

TEMPORAL ASPECTS OF HEPARIN-INDUCED THROMBOCYTOPENIA

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ABSTRACT

Background Heparin-induced thrombocytopenia is a relatively common antibody-mediated drug reaction. We studied the temporal relation between previous or current heparin therapy and the onset of heparin-induced thrombocytopenia.

Methods We examined the time between the start of heparin therapy and the onset of thrombocytopenia in 243 patients with serologically confirmed heparin-induced thrombocytopenia. We also investigated the persistence of circulating heparin-dependent antibodies by performing a platelet serotonin-release assay and an assay for antibodies against platelet factor 4. The outcome in seven patients who had previously had an episode of heparin-induced thrombocytopenia and were later treated again with heparin was also examined.

Results A fall in the platelet count beginning four or more days after the start of heparin therapy occurred in 170 of the 243 patients (70 percent); in these patients, a history of previous heparin treatment did not influence the timing of the onset of thrombocytopenia. In the remaining 73 patients (30 percent), the onset of thrombocytopenia was rapid (median time of onset, 10.5 hours after the start of heparin administration); all these patients had been treated with heparin within the previous 100 days. During recovery from thrombocytopenia, heparin-dependent antibodies in the serum fell to undetectable levels at a median of 50 to 85 days, depending on the assay performed. In the seven patients who were given heparin again after the disappearance of heparin-dependent antibodies, a new episode of heparin-induced thrombocytopenia did not occur.

Conclusions Heparin-induced thrombocytopenia can begin rapidly in patients who have received heparin within the previous 100 days. Heparin-dependent antibodies do not invariably reappear with subsequent heparin use. (N Engl J Med 2001;344:1286-92.)

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HEPARIN-INDUCED thrombocytopenia is a syndrome of antibody-mediated thrombocytopenia that paradoxically is often associated with thrombosis.¹⁻⁵ Most patients with this disorder produce IgG antibodies^{6,7} against complexes of platelet factor 4 and heparin.⁸⁻¹¹ Platelet factor 4, a small peptide stored within the alpha granules of platelets, binds to heparin and is released into the blood during treatment with heparin.¹² In vitro, IgG-platelet factor 4-heparin complexes can activate platelets,^{13,14} a finding that raises the possibil-

ity that platelet activation in vivo contributes to the thrombotic complications of heparin-induced thrombocytopenia.^{15,16}

Typically, heparin-induced thrombocytopenia begins with the appearance of thrombocytopenia about a week after the start of heparin therapy.^{4,5} Occasionally, a more rapid fall in the platelet count occurs if the patient has previously been treated with heparin.^{2,5,17-19} We report here a study of the timing of the onset of thrombocytopenia in relation to heparin treatment, including previous treatment with heparin, in 243 patients with serologically confirmed heparin-induced thrombocytopenia.

METHODS**Patients, Data Extraction, and Definitions**

We reviewed the medical and laboratory records of all the patients in Hamilton, Ontario, Canada, in whom a diagnosis of heparin-induced thrombocytopenia was serologically confirmed during the 15-year period ending June 30, 1998. We recorded the date and time that heparin treatment was started, as well as the route of administration and the dose administered; the date and time of the onset of thrombocytopenia; and whether or not heparin treatment had been given previously.

Heparin-induced thrombocytopenia was considered present if both of the following criteria were met: a decrease in the platelet count to less than 150,000 per cubic millimeter (with a minimal decrease of 30 percent of the platelet count) or a 50 percent or greater decrease in the platelet count; and a positive serologic test for heparin-induced thrombocytopenia.

We defined the first day of the course of heparin that resulted in heparin-induced thrombocytopenia as day 0. With that point as a reference, the time when the platelet count began to fall was identified (and rounded to the nearest day). We used this day in our analyses because it corresponds closely with the day on which heparin-dependent antibodies become detectable.⁴ In the case of 61 patients, daily platelet counts were not available, so we could not determine the day of onset of thrombocytopenia; for these patients, the range of possible days of onset (e.g., days 10 to 12) was determined, and the mean value was used for analysis.

We classified heparin-induced thrombocytopenia as having a typical onset if the fall in the platelet count began four or more days after the start of heparin therapy.^{4,17} Heparin-induced thrombocytopenia was classified as having a rapid onset if the fall in the platelet count began less than four days after heparin therapy was started. We defined previous use of heparin as "definite" if it could be documented in the patient's medical records, as "possible" if there had been at least one previous hospitalization for a surgical procedure or illness during which treatment with heparin would have been likely, and as "unlikely" if there had been no hospitalization or only a hospitalization during which heparin therapy would have

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been unlikely. Previous treatment with heparin was considered recent if heparin had been given during the 100 days preceding the first day of the current course of treatment.

Assays for Heparin-Dependent Antibodies

We used the platelet serotonin-release assay (hereafter referred to as the activation assay)^{20,21} to confirm the diagnosis of heparin-induced thrombocytopenia and to study changes in the levels of heparin-dependent antibodies in serum over time. We also used an assay that detects IgG, IgA, and IgM antibodies against platelet factor 4 bound to polyvinylsulfonate²² (hereafter referred to as the antigen assay; GTI-PF4, Genetic Testing Institute, Brookfield, Wis.).

Both the activation assay and the antigen assay were used to test blood samples that were obtained within 180 days after the initial positive serologic test. The date midway between the date of the last positive sample and the date of the first subsequent negative sample was arbitrarily defined as the date the test result became negative.

Use of Heparin in Patients with Previous Heparin-Induced Thrombocytopenia

We identified three patients with serologically confirmed heparin-induced thrombocytopenia who had inadvertently received a course of heparin that was started more than 100 days after an initial episode of heparin-induced thrombocytopenia. Platelet counts and the results of repeated heparin-dependent antibody tests (available in two of the three patients) were reviewed to determine whether heparin-induced thrombocytopenia had recurred. We also reviewed the records of four patients with a previous episode of serologically confirmed heparin-induced thrombocytopenia who later required anticoagulation for cardiac or vascular surgery, at a time when heparin-dependent antibodies were undetectable in their serum. After written informed consent was obtained, heparin was used during the surgery as an anticoagulant. Blood samples obtained daily until discharge were tested for heparin-dependent antibodies with use of both the activation assay and the antigen assay. In these four patients, heparin was used only during the surgical procedure.

Statistical Analysis

The distribution of the data corresponding to the day of onset of heparin-induced thrombocytopenia and to the nadir of the platelet count was skewed to the right. Accordingly, we analyzed log-transformed data with use of the t-test to compare the groups of patients. The groups were compared with respect to binary variables with use of Fisher's exact test.

The time to the disappearance of detectable heparin-dependent antibodies was analyzed by means of techniques used for survival analysis to allow for the varying duration of follow-up. The Kaplan-Meier method²³ was used to estimate the cumulative proportion of assays remaining positive over time; after log transformation, 95 percent confidence intervals were computed by means of Greenwood's method for calculating standard errors.²³ A sign test²⁴ was used to compare the activation and antigen assays with respect to the time to negative results in the patients whose serum was analyzed with both assays. This test was used because of the discrepancy in the number of patients for whom the results of the activation assay became negative more quickly than did the results of the antigen assay, as compared with the number of patients for whom the reverse was true.

RESULTS

We identified 243 patients with serologically confirmed heparin-induced thrombocytopenia. Of these patients, 170 (70 percent) had heparin-induced thrombocytopenia with a typical onset (i.e., the fall in the platelet count began four or more days after the start of heparin therapy). In the remaining 73 patients (30 percent), the onset was rapid (i.e., the decrease began less than four days after the start of heparin therapy).

Table 1 shows the characteristics of the patients with typical-onset heparin-induced thrombocytopenia and of those with rapid-onset heparin-induced thrombocytopenia. The two groups were similar with respect to sex, age, the severity of thrombocytopenia, the incidence of new thrombotic complications, the incidence of fatal hemorrhage, and 30-day mortality.

Of the 170 patients with typical-onset heparin-induced thrombocytopenia, 47 (28 percent) had definitely received previous treatment with heparin, 49 (29 percent) had possible previous treatment with heparin, and 74 (44 percent) were unlikely to have previously received heparin. Thrombocytopenia usually began 5 to 10 days after the start of heparin treatment (Fig. 1A) and did not begin more quickly in patients who had definitely received a previous course of heparin (Table 2).

Heparin-induced thrombocytopenia of rapid onset occurred soon after the initiation of heparin use (median, 10.5 hours after the start of therapy; interquartile range, 2.1 to 18.1 hours). All 73 patients in this category had definitely received heparin within the previous 100 days, whereas only 16 of the 47 patients with a typical onset (34 percent) had recently received heparin (P<0.001) (Fig. 1B). Blood samples obtained within two days before the start of the current course of heparin were available from eight of the patients with rapid-onset heparin-induced thrombocytopenia. Heparin-dependent antibodies were detected in all eight samples.

TABLE 1. CHARACTERISTICS OF THE PATIENTS ACCORDING TO THE TIME OF ONSET OF HEPARIN-INDUCED THROMBOCYTOPENIA.*

CHARACTERISTIC	TYPICAL-ONSET HEPARIN-INDUCED THROMBOCYTOPENIA (N=170)	RAPID-ONSET HEPARIN-INDUCED THROMBOCYTOPENIA (N=73)
Sex — no. of patients (%)		
Male	75 (44)	31 (42)
Female	95 (56)	42 (58)
Age — yr	65.9±12.6	67.0±10.2
Lowest platelet count — per mm ³		
Median	54,000	59,000
Interquartile range	33,000–82,000	34,000–92,000
New thrombosis during or after the course of heparin — no. of patients (%)	120 (71)	50 (68)
Fatal hemorrhage — no. of patients (%)†	2 (1)	1 (1)
Death within 30 days after onset of heparin-induced thrombocytopenia — no. of patients (%)	26 (15)	9 (12)

*Plus-minus values are means ±SD. There were no significant differences between groups with respect to any characteristic.

†Of the three patients who died of hemorrhage, two died during treatment with alternative anticoagulants for heparin-induced thrombocytopenia, and one died during continued treatment with heparin and warfarin because of a delay in the diagnosis of heparin-induced thrombocytopenia.

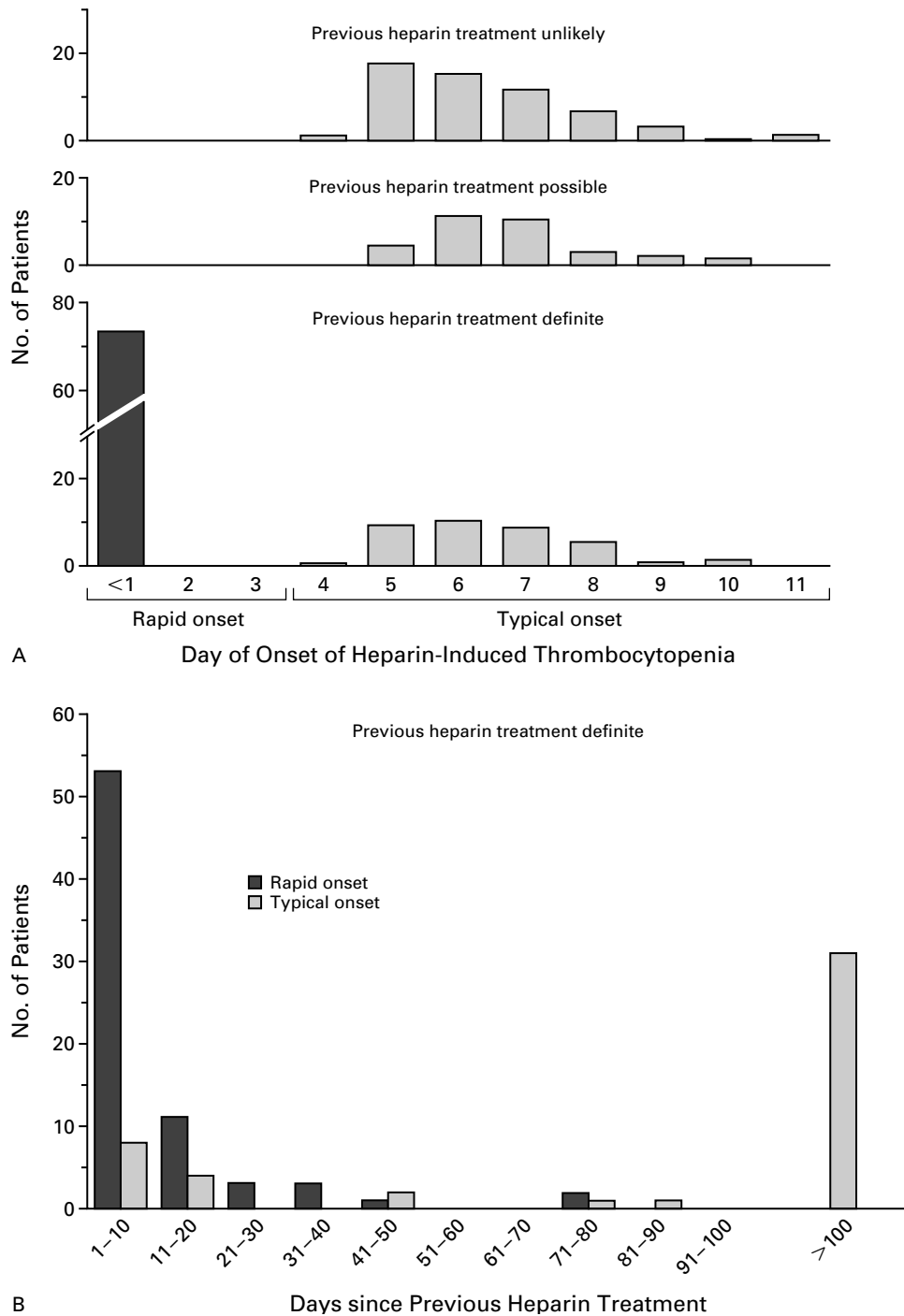


Figure 1. Temporal Patterns of Heparin-Induced Thrombocytopenia in Relation to Previous Treatment with Heparin. Panel A shows data for the 202 patients in whom the day of onset of thrombocytopenia could be determined within a three-day period. Within the subgroup of patients who definitely had previously undergone treatment with heparin, two temporal patterns of thrombocytopenia (rapid onset and typical onset) were observed (Panel A). Within this subgroup, an analysis of the time elapsed since the previous heparin treatment revealed that patients with rapid-onset heparin-induced thrombocytopenia were more likely to have received heparin within the past 100 days than patients with typical-onset heparin-induced thrombocytopenia (73 of 73 vs. 16 of 47, respectively; $P < 0.001$) (Panel B). None of the patients whose prior heparin treatment had occurred more than 100 days earlier had rapid-onset thrombocytopenia.

TABLE 2. DAY OF ONSET OF THROMBOCYTOPENIA IN RELATION TO PREVIOUS HEPARIN USE AMONG PATIENTS WITH TYPICAL-ONSET HEPARIN-INDUCED THROMBOCYTOPENIA.*

VARIABLE	PREVIOUS HEPARIN USE		
	DEFINITE	POSSIBLE	UNLIKELY
No. of patients	47	49	74
Onset of thrombocytopenia (days after start of heparin treatment)			
Median	6.5	7.0	6.0
Interquartile range	5.5–7.8	6.0–8.0	5.2–7.5

*Among the 170 patients with typical-onset heparin-induced thrombocytopenia, those who definitely had received previous treatment with heparin did not have a more rapid onset of thrombocytopenia than those who were unlikely to have been treated previously with heparin ($P=0.88$).

Figure 2 shows the proportion of patients over time in whom heparin-dependent antibodies remained detectable. The antigen assay tended to become negative more slowly than did the activation assay. The difference was statistically significant according to a comparison of the two curves by the sign test ($P=0.007$). The median time to a negative test according to the Kaplan–Meier analysis was 50 days (95 percent con-

fidence interval, 32 to 64) in the case of the activation assays and 85 days (95 percent confidence interval, 64 to 124) in the case of the antigen assays.

Five patients had a typical onset of thrombocytopenia in association with an initial course of heparin but a rapid onset when heparin was given again within the next 100 days. Figure 3 shows a representative case of this kind of dual pattern of heparin-induced thrombocytopenia.

Table 3 lists outcomes in seven patients with a history of serologically confirmed heparin-induced thrombocytopenia who received a subsequent course of heparin. Three of these patients were inadvertently given heparin for 8 to 19 days between 10 months and 13.5 years after an initial episode of heparin-induced thrombocytopenia. In none of these three patients did thrombocytopenia recur, and heparin-dependent antibodies could not be detected in the two patients whose serum was tested. Thrombocytopenia or thrombotic complications did not occur in any of the four patients who received an elective, brief course of heparin in preparation for cardiopulmonary-bypass surgery (two patients) or vascular surgery (two patients). Heparin-dependent antibodies were found in the serum of one of these four patients beginning on postoperative day 6.

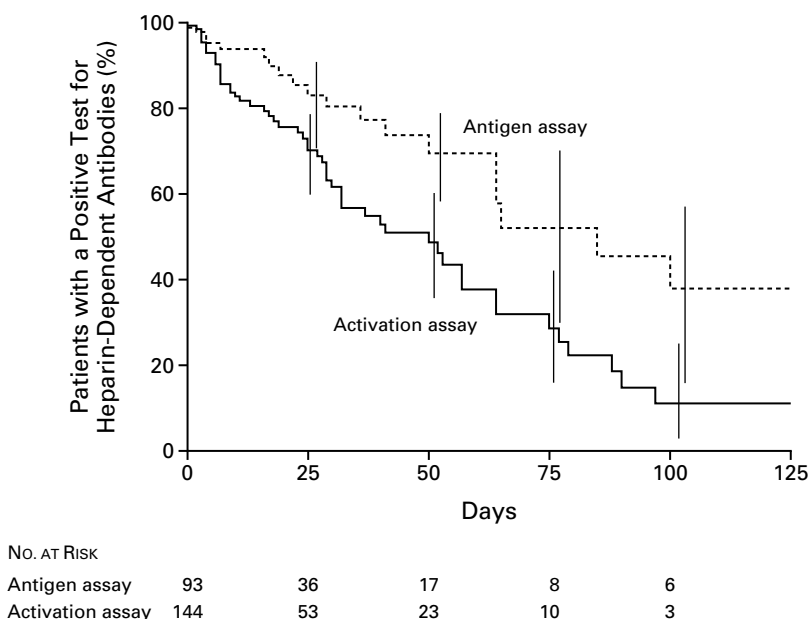


Figure 2. Kaplan–Meier Analysis of the Proportion of Patients with Heparin-Dependent Antibodies after an Episode of Heparin-Induced Thrombocytopenia.

The time (in days) to a negative test by the activation assay (144 patients) or the antigen assay (93 of the 144 patients) is shown. All 144 patients initially had positive tests for heparin-dependent antibodies and underwent subsequent testing within 180 days. The date the test result became negative was estimated to be the date midway between the date of the last positive test and the date of the first negative test. The antigen assay tended to become negative more slowly than did the activation assay ($P=0.007$ by the sign test). The bars indicate 95 percent confidence intervals.

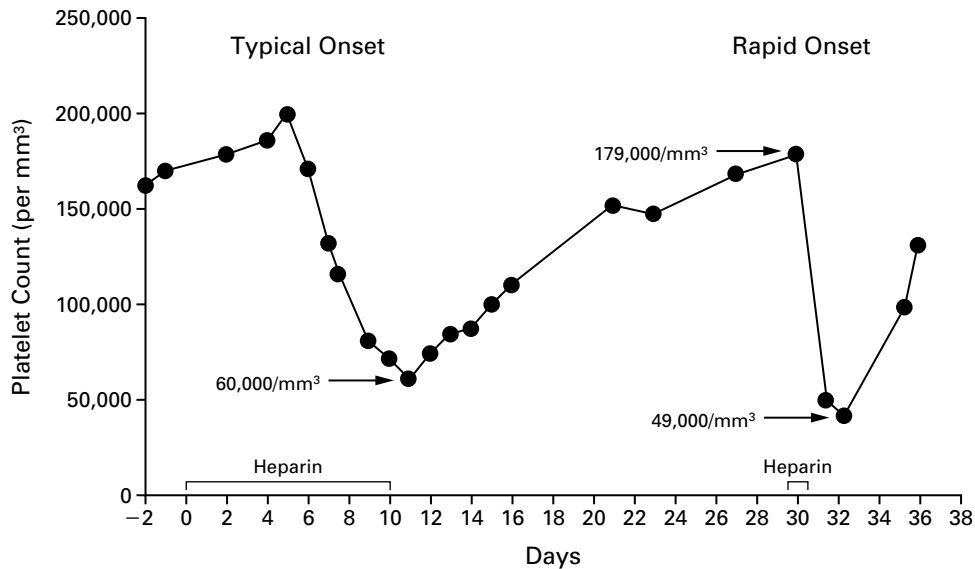


Figure 3. Representative Case of Typical-Onset Heparin-Induced Thrombocytopenia, Followed by a Rapid-Onset Episode. The patient initially received a 10-day course of heparin (10,000 U per day by subcutaneous injection). Typical-onset heparin-induced thrombocytopenia developed on day 6, according to a positive test for heparin-dependent antibodies. On day 30, the patient received heparin again (5000 U as a bolus injection followed by intravenous infusion), and rapid-onset thrombocytopenia developed.

DISCUSSION

In this study of serologically confirmed heparin-induced thrombocytopenia we examined the time of onset of the disorder in relation to previous treatment with heparin. We also investigated the persistence of heparin-dependent antibodies after an episode of heparin-induced thrombocytopenia. In 70 percent of the 243 patients we studied, the platelet count began to fall four or more days after the start of heparin therapy (typically between days 5 and 10). In the remaining 30 percent the thrombocytopenia began a median of 10.5 hours after the initiation of heparin therapy. All of the latter patients had recently been exposed to heparin, usually within the previous 3 weeks and invariably within the previous 100 days. In addition, we found that the presence of heparin-dependent antibodies in the blood was usually transient and did not always recur with subsequent heparin therapy.

The transience of heparin-dependent antibodies may explain these contrasting patterns of heparin-induced thrombocytopenia. Using an activation assay, Cines and colleagues²⁵ observed a rapid decline (over a period of a few weeks) in the levels of heparin-dependent antibodies in two patients. We confirmed such observations and also showed a rapid decline in the levels of antibodies against platelet factor 4 (Fig. 2). The median time to a negative activation assay was 50 days, and the median time to a negative antigen assay was

85 days. This difference is consistent with the relatively high sensitivity of the antigen assay as compared with the activation assay^{10,22} (although the activation assay has superior operating characteristics for diagnosis²⁶).

In contrast to heparin-dependent antibodies, antibodies induced by exposure to quinine, quinidine, or sulfonamides can persist for years after an episode of drug-dependent thrombocytopenia.^{27,28} In these cases, the onset of thrombocytopenia on reexposure to one of these drugs is abrupt, even many years after its previous use.²⁹⁻³¹

Our study suggests that patients in whom thrombocytopenia develops within hours after exposure to heparin already have circulating heparin-dependent antibodies that arose during a recent treatment with heparin. Several of our observations support this interpretation. First, rapid-onset thrombocytopenia occurred in the patients who had received heparin within 100 days before the current treatment, an interval consistent with the persistence of heparin-dependent antibodies. Second, each of the eight patients from whom blood samples were available before the initiation of the heparin treatment that caused rapid-onset thrombocytopenia had positive tests for heparin-dependent antibodies. Third, among the patients with rapid-onset heparin-induced thrombocytopenia, the interval between the initiation of heparin administra-

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TABLE 3. OUTCOME IN SEVEN PATIENTS WITH A HISTORY OF HEPARIN-INDUCED THROMBOCYTOPENIA WHO RECEIVED A SUBSEQUENT COURSE OF HEPARIN AFTER THE LOSS OF HEPARIN-DEPENDENT ANTIBODIES.*

PATIENT No.	AGE (YR)/SEX†	PREVIOUS EPISODE OF HEPARIN-INDUCED THROMBOCYTOPENIA		INTERVAL BEFORE SUBSEQUENT HEPARIN TREATMENT	RESULT OF SUBSEQUENT COURSE OF HEPARIN		
		DAY OF ONSET	LOWEST PLATELET COUNT per mm ³		COMPLICATIONS	CLINICAL EFFECTS	RESULTS OF ANTIBODY TESTING
1	54/M	6	53,000	None	10 mo	No decrease in platelet count or thrombosis during 8-day treatment	Not done
2	55/M	8	41,000	Deep venous thrombosis	13.5 yr	No decrease in platelet count or thrombosis during 11-day treatment	Negative activation assay on day 12
3	65/F	6	23,000	Limb-artery thrombosis	9.3 yr	No decrease in platelet count or thrombosis during 19-day treatment	Negative activation assay on day 19
4	60/M	7	65,000	Adrenal infarct	2.5 yr	No decrease in platelet count or thrombosis‡	All tests negative from day 0 to day 5; the antigen assay became positive on day 6; the activation assay became positive on day 8‡
5	48/M	6	34,000	None	2 mo	No decrease in platelet count or thrombosis§	All tests negative, day 0 to day 18, inclusive§
6	60/F	1	44,000¶	Digital ischemia	1.5 mo	No decrease in platelet count or thrombosis§	All tests negative, day 0 to day 9, inclusive§
7	65/M	1	193,000	Transient global amnesia	6 yr	No decrease in platelet count or thrombosis§	All tests negative, day 0 to day 9, inclusive§

*Patients 1, 2, and 3 inadvertently underwent a subsequent full course of heparin. The other four patients underwent a planned brief course of heparin (<2 hr) to permit cardiac surgery (in Patients 4 and 5) or vascular surgery (in Patients 6 and 7).

†The ages shown are those at the time of the initial episode of heparin-induced thrombocytopenia.

‡Despite seroconversion of heparin-dependent antibodies, the platelet count rose to 190,000 per cubic millimeter by day 8 and to a maximal level of 512,000 per cubic millimeter on day 20.

§There was no seroconversion of heparin-dependent antibodies, according to the antigen or activation assay; the platelet count increased during the postoperative period.

¶The platelet count fell rapidly, to 44,000 per cubic millimeter, during heparin use because of heparin-dependent antibodies that were already circulating as a result of heparin use 24 days earlier.

||The platelet count fell rapidly, to 193,000 per cubic millimeter, after administration of a bolus dose of heparin, because of heparin-dependent antibodies that were already circulating as a result of heparin use 11 days earlier.

tion and the fall in the platelet count was very short (median, 10.5 hours). This decrease seems too rapid to be a secondary (anamnestic) immune response, which generally would not begin until at least three days after reexposure to the antigen.³²

Seven patients with a history of serologically confirmed heparin-induced thrombocytopenia received heparin again after the disappearance of heparin-induced antibodies. Heparin-induced thrombocytopenia did not recur in any of these seven patients, and heparin-dependent antibodies were found in only one, six days after brief, intraoperative use of heparin. These findings are consistent with the description by Pötzsch and colleagues³³ of 10 patients with a previous episode of serologically confirmed heparin-induced thrombocytopenia who briefly received heparin again in preparation for heart surgery at a time when heparin-dependent antibodies were no longer detectable. In none of these 10 patients did heparin-dependent antibodies reappear (according to the results of the antigen assay). These observations suggest that in the ab-

sence of heparin-dependent antibodies, the risk of a recurrence of heparin-induced thrombocytopenia after another brief exposure to heparin is low.

We believe that the use of heparin in patients with a history of heparin-induced thrombocytopenia should be restricted to patients with a compelling indication for its use, such as cardiac or vascular surgery, and that it should be considered only if heparin-dependent antibodies cannot be detected by a sensitive assay. Because the risk of a recurrence of heparin-induced thrombocytopenia in such patients is unknown, it would be prudent to limit the use of heparin to the surgical procedure itself and to use an alternative anticoagulant for postoperative antithrombotic prophylaxis or therapy.

Supported by grants (B-3763 and T-4502, to Dr. Warkentin, and T-4404, to Dr. Kelton) from the Heart and Stroke Foundation of Ontario.

We are indebted to Robin S. Roberts for assistance with statistical analysis and to Jo-Ann I. Sheppard for technical assistance.

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