

A survey of factor prophylaxis in the Canadian haemophilia A population

P. BLANCHETTE,* ‡‡ G. RIVARD,† S. ISRAELS,‡ S. ROBINSON,§ K. ALI,¶ I. WALKER,** A. M. STAIN,†† and V. BLANCHETTE‡‡ ON BEHALF OF THE ASSOCIATION OF HEMOPHILIA CLINIC DIRECTORS OF CANADA (AHDC) AND THE CANADIAN ASSOCIATION OF NURSES IN HEMOPHILIA CARE

**Institute of Medical Sciences, University of Toronto, Toronto; †Hôpital Ste Justine, Montreal; ‡Health Sciences Center, Winnipeg; §Queen Elizabeth II Health Sciences Center, Halifax; ¶Comprehensive Care Hemophilia Program, Saskatoon; **McMaster University Medical Center, Hamilton; ††Department of Nursing, Hospital for Sick Children, Toronto; and ‡‡Division of Hematology/Oncology, Hospital for Sick Children and Division of Pediatrics, Toronto, Canada*

Summary. High-dose factor prophylaxis, defined as the infusion of 25–40 factor (F) VIII International Units (IU) kg bodyweight (bw)⁻¹ \geq \times 3 per week, started at age 1–2 years of life in boys with severe haemophilia A prevents the development of significant bleed-related arthropathy. However, programmes of prophylaxis are very expensive and venous access is a challenge. To ascertain patterns of prophylaxis in Canada during the period of a global shortage of recombinant FVIII concentrate a survey was conducted in 2001. The response rate was 83% and the survey identified 247 inhibitor-negative haemophilia A cases receiving prophylaxis, defined as the regular administration of FVIII at least once weekly, from 14 Canadian haemophilia treatment centres. The median age of the group identified was 13 years (range: 1–65) and 95% of cases had severe haemophilia A defined

by a circulating factor level of <1%. The median FVIII infusion dose was 26 (range: 16–33) IU kg⁻¹; infusions were administered \geq \times 3 per week in 67% of cases. High-dose factor prophylaxis was used most frequently in boys <5 years of age (23 of 28 cases, 82%) as compared with 56% (56 of 100), 66% (40 of 61) and 62% (36 of 58) of males ages 5–12, 13–18 and >18 years. Prophylaxis accounted for 50% of the annual Canadian FVIII consumption and was a major driving force in the 10% increase (=19.3 million FVIII IU) in the FVIII consumption in Canada in the 4-year period 1999–2003. Given the economic implications of increased use of prophylaxis prospective studies are warranted to better define optimal prophylaxis regimens in the haemophilia A population.

Keywords: haemophilia A, prophylaxis

Introduction

The haemophilias are sex-linked inherited coagulation disorders caused by deficiencies of factor (F) VIII (haemophilia A) or FIX (haemophilia B) [1]. They are the most frequent of the clinically severe inherited bleeding disorders. Traditionally, the haemophilias are classified as severe, moderate or mild based on circulating factor levels of 1% or less, 2–5% or above 5%.

The clinical hallmark of the severe haemophilias is recurrent bleeding into muscles and joints from an early age of life. The first joint bleed in boys with severe haemophilia generally occurs after the first 6 months of life, and by the second birthday [2]. The consequence of repeated bleeding into joints is the premature development of arthritis, termed haemophilic arthropathy. This unwanted complication is manifest by age 20 years in males with severe haemophilia who are inadequately treated, or who have limited or no access to FVIII or FIX replacement therapy. The development of arthropathy in boys with severe haemophilia can be effectively prevented by starting a programme of factor prophylaxis at age 1–2 years of life and continued until at least age 20 years of age and perhaps lifelong [3,4]. However, such programmes are demanding (because of the need

Correspondence: Dr Victor Blanchette, Division of Haematology and Oncology, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada.
Tel.: (416) 813-5852; fax: (416) 813-5852;
e-mail: victor.blanchette@sickkids.ca

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to assure venous access for factor infusions as often as every other day), and very expensive (because of the high cost of factor replacement therapy).

In this report, we describe the patterns of factor prophylaxis in persons with haemophilia resident in Canada in 2001. The data is based on responses to a questionnaire sent to Medical Directors of Canadian Comprehensive Care Hemophilia Treatment Centres that requested information about patterns of factor prophylaxis during a period of global shortage of a recombinant factor concentrate (Kogenate® FS; Bayer, Berkeley, CA, USA) that was widely used in Canada. The results of this survey provide important messages about prophylaxis, a highly effective but very expensive preventative strategy of haemophilia care.

Materials and methods

Patients

Patients eligible for this study were those with a diagnosis of FVIII deficiency registered and followed in a Canadian Comprehensive Care Hemophilia Treatment Centre in 2001, and who were receiving factor prophylaxis defined as the administration of FVIII at least once weekly with the aim of preventing bleeding.

Survey

A questionnaire was mailed to all Canadian Comprehensive Care Hemophilia Treatment Centres in May 2001 requesting the following information on persons with haemophilia receiving factor prophylaxis as defined above: factor levels; date of birth; body weight (bw); [kilogram, (kg)]; type(s) of factor concentrate infused; frequency of infusions; and usual infusion dose (FVIII Units).

Analysis

A chi-square analysis was used to compare the proportion of subjects receiving full-dose factor prophylaxis in different age groups.

Results

Responses were received from 14 haemophilia treatment centres: Vancouver, Edmonton, Calgary, Winnipeg, Ottawa, Kingston, Toronto (adult haemophilia program – St Michael's Hospital and paediatric haemophilia program – The Hospital for Sick Children), Hamilton, London, Montreal

(St Justine Hôpital), Quebec City, Halifax and Newfoundland. These centres collectively followed 83% of the 2180 haemophilia A cases and 81% of the severe haemophilia A cases entered into the Canadian Hemophilia Assessment and Resource Management Information System (CHARMS) Registry (I. Walker, 2004, personal communication).

A total of 266 patients with haemophilia A were identified as receiving prophylaxis defined as the infusion of FVIII at least once weekly with the aim of preventing bleeding. Ninety-three percent (247 of 266) were inhibitor-negative and 7% (19 of 266) inhibitor-positive. Ninety-five percentage (253 of 266) of cases had severe haemophilia, and 5% (13 of 266) mild/moderate haemophilia.

Inhibitor-negative cases

Two hundred and forty seven inhibitor-negative cases were identified to be receiving factor prophylaxis. The mean and median age of this subgroup of cases was 13 years (range: 1–65). Ninety-five percent of cases (235 of 247) had severe haemophilia A and 5% (12 of 247) mild/moderate haemophilia A (moderate – 11; mild – 1). The mean and median FVIII infusion doses used for prophylaxis in the 247 cases were 28 and 26 International Units (IU) kg⁻¹ respectively. The number of cases receiving a FVIII dose in the range of 25–40 FVIII IU kg⁻¹ was 38%.

The frequency of infusions varied from daily to once weekly (Table 1). In 67% of cases the frequency of infusion was $\geq \times 3$ per week. Data for this group of patients is provided in Table 2; the percentage of patients receiving full-dose prophylaxis (defined as factor infusions $\geq \times 3$ per week) in the age group ≤ 5 years was significantly greater than for those older than 5 years of age ($P = 0.02$, Table 2).

The annual FVIII use for prophylaxis in the 14 haemophilia treatment centres, based on the data reported in 2001 was 44 273 069 IU FVIII. The median infusion dose for each of the 14 centres

Table 1. Frequency of factor VIII infusion.

Frequency	Number of cases	%
Daily	11	4
Alternate days	33	13
$\times 3-4$ per week	2	1
$\times 3$ per week	110	45
$\times 2-3$ per week	9	4
$\times 2$ per week	55	22
Every third day	6	2
$\times 1$ per week	21	9
	247	100

Table 2. Full-dose prophylaxis (infusion ≥ 3 per week).

Age (year)	Number of cases	Number on full-dose prophylaxis (%)	Median infusion dose (factor VIII Units kg^{-1})
<5	28	23 (82)	42.5
5–12	100	56 (56)	29.8
13–18	61	40 (66)	24.4
>18	58	36 (62)	29.8

ranged from 16 to 33 IU kg^{-1} with 71% (10 of 14) of centres reporting a median infusion dose in the range of 25–40 IU kg^{-1} .

Inhibitor-positive cases

Nineteen inhibitor-positive cases were identified to be receiving factor prophylaxis. All 19 cases were receiving FVIII ≥ 3 per week; seven of the 19 cases were receiving daily infusions of FVIII. The annual FVIII used for this group was 14 466 100 IU.

Canadian factor VIII utilization

The FVIII utilization in Canada for the 4-year period 1999–2003 is illustrated in Fig. 1. The percent recombinant FVIII (rFVIII):plasma-derived (pd) FVIII in this 4-year period was 98%:2%. The 20% overall increase in FVIII use (97.6–116.9 million FVIII Units) was interrupted by a 13% decrease in FVIII use in 2001/2002 reflecting the global shortage of rFVIII (Kogenate® FS; Bayer, Berkley, CA, USA). Based on data reported by Canadian Comprehensive Care Hemophilia Centres in 2001, factor prophylaxis and immune tolerance therapy (ITT) for management of individuals with FVIII inhibitors accounted for 50% (44 273 069 Units) and 16%

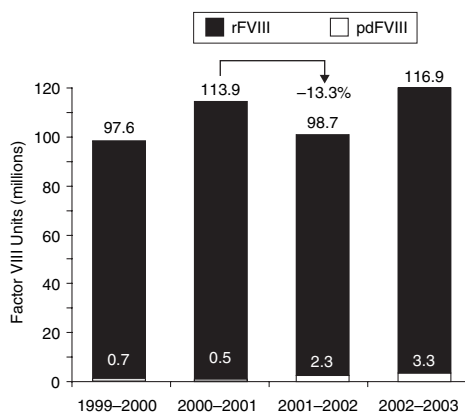


Fig. 1. Factor FVIII consumption (International Units) in the Canadian haemophilia A population during the period 1999–2003. rFVIII = recombinant FVIII; pdFVIII = plasma-derived FVIII.

(14 460 000 Units) respectively of the total FVIII (88 123 000 Units) used by the population of haemophilia A patients in Canada. Overall, therefore, these two programmes accounted for 67% of the FVIII used in Canada during 2001.

Discussion

The results of this survey, conducted during a time of global shortage of a rFVIII concentrate, are instructive. They indicate that in a country where individuals with haemophilia have free access to safe FVIII concentrates, programmes of factor prophylaxis and ITT account for the majority of FVIII used to support the haemophilia population. Relevant percentages for Canada in 2001 were 50% (for factor prophylaxis) and 16% (for ITT). How can these very expensive programmes in haemophilia be best justified? Our data, obtained during a period of an unexpected shortage of rFVIII concentrate, are relevant in this regard.

The pioneering studies of factor prophylaxis by Prof. Inga Marie Nilsson and her colleagues in Sweden, started in the late-1950s and reported in the early 1990s set the ‘gold standard’ for factor prophylaxis in young boys with severe haemophilia A [3,4]. These studies suggest that the administration of 25–40 IU of FVIII concentrate per kg of bw commenced at 1–2 years of life in boys with severe haemophilia and administered on alternate days (minimum $\times 3$ per week) or the same dose of FIX administered twice weekly to boys with severe haemophilia B, virtually eliminates joint bleeding and preserves a normal musculoskeletal status. The Swedish data suggests that primary prophylaxis should be continued until at least 20 years of age, and possibly longer [3,4]. Although very effective, full-dose factor prophylaxis (the Malmö protocol) has certain drawbacks: venous access is often difficult and necessitates the placement of a central venous access catheter (port-a-catheter) in many young boys with the attendant risk of infection and thrombosis [5–7]; the programme likely represents over-treatment of approximately 10% of boys with severe haemophilia who bleed relatively infrequently [8]; and the programme is very expensive. To address these barriers to primary prophylaxis in very young boys with severe haemophilia, Petrini advocates starting factor prophylaxis at 1–2 years of life with once weekly infusions (50 IU kg^{-1}) followed by escalation to the full-dose Malmö protocol over the following 18 months to 2 years [9]. In an ongoing Canadian primary prophylaxis study, boys with severe haemophilia are started on once weekly

treatment (50 IU kg⁻¹) with dose escalation based on the pattern of bleeding [10].

A key question is when should primary prophylaxis be started? Kreuz *et al.* recommend that primary prophylaxis be started at or before the first joint bleed using a FVIII dose of 30–50 IU kg⁻¹ every other day or three times per week in haemophilia A cases, and twice a week or every 3 days in haemophilia B cases [11]. By contrast, Liesner *et al.* wait until boys with severe haemophilia have three joint bleeds or two successive bleeds into the same joint before starting infusions of 15–25 IU kg⁻¹ of FVIII three times per week or FIX twice weekly in boys with severe haemophilia A and B [12]. Overall, there is consensus that, in order to achieve maximum benefit from primary prophylaxis, programmes should be started before the age of 3 years [13], and by the third joint bleed [14]. An important finding from the Swedish groups is that in boys with severe haemophilia <3 years of age primary prophylaxis can be started with once weekly replacement therapy without compromise of an excellent musculoskeletal status in later life. In this way, it becomes possible to avoid port-a-catheter placement in the majority of subjects, with avoidance of catheter-related complications such as infection and thrombosis.

Our survey indicates that, in 2001, approximately two-thirds of individuals with haemophilia on prophylaxis were receiving FVIII infusions at least three times weekly, i.e. full-dose prophylaxis. The frequency of this management strategy in boys <5 years of age was 82%, a number that was significantly higher than in older subjects. These statistics reflect an increasing awareness of the benefits of factor prophylaxis started at an early age in life. An interesting finding from our survey was the relatively wide variation in median dose of FVIII used for prophylaxis between haemophilia treatment centres in the same country; values ranged from 16 to 33 IU kg⁻¹ with 71% (10 of 14) of centres reporting a median dose in the range 25–40 IU kg⁻¹, i.e. the dose used in the Malmö prophylaxis protocol, while four clinics reported median values of 16, 17, 20 and 22 IU kg⁻¹. Our survey does not allow us to provide commentary on the relative outcomes of these different dose regimens. It is possible, however, that a lower dose prophylaxis regimen with escalation based on individual bleeding patterns is a more cost-efficient way to deliver primary prophylaxis than the fixed full-dose regimen reported by the Swedish group. The recent report by Fischer *et al.* from the van Creveldkliniek is supportive of this approach [15]. In the Netherlands, prophylaxis in young boys

with severe haemophilia A is administered at an intermediate dose range of 15–25 IU kg⁻¹ two to three times weekly for haemophilia A cases or 30–50 IU kg⁻¹ twice weekly for haemophilia B cases. Prophylaxis is aimed at preventing joint bleeds and doses are adjusted in the event of breakthrough bleeding without taking trough FVIII or FIX levels into account. The result is a significant saving in factor use when compared with the full-dose Swedish (Malmö) prophylactic regimen [15].

A key finding from the Canadian experience is that, faced with a potential shortage of rFVIII, the haemophilia community and the health care teams involved with care of persons with haemophilia adhered to a conservation approach that was both reasonable and effective. The approach involved measures such as deferral of elective surgery, use of plasma-derived rather than rFVIII concentrates for ITT, and reduction in the dose of factor concentrates used for prophylaxis when the infusion dose exceeded 30 IU kg⁻¹. These measures resulted in an annual decrease in FVIII consumption of 13.3% or 15.2 million Units of FVIII. The negative impact, if any, for this approach cannot be assessed from our survey and the annual FVIII use increased following the period of shortage to an unprecedented high. This increase in FVIII consumption is, in our opinion, expected and likely to continue as a result of the increased use of primary prophylaxis in young boys with severe haemophilia and of programmes of ITT in individuals with haemophilia and high-titre inhibitors. Given this trend, it is important that the haemophilia community and the health care teams caring for these group of patients critically examine the regimens of prophylaxis and ITT used in their clinics to ensure that over-treatment is identified and corrected. The regimens selected should be those reported to be effective and, wherever possible, patients should be enrolled in prospective clinical trials that are well designed and that will answer important clinical questions, e.g. the currently open randomized international study of high-dose vs. intermediate-dose FVIII for immune induction therapy in patients with haemophilia and high-titre inhibitors.

In conclusion, the successful Canadian response to the recent global FVIII concentrate shortage attests to the fact that significant changes in FVIII consumption can be achieved through a collaborative effort between patients and treaters. Based on this experience, it is our opinion that education and monitoring programmes that involve patients, families and health care professionals can be used to ensure that excessive use of factor concentrates for

primary prophylaxis and ITT programmes is minimized thereby facilitating availability of clotting factor concentrates and financial support for these very expensive but highly effective programmes.

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