Biological and clinical response to desmopressin (DDAVP) in a retrospective cohort study of children with low von Willebrand factor levels and bleeding history

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Summary

The diagnosis and management of von Willebrand disease (VWD) in paediatrics is challenging. Our aim was to review patient's characteristics related to biological and clinical response to DDAVP in children with low von Willebrand factor (VWF) levels and bleeding history from a single institution. We included a retrospective cohort of 221 children (median age 11 years; 137 females): 27 type 1 (VWF levels within 15–30 IU dL^{-1}) and 194 possible type 1 (VWF levels within 31–49 IU dL^{-1}). The DDAVP infusion-test was performed in 214/221 children, 93.4% of whom showed good response. Patients with type 1 were at higher risk of DDAVP-test failure: 9/26 (34.6%) vs. 18/188 (9.6%) with possible type 1 (RR 3.44, 1.75–6.79; p= 0.002, Fisher's exact test). In 68 children, the clinical response to DDAVP was evaluated 87 times: i) to stop bleeding: menorrhagia (13), mucocutaneous (12), haemarthrosis (1); and ii) to prevent surgical bleeding: adenotonsillectomy (17), major (15) and minor surgery (10); and dental procedures (19). No major adverse events or bleeding were observed. The treatment was effective with one single dose of DDAVP in almost all patients, without antifibrinolytic or local therapy, except in a girl with severe haemorrhage during menarche who required replacement therapy. In conclusion, patients with VWD type 1 were at higher risk of no response to DDAVP infusion-test. In this series, one dose of DDAVP proved effective and safe for children with VWD. Since this is a safe, effective and affordable therapy, we consider that a wider use should be promoted, especially in developing countries.

Keywords

Biological response, clinical response, children, desmopressin, von Willebrand disease

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Introduction

von Willebrand disease (VWD) is the most common inherited bleeding disorder with an estimated prevalence of 1% in general population, while recent population-based studies suggest that approximately just 1:1,000 subjects experience clinical symptoms as a result of this condition (1). The bleeding tendency, spontaneous or post-surgery, varies from mild to severe according to the type and degree of the von Willebrand factor (VWF) defect (2). There are two main treatment options to prevent or control bleeding in patients with VWD, either replacement with plasma derived factor VIII/VWF (FVIII/VWF) concentrates or treatment with desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]) (3–6). DDAVP, a synthetic analogue of vasopressin, increased FVIII and VWF plasma concentrations without important side effects when administered to healthy volunteers (7–8). Because of structural differences, DDAVP has both greater antidiuretic effect, about 10-fold, and a more prolonged action, with a negligible effect over smooth muscle and a markedly decreased pressor activity, approximately 0.05%, compared to the natural hormone.

DDAVP was used for the first time in 1977 to treat patients with haemophilia A and VWD (9), and since that time, it has become a major therapeutic option for the prevention and treatment of bleeding in patients with VWD, mostly type 1 (5). There are only a few papers on DDAVP use in children with VWD in the literature (10–15). In a paediatric cohort of 75 patients (13), mostly VWD type 1, 76% were responders to DDAVP.

The aim of this retrospective cohort study was to report our experience on the use of DDAVP, a very safe and affordable drug, in children with low VWF levels and bleeding symptoms.

Patients and methods

Study cohort

The retrospective cohort study involved the records of children up to 18 years old with low VWF levels and bleeding symptoms, who underwent a DDAVP infusion-test. Also, we included those patients whom had used DDAVP to stop bleeds and/or to prevent excessive bleeding related to surgical procedures. The patients had a minimum of two laboratory results; as is usual in clinical practice, the most abnormal value for any given test being considered for the analysis. Patients were classified as type 1 for people with VWF levels within 15–30 IU dL^{-1} and the possible type 1 VWD with levels within 31–49 IU dL^{-1} at a ratio of VWF:RCo/VWF:Ag > 0.7 (5). The study entailed reports of 252 children with VWD diagnosis attending the Departamento de Hemostasia y Trombosis, between January 1999 and December 2007. Thirty-one patients were lost to follow-up. Patients with other factor deficiencies and thrombocytopathies were excluded from analysis. We evaluated: i) the biological response to DDAVP (DDAVP infusion-test) in 214 children; ii) the clinical response in 61/214 and iii) seven children who used the drug to treat or prevent bleeding, but without previous infusion-test.

The medical records were thoroughly reviewed for a personal and family history of bleeding. For each patient, the severity of each symptom was summarised using the MCMDM-1 VWD scoring system (16), considering the most severe occurrence. As it was recently reported (17), other paediatric-specific bleeding symptoms were included: umbilical stump bleeding, cephalohaematoma, post-circumcision bleeding, post-venipuncture bleeding, and macroscopic haematuria.

Major adverse events were considered as DDAVP-related side effects if medical condition appeared until 48 hours (h) after administration, based on parents report and/or confirmed by attending physician: vomiting, hyponatraemia, and seizures. Exclusion criteria for DDAVP testing were: children under two years of age, platelet counts below 50,000 µL^{-1}, and/or concomitant bleeding event or surgery. Written informed consent was obtained from each parent or the legal guardian. The Institutional Review Board approved the study.

Laboratory assays

The following laboratory data were collected from the clinical histories: FVIII:C, VWF:Ag (VWF antigen), and VWF:RCo (ristocetin cofactor activity) values. FVIII:C was assayed by the one-stage method (18) (normal range = 50–150 IU dL^{-1}), VWF:Ag by ELISA (19) (50–150 IU dL^{-1}), and VWF:RCo by the method of Macfarlane (20) (50–150 IU dL^{-1}). VWF values were not adjusted for blood group.

Standard plasma

The standard was "in-house" normal plasma pool from at least 20 healthy donors. APTT and FVIII were checked in each donor. It was calibrated for FVIII, VWF:Ag, and VWF:RCo against the International Reference Preparation for Factor VIII:C Related Activities in Plasma (IRP) (codes: 87/718 and 97/586, National Institute for Biological Standards and Controls, London, UK).

DDAVP infusion-test

Intravenous infusion of 0.3 µg kg^{-1} body weight DDAVP, diluted in 30 ml saline over 20 minutes (min), was given under medical supervision. Venous blood was withdrawn at baseline and 1 and 2 h after the end of the infusion (N= 203). Aliquots of platelet-poor plasma samples were obtained and frozen at –70ºC until tested (VWF:Ag and VWF:RCo). The recommendation of fluid restriction in the first 24 h after infusion was given to the parents (12). In children below 20 kg of weight, venous blood samples were taken just at baseline and at 90 min (N= 11). Parents were required to attend an emergency room in case they noticed any changes in medical status, especially the appearance of vomiting and/or the retention of urine and/or seizures.

Biological and clinical response to DDAVP

Patients were defined as follows (21–22): complete responders: both VWF:RCo and FVIII:C were 50 IU dL^{-1} or higher after DDAVP infusion; partial responders: VWF:RCo or FVIII:C were lower than 50 IU dL^{-1} but increased at least three-fold; and non-responders: neither criteria. Partial and non-responders were grouped as non-responders for analysis.

One dose of DDAVP (0.3 µg kg^{-1}) was prescribed 87 times in 68 children: i) to stop bleeding, and ii) to prevent excessive bleeding in surgery. No patient received epsilon aminocaproic acid neither local haemostatic therapy (i.e. fibrin glue). The bleeding episodes evaluated were: menorrhagia, N=13; epistaxis, N= 9; haematoma, N= 2; haemarthrosis post-trauma, N= 1; and teething, N= 1. In girls with menorrhagia, DDAVP was given by subcutaneous injection (s.c., 0.3 µg kg^{-1}) on the second and the third day of menses. Surgical procedures were divided into four main groups (23): adenotonsillectomy, N= 17; major surgeries (abdominal, N= 6; urological, N= 3; gynaecological –haemorrhagic ovarian follicle-, N= 2; orthopaedic, N= 2; reconstructive plastic surgery, N= 2); minor surgeries, N= 10 (biopsies, invasive procedures, such as arthroscopy, endoscopy, and skin excision); and dental procedures, N= 19. The clinical response was defined as good when surgical bleeding, clinically, was not different from normal and when the spontaneous bleeding stopped after the infusion of the drug.

Table 1: Characteristics of patients and laboratory parameters according to type 1 and possible type 1 VWD.

	Type 1	Possible type 1	P-value
Number of patients	27	194	
Gender			0.086
Female	13	124	
Male	14	70	
Blood group			0.320
O	15	124	
No O	7	41	
Missing	5	29	
Age at VWD diagnosis (years)			0.038
Median	9	12	
CI95%	7.7–11.4	10.7–11.8	
Age at first DDAVP (years)			0.347
Median	13	13	
CI95%	10.5–14.2	12.5–13.4	
Bleeding score			0.212
Median	3	3	
Range	1–11	1–10	
FVIII:C (IU dL^{-1})			
Mean	38	55	
CI95%	32–44	51–58	
VWF:Ag (IU dL^{-1})			
Mean	26	42	
CI95%	21–31	41–43	
VWF:RCo (IU dL^{-1})	23	43	
Mean	19–27	42–44	
CI95%			

Statistical analysis

Descriptive statistics are reported as mean, median, standard deviation (SD) and 95% confidence interval (CI95%) as appropriate for continuous variables; and frequencies for categorical variables. Analysis of categorical variables was performed using two-tailed Fisher's exact test. Comparison of continuous variables was performed by the Mann-Whitney rank sum test. Relative risk (RR) and CI95% were also calculated, to evaluate the degree of association between DDAVP response and age, gender, and VWF levels. SPSS software, version 16.01 was used. A p-value < 0.05 was considered statistically significant.

Results

Patients

Two hundred twenty-one children (137 female, 84 male) were included, median age 11 years: of these, 27 had type 1 and 194 possible type 1 VWD. Median bleeding score (BS) was 3, with 82.4% of

patients with BS ≥2. Main characteristics of population according to type 1 group and possible type 1 group are described in ▶ Table 1. As it is shown, no difference in the representation of blood groups was observed between the groups (p= 0.320) and there were no significant differences observed in the magnitude of bleeding in BS between VWD type 1 and possible type 1. Patients with type 1 were younger than possible type 1 (p= 0.038). Girls were more frequently diagnosed as possible type 1 (p= 0.086), and they were significantly older than boys at diagnosis (median age 12 years, 11–12.2, vs. median age 10 years, 9.1–11, p= 0.005, Mann-Whitney test).

The most frequent bleeding symptoms were epistaxis (61.5%), easy bruising-haematoma (58.4%), gums (27.2%), tooth extraction (13.6%) or after surgery (13.2%). In girls, the prevalence of menorrhagia was 51.8%. Other unfrequent symptoms were bleeding from gastrointestinal and urinary tracts, teething and umbilical stump bleeding. Previous to VWD diagnosis, 26 (11.8%) patients had been transfused, more frequently in those with type 1 (p= 0.076, Fisher's exact test), independently of age and gender. There was a family history of VWD in 92.6% (25/27) of patients with type 1 vs. 73.3% (137/187) of patients with possible type 1 (p= 0.018, Fisher's exact test). Seven children (2.5%) were adopted and unaware of their family history. Laboratory parameters, FVIII:C, VWF:Ag and VWF:RCo, by type 1 group and possible type 1 group are described in Table 1.

Biological and clinical response to DDAVP

Overall, 200/214 (93.4%) children were good responders to the DDAVP infusion-test. FVIII:C, VWF:Ag and VWF:RCo levels in these patients are shown in ▶ Figure 1, by groups. DDAVP response did not differ between female and male patients (95.5% and 90% of good responders, respectively, p= 0.152, Fisher's exact test). There were no relationship on the type of responses to DDAVP and age (p= 0.653, Mann-Whitney test). The 14 partial responder children were: seven type 1 and seven possible type 1. There were no differences in the response to DDAVP between blood groups: 13.4% of 135 patients with blood group type O were non-responders vs. 17.4% of 46 patients from non-O-blood group (p= 0.236).

VWF baseline levels below 30 IU dL^{-1}, i.e VWD type 1, were associated to a higher rate of failure to DDAVP-test: 9/26 (34.6%) patients with type 1 vs. 18/188 (9.6%) with possible type 1 (RR 3.44, CI95% 1.75–6.79; p= 0.002, Fisher's exact test). No relationship was found between DDAVP response and baseline FVIII:C.

One dose of DDAVP was prescribed 87 times in 68 children to prevent excessive bleeding in major surgery and to treat bleeding. Of these patients, 67/68 showed adequate haemostatic response without adverse effects. One girl did not respond clinically and required replacement therapy because of profuse bleeding related to menarche. In 7/68 children DDAVP was used therapeutically, without previous infusion-test, nonetheless all children showed good clinical response. The age of these seven children was signifi-
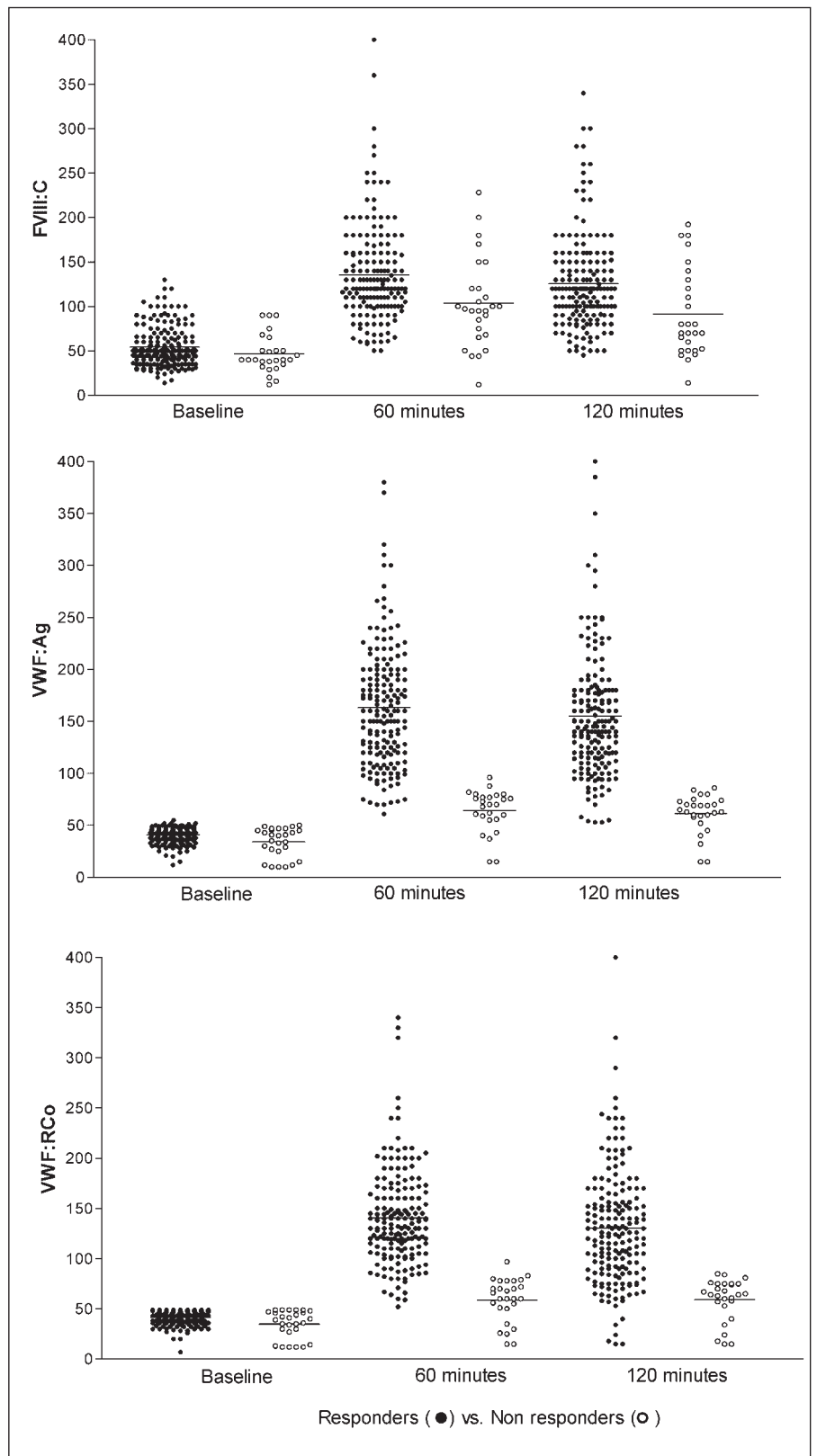
Figure 1: DDAVP infusion-test: factor VIII (FVIII:C) and von Willebrand factor (VWF:Ag and VWF:RCo): at baseline, 1 and 2 hour levels after the end of infusion, grouped by responders and non responders patients. FVIII:C: factor VIII; VWF:Ag: von Willebrand antigen; VWF:RCo: ristocetin cofactor activity.

What is known about this topic?

- In paediatrics, von Willebrand disease (VWD) diagnosis and management is challenging.
- Although mildest forms of VWD may not require treatment, improper management can lead to severe haemorrhage complications.
- In VWD, DDAVP is the first option of therapy, especially for type 1.

What does this paper add?

- Although the possible type 1 was more frequent, there were no differences in the bleeding symptoms between groups.
- Girls were diagnosed often with milder forms and were usually older than boys.
- Type 1 VWD was at increased risk of no response to DDAVP infusion-test.
- This retrospective cohort study showed that the DDAVP is effective and safe for children with low von Willebrand factor levels and bleeding history, when the emphasis is placed on the concentration and volume of the drug and rate of infusion, and with appropriate fluid restriction.

cantly lower than that of the children whit DDAVP infusion-test performed: median age eight years, 3.2–12.2 vs. 13 years, 12.6–13.4 (p< 0.003, Mann-Whitney test). No differences in the response to DDAVP by gender were found.

Discussion

The VWD in children requires a high index of suspicion (24, 25), since many of them have no a previous haemostatic challenge to evidence the bleeding tendency.

In paediatrics, there is some reluctance to use DDAVP (10, 11), especially in small children, because of the risk of symptomatic hyponatraemia and seizures. The NHBLI guidelines on VWD (5) reported that, like us, many pediatric hematologists do not use DDAVP in children under the age of two years. Hyponatraemia and volume overload due to the antidiuretic effects of DDAVP are relatively rare; just a few cases have been described, typically in young children who received repeated infusions and with poor fluid restriction (26–28). We apply strict fluid restriction therapy to prevent the hiponaetraemia and we have seen no major complications.

Mildest forms of VWD remain without definite diagnosis (29, 30). In our series, while children with type 1 were younger than those with possible type 1, girls were diagnosed more frequently as possible type 1, older than boys at diagnosis and outnumbered them. The Universal Data Collection Program of CDC (31), with over 1,400 women registered up to 2002, reported nearly 75% with the mildest type of VWD and a VWD diagnosed at median age of 13 years. Given the immense challenge of menstruation in girls, it is not surprising that they show the bleeding symptom for the first time later than boys, i.e. close to menarche, and with milder forms of the disease.

There is no standardised approach to test the biological response to DDAVP in paediatric setting (11–15). In our protocol of study, we modify the DDAVP-testing only for children below 20 kg of weight, performing the baseline and post-90 min evaluation. Overall, more than 90% of our patients showed good biological response to DDAVP. This rate is close to the 83% reported by the European Study MCMDM –1VWD (22), which included only 11 type 1 patients. Revel-Vilk et al. (13) evaluated 75 children with moderate and mild VWD and identified 76% of good responders. We found no relationship between response to DDAVP and age or gender, but we had no patients below two years of age.

Regarding VWF baseline profile, a positive association between FVIII and VWF:RCo baseline levels with good DDAVP response have been previously described in children and adults (11, 13). Concerning baseline FVIII levels, we agree with Nolan et al. that FVIII was an unreliable guide to the response to DDAVP in VWD (11). In addition, the range of FVIII at baseline in the cohort of non-responders from Revel-Vilk et al. (13) was wide and overlaped the level of the responders. Taken altogether, our findings suggest that DDAVP infusion-test should be performed in all children with low VWF levels and bleeding history, particularly those with VWF below 30 IU dL^{-1}, who are at higher risk of no adequate response. We believe that our successful results derive to some extent from the personalised management of the patients by our specialists and the emphasis that they place on being precise with concentration and volume of the drug and rate of infusion. Although we think that the infusion-test is really necessary, we have used DDAVP in surgeries with good results in seven children with VWF levels over 30 IU dL^{-1}, without performing the infusion-test in advance.

Our retrospective study of VWD children that received DDAVP to evaluate biological and clinical response, illustrates a cohort of patients occurring in clinical practice. Over the study period, patients have been diagnosed and treated by the same team, using homogeneous criteria for the diagnosis and management of bleeding disorders. DDAVP was well tolerated and caused no serious adverse events when it was administered in one single dose giving special attention to concentration of drug, rate of infusion and fluid restriction. As we report in this series, single infusions of DDAVP have been recommended (5) to stop mild bleeding as well as for minor surgical procedures. DDAVP demonstrated to be a safe and effective option in the VWD management in children, valuable in emergencies even if the DDAVP-test has not been performed before. Considering our results, we hope to encourage the paediatricians to a wider use of DDAVP, especially in children from developing countries.

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