The use of desmopressin in acquired haemophilia A: a systematic review

Massimo Franchini,[1] Giuseppe Lippi[2]

[1]Service of Immunohaematology and Transfusion Medicine, Department of Laboratory Medicine and Pathology; [2]Blood-Chemistry Diagnostics Unit, University Hospital of Parma, Parma, Italy

Introduction

Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) is a synthetic analogue of the antidiuretic hormone vasopressin, which was originally developed for the treatment of *diabetes insipidus*[1,2]. Following its original clinical use in 1977, DDAVP rapidly emerged as the treatment of choice for patients with type 1 von Willebrand's disease (VWD) and mild haemophilia A (factor VIII coagulant activity [FVIII:C] >5%)[3-7]. The widespread clinical use of this synthetic compound over the past 30 years has been mainly due to the fact that it is relatively inexpensive and safe, being associated with a very low rate of adverse reactions and no risk of transmission of blood-borne viral infections[8]. This latter aspect saved numerous patients with VWD and mild haemophilia A from the catastrophic consequences of human immunodeficiency virus (HIV) transmission with non-virus inactivated clotting factor concentrates prior to 1985[9].

The mechanisms of action of DDAVP are still incompletely understood, despite its extensive clinical use. Desmopressin induces a remarkable increase in the levels of plasma von Willebrand factor (VWF), FVIII:C, and tissue plasminogen activator (t-PA), and also exerts a vasodilatory effect. Desmopressin shortens the prolonged activated partial thromboplastin time (APTT) and the bleeding time. These effects probably result from increases in FVIII:C and VWF, both of which play a rate-accelerating role in these global tests of intrinsic coagulation and primary haemostasis[10]. The effects of desmopressin on VWF and t-PA, as well as its vasodilatory action, are explained by a direct effect on the endothelium, via activation of the endothelial vasopressin V2 receptor (V2R) and c-AMP-mediated signalling. This leads to exocytosis of VWF and t-PA from endothelial cell Weibel-Palade bodies where VWF and t-PA are stored[11]. The cellular mechanisms leading to the DDVAP-induced release of FVIII are, however, less certain. One hypothesis is that the close correlation between FVIII:C and VWF plasma levels could be explained by co-secretion, but a cell type that stores and secretes both proteins has not yet been identified as yet. Another reasonable hypothesis is that the effect of DDAVP on FVIII is mediated by indirect mechanisms, via VWF secretion, thereby making more binding sites for FVIII available within the VWF molecules[11,12].

Desmopressin can be administered by intravenously (0.3 μg/kg diluted in 50-100 mL of isotonic saline and infused over 30 minutes), subcutaneously (0.3 μg/kg) or via the intranasal route (300 μg). The FVIII levels usually increase by 2- to 6-fold over baseline values but the response is not always linked to the basal FVIII:C levels[13-18]. For this reason and also considering that there is a high consistency of responses to separate DDAVP treatments, a test infusion/injection should be carried out in every patient to assess his/her level of response[19]. The level of the FVIII:C elicited after DDAVP administration peaks in the first hour while its half-life ranges between 5 and 8 hours, with inter-individual heterogeneity[2]. Decreased responsiveness after repeated administrations of DDAVP at 12-24 hour intervals has been reported in some patients. This phenomenon, known as tachyphylaxis, is thought to be due to FVIII:C depletion from cellular stores[19,20].

Desmopressin has also been used successfully for the treatment of patients with autoantibodies against coagulation FVIII, a therapeutic use analysed in this article by systematically reviewing the published literature.

Search methods

We performed a search of MEDLINE, EMBASE, OVID, and SCOPUS using the following terms without time limits:

- "desmopressin",
- "DDAVP",

Blood Transfus 2011;9:377-82 DOI 10.2450/2011.0113-10

- "acquired inhibitors",
- "acquired factor VIII inhibitors",
- "acquired inhibitors and coagulation factors",
- "autoantibodies and coagulation factors",
- "anti-factor VIII antibodies",
- "factor VIII autoantibodies",
- "autoimmune factor VIII inhibitors",
- "haemophilia and inhibitors",
- "haemophilia and autoantibodies", and
- "spontaneous inhibitors and factor VIII".

Only articles or abstracts written in English were considered. The references of all retrieved studies and reviews were assessed for additional reports of clinical trials.

Figure 1 shows the flow-chart of the inclusion of the studies.

Literature results and discussion

Acquired haemophilia A is an uncommon (incidence of 0.2-1.0 cases per 1 million persons per year) but potentially life-threatening clinical syndrome characterised by autoantibodies directed against functional epitopes of FVIII causing neutralisation of this clotting factor and/or its accelerated clearance from the plasma[21-23]. Acquired anti-FVIII inhibitors are distributed equally between sexes and have an typically biphasic age distribution, with a small peak between 20 and 30 years (mainly post-partum inhibitors) and a larger peak in patients aged 70-80 years old. In approximately 50% of cases FVIII autoantibodies occur in patients without concomitant diseases, while the remaining cases are associated with a variety of conditions, including pregnancy, autoimmune disorders, cancers and drugs[24-27].

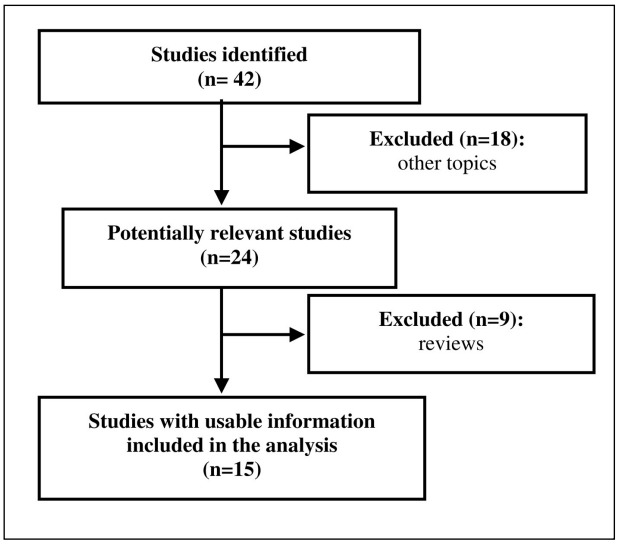

Figure 1 - Flow-chart of the inclusion of the studies.

The clinical picture of acquired haemophilia is typically characterised by bleeding into the skin, muscles, soft tissues and mucous membranes, whereas haemarthroses, a typical manifestation of congenital haemophilia A, are unusual. Not rarely the haemorrhages in acquired haemophilia are serious or life-threatening, as in the case of cerebral haemorrhage or rapidly progressive retroperitoneal haematomas[22]. The diagnosis of acquired haemophilia is based on the demonstration of an isolated prolongation of the activated partial thromboplastin time (APTT), not corrected by incubating the patient's plasma with equal volumes of normal plasma (mixing study), associated with low FVIII levels and evidence of a FVIII inhibitor (which can be titrated in Bethesda units [BU]), in a patient with no previous personal or family history of bleeding[22]. The treatment priorities of acquired haemophilia are to arrest the acute bleeding and to eradicate the FVIII autoantibody[28,29]. Acute bleeding episodes in patients with low-titre inhibitors can be treated using FVIII concentrates, whereas FVIII bypassing agents, such as activated prothrombin complex concentrates (APCC) or recombinant activated factor VII (rFVIIa), are effective for the treatment of those with high titre inhibitors. Inhibitor elimination may be achieved by using immunosuppressive agents such as corticosteroids alone or in association with cyclophosphamide[29].

Second-line eradicating therapies include high-dose immunoglobulins, cyclosporine and rituximab[6].

Following the first report on the use of DDAVP in non-haemophilic patients with acquired FVIII inhibitors in 1985, by De la Fuente and colleagues[30], a number of other case reports or small case series on this subject have been published[31-44]. Di Bona and colleagues reported on 17 cases of acquired haemophilia A cases diagnosed at two Italian haemophilia centres between 1979 and 1995. Desmopressin was used successfully for minor haemorrhagic episodes in five patients with low-titre inhibitor and measurable FVIII:C levels. Although FVIII:C levels increased by approximately 6-fold

over the mean basal level, the increment was short-lived and additional infusions at 24-hour intervals failed to elicit an increase of FVIII:C because of tachyphylaxis.

Three additional patients with acquired haemophilia A successfully treated with DDAVP for non-life threatening haemorrhages have been described by our group. One patient had a low-inhibitor titre, while the other two patients had a previous high-titre inhibitor which responded to immunosuppressive therapy thus allowing the use of DDAVP. All the three patients reported by Collins and colleagues responded to DDAVP, which was used to cover two minor invasive procedures and a minor bleeding episode. However, the largest experience is that reported by Nilsson and Lethagen[36]: in six of 11 patients with acquired haemophilia A treated with DDAVP, a satisfactory increase of FVIII:C levels and a haemostatic effect were obtained. By contrast, in the patients with high antibody titres and no measurable or very low FVIII:C concentrations, DDAVP had no effect. A literature review published by Mudad and Kane[37], reporting on 22 cases of acquired haemophilia A treated with DDAVP revealed that in all 11 patients with initial FVIII:C levels greater than 5%, DDAVP induced a rise in FVIII:C levels to between 15 and 140%. The five patients in this group with inhibitor titres of less than 2 BU had the best responses with peak FVIII:C levels of greater than 80%. Responses were also documented in three of the ten patients with FVIII:C levels of less than 5%.

Our systematic analysis of the available literature, the largest published so far, has documented a total of 37 patients collected from 15 case reports published during the period 1985-2005 (see Table I). The male to female ratio was 1.3 (21 males and 16 females) while the median age was 65.5 years (range, 12-83 years). As regards the most frequent associated conditions, 11 of the 26 evaluable cases (42.3%) were idiopathic, while six cases (23.1%) occurred in the post-partum period and four cases (15.4%) were associated with bronchial asthma. In all cases DDAVP was used for the treatment of non-life-threatening haemorrhages or to cover minor surgical, invasive or dental procedures. In the great majority of the cases (28/32, 87.5%), DDAVP was administered intravenously at a dose of 0.3 μg/kg.

The median number of doses administered was 2 (range, 1-26 doses). The median inhibitor titre was 5.3 BU (range, 0-444 BU). The median FVIII:C level prior to DDAVP administration was 5% (range, 0-40%), while the median FVIII:C level following DDAVP administration was 24.7% (range, 0-140%). Thus, the use of DDAVP led to an approximately 5-fold increase of FVIII:C levels. In 15 of the 26 evaluable cases (57.7%), a concomitant haemostatic therapy was given. However, as antifibrinolytic agents were used only in two patients[30,32], their role in improving the efficacy of DDAVP cannot be evaluated. Finally, DDAVP produced a haemostatic effect in 28 of 37 cases (75.7%).

In line with the results of the systematic review by Mudad and Kane[37], the best responses (19/20 cases [95%] with an increase in FVIII:C levels between 8 and 133%) were observed in patients with basal FVIII:C levels higher than 5%. Similarly, all the 11 evaluable patients with inhibitor titres less than 5 BU responded to DDAVP. A comparison between patients who responded to DDAVP and those who did not showed statistically significant difference between the two groups with regards to both median inhibitor titre (4 BU versus 48.5 BU, $P<0.001$, Student's *t*-test) and basal FVIII:C level (7% versus 1.5%, $P<0.01$, Student's *t*-test). Thus, our systematic review shows that a low inhibitor titre (<5 BU) and a residual FVIII:C level greater than 5% were predictive of a clinical response to DDAVP in patients with acquired haemophilia A.

Conclusions

This analysis of the literature supports the role of DDAVP in the treatment of minor bleeding episodes or prophylaxis of minor surgical/invasive procedures in patients with acquired haemophilia A with a low inhibitor titre and measurable baseline levels of circulating plasma FVIII:C. Nevertheless, experience in using DDAVP in this setting is limited to a few case reports.

The data in the large multicentre European Acquired Haemophilia Registry (EACH2), which has collected information on more than 300 cases of acquired haemophilia, will help us to clarify the role of this agent in acquired haemophilia A.

Keywords: desmopressin, DDAVP, acquired haemophilia A, inhibitors.

Table I - The clinical use of desmopressin in acquired haemophilia A: analysis of the literature data.

Author, year[Ref.]	Age/Sex	Associated condition	Reason for DDAVP use	Doses[1], route / inhibitor titer[2]	FVIII: C (%)		Concomitant anti-hemorrhagic therapy	Clinical outcome
					Pre-DDAVP	Post-DDAVP		
De la Fuente, 1985[30]	47/M	Idiopathic	Dental procedure	0.3x1, IV/1.8	18	80	EACA	Haemostatic efficacy
Vincente, 1985[31]	NR/F	Post-partum	DDAVP test	0.4x1, IV/13	3	5	No	No response
Hasson, 1986[32]	64/M	Idiopathic	Dental procedure	0.3x1, IV/0.6	51	130	EACA	Haemostatic efficacy
Chistolini, 1987[33]	60/M	Idiopathic	DDAVP test	0.3x1, SC/1	6.5	110	No	Haemostatic efficacy
Naarose-Abidi, 1988[34]	75/F	Idiopathic	Haematuria	0.3x1, IV/NR	7	140	No	Haemostatic efficacy
	20/F	Post-partum	Soft-tissue bleeding	0.3x1, IV/4	1	18	No	Haemostatic efficacy
	27/F	Post-partum	Soft-tissue bleeding	0.3x2, IV/NR	2	27	No	Haemostatic efficacy
Muhm, 1990[35]	12/M	Idiopathic	RPH, haemarthrosis, MH	0.4x9, IV/4.6	15	90	hFVIII	Haemostatic efficacy
	77/M	Asthma	Haematuria, SCH	0.4x8, IV/267	2.9	15	hFVIII	Haemostatic efficacy
	73/M	Asthma	MH	0.4x1, IV/444	<1	<1	APCC	No response
Nilsson, 1991[36]	55/F	NR	NR	0.3x17, IV/1:10,00[3]	9.6	24.1	NR	Haemostatic efficacy
	60/F	NR	NR	0.3x1, IV/1:2[3]	26	69	NR	Haemostatic efficacy
	76/F	NR	NR	0.3x26, IV/1:10[3]	5.5	16	NR	Haemostatic efficacy
	67/F	NR	NR	0.3x2, IV/1:50[3]	14	48.5	NR	Haemostatic efficacy
	68/M	NR	NR	0.3x19, IV/1:100[3]	15.4	24.7	NR	Haemostatic efficacy
	69/F	NR	NR	0.3x5, IV/1:2[3]	9.8	23.6	NR	Haemostatic efficacy
	83/M	NR	NR	0.3x1, IV/1:10[3]	<0.5	3.6	NR	No response
	71/M	NR	NR	0.3x7, IV/1:1,00[3]	1.1	4.8	NR	No response
	60/M	NR	NR	0.3x1, IV/1:20[3]	1.5	3	NR	No response
	80/F	NR	NR	0.3x5, IV/1:21[3]	2	8.8	NR	No response
	69/M	NR	NR	0.3x4, IV/1:2,00[3]	<0.5	<0.5	NR	No response
Mudad and Kane, 1993[37]	80/F	Asthma, RA	GI bleeding	0.3x1, IV/1.9	10	88	No	Haemostatic efficacy
Vivaldi, 1993[38]	82/M	Idiopathic	Cutaneous bleeding	0.3x1, IV/15	6	NR	APCC	Haemostatic efficacy
Di Bona, 1997[39]	59/M	Diabetes, LAC	RPH, SCH, MH	0.3x1, IV/14	4	30	hFVIII, pFVIII, APCC	No response
	69/M	Idiopathic	MH, RPH	0.3x4, IV/4	5	78	hFVIII, pFVIII	Haemostatic efficacy
	28/F	Post-partum	MH	0.3x4, IV/140	12	20	pFVIII	Haemostatic efficacy
	70/M	MGUS	MH	0.3x4, IV/3.6	5	40	hFVIII	Haemostatic efficacy
	59/F	Asthma	SCH	0.3x1 IV/34	1	18	hFVIII	Haemostatic efficacy
Burnet, 2001[40]	70/M	Quinine	NR	NR/3.4	2	NR	TA	Haemostatic efficacy
Delgado, 2002[41]	28/F	Post-partum	Vaginal bleeding, MH	NR/83	8	NR	APCC	No response
Howland, 2002[42]	38/F	Post-partum	Vaginal bleeding	0.3x1 IV/2	16	NR	TA	Haemostatic efficacy
Collins, 2004[43]	41/M	Idiopathic	Cystoscopy	NR/7	<1	NR	No	Haemostatic efficacy
	51/M	Castlemann disease	Minor surgery	NR/35	3.5	NR	No	Haemostatic efficacy
	80/M	Idiopathic	SCH	NR/6	4	NR	No	Haemostatic efficacy
Franchini, 2005[44]	75/F	Idiopathic	Rectosigmoidoscopy	03.x5, SC/6	40	NR	TA	Haemostatic efficacy
	45/M	Idiopathic	Haemarthrosis, MH	0.3x3, SC/1	4	38	No	Haemostatic efficacy
	64/M	ATD	Conjunctival haemorrhage	0.3x2, SC/2	16	54	No	Haemostatic efficacy

Legend:
IV, intravenously; SC, subcutaneously; DDAVP, desmopressin; FVIII:C, factor VIII coagulant activity; EACA, epsilon aminocaproic acid; NR, not reported; RPH, retroperitoneal haemorrhage; hFVIII, human factor VIII concentrate; pFVIII, porcine factor VIII concentrate; APCC, activated prothrombin complex concentrate; SCH, subcutaneous haematoma; MH, muscle haematoma; RA, rheumatoid arthritis; GI, gastrointestinal; LAC, lupus anticoagulant; MGUS, monoclonal gammopathy of undetermined significance; TA, tranexamic acid; ATD, autoimmune thyroid disease. [1]μg/kg; [2]Bethesda Units; [3]The maximum dilution of inhibitor plasma that prolongs the clotting time of normal plasma is reported.

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Received: 21 December 2010 - Revision accepted: 9 March 2011
Correspondence: Massimo Franchini
Immunohematology and Transfusion Center
Department of Laboratory and Pathology Medicine
University Hospital of Parma
Via Gramsci 14
43100 Parma Italy
e-mail: mafra66@libero.it