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Incidence of bleeding symptoms in 100 patients with inherited afibrinogenemia or hypofibrinogenemia

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To cite this article: Peyvandi F, Haertel S, Knaub S, Mannucci PM. Incidence of bleeding symptoms in 100 patients with inherited afibrinogenemia or hypofibrinogenemia. *J Thromb Haemost* 2006; **4**: 1634–7.

Congenital deficiency of plasma fibrinogen is a hereditary bleeding disorder with an autosomal recessive pattern of inheritance [1] and an estimated incidence of 1–2 per million in the general population [1]. Due to the rarity of the disorder, the available data on the incidence of bleeding episodes, prevalent clinical manifestations and treatment modalities are scarce [2–7]. Afibrinogenemia is sometimes associated with symptoms that are unusual in patients with defects of coagulation factors, such as thrombotic complications and miscarriages [8–12]. However, knowledge on the incidence and significance of these unusual symptoms is influenced by publication bias. Fresh frozen plasma, cryoprecipitate (cryo) and lyophilized fibrinogen concentrates are the main sources of fibrinogen for replacement therapy, but there is limited knowledge on optimal dosages and target plasma levels. Finally, there is little experience on the use of prophylactic replacement therapy. In order to fill these gaps of knowledge, we report here on the results of a questionnaire survey based upon the data obtained in 100 a- or hypofibrinogenemic patients.

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Received 27 March 2006, accepted 12 April 2006

In Europe and Canada the questionnaire was sent to 14 physicians known to treat patients with fibrinogen deficiency from their publications, from marketing information (use of the fibrinogen concentrate manufactured by ZLB Behring, Marburg, Germany) or from asking hemophilia centers. In the USA, the questionnaire was sent to 97 hemophilia centers from the national registry. This survey and its design were agreed upon by the Food and Drug Administration, because there is no fibrinogen concentrate in the USA and little is known about the incidence of bleeding and treatment practice in patients with fibrinogen deficiency. The general part of the questionnaire (available upon request) was meant to gather information on the number of patients under the care of each physician, the peak levels of plasma fibrinogen considered necessary for hemostasis, the laboratory assay used to measure plasma fibrinogen, and the types of products used for treatment. A part specific for each patient collected demographic variables and the protocol adopted for prophylactic or on-demand treatment of spontaneous, post-traumatic or surgical bleeding episodes categorized according to location. The incidence of bleeding episodes was calculated for each patient starting from the time period when she/he started to be followed up regularly at the treatment center. Analysis was done separately for patients on prophylaxis or on-demand treatment, and for each of the main replacement products.

Thirty-four physicians from 10 different countries [USA (11), Italy (9), Canada (3), Austria (2) Iran (2), Germany (2),

Spain (2), Switzerland (1), Turkey (1) and UK (1)] responded to the questionnaire because they followed at least one patient with a- or hypofibrinogenemia. Data from 100 patients (53 males and 47 females, median age 20.5 years, range 7 months to 75 years) were obtained. The most common method used for plasma fibrinogen determination was the Clauss fibrin polymerization assay. Patients' fibrinogen levels ranged from 0 to 116 mg dL^{-1}, with a median level of 6 mg dL^{-1}. Seventy-two patients had levels of < 10 mg dL^{-1}, 26 between 10 and 50 mg dL^{-1}, and one more than 50 mg dL^{-1} (1 missing). The only patient with relatively high fibrinogen value (116 mg dL^{-1}) was reported to be a bleeder and not to have dysfibrinogenemia (values of immunoreactive fibrinogen were similar to those of functional fibrinogen).

A total of 517 bleeding episodes (322 spontaneous, 100 trauma-related, 79 surgery-related and 16 'other' or 'unspecified') were reported. The mean annual incidence of bleeding episodes was 0.5 for patients on prophylactic replacement therapy (range 0–2.6) and 0.7 for patients on on-demand therapy (range 0–16.5). Although the incidence of bleeding appears to be low, there were 15 patients treated on demand who had an annual incidence equal or greater than one per year (Table 1). Of these 15 more frequent bleeders (13 had fibrinogen levels of < 10 mg dL^{-1}), some had been followed at the hemophilia centers for < 12 months, so their reported incidence of bleeding may be somewhat inaccurate (Table 1). Of the reported bleeding episodes, 40% were of mucosal type, 54% non-mucosal, and 6% unspecified. Among the 72 patients with severe fibrinogen deficiency (< 10 mg dL^{-1}), the most frequent hemorrhages were hemarthrosis (25%), muscle hematoma (17%), gastrointestinal (GI) bleeding (17%), epistaxis (10%) and menorrhagia (7%). Central nervous system (CNS) and intra-retroperitoneal bleeding were reported rarely (4% each). Two patients had a thrombotic episode (see below) and four of 30 women of childbearing age had a miscarriage. Among the 26 patients with milder fibrinogen deficiency (10 mg dL^{-1} or more) the most frequent hemorrhagic symptom was menorrhagia (in 46% of patients), whereas hemarthrosis (14%), muscle hematoma (12%), GI bleeding (5%) and epistaxis (6%) were less frequent than in patients with severe deficiency. There was no case of CNS and intra-retroperitoneal bleeding, thrombosis and miscarriage.

For life-threatening bleeding episodes such as CNS bleeding the target of treatment indicated by all the questionnaire respondents was to achieve postinfusion peaks of plasma fibrinogen of 150 mg dL^{-1} for a time period varying between 4 and 14 days. For less severe bleeding episodes, peaks between 50 and 70 mg dL^{-1} for 1–5 days (median 2 days) or of 100 mg dL^{-1} for shorter periods (1–2 days), were indicated. For major surgery, duration of treatment ranged between 4 and 14 days, with peaks of 150 mg dL^{-1}, but a higher level (200 mg dL^{-1} or more for 10–14 days) was adopted by USA physicians. For minor surgery the duration of treatment was between 1 and 7 days, with peaks of 100 mg dL^{-1}.

Seventy-six patients were treated on demand and 19 were on regular prophylactic treatment; five patients had been, at different times, on both on-demand and prophylactic treatment. For the patients treated on demand the bleeding episodes that most frequently required treatment were hemarthroses, hematomas and GI bleeding. Of the 74 surgical procedures 52 (70%) were minor and 15 (20%) major, seven (10%) procedures were not specified. The types of replacement material were fibrinogen concentrates (in 52% of the procedures), and cryo (in 42%). Fibrinogen concentrate and cryo were judged to be equally effective (excellent/good haemostatic efficacy > 90%).

Nineteen patients were on regular prophylaxis (17 with fibrinogen concentrates and two with cryo). Typical reasons for this mode of treatment delivery were previous CNS bleeding and frequent spontaneous bleeding. Daily doses of fibrinogen

Table 1 Details of patients treated on demand with at least one bleeding episode per year

Patients code	Plasma fibrinogen levels (mg dL^{-1})	Duration of follow-up (years)	Number of events*	Incidence per year	Treatment products
2001	< 10	8.0	11	1.4	Concentrate†
2002	< 10	0.3	3	9.0	Mixed
2003	< 10	6.9	15	2.1	Mixed
7001	< 10	0.8	2	2.6	Mixed
7002	< 10	5.0	18	3.6	Concentrate
12001	< 10	23.6	61	2.6	Mixed
15001	< 10	2.8	46	16.5	Mixed
18002	< 10	0.1	1	7.6	Mixed
19002	< 10	1.0	1	1.0	Cryoprecipitate
20001	< 10	0.5	1	2.1	Mixed
20002	32	0.5	1	1.8	Other
21001	< 10	0.2	1	4.2	Concentrate
21002	< 10	0.9	1	1.0	Concentrate
26001	< 10	3.4	15	4.4	Concentrate
33001	89	0.2	1	4.0	Cryoprecipitate

*If the first event occurred on the start date of on-demand treatment, it was not taken into account.
†Concentrate denotes commercial fibrinogen concentrates.

ranged from 18 to 120 mg kg^{-1}, with a median of 53 mg kg^{-1}. Most patients (59%) received weekly doses, the remaining patients were treated every 2 weeks or once a month. The two patients on cryo received weekly doses of 10 and 18 bags of cryo, respectively. Nine of the 19 patients treated prophylactically had no breakthrough bleeding, five of 19 suffered from 1–2 episodes per year, two from two to four episodes, and two patients experienced CNS bleeding during prophylaxis (on weekly treatment, one with cryo, one with fibrinogen). No information was provided on the fibrinogen levels attained at the time of these breakthrough bleeding episodes. Ischemic stroke occurred in a patient treated bi-weekly with 63 mg kg^{-1}, which was changed to the same dosage every 3 weeks but with this schedule a CNS bleeding occurred. With 42 mg kg^{-1} no event occurred in the last 3 years. For another patient on prophylaxis with cryo the dose was changed due to 'thrombosis', but the type of the thrombosis was not specified.

This survey is retrospective and based upon a questionnaire, and has therefore all the limits and biases of this type of analysis. According to previous reports [1–6], bleeding manifestations are highly heterogeneous in fibrinogen-deficient patients, ranging from mild to catastrophic in severity. This survey is the first that attempts to provide data on the incidence of bleeding episodes in these patients. The mean annual incidence in patients treated on-demand was 0.7 (0–16.5). These wide ranges confirm the heterogeneity of the disease: some patients do not bleed at all, others bleed more frequently, for example, 15 patients had more than one bleeding event per year (Table 1). A few patients among the frequent bleeders had been followed up for < 12 months, so that their reported incidence of bleeding may be inaccurate. However, even if the calculated incidences were doubled, the mean number of bleeding episodes per year would still be close to one per year, which is unexpectedly low. In hemophilia A and B, for instance, the average frequency of bleeding is no $<$ 10–15 episodes per year [13].

This survey also indicates that the therapeutic approaches of the participating physicians were variable. The peak fibrinogen level most often recommended for on-demand treatment of minor bleeding was approximately 100 mg dL^{-1}, but the target level for major episodes such as CNS bleeding was higher (150 mg dL^{-1}). Minor episodes, like epistaxis, were usually treated with target peaks of 50–70 mg dL^{-1}. Duration of treatment ranged from 1 to 2 weeks for major events, from 1 to 7 days for minor events. The main types of replacement material used (fibrinogen concentrates and cryo) seem to be equally effective, but fibrinogen concentrates have a better safety profile because they are virus-inactivated. The volume of infusion required for adequate hemostasis is much larger for cryo and high amounts of unnecessary proteins such as factor VIII and von Willebrand factor are infused with this blood product. Finally, more precise dosing can be accomplished with fibrinogen concentrates in order to achieve the desired target plasma levels, because their potency is known, in contrast to cryo.

There were only few data to compare bleeding events before and after the start of prophylaxis, so that it is difficult to assess the efficacy of this mode of treatment delivery. Surprisingly, the mean incidence of bleeding episodes in patients on prophylaxis was not much lower than that in patients treated on demand. A severe manifestation such as intracranial bleeding occurred in two patients on prophylaxis. Unfortunately, there were no data about the plasma levels of fibrinogen at the time of the events. As the pharmacokinetics of fibrinogen after replacement therapy show a large between-patients variability [14], adjustment of the prophylactic schedule to the pharmacokinetic data of the individual patient might be an option. Four of 30 women in the fertile age had a miscarriage, so that this complication appears frequently in this series as in others [3,5]. Two patients experienced thrombotic events under prophylactic treatment. Occurrence of thrombosis in patients with fibrinogen deficiency has been repeatedly described [3,5–12]. The prevailing hypothesis on the mechanism of this complication is that thrombin activity, which forms at a normal rate in patients with fibrinogen deficiency, is poorly neutralized because the thrombin-neutralizing activity of fibrin is lacking (so called antithrombin VI) [7,12]. This hypothesis, however, is not consistent with the observation that in this as well as in other reported cases, thrombosis developed not only in untreated patients but also in those receiving replacement therapy. More studies should be done to understand the mechanism of thrombosis but they are rendered difficult by the rarity of fibrinogen deficiency.

Acknowledgements

This study was jointly planned and written by the authors of the Hemophilia and Thrombosis Center and those of ZLB Behring that supported the study.

The following participants in the study are acknowledged: S. A-Acharya, USA; J. A. Aznar, Spain; S. Bernasconi, Italy; L. Boggio, USA; H. Britton, USA; D. Brown, USA; E. Broxon, USA; G. Cantin, Canada; G. Castaman, Italy; J. Ducore, USA; G. Growe, Canada; J. Hambleton, USA; K. Hoots, USA; V. Jiménez-Yuste, Spain; M. Karimi, Iran; K. Kavakli, Turkey; D. Keeling, UK; C. Kessler, USA; W. Kreuz, Germany; P. A. Kyrle, Austria; M. Lak, Iran; P. Leblond, Canada; B. Lewis; USA; L. J. Logan, USA; G. Mancuso, Italy; P. M. Mannucci, Italy; P. Marks, USA; E. O. Meili, Switzerland; M. Morfini, Italy; G. Piseddu, Italy; H. Pollmann, Germany; G. Rivard, Canada; M. Schiavoni, Italy; R. Schwarz, Austria; A. D. Shapiro, USA; R. Targhetta, Italy; F. Tarin, Spain; A. R. Thompson, USA; E. Williams, USA; E. Zanon, Italy.

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MedWatch: an important instrument for postlicensing surveillance

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To cite this article: Aledort LM. MedWatch: an important instrument for postlicensing surveillance. *J Thromb Haemost* 2006; **4**: 1637.

In 2004, the *Journal of Thrombosis and Haemostasis* published a controversial paper on thrombotic events occurring postlicensing for factor VIII inhibitor bypass activity (FEIBA) vs. recombinant factor VIIa (rFVIIa) [1]. In 2006, the *Journal of the American Medical Association (JAMA)* published a paper [2] that extends these previously published observations. The results of this article are in keeping with the prior report but now focus only on off-label use of rFVIIa to January 1, 2005. These earlier off-label thrombotic episodes from MedWatch were reported [3] and responded to [4]. Of the deaths reported in the *JAMA* paper, 72% were due to thromboembolic events. As in the initial report [1], cerebrovascular and myocardial events led the list. Of note is that, for on-label use in hemophilia, the reported rate of thrombosis for rFVIIa is equal to that of FEIBA. As in prior reports [1,3] few data are available regarding dose relationship to these adverse events.

These reports should put patients and treatment-givers on notice that when making therapeutic choices that are not made on evidence-based data, they can be accompanied by complications, most unwanted, and not inconsequential morbidity and mortality. Caveat emptor.

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Received 13 April 2006, accepted 19 April 2006