REVIEW

How do you treat bleeding disorders with desmopressin?

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Postgrad Med J 2007;**83**:159–163. doi: 10.1136/pgmj.2006.052118

Desmopressin is an analog of vasopressin that exerts a substantial haemostatic effect by inducing the release of von Willebrand factor from its storage sites in endothelial cells. It has proved useful in treating or preventing bleeding episodes in patients with von Willebrand disease, haemophilia A and platelet function defects. Its efficacy in achieving a satisfactory level of haemostasis has reduced the use of blood products to treat bleeding episodes. Clinicians need to become familiar with the use of this drug that has become a home medication for many patients with inherited bleeding disorders.

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Received 5 August 2006
Accepted
26 September 2006

Desmopressin is one of the several non-transfusional pharmacological agents within the clinician's armamentarium for treating bleeding episodes, which include, among others, anti-fibrinolytic agents tranexamic acid, ϵ-amino-caproic acid and aprotinin; recombinant human factor VIIa; and the conjugated oestrogens.[1] Its properties of ease of use, low cost and versatility in preventing and treating bleeding from various sites of the body in a variety of bleeding disorders make it a useful haemostatic drug. Importantly, it carries no risk of transmitting bloodborne infectious agents. Since its introduction into clinical use in 1977, it has revolutionised the treatment of bleeding disorders, leading to a marked reduction in the use of blood products for the prevention and treatment of bleeding episodes.[2 3]

This review outlines the basic knowledge on desmopressin, and attempts to reintroduce it to the primary care clinician, who could be an emergency room physician treating epistaxis in a patient with mild haemophilia A, a nurse practitioner treating gum bleeding in a patient with end-stage renal disease, a dentist anticipating wisdom tooth extraction in a patient with type 1 von Willebrand disease (VWD), or a paediatrician treating a female adolescent patient with type 1 VWD experiencing excessive menstrual bleeding. In these clinical scenarios, understanding the pathogenesis of the disease process and the mechanism of action of desmopressin will enable the clinician to formulate a plan of action for the patient in conjunction with the haematologist and avoid delay in patient management.

PHYSIOLOGY OF THE VON WILLEBRAND FACTOR

Insight into the normal and pathological physiology of the von Willebrand factor (VWF) will facilitate understanding of the mechanism of action of desmopressin. Both the factor and the disease are named after Dr Erik von Willebrand, a Finnish physician who, in 1926, first described a hereditary haemorrhagic disease with autosomal dominant inheritance pattern in a large kindred from the Åland islands, an archipelago off the western coast of Finland.[4] His index patient was a young girl who died of menstrual haemorrhage soon after her menarche, clearly epitomising the involvement of females in this bleeding disorder as opposed to that in haemophilia A or B. It was only years later, well into the late 20th century, that it was appreciated that the disease originated from a quantitative or qualitative deficiency of a plasma protein of high importance in the normal haemostatic mechanism.

VWF is a complex multimeric glycoprotein with two important roles in haemostasis: it binds to platelet receptors, bridging them to other platelets and subendothelial tissue that is exposed after vascular injury, and also acts as a carrier protein for the coagulation factor VIII (FVIII), thus preventing its proteolytic inactivation in the plasma. Without the VWF, FVIII plasma levels decline rapidly; and depending on the severity of the disorder, a haemostatic defect similar to haemophilia A emerges.[4 5]

The gene for VWF is located on chromosome 12. During its synthesis in endothelial cells and megakaryocytes, VWF undergoes extensive processing in the Golgi apparatus of these cells, including polymerisation into a large molecule with a molecular weight of 20 000 kDa. Stored inside specialised storage organelles, the Weibel–Palade bodies of endothelial cells and α-granules of platelets, VWF is released into circulation both constitutively and on stimulation.[5] Myriad substances act as secretagogues of the VWF, including histamine, thrombin, epinephrine and vasopressin.[5]

VWF is released into plasma as a large multimer, which is instantaneously broken down by a protease into several molecules of varying molecular sizes: multimers with high, intermediate and low molecular weight. The protease that cleaves VWF immediately on its release into the plasma, ADAMTS13, has recently gained clinical relevance when it was understood that its deficiency underlies the pathogenesis of thrombotic thrombocytopenic purpura.[6] In this disorder, platelet aggregation occurs around the unusually large VWF molecules in circulation, leading to disseminated thrombosis and multiorgan dysfunction.

The high-molecular-weight multimers, by virtue of their strong affinity to platelet receptors, are considered more potent than the other multimers.

Abbreviations: FVIII, coagulation factor VIII; VWD, von Willebrand disease; VWF, von Willebrand factor

Box 1: Synopsis of the physiology of the von Willebrand factor

- Gene located on chromosome 12
- Multimeric glycoprotein with molecular weight ranging from 500 to 20 000 kDa
- Synthesis by endothelial cells and megakaryocytes
- Storage in Weibel–Palade bodies of endothelial cells and α-granules of platelets
- Release into plasma as a large molecule, followed by breakdown into varying sizes of multimeric molecules by a plasma protease
- Functions include platelet adhesion and protecting coagulation factor VIII from proteolytic inactivation in the plasma

The absence of these multimers leads to a defect in platelet adhesion, prolonging the bleeding time. Ristocetin is an antibiotic that enhances the interaction between the VWF and the platelet receptors. On the basis of this effect, ristocetin cofactor activity test is used as a surrogate marker of the functional activity of the VWF.[4] Box 1 summarises the physiology of VWF.

MECHANISM OF ACTION OF DESMOPRESSIN

Vasopressin is a secretagogue of VWF. This hormone functions through two receptors, termed V1 and V2, which activate different intracellular second messengers.[7] Agonist activity at V2 receptors leads to a rise in intracellular concentrations of cyclic adenosine monophosphate, which in turn induces exocytosis of VWF from its storage sites (ie, Weibel–Palade bodies of endothelial cells) into the circulation. Interestingly, tissue plasminogen activator, a molecule involved in fibrinolysis and therefore in opposition to the effects of VWF, is also released into circulation along with VWF. Desmopressin (1-desamino-8-D-arginine vasopressin, also abbreviated DDAVP) is a synthetic analogue of vasopressin, which activates only V2 receptors and thus lacks its vasoconstrictor and uterotonic properties. Intravenous or intranasal administration of desmopressin to healthy individuals is followed by a rise in levels of both VWF and its precious cargo, FVIII.[2] Individuals who lack V2 receptors—that is, patients with nephrogenic diabetes insipidus—expectedly do not show this increase in VWF and FVIII levels.[1 3 7 8]

Although originally designed for the treatment of diabetes insipidus, desmopressin emerged as a haemostatic agent, with the appreciation of its effects on coagulation and the lack of the severe side effects associated with vasopressin. The next section discusses the bleeding disorders amenable to treatment with this drug.

BLEEDING DISORDERS TREATED WITH DESMOPRESSIN

von Willebrand disease

von Willebrand disease (VWD) is categorised into three major types. Mild quantitative deficiency of VWF molecule with a normal multimer pattern is the cause of type 1 VWD, the most common inherited bleeding disorder, affecting up to 1% of the population. Total or near-total absence of VWF leads to type 3 VWD, which is the most severe but fortunately a rare type.[5] Understandably, desmopressin is a useful therapeutic agent in type 1 VWD, where there is residual VWF in the endothelial storage sites to provide haemostasis, at least temporarily. Owing to presence of little or no VWF in the storage sites in type 3 VWD, desmopressin shows no therapeutic benefit in this disease.[4 9 10] Type 2 VWD is characterised by a qualitative defect in the VWF molecule. Some patients with type 2 VWD will show absence of the high-molecular-weight multimers (types 2A and 2B). Type 2B is characterised by a gain-of-function type of interaction between platelets and VWF, leading to spontaneous platelet aggregation and thrombocytopenia due to clearance of the platelet–VWF complexes from circulation. Other patients with type 2 VWD will have a normal multimer pattern, but laboratory evaluation will detect either a deficient interaction with the platelet receptors (type 2M) or a deficient FVIII-carrying activity (type 2N). Type 2N is characterised by rapid proteolysis of FVIII, and the clinical picture is much like that of haemophilia A.[4 9 10] Theoretically, desmopressin is not expected to provide any haemostatic effect in type 2 VWD, because the VWF released from the storage sites will still be abnormal. Surprisingly, however, some patients with type 2 VWD will have a laboratory and clinical response to desmopressin.[11] Notably, type 2B constitutes a theoretical contraindication to the use of desmopressin, as the release of abnormal VWF molecules with a gain-of-function defect is expected to trigger spontaneous platelet aggregation and thrombocytopenia.[10] Table 1 shows a synopsis of the types of VWD and the response to desmopressin in individual types.

Haemophilia A

FVIII has a critical role in the coagulation cascade by acting as a cofactor for factor IXa in the activation of factor X, the common-pathway protease that will subsequently activate thrombin, the real propeller of the coagulation machine. In the absence of FVIII, the activation of factor X is sluggish, leading to an intolerable delay in coagulation. Many different mutations of the FVIII gene on the X chromosome, but most commonly inversion of one of the introns of the FVIII gene, disrupt the synthesis of the product molecule. Patients with such mutations have no detectable levels of FVIII, and are clinically at the most severe end of the spectrum, exhibiting potentially crippling or fatal, spontaneous bleeding episodes. Unfortunately, these patients do not benefit from administration of desmopressin, because increases in plasma levels of VWF alone without its precious cargo, the FVIII molecule, will not translate into a haemostatic effect. Some patients with haemophilia A, however, have detectable FVIII levels because a single nucleotide substitution in the FVIII gene will still allow the translation of a mutant FVIII molecule, albeit with diminished factor activity. These patients are classified into the category of mild or moderate haemophilia, and may fortunately respond to desmopressin.[12]

Other bleeding disorders

Various acquired or inherited disorders of bleeding have been documented to respond to desmopressin.[3] The exact mechanism underlying this therapeutic effect is not known but may be related to several events associated with the release of VWF. First of all, sheer increase in FVIII levels will accelerate the activation of factor X, thus providing a faster coagulation. Secondly, unlike its constitutive release into the lumen of vessels, stimulated release of VWF is thought to occur on the abluminal surface of the endothelial cell, directly bringing VWF into contact with the subendothelial tissues. This may in turn provide a more efficient platelet adhesion, a process that is possible only through interaction between platelets and VWF. Finally, desmopressin induces the release of the unusually large VWF molecules, which are more adhesive than the regular-sized VWF molecules in circulation.[3]

Table 1 Desmopressin use in various types of von Willebrand disease

Type of VWD	Characteristic features	Desmopressin use
Type 1	Mild to moderate decrease in plasma VWF levels with a normal multimer pattern	Trial needed before use
Type 2A	Absence of multimers with high and intermediate molecular weight	Trial needed before use
Type 2B	Increased affinity for platelet receptors, ultimately leading to excessive platelet activation and thrombocytopenia	Trial needed before use? Contraindicated
Type 2N	Mutation in FVIII-binding region of the VWF, disrupting FVIII-carrying function	Trial needed before use
Type 2M	Mutation in the region of the VWF that binds to platelet receptors, disrupting platelet adhesion	Trial needed before use
Type 3	Undetectable levels of the VWF with severe bleeding diathesis	Not useful

FVIII, coagulation factor VIII; VWD, von Willebrand disease; VWF, von Willebrand factor.

USE OF DESMOPRESSIN IN THE TREATMENT OF BLEEDING DISORDERS

Desmopressin has been successfully used in the prophylaxis and treatment of bleeding episodes in some patients with VWD types 1 and 2, mild to moderate haemophilia A, platelet function defects related to aspirin use, uraemia and inherited platelet disorders, bleeding related to cirrhosis (excluding acute gastrointestinal bleeding), or heparin use.[1 3 6] Patients with inherited disorders should undergo a trial to document an improvement in laboratory parameters, which could be an increase in VWF and ristocetin cofactor activity levels for patients with VWD, increase in FVIII levels for patients with haemophilia A, and normalisation of bleeding time or platelet function analysis test for patients with inherited platelet disorders. Before starting treatment, it is important to inquire about response to desmopressin trial, and the patient's haematologist should be contacted if in doubt. The haematologist should definitely be consulted for the management of a patient with bleeding disorders who has never used desmopressin before.

Desmopressin can raise VWF and FVIII levels by 3–5-fold. As the response to desmopressin in an individual patient is consistent on different occasions, knowledge of the expected response and baseline levels of factor is essential to determine the optimal mode of treatment. For example, for a patient with haemophilia with baseline FVIII levels of 10% that responds to desmopressin by a fourfold increase, a combination of desmopressin and oral antifibrinolytics could be sufficient prophylaxis before a simple dental extraction. The same patient would need to be treated with FVIII concentrates for the treatment of a limb or life-threatening haemorrhage, or in preparation for major surgery.

The efficacy of desmopressin in preventing or treating menorrhagia in patients with bleeding disorders is not clear because of conflicting results from studies in which desmopressin was used in the treatment of menorrhagia in women with VWD.[13] Desmopressin paradoxically causes release of the tissue plasminogen activator, a fibrinolytic substance, along with the VWF, and thus may actually increase menstrual bleeding. A therapeutic trial can be undertaken for each individual woman to gauge the clinical response, as a guide for future plan of action. Pictorial chart assessment can be used to estimate menstrual blood loss. It is important to exclude other causes of menorrhagia, such as dysfunctional uterine bleeding, before the use of haemostatic agents.

Both intranasal and subcutaneous desmopressin was found to be effective in the treatment of menorrhagia in women with VWD.[14–16] Unfortunately, the optimal dosing schedule to prevent menstrual bleeding is not known, although a tentative approach would be a dose at the onset of menses followed by two subsequent doses every 24 h.[15] Alternative treatment strategies would include oral tranexamic acid, oral contraceptives, levonorgesterel-releasing intrauterine systems and endometrial ablations.[17]

DOSING AND ADMINISTRATION

Desmopressin can be given through intravenous, subcutaneous and intranasal routes. The dose for both intravenous and subcutaneous routes is 0.3 μg/kg. When giving intravenously, the drug is diluted in normal saline and infused over 15–30 min. The dilution volume of normal saline is 15–30 ml for children and 50–100 ml for adults. The intranasal dose is 150 μg for patients weighing <50 kg (one puff into one nostril) and 300 μg for patients weighing ⩾50 kg (one puff into each nostril). The intranasal solution of desmopressin used in the treatment of bleeding disorders (Stimate, Ferring AB, Limhamn, Sweden) is more concentrated than that used in the treatment of nocturnal enuresis or diabetes insipidus. The peak effect is achieved 30–60 min after intravenous infusion, and 60–90 min after an intranasal or subcutaneous dose. This timing should be taken into account when desmopressin is given as prophylaxis before procedures. Owing to the shorter time required to achieve the haemostatic effect, intravenous route is preferred to subcutaneous and intranasal routes when treating acute bleeding episodes. High levels of FVIII and VWF are maintained for 6–8 h.[1 10] Table 2 provides a summary of dosing of desmopressin.

The dose can be repeated every 12–24 h depending on the type and severity of bleeding; however, most patients with moderate haemophilia A (and to a lesser extent, those with VWD) respond less with each consecutive dose (tachyphylaxis) because of exhaustion of VWF stores. Therefore, to achieve longlasting haemostasis during recovery from major trauma or surgery, specific factor concentrates or platelet transfusions should be provided, depending on the underlying disease.

The response to desmopressin can be monitored using laboratory tests specific for the bleeding disorder. Platelet function analyzer PFA-100 (Dade International, Miami, Florida, USA), which has been introduced as an alternative to bleeding time, is a new in vitro tool to test platelet function globally. The results are given as closure times representing formation of a platelet aggregate within its two cartridges that contain either adenosine diphosphate or epinephrine, agonists for platelet activation.[18] PFA-100 may be a be a useful adjunct to monitor response to desmopressin in patients with type 1

Table 2 Doses and preparations of desmopressin

Mode of delivery	Dose and preparation
Intranasal	Stimate 150 μg for body weight <50 kg (one spray into one nostril) 300 μg for body weight >50 kg (one spray into each nostril)
Intravenous	0.3 μg/kg body weight diluted in normal saline (15–30 ml for children, 50–100 ml for adults) and given over 15–30 min
Subcutaneous	0.3 μg/kg body weight

VWD.[19] As PFA-100 is an expensive test and knowledge regarding its utility in monitoring haemostasis is yet evolving, at the time of writing this manuscript, the general practitioner is advised only to become familiar with the interpretation of its results but not to use it as a routine test to monitor response to desmopressin.

ADVERSE EFFECTS, PRECAUTIONS, AND CONTRAINDICATIONS

The most common side effects encountered with the use of desmopressin are tachycardia (mild), flushing and headache (mild).[3] As desmopressin is a potent antidiuretic agent, it can cause hyponatraemia and even seizures in patients receiving generous amounts of hypotonic intravenous or oral fluids, necessitating fluid restriction during desmopressin treatment. This fact is especially important in the context of treatment of minor bleeding episodes at home, and the patients or care givers should be instructed to observe fluid restriction after giving desmopressin. For young children who are inpatients (ie, postoperative patients), hypotonic intravenous fluids should be avoided and total fluid intake should be reduced to 75% of maintenance requirements in the 24 h after use of desmopressin. Monitoring serum sodium levels and osmolality before and after desmopressin use would be prudent in young children, especially if more than one dose is used over a 24-h period.[20]

A rare but serious side effect in patients receiving desmopressin is the occurrence of arterial thrombotic events, such as stroke or acute myocardial infarction.[21 22] Caution should be exercised, therefore, with the use of desmopressin in elderly patients with atherosclerotic disease. Venous thrombosis is likewise rare after desmopressin administration, and has been observed only in patients who had received desmopressin after transfusion of FVIII/VWF concentrates.[22] Patients with thrombocytopenic purpura should not receive desmopressin because further release of the unusually large VWF molecules into plasma is thought to add more fuel to the ongoing thrombotic event in these patients.[23] Thrombocytopenia can easily develop in patients with type 2B VWD after desmopressin use, and this disease represents a classic contraindication to the use of desmopressin; however, some patients with type 2B VWD have had a therapeutic response to desmopressin without developing thrombotic complications.[24] Therefore, desmopressin should be used in patients with type 2B VWD only under the guidance of a haematologist.

It is also important to recognise disorders where desmopressin will not be effective, such as type 3 VWD and severe haemophilia A. Recombinant or plasma-derived factor concentrates and other non-transfusional agents, such as conjugated oestrogens or antifibrinolytics, can be helpful in the management of patients with such bleeding problems.

Desmopressin does not provide any haemostatic benefit in severe haemophilia B, deficiency of factor IX. Factor IX and FVIII work together to activate factor X, so artificially increasing the levels of one factor is not expected to compensate for the lack of the other. Nevertheless, response to desmopressin has been reported in patients with mild to moderate haemophilia B, perhaps because of a generalised haemostatic effect.[25] Box 2 summarises the guidelines for the use of desmopressin in bleeding disorders.

Box 2: Guidelines for the use of desmopressin in bleeding disorders

- Inquire about response to trial
- Administer 30–60 min before procedure
- Restrict fluid intake
- Monitor serum sodium level and osmolality in young children
- Anticipate tachyphylaxis after repeated doses
- Monitor therapeutic response with an appropriate test for the individual bleeding disorder

CONCLUSION

Desmopressin has revolutionised the treatment of bleeding disorders since its introduction to haematology in 1977. The resultant avoidance of blood products has saved numerous lives since then. Intranasal and subcutaneous routes render it convenient for treatment at home, avoiding emergency room or office visits for simple bleeding problems. Clinicians in primary care should familiarise themselves with the indications, dosing, side effects and contraindications of this versatile tool for haemostasis.

Key references

- Mannucci PM. Hemostatic drugs. *N Engl J Med* 1998;**339**:245–53.
- Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997;**90**:2515–21.
- Mannucci PM. Treatment of von Willebrand's Disease. *N Engl J Med* 2004;**351**:683–94.
- Lee CA, Abdul-Kadir R. von Willebrand disease and women's health. *Semin Hematol* 2005;**42**:42–8.
- Scott H. Use of desmopressin, antifibrinolytics, and conjugated estrogens in hemostasis. In: Goodnight J, Hathaway WE, eds. *Disorders of Hemostasis & Thrombosis: a clinical guide*. 2nd edn. Philadelphia: McGraw-Hill, 2001: 528–42.

SELF-ASSESSMENT QUESTIONS; ANSWERS AT THE END OF REFERENCES

1. Desmopressin exerts its haemostatic effect by:

A. Inducing synthesis of the von Willebrand factor (VWF) by endothelial cells
B. Stimulating release of the VWF from its storage sites in endothelial cells
C. Cleaving the large VWF multimers circulating in plasma into smaller multimers
D. Enhancing interaction between platelets and the VWF
E. Binding to VWF receptors on platelets

2. Desmopressin is not expected to show any haemostatic effect in patients with:

A. Uraemia
B. Type 1 von Willebrand disease (VWD)
C. Type 3 VWD
D. Mild haemophilia A
E. Platelet function defect secondary to aspirin use

3. A 2-year-old boy with mild haemophilia A, known to be responsive to desmopressin, is hospitalised for elective surgery. He receives a single intravenous dose before and

two more doses 12 h apart after surgery, which proceeds without any haemorrhagic complications. To thwart serious side effects of desmopressin, postoperative care should include:

A. Monitoring serum sodium levels
B. Serial electrocardiograms
C. Chest radiograph
D. Prothrombin time and partial thromboplastin time
E. Platelet count

4. A 20-year-old woman (weight 54 kg) with type 1 VWD is going to have wisdom tooth extraction. The appropriate dose and timing for the intranasal solution is:

A. One puff (150 μg) to one nostril 10 min before the procedure
B. One puff to each nostril (total dose 300 μg) 10 min before the procedure
C. One puff (150 μg) to one nostril 60 min before the procedure
D. One puff to each nostril (total dose 300 μg) 60 min before the procedure
E. Two puffs to each nostril (total dose 600 μg) 60 min before the procedure

5. Which of the following is NOT part of the guidelines for the use of desmopressin in children for the treatment of bleeding episodes?

A. Inquiry about response to a previous trial of desmopressin
B. Generous use of intravenous fluids
C. Anticipation of reduced haemostatic effect after repeated doses
D. Monitoring serum sodium and osmolality in patients receiving multiple doses
E. Monitoring the therapeutic response with appropriate tests

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Competing interests: None.

REFERENCES

1 **Mannucci PM**. Hemostatic drugs. *N Engl J Med* 1998;**339**:245–53.
2 **Warrier AI**, Lusher JM. DDAVP: a useful alternative to blood components in moderate hemophilia A and von Willebrand disease. *J Pediatr* 1983;**102**:228–33.
3 **Mannucci PM**. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997;**90**:2515–21.
4 **Ginsburg D**. von Willebrand disease. In: Beutler E, Coller BS, Lichtman MA, Kipps TJ, eds. *Williams hematology*.6th edn. Philadelphia: McGraw-Hill, 2001:1813–28.
5 **Castaman G**, Federici AB, Rodeghiero F, *et al*. Von Willebrand's disease in the year 2003: towards the complete identification of gene defects for correct diagnosis and treatment. *Haematologica* 2003;**88**:94–108.
6 **Levy GG**, Motto DG, Ginsburg D. ADAMTS13 turns 3. *Blood* 2005;**106**:11–17.
7 **Thibonnier M**. Vasopressin agonists and antagonists. *Horm Res* 1990;**34**:124–8.
8 **Scott H**. Use of desmopressin, antifibrinolytics, and conjugated estrogens in hemostasis. In: Goodnight J, Hathaway WE, eds. *Disorders of hemostasis & thrombosis:a clinical guide*. 2nd edn. USA: McGraw-Hill, 2001:528–42.
9 **Lusher JM**. Response to 1-deamino-8-D-arginine vasopressin in von Willebrand disease. *Haemostasis* 1994;**24**:276–84.
10 **Mannucci PM**. Treatment of von Willebrand's disease. *N Engl J Med* 2004;**351**:683–94.
11 **Federici AB**, Mazurier C, Berntorp E, *et al*. Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study. *Blood* 2004;**103**:2032–8.
12 **Kaufman RJ**, Antonarakis SE. Structure, biology, and genetics of factor VIII. In: Hoffman R, Edward J, Benz J, Shattil SJ, Furie B, Cohen HJ, *et al*, eds. *Hematology:basic principles and practice*.3rd edn. Philadelphia: Churchill Livingstone, 2000:1850–68.
13 **Kujovich JL**. von Willebrand's disease and menorrhagia: prevalence, diagnosis, and management. *Am J Hematol* 2005;**79**:220–8.
14 **Leissinger C**, Becton D, Cornell C Jr, *et al*. High-dose DDAVP intranasal spray (Stimate) for the prevention and treatment of bleeding in patients with mild haemophilia A, mild or moderate type 1 von Willebrand disease and symptomatic carriers of haemophilia A. *Haemophilia* 2001;**7**:258–66.
15 **Amesse LS**, Pfaff-Amesse T, Leonardi R, *et al*. Oral contraceptives and DDAVP nasal spray: patterns of use in managing vWD-associated menorrhagia: a single-institution study. *J Pediatr Hematol Oncol* 2005;**27**:357–63.
16 **Rodeghiero F**, Castaman G, Mannucci PM. Prospective multicenter study on subcutaneous concentrated desmopressin for home treatment of patients with von Willebrand disease and mild or moderate hemophilia A. *Thromb Haemost* 1996;**76**:692–6.
17 **Lee CA**, Abdul-Kadir R. von Willebrand disease and women's health. *Semin Hematol* 2005;**42**:42–8.
18 **Harrison P**. The role of PFA-100 testing in the investigation and management of haemostatic defects in children and adults. *Br J Haematol* 2005;**130**:3–10.
19 **Franchini M**, Gandini G, Manzato F, *et al*. Evaluation of the PFA-100 system for monitoring desmopressin therapy in patients with type 1 von Willebrand's disease. *Haematologica* 2002;**87**:670.
20 **Das P**, Carcao M, Hitzler J. DDAVP-induced hyponatremia in young children. *J Pediatr Hematol Oncol* 2005;**27**:330–2.
21 **Mannucci PM**, Lusher JM. Desmopressin and thrombosis. *Lancet* 1989;**2**:675–6.
22 **Girolami A**, Tezza F, Scapin M, *et al*. Arterial and venous thrombosis in patients with von Willebrand's disease: a critical review of the literature. *J Thromb Thrombolysis* 2006;**21**:175–8.
23 **Overman M**, Brass E. Worsening of thrombotic thrombocytopenic purpura symptoms associated with desmopressin administration. *Thromb Haemost* 2004;**92**:886–7.
24 **McKeown LP**, Connaghan G, Wilson O, *et al*. 1-Desamino-8-arginine-vasopressin corrects the hemostatic defects in type 2B von Willebrand's disease. *Am J Hematol* 1996;**51**:158–63.
25 **Ehl S**, Severin T, Sutor AH. DDAVP (desmopressin; 1-deamino-cys-8-D-arginine-vasopressin) treatment in children with haemophilia B. *Br J Haematol* 2000;**111**:1260–2.

ANSWERS

1. (B) 2. (C) 3. (A) 4. (D) 5. (B)