The use of desmopressin in congenital factor XI deficiency: a systematic review

Massimo Franchini, Franco Manzato, Gian Luca Salvagno, Martina Montagnana, Giuseppe Lippi

Ann Hematol (2009) 88:931–935
DOI 10.1007/s00277-009-0792-9

REVIEW ARTICLE

The use of desmopressin in congenital factor XI deficiency: a systematic review

Massimo Franchini · Franco Manzato · Gian Luca Salvagno · Martina Montagnana · Giuseppe Lippi

Received: 23 March 2009 / Accepted: 6 July 2009 / Published online: 17 July 2009

Abstract Factor XI (FXI) deficiency is a rare inherited coagulation disorder characterized by infrequent spontaneous bleeding, but increased risk of hemorrhagic complications especially after trauma or surgery. Treatment options for FXI-deficient patients include virus-inactivated fresh frozen plasma, plasma-derived FXI concentrates, and activated recombinant FVII. Inhibitors of fibrinolysis, such as tranexamic acid, and desmopressin (DDAVP) have also been used in these patients, especially in mild cases. The current knowledge on the use of the latter agent in this congenital bleeding condition is systematically reviewed here. Although limited, the available literature data suggest the potential role of DDAVP for either treatment of bleeding episodes or the prevention of postoperative bleeding in patients with milder FXI defects. However, these findings need to be supported by further trials on large population of patients.

Keywords Factor XI deficiency · Desmopressin · Bleeding · Therapy

M. Franchini (✉)
Servizio di Immunoematologia e Medicina Trasfusionale,
Dipartimento di Patologia e Medicina di Laboratorio,
Azienda Ospedaliero-Universitaria di Parma,
Parma, Italy
e-mail: massimo.franchini@azosp.vr.it

F. Manzato
Laboratorio di Patologia Clinica, Ospedale "Carlo Poma",
Mantova, Italy

G. L. Salvagno · M. Montagnana · G. Lippi
Sezione di Chimica Clinica, Dipartimento di Scienze Biomediche
e Morfologiche, Università di Verona,
Verona, Italy

Introduction

Inherited factor XI (FXI) deficiency, originally named hemophilia C, is an uncommon autosomal recessive disorder, which is characterized by a more variable bleeding tendency than hemophilia A or B [1–6]. Indeed, patients with severe FXI deficiency (plasma FXI activity [FXI:C] <15 U/dL) do not usually bleed spontaneously but may suffer excessive injury- or surgery-related bleeding [5]. In patients with milder defects (plasma FXI:C 15–60 U/dL), bleeding is, however, difficult to predict because it correlates poorly with FXI levels, thus making the clinical management of such patients particularly challenging [6].

Replacement therapy with virally inactivated fresh frozen plasma (solvent–detergent-treated fresh frozen plasma (FFP)) or FXI concentrates is the mainstay of treatment of severe FXI deficiency, the latter one being, however, associated with an increased thrombotic risk [7–10]. Activated recombinant factor VII has also been successfully used in patients with alloantibodies against FXI [11–13]. Antifibrinolytic agents such as tranexamic acid have been useful for the management of mild cases, for minor surgical procedures (e.g., tooth extraction), in severe FXI deficiency, or as an adjunct in more severe cases or procedures [14]. These drugs have also been used successfully in the management of women with FXI deficiency and menorrhagia [15, 16]. Desmopressin (DDAVP), a synthetic analog of the natural antidiuretic hormone vasopressin traditionally used in a variety of congenital and acquired bleeding disorders [17–19], has also been recently administered in the prophylaxis of surgical bleeding in patients with partial symptomatic FXI deficiency [5]. The main advantages of this agent are safety, low cost, ease of use, and no risk of blood-borne

virus transmission. In this review, we briefly summarize the available scientific literature on the role of DDAVP in the management of patients with FXI deficiency.

Search methods

We firstly performed an electronic search on MEDLINE, EMBASE, SCOPUS, OVID, and the Cochrane Library without temporal limits and using different combinations of the following keywords: "congenital haemophilia C", "factor XI deficiency", "FXI deficiency", "desmopressin", and "DDAVP". Only full-text articles with at least an English abstract were considered. The bibliographic references of all retrieved studies and reviews were assessed for additional reports of clinical trials. Unpublished works were identified by searching the abstract books of the most important meetings on this topic of the last 15 years (International Society on Thrombosis and Haemostasis, American Society of Hematology, European Hematology Association, World Federation of Hemophilia, Italian Society of Hematology). Overall, we identified 76 published references through the electronic (last access: 28 February 2009) and hand searches. After reading the full text of the articles/abstracts, we excluded 59 references focusing on other topics and retrieved 17 potentially relevant references for further assessment. A further nine studies were excluded because they were reviews. Thus, we have considered for this systematic review eight case series (seven full text articles and one abstract). The flowchart of the inclusion of the studies is reported in Fig. 1. For statistical analysis, we used paired *t* tests. A P value <0.05 was considered significant.

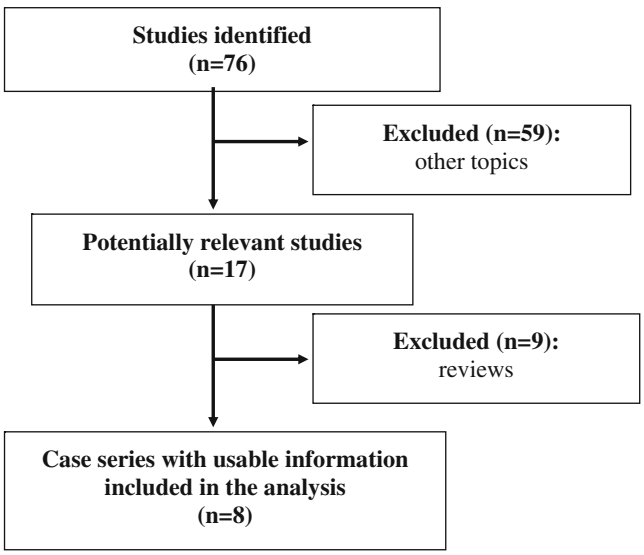

Fig. 1 Flowchart of the inclusion of the studies

Results

Only few case reports have been reported so far on the use of desmopressin for the treatment of bleeding or as surgical prophylaxis in patients with inherited deficiency of FXI [20–27]. Castaman and colleagues [21] reported about two patients with partial FXI deficiency and previous bleeding histories who received DDAVP infusions before carpal tunnel surgery and dental extraction. The authors showed an increase of both FXI activity (16 and 23 U/dL, respectively) and antigen (FXI:Ag) levels (24 and 25 U/dL, respectively) 60 min after a DDAVP test infusion. A single DDAVP infusion was sufficient (in the patient undergoing dental extraction, it was associated with oral tranexamic acid) to provide an efficient perioperative hemostasis. As the authors also documented an immediate (30 min) rise of FXI levels after DDAVP infusion, they hypothesized a drug-induced release of FXI from storage compartment rather than increased synthesis as a leading mechanism of action. Interestingly, the investigators found an increase of FXI activity and antigen levels also in two normal subjects and type 1 von Willebrand disease (VWD) patients. Their results were supported by a previous double-blind, placebo-controlled crossover study published by Agnelli and colleagues [28] in patients with chronic liver disease. The authors found a 22% increase of FXI:C levels after DDAVP infusion (0.5 μg/kg). However, these findings were not replicated by a more recent study by White and colleagues [29], who failed to found any significant increase of FXI:C and FXI:Ag levels in 33 individuals with VWD or mild hemophilia A. The lack of rise of FXI:C levels after DDAVP infusion was also observed by De Angelis and colleagues [20] in a patient with combined factor VIII (FVIII) and FXI deficiency. These contradictory results may reflect methodological differences among the various case reports. Alternatively, the response to DDAVP infusion could be genetically determined, thus depending on the type of mutation causing the FXI defect. It is also conceivable that the beneficial effect of DDAVP in such cases could depend on the pronounced increase in the levels of VWF and FVIII rather than to the slight rise of FXI.

The successful use of DDAVP for the prevention of bleeding in a patient with a mild FXI defect undergoing a neurosurgery operation was reported by Bauduer and colleagues [22]. The largest experience in this field has been described by our group [23]. Indeed, we reported six patients with a heterozygous defect FXI:C levels, ranging from 32 to 45 U/dL, undergoing various surgical procedures under hemostatic coverage with DDAVP and antifibrinolytic agents. A DDAVP test produced a slight increase of FXI:C levels (median 12 U/dL, range 9–14 U/dL) after subcutaneous injection. No bleeding complications or drug-related adverse effects were documented.

Table 1 Summary of the literature data on the use of desmopressin in congenital FXI deficiency

Author [reference]	Patient no.	Age	Sex	Bleeding tendency	Surgical prophylaxis or bleeding episode	FXI:C levels (U/dL)		No. of DDAVP[d] doses (days)	DDAVP dose	Concomitant therapy	Bleeding complications	Drug-related adverse events
						Basal	1h post-DDAVP					
De Angelis [20]	# 1[a]	19	M	Yes	Accidental wound	40	40	4 (4)	0.4 μg/kg i.v.	No	No	No
Castaman [21]	# 1	58	M	Yes	Dental extraction	34	58	1 (1)	0.3 μg/kg i.v.	Tranexamic acid	No	No
	# 2	50	F	Yes	Carpal tunnel surgery	35	60	1 (1)	0.3 μg/kg i.v.	No	No	No
Bauduer [22]	# 1	4	M	No	Hydrocele surgery	<1	<1	1 (1)	0.3 μg/kg i.v.	No	No	No
	# 2	43	M	No	Meningioma excision	45	57	2 (1)	0.4 μg/kg i.v.	No	No	No
Franchini [23]	# 1	56	F	Yes	Endoscopic cholecystectomy	32	46	5 (4)	0.3 μg/kg s.c.	Tranexamic acid	No	No
	# 2	65	M	Yes	Knee ligaments reconstruction	42	54	5 (5)	0.3 μg/kg s.c.	Tranexamic acid	No	No
	# 3	29	M	Yes	Knee ligaments reconstruction	40	52	5 (5)	0.3 μg/kg s.c.	Tranexamic acid	No	No
	# 4	67	F	Yes	Saphenectomy	45	54	5 (5)	0.3 μg/kg s.c.	Tranexamic acid	No	No
	# 5	6	M	Yes	Urethra reconstruction	36	50	5 (5)	0.3 μg/kg s.c.	Tranexamic acid	No	No
	# 6	16	M	Yes	Hydrocele surgery	34	45	5 (5)	0.3 μg/kg s.c.	Tranexamic acid	No	No
Garcia-Fernandez [24]	# 1	6	M	Yes	Amigdalectomy	43	49	5 (5)	0.3 μg/kg i.v.	Tranexamic acid	No	No
Heim [25]	# 1	9	F	Yes	Postoperative bleeding	8	31	1 (1)	0.3 μg/kg i.v.	No	No	No
Ruiz-Saez [26]	# 1[b]	NI	NI	NI	Surgical procedure	40	61	NI	NI	No	No	No
Franchini [27]	# 1	44	F	Yes	Total thyroidectomy	42	53	5 (5)	0.3 μg/kg s.c.	No	No	No
	# 2	56	F	Yes	Total thyroidectomy	40	55	5 (5)	0.3 μg/kg s.c.	No	No	No
Total	16	35.2[c]	9M/6F			34.5[c]	47.9[c]	3.7 (3.5)[c]				

FXI:C factor XI activity, *M* male, *F* female, *DDAVP* desmopressin, *NI* not indicated

[a] Combined FXI and factor VIII deficiency (29 U/dL)

[b] Combined FXI deficiency and von Willebrand disease

[c] Median values

[d] 0.3 μg/kg given intravenously diluted in 100 mL of isotonic saline and infused over 30 min or subcutaneously as bolus injection

Heim and colleagues [25] reported a 9-year-old girl with FXI deficiency (basal FXI:C 8%) with postoperative bleeding which was stopped after DDAVP infusion. Interestingly, DDAVP was associated with an increase in FXI:C up to 31%. No adverse events were recorded. We recently published two additional cases [27]: Subcutaneous injection of DDVP was effective in preventing postoperative bleeding in two patients with heterozygous FXI deficiency and multinodular goiter undergoing total thyroidectomy.

Ruiz-Saez and colleagues [26] reported the successful use of DDAVP in a patient with combined FXI deficiency and VWD. Finally, in a double-blind crossover study, Kadir and colleagues [30] randomized 39 women with menorrhagia and inherited bleeding disorders (two patients with FXI deficiency and three with combined VWD and FXI deficiency) to start 2 months' therapy with placebo or DDAVP spray (300 μg). No previous DDAVP response was assessed. No statistically significant difference (P=0.5) in pictorial blood assessment chart scores was observed in women receiving DDAVP than in those receiving placebo.

The case series reporting the use of DDAVP in FXI-deficient patients are summarized in Table 1. Overall, 16 cases have been reported so far in the literature. The ratio male/female was 1.5, while the median age was 35.2 years (range 4–67 years). Although DDAVP was used also in four children without adverse events, we advise particular caution when administering this agent in young patients due to its antidiuretic effects. Table 1 shows that in the majority of cases, DDAVP was used for the management of minor bleeding episodes or surgical procedures. However, in a few cases, this agent was used to prevent postoperative bleeding in major surgeries. The median increase of FXI:C levels following the administration of DDAVP was statistically significant (basal FXI:C levels 34.5 U/dL [range 1–4 U/dL] versus 47.9 U/dL [range 1–60 U/dL] 1 h after DDAVP administration, P<0.01). The median number of doses of DDAVP administered was 3.7 (range 1–5 doses) and the median number of days of therapy was 3.5 (rang 1–5 days). However, these ranges are too wide, so that definitive evidences about doses and duration of DDAVP therapy in this clinical setting are yet to be established. In half of the cases, antifibrinolytic agents were associated with DDAVP therapy. As antifibrinolytic agents have a confirmed efficacy alone in some surgical procedures [31], this concomitant therapy could mask the real efficacy of DDAVP in congenital FXI-deficient patients. In most cases (14/16, 87.5%), DDAVP was used as prophylaxis of surgical-related bleeding. The majority of these patients (12/14, 85.7%) had a positive family or personal bleeding history, which justified the prophylactic use of this agent. However, it is also possible that preventive treatment with DDAVP was unnecessary and that such patients would not have bled without treatment, as recently reported by Salomon and colleagues [32]. Indeed, the authors retrospectively analyzed bleeding manifestations related to vaginal and/or cesarean deliveries in 62 women with severe FXI deficiency and concluded that the use of FFP is not mandatory in such patients, but it can be reserved for cases with excessive bleeding. Nevertheless, DDAVP appeared to be safe and effective in the cases series reported as no bleeding complications or drug-related adverse events occurred.

Conclusions

Overall, the published literature data suggest the potential role of DDAVP for both management of bleeding episodes and surgical prophylaxis in patients with milder congenital FXI defects. However, as these findings are only supported by few case reports, proper trials on large patient population are needed to definitely assess the efficacy of this agent in the management of FXI deficiency. Further studies will also help to elucidate the biological effect of DDAVP in FXI deficiency since the literature results are conflicting in relation to the FXI levels achieved.

References

1. Smith JK (1996) Factor XI deficiency and its management. Haemophilia 2:128–136
2. Bolton-Maggs PHB (1995) Factor XI deficiency: a review. Haemophilia 1:217–221
3. Bolton-Maggs PHB, Perry DJ, Chalmers EA, Parapia LA, Wilde JT, Williams MD, Collins PW, Kitchen S, Dolan G, Mumford AD (2004) The rare coagulation disorders—review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. Haemophilia 10:593–628
4. Salomon O, Seligsohn U (2004) New observations on factor XI deficiency. Haemophilia 10(Suppl. 4):184–187
5. Franchini M, Veneri D, Lippi G (2006) Inherited factor XI deficiency: a concise review. Hematology 11:307–309
6. O'Connell NM (2003) Factor XI deficiency—from molecular genetics to clinical management. Blood Coagul Fibrinolysis 14 (Suppl. 1):S59–S64
7. Bolton-Maggs PHB (1998) The management of factor XI deficiency. Haemophilia 4:683–688
8. Bolton-Maggs PH, Colvin BT, Satchi BT, Lee CA, Lucas GS (1994) Thrombogenic potential of factor XI concentrate. Lancet 344:748–749
9. Mannucci PM, Bauer KA, Santagostino E, Faioni E, Barzegar S, Coppola R, Rosenberg RD (1994) Activation of the coagulation cascade after infusion of a factor XI concentrate in congenitally deficient patients. Blood 84:1314–1319
10. O'Connell NM (2004) Factor XI deficiency. Semin Hematol 41 (Suppl 1):76–81
11. Lawler P, White B, Pye S, Hermans C, Riddell A, Costello C, Brown S, Lee CA (2002) Successful use of recombinant factor VIIa in a patient with inhibitor secondary to severe factor XI deficiency. Haemophilia 8:145–148

12. Bern MM, Sahud M, Zhukov O, Qu K, Mitchell W Jr (2005) Treatment of factor XI inhibitor using recombinant activated factor VIIa. Haemophilia 11:20–25
13. Schulman S, Nemeth G (2006) An illustrative case and a review on the dosing of recombinant facto VIIa in congenital factor XI deficiency. Haemophilia 12:223–227
14. Berliner S, Horowitz I, Martinowitz U, Brenner B, Seligsohn U (1992) Dental surgery in patients with severe factor XI deficiency without plasma replacement. Blood Coagul Fibrinolysis 3:465–468
15. Kadir RA, Economides DL, Lee CA (1999) Factor XI deficiency in women. Am J Hematol 60:48–54
16. Rodeghiero F (2008) Management of menorrhagia in women with inherited bleeding disorders: general principles and use of desmopressin. Haemphilia 14(Suppl. 1):21–30
17. Cattaneo M (1997) Review of clinical experience of desmopressin in patients with congenital and acquired bleeding disorders. Eur J Anaesthesiol 14(Suppl. 14):10–18
18. Franchini M (2007) The use of desmopressin as a hemostatic agent: a concise review. Am J Hematol 82:731–735
19. Crescenzi G, Landoni G, Biondi-Zoccai G, Pappalardo F, Nuzzi M, Bignami E, Fochi O, Maj G, Calabrò MG, Ranucci M, Zangrillo A (2008) Desmopressin reduces transfusion needs after surgery. Anesthesiology 109:1063–1076
20. Angelis De, Orazi BM, Santarossa L, Molaro G (1990) Combined factor VIII and factor XI congenital deficiency: a case report. Haematologica 75:272–273
21. Castaman G, Ruggeri M, Rodeghiero F (1996) Clinical usefulness of desmopressin for prevention of surgical bleeding in patients with symptomatic heterozygous factor XI deficiency. Br J Hematol 94:168–170
22. Bauduer F, Bendriss P, Freyburger G, Ducout L, Marti B (1998) Use of desmopressin for prophylaxis of surgical bleeding in factor XI-deficient patients. Acta Haematol 99:52–53
23. Franchini M, de Gironcoli M, Lippi G, Manzato F, Aprili G, Gandini G (2000) Prophylactic use of desmopressin in surgery of six patients with symptomatic heterozygous factor XI deficiency. Haematologica 85:106–107
24. Garcia Fernandez JR, Sánchez Forte M, Diego Fernández P, López Berenguel F, Moreno Madrid F (2002) Familial study of factor XI deficiency. Presurgical prophylactic treatment with desmopressin plus antifibrinolytics. An Esp Pediatr 57:373–377
25. Heim MU, Lutze G, Aumann V, Schumacher J, Freigang B (2002) Postoperative haemorrhagia in a girl with congenital factor XI deficiency—successful treatment with desmopressin (DDAVP, Minirin). Klin Padiatr 214:128–131
26. Ruiz-Saez A, Arguello A, Boadas A, Feijoo R, Bosch N (2003) Factor XI deficiency in Mestizo Venezuelan population. J Thromb Haemost 1(Suppl. 1):P1205 abstract
27. Franchini M, Zugni C, Veneri D, Gandini G, Lippi G, Manzato F, Brazzarola P (2004) High prevalence of acquired von Willebrand's syndrome in patients with thyroid diseases undergoing thyroid surgery. Haematologica 89:1341–1346
28. Agnelli G, Parise P, Levi M, Cosmi B, Nenci GG (1995) Effects of desmopressin on hemostasis in patients with liver cirrhosis. Haemostasis 25:241–247
29. White B, Lawler P, Riddell A, Nitu-Whalley IC, Hermans C, Lee CA, Brown SA (2004) Response to desmopressin of factors XI, X and V in patients with factor VIII deficiency and von Willebrand disease. Br J Haematol 126:100–104
30. Kadir RA, Lee CA, Sabin CA, Pollard D, Economides DL (2002) DDAVP nasal spray for treatment of menorrhagia in women with inherited bleeding disorders: a randomized placebo-controlled crossover study. Haemophilia 8:787–793
31. Mannucci PM (1998) Hemostatic agents. N Engl J Med 339:245–253
32. Salomon O, Steinberg DM, Tamarin I, Zivelin A, Seligsohn U (2005) Plasma replacement therapy during labor is not mandatory for women with severe factor XI deficiency. Blood Coagul Fibrinolysis 16:37–41