users of specific compounds,[6] but the case definitions and estimates of the numerators and denominators were unsatisfactory. From 1983 to 1991, we conducted a case-control study in the northeastern United States of three blood dyscrasias: agranulocytosis, aplastic anemia, and TP. We report here findings for acute TP.

MATERIALS AND METHODS

Data were collected in eastern Massachusetts and Rhode Island from February 1983 to November 1991, and in the Philadelphia region from January 1986 to February 1988. Cases of TP were identified by contacting relevant personnel in hospitals in the study regions (55 in Massachusetts/Rhode Island and 36 in Philadelphia) either by telephone or in person, at least every other week. The diagnoses were subsequently confirmed by a panel of hematologists (A.S. and D.H.), who had no knowledge of patients' drug use. Controls were selected from other patients admitted to the same hospitals.

All subjects were interviewed by trained nurses. The information obtained included demographic data, relevant medical history, and limited data on exposure to radiation, chemicals, and insecticides. Detailed histories of drug use were elicited by asking about use for a list of indications followed by a list of commonly used generic and trade names of drugs of particular interest. Drug histories for the 4 weeks immediately preceding admission were recorded week by week; information for earlier exposure was less detailed.

The course of the illness to the time of admission was also recorded. In addition to the information obtained by interview, relevant data were abstracted from the medical records. For cases, all blood counts were recorded, and smears, bone marrow (BM) aspirates, and biopsy sections were obtained whenever possible to confirm the diagnosis.

Cases. Patients eligible for enrollment as cases were over the age of 16 years and were admitted to a hospital with petechiae, bleeding from gums, easy bruising, or other bleeding, and with platelets ≤30,000/μL, white blood cell count (WBC) ≥3,500/μL, hematocrit ≥30%, and hemoglobin (HgB) ≥10 G/100 mL (lower values for hematocrit and HgB were acceptable if they could be explained by other conditions, or by bleeding due to thrombocytopenia). Younger patients were not included because of the difficulty of excluding viral etiologies.[18] If blood counts did not return to normal levels, a BM biopsy was required, and the diagnosis was based on the presence of thrombocytopenia with normal or increased megakaryocytes in the BM. Patients were not eligible if they were undergoing chemotherapy, immunotherapy, or radiotherapy, or if they had any of the following conditions: splenomegaly, Felty's syndrome, disseminated intravascular coagulopathy, human immunodeficiency virus-positivity or acute immunodeficiency syndrome, systemic lupus erythematosus, infectious mononucleosis, malignant blood disease, megaloblastic anemia, renal failure, cirrhosis, benign or malignant granulomatous disease, or any other disease that could be associated with an increased risk of TP. Cases were observed for up to 6 months to determine the pattern of recovery.

Of the 450 initially identified possible cases, 8% were not approached for interview because they could not be located, 8% because they were identified too long after admission to be included, and 10% for a variety of other reasons (eg, death or patient did not speak English). A further 10% refused to participate. Of the re-

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.

Supported by Grant No. R01 HL31768 from the National Heart, Lung, and Blood Institute, and by Ciba-Geigy, Ltd. The Slone Epidemiology Unit has also received general support during the course of the study from Merrell Dow Pharmaceuticals and Hoffmann-La Roche, Inc.

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

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" *in accordance with 18 U.S.C. section 1734 solely to indicate this fact.*

0006-4971/93/8209-0020$3.00/0

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 $\geq$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 agranulocytosis 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, sulfonamides, sulfonylureas, salicylates, and paracetamol.

Table 1. Drug Use in the Week Before the Index Day Among 2,625 Controls According to Diagnosis

	Trauma (1,232)		Infection (804)		Other (589)	
Drug	No.	%*	No.	%*	No.	%*
Quinidine/quinine	4	0.3	4	0.7	5	0.7
Digoxin	26	1.9	24	3.4	23	4.6
Beta-blockers	98	7.3	47	7.0	45	7.9
Dipyridamole	16	1.4	3	0.4	3	0.5
Furosemide	32	2.5	25	3.5	17	3.4
Thiazides	120	8.4	42	6.7	32	6.4
Sulfonamides	11	0.9	6	0.8	5	0.9
Sulfonylureas	20	1.5	19	2.8	12	2.4
Salicylates	218	18	149	19	99	16
Paracetamol	190	16	155	18	109	19

* Adjusted to the overall distribution of the controls according to age, sex, and geography.

To control confounding by the concomitant use of more than one possibly causal drug, as well as by other factors, multiple logistic regression[19] was used. Apart from drugs, the following factors were included in the multivariate model: age (<30, 30 to 49, 50 to 69, and $\geq$70 years); sex; body mass index (weight/height^2 <20, 20 to 24, 25 to 29, and $\geq$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 $\geq$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 (3.15%) was applied to the MHDC total to yield the numerator, 148 cases. The denominator population was derived from 1980 US Census data[20] 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.

Table 2. Drug Use in the Week Before the Index Day Among 62 Cases of Acute TP and 2,625 Controls

Drug	Cases	Controls	Multivariate RR Estimate (95% CI)*
Quinidine/quinine	14	13	101 (31-324)
Digoxin	9	73	1.5 (0.4-5.5)
Beta-blockers†	10	190	1.3 (0.5-3.6)
Dipyridamole	8	22	14 (3.5-54)
Furosemide	6	74	2.8 (0.8-10)
Thiazides‡	6	194	0.4 (0.1-1.7)
Sulfonamides§	6	22	40 (10-162)
Sulfonylureas‖	5	51	4.8 (1.5-16)
Salicylates¶	23	466	2.6 (1.3-5.0)
Paracetamol	10	454	0.7 (0.3-1.5)

* 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 labetolol (0, 4).

‡ Includes hydrochlorothiazide (5 cases, 170 controls); methylclothiazide (1, 10); chlorothiazide (0, 8); bendroflumethiazide (0, 2); trichloromethiazide (0, 2); hydroflumethiazide (0, 1); and metolazone (0, 1).

§ Includes trimethoprim/sulfamethoxazole (6 cases, 12 controls); sulfasalazine (0, 6); sulfadiazine (0, 2); sulfacetamide (0, 1); and sulfisoxazole (0, 1).

‖ Includes glyburide (2 cases, 21 controls); tolazamide (2, 9); glipizide (1, 5); 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); diflunisal (0, 3); aspirin + salicylamide (0, 2); magnesium choline trisalicylate (0, 2); salicylic acid (0, 2); salicylamide (0, 2); magnesium salicylate (0, 1); sodium salicylate (0, 1); salsalate (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[21] (EF; a measure of the proportion of cases that are due to the exposure), and the overall weekly incidence (I) of acute TP, with the method used in the International Agranulocytosis and Aplastic Anemia Study.[22] The incidence in the nonexposed was calculated as $(1 - EF) \times (I)$, and the incidence in the exposed as $(RR) \times (1 - EF) \times (I)$. The difference between the two rates was the excess risk. Excess risk estimates were expressed as the number of acute cases per million persons exposed to the drug in a 1-week period.

RESULTS

The use of drugs among cases and controls is shown in Table 2, along with the multivariate RR estimates. The RR estimate for quinidine/quinine was 101 (95% CI, 31 to 324); of the users, 10 cases and 9 controls took quinidine specifically, with an RR estimate of 125 (33 to 474). Other significantly associated drugs were dipyridamole, with an RR estimate of 14 (3.5 to 54); sulfonamides, 40 (10 to 162); sulfonylureas, 4.8 (1.5 to 16); and salicylates, 2.6 (1.3 to 5.0). Among the sulfonamide users, all 6 cases and 12 of 22 controls took trimethoprim/sulfamethoxazole, with an RR estimate of 124 (19 to 821). No individual compound predominated among the users of sulfonylureas. Among the beta-blocker users, 4 cases and 52 controls took propranolol.

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 sulfonylureas (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 sulfonylureas, and 0.4 per million for salicylates.

DISCUSSION

The present results confirm previously reported associations[3,4,6,8,9,23] between the use of quinidine/quinine, sulfonamides, sulfonylureas, 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,[6] 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 3. Median Durations* of Use of Associated Drugs Among Cases of Acute TP and Controls

Drug	Cases		Controls	
	Median	No. of Users	Median	No. of Users
Quinidine	45	10	758	9
Dipyridamole	77	8	1,488	22
Sulfonamides	5	6	5	22
Sulfonylureas	566	5	1,021	51
Salicylates	26	23	3	466

*Consecutive days of use before the index day.

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 grounds[26] and to elucidate mechanisms.[7,27-29] 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,[6,8,9,30] quinine,[6,8-10,31-33] sulfonamides,[11-14,26] and sulfonylureas.[23] Various other drugs (eg, heparin[15,16,34] and gold salts[17,35]) 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.[3,36] 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.[6] 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).[5,14] 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.

ACKNOWLEDGMENT

The authors are indebted to the nurses, staff, physicians, and patients of the participating hospitals. We also wish to thank the coordinators of the study, Beverly McKean, James Hogan, Carol Wells, Lynne Schoaf, and Margaret Dunn; the interviewers, Patricia Benson, Joan Cole, Barbara Durney, Deborah Hickson-Dorsey, Laurie Kilcoyne, Tammy Martin, Marguerite Schaepe, Sally Somers, Cynthia Syverson-Mercer, and Sally Weedon; the research pharmacist, Mark Samuelson; John Farrell for data management; Dorothy Roach for word processing; and Dr Surapol Issaragrisil for his advice.

REFERENCES

1. Bithell TC: Thrombocytopenia, in Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN (eds): Wintrobe's Clinical Hematology (ed 9). Philadelphia, PA, Lea and Febiger, 1993, p 1325
2. Hedge UM, Zuiable A, Ball S, Roter BLT: The relative incidence of idiopathic and secondary autoimmune thrombocytopenia: A clinical and serological evaluation in 508 patients. Clin Lab Hematol 7:7, 1985
3. Moss RA: Drug-induced thrombocytopenia. Am J Hematol 9:439, 1980
4. Miescher PA, Miescher A: Immunologic drug-induced blood dyscrasias. Klin Wochenschr 56:1, 1978
5. Bottiger LE, Westerholm B: Thrombocytopenia. I. Incidence and aetiology. Acta Med Scand 191:535, 1972
6. Bottiger LE, Westerholm B: Thrombocytopenia. II. Drug-induced thrombocytopenia. Acta Med Scand 191:541, 1972
7. Christie DJ, Diaz-Arauzo H, Cook JM: Antibody-mediated platelet destruction by quinine, quinidine, and their metabolites. J Lab Clin Med 112:92, 1988
8. Danielson DA, Douglas SW, Herzog P, Jick H, Porter JB: Drug-induced blood disorders. JAMA 252:3257, 1984
9. Van der Weerdt CM: Thrombocytopenia due to quinidine or quinine. Report on a series of 28 patients. Vox Sang 12:265, 1967
10. Belkin GA: Cocktail purpura. An unusual case of quinine sensitivity. Ann Intern Med 66:583, 1967
11. Keisu M, Wilholm B-E, Palmblad J: Trimethoprim-sulphamethoxazole–associated blood dyscrasias. Ten years' experience of the Swedish spontaneous reporting system. J Intern Med 228:353, 1990
12. Dickson H: Trimethoprim-sulphamethoxazole and thrombocytopenia. Med J Aust 2:5, 1978
13. Heimpel H, Raghavachar A: Hematological side effects of cotrimoxazole. Infection 15:248, 1987 (suppl 5)
14. Bottiger LE, Bottiger B: Incidence and cause of aplastic anemia, hemolytic anemia, agranulocytosis and thrombocytopenia. Acta Med Scand 210:475, 1981
15. MacLean JA, Moscicki R, Bloch KJ: Adverse reactions to heparin. Ann Allergy 65:254, 1990
16. Majerus PW, Broze GJ, Miletich JP, Tollefsen DM: Anticoagulant, thrombolytic, and antiplatelet drugs, in Goodman GA, Rall TW, Nies AS, Taylor P (eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics (ed 8). New York, NY, Pergamon, 1990, p 1316
17. Adachi JD, Bensen WG, Kassam Y, Powers PJ, Bianchi FA, Cividino A, Kean WF, Rooney PJ, Craig GL, Buchanan WW, Tugwell PX, Gordon DA, Lucarelli A, Singl DP: Gold induced thrombocytopenia: Twelve cases and a review of the literature. Semin Arthritis Rheum 16:287, 1987
18. Shende A: Idiopathic thrombocytopenic purpura in children. Pediatr Ann 14:609, 1985
19. Schlesselman JJ: Case-Control Studies: Design, Conduct, Analysis. New York, NY, Oxford, 1982
20. Bureau of the Census: 1980 Census of Population: Volume 1: Characteristics of the Population. Washington, DC, US Department of Commerce, 1982, p 23
21. Miettinen OS: Proportion of disease caused or prevented by a given exposure, trait or intervention. Am J Epidemiol 99:325, 1974
22. Kaufman DW, Kelly JP, Levy M, Shapiro S: The Drug Etiology of Agranulocytosis and Aplastic Anemia: The International Agranulocytosis and Aplastic Anemia Study. New York, NY, Oxford, 1991
23. Israeli A, Matzner Y, Or R, Raz I: Glibenclamide causing thrombocytopenia and bleeding tendency: Case reports and a review of the literature. Klin Wochenschr 66:223, 1988
24. Grandjean LC: A case of purpura haemorrhagica after administration of quinine with specific thrombocytopenia demonstrated in vitro. Acta Med Scand 121:165, 1948 (suppl 213)
25. Ackroyd JF: The pathogenesis of thrombocytopenic purpura due to hypersensitivity to sedormid. Clin Sci 7:249, 1949
26. Hamilton HE, Sheets RF: Sulfisoxazole-induced thrombocytopenic purpura. JAMA 239:2586, 1978
27. Kelton JG, Meltzer D, Moore J, Giles AR, Wilson WE, Barr R, Hirsh J, Neame PB, Powers PJ, Walker I, Bianchi F, Carter CJ: Drug-induced thrombocytopenia is associated with increased binding of IgG to platelets both in vivo and in vitro. Blood 58:524, 1981
28. Peterson BH, Heim MC, White JF: Experimental drug-induced immune thrombocytopenia in monkeys. Diag Clin Immunol 5:349, 1988
29. Connellan JM, Deacon S, Thurlow PJ: Changes in platelet function and reactivity induced by quinine in relation to quinine (drug) induced immune thrombocytopenia. Thromb Res 61:501, 1991
30. Reid DM, Shulman R: Drug purpura due to surreptitious quinidine intake. Ann Intern Med 108:206, 1988
31. Powell SE, O'Brien SJ, Barnes R, Warren RF, Wickiewicz TL: Quinine-induced thrombocytopenia. A case report. J Bone Joint Surg 7:1097, 1988
32. Boyd IW: Nocturnal cramps, quinine, and thrombocytopenia. Arch Intern Med 151:1021, 1991 (letter)
33. Freiman JP: Fatal quinine-induced thrombocytopenia. Ann Intern Med 112:308, 1990
34. Eichinger S, Kyrle PA, Brenner B, Wagner B, Kapiotis S, Lechner K, Korninger HC: Thrombocytopenia associated with low-molecular-weight heparin. Lancet 337:1425, 1991
35. Cicuttini FM, Wiley JS, Fraser KJ: Immune thrombocytopenia in association with oral gold treatment. Arthritis Rheum 31:299, 1988
36. Scheinberg IH: Thrombocytopenic reaction to aspirin and acetaminophen. N Engl J Med 300:678, 1979 (letter)