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REVIEW

Desmopressin in treatment of haematological disorders and in prevention of surgical bleeding

Peter J. Svensson [a,1], Peter B.F. Bergqvist [b,2], Kristian Vinter Juul [b,3], Erik Berntorp [a,*]

[a] Lund University, Centre for Thrombosis and Haemostasis, Skane University Hospital, 205 02 Malmö, Sweden
[b] Ferring Pharmaceuticals A/S, Kay Fiskers Plads 11, 2300 Copenhagen S, Denmark

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ABSTRACT

Stimulation with the vasopressin analogue desmopressin (DDAVP) of extrarenal arginine vasopressin (AVP) V2-receptors in endothelial cells and possible in platelets increases the circulating levels of coagulation factor VIII (FVIII), von Willebrand factor (VWF) and tissue plasminogen activator (t-PA). The purpose of this paper is to provide an updated review of current information on the efficacy and safety of DDAVP in the treatment of haemophilia, von Willebrand disease (VWD), uremia, liver cirrhosis, and in congenital or drug-induced platelet dysfunction — under surgical or non-surgical conditions. In summary, desmopressin is an effective haemostatic drug that when administered i.v., s.c. or intranasally increases plasma levels of FVIII and VWF 2–6 times and improves platelet function. It has a proven haemostatic efficacy in mild haemophilia A and VWD as well as in uremia, liver cirrhosis and in congenital and acquired, drug induced platelet dysfunction. Desmopressin has few side effects but observation is advised in small children and elderly.

1. Introduction

Stimulation with the vasopressin analogue desmopressin (DDAVP) of extrarenal arginine vasopressin (AVP) V2-receptors in endothelial cells (ECs) and possible in platelets increases the circulating levels of coagulation factor VIII (FVIII), von Willebrand factor (VWF) and tissue plasminogen activator (t-PA) (Fig. 1) [1–3].

The mode of action is that desmopressin stimulates endothelial V2R to induce EC Weibel-Palade Body (WPB)-aversion [3], which in turn increases membrane-bound and circulating VWF as well as FVIII [4]. In addition to VWF and factor VIII, desmopressin also induces the release and membrane presentation of P-selectin [5], which mediates platelet rolling on ECs under high shear conditions through PSGL-1/P-selectin interaction [6]. A recent study confirmed that desmopressin has no direct effects on platelets in vitro, but demonstrated the novel observation that desmopressin increases endothelial adhesiveness for platelets and platelet adhesion to collagen by releasing a proadhesive factor, likely VWF, from ECs [7].

As a result of the increase in VWF, there is an increase in the number of factor VIII binding sites, on the one hand, and factor VIII is therefore better protected against proteolytic breakdown, on the other [1]. On average, a rapid, three-fold increase in the factor VIII and VWF values can be expected after intravenous administration of desmopressin [8–11].

Since the pioneering studies of Mannucci et al. [12,13] in the mid 1970s DDAVP has been used to treat patients with primary haemostatic disorders of varying origin, in particular with VWD [14] or mild haemophilia A (residual activity >5%) [15], and to stimulate Factor VIII-release in plasma donors. In these conditions, the bleeding and clotting times in the majority of cases can be reduced or normalised with desmopressin [16–18]. Later studies established that even major surgical interventions can be carried out under the protection of elevated coagulation factor levels induced by several doses of desmopressin and that desmopressin is also valuable in the treatment of spontaneous and traumatic bleeding episodes [19,20]. In contrast to AVP, desmopressin is relatively inactive at V1 receptors, even at high doses, thus avoiding V1-receptor mediated contraction of smooth muscle in the GI tract and blood vessels [21,22].

The primary purpose of this paper is to provide an updated review of current information on the efficacy and safety of DDAVP in the treatment of haemophilia, von Willebrand disease (VWD), uremia, liver cirrhosis, and in congenital or drug-induced platelet dysfunction — under surgical or non-surgical conditions. Off-label indications will also be reviewed where evidence is available.

* Corresponding author. Tel.: +46 40331000; fax: +46 40336255.
E-mail addresses: peter.svensson@med.lu.se (P.J. Svensson), pbe@ferring.com (P.B.F. Bergqvist), kvj@ferring.com (K.V. Juul), erik.berntorp@med.lu.se (E. Berntorp).
[1] Tel.: +46 40337498; fax: +46 40336255.
[2] Tel.: +45 2878 7478; fax: +45 2817 6478.
[3] Tel: +45 2878 7544; fax: +45 28176548.

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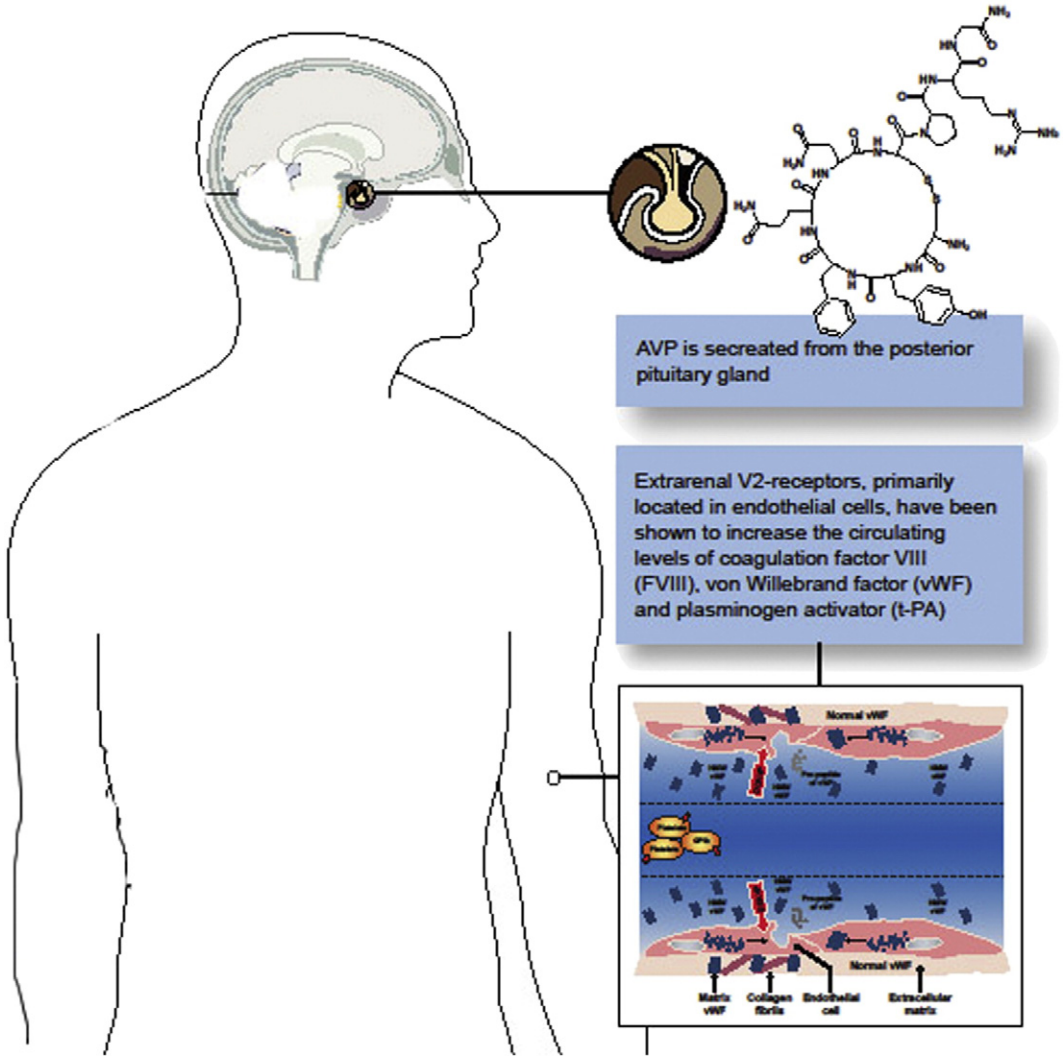

Fig. 1. AVP release from anterior pituitary. Location and function of AVP V2-receptor in endothelium.

2. Haemophilia and von Willebrand disease (VWD)

2.1. Effects of desmopressin in patients not undergoing surgery

Most patients with Type 1 VWD and FVIII/VWF levels >10 IU/mL do respond to DDAVP [23] whereas Type 2 has a more variable response pattern [24]. The use in most cases of Type 2B is contraindicated due to the risk of platelet aggregation and thrombocytopenia and Type 3 VWD is nonresponsive.

In patients who treat themselves in case of acute bleeds or e.g. heavy menstruations, subcutaneous or especially nasal administration has the added benefit that patients also can administer desmopressin at home as self-treatment [10]. The licensed product in Sweden is formulated as 15 μg/mL and is diluted in 10 mL of saline injected during 10 min in case of i.v. injection and undiluted as s.c. injection. Two other formulations, 4 μg/mL desmopressin or 40 μg/mL desmopressin, have also been used with no differences found in terms of efficacy [11]. Intranasal administration is given as a spray, 150 μg per dose, one in each nostril. For testing DDAVP responsiveness blood samples are taken after i.v. injection as a minimum after 30–60 min and 4 h in order to get a reliable figure on recovery and clearance of FVIII and VWF postinfusion [25]. As the s.c. and intranasal routes give a slower response the first sample should be taken after 60 to 90 min. The i.v. route should be used to test responsiveness as the other routes may give a variable adsorption of DDAVP. The requirement for responsiveness varies with which kind of haemostatic effect is needed. For major surgery levels of 50 IU/mL are a minimum whereas for minor surgery and bleeds levels in the range of 30 IU/mL may suffice.

In patients with VWD and platelet dysfunctions bleeding time is significantly reduced after administration of desmopressin, although nowadays bleeding time is considered not to be a good predictor of haemostasis. An example is shown below in Fig. 2, adapted from a study by Schulman [26], investigating the effects of s.c. administration with the 15 μg/mL preparation.

Similar results in terms of shortening bleeding time have been shown with doses of 10 $\mu g/m^2$ (maximum dose of 24 μg) i.v. desmopressin in VWD, platelet function defects, VWD and platelet defects together, or isolated prolongation of the bleeding time [27]. Shortening of the bleeding time was also observed in two patients with aspirin-induced platelet defects and even in two normal subjects.

In patients with VWD or platelet dysfunction mean bleeding time was reduced from 20.0 min pre-treatment to 10.3 min after treatment with s.c. desmopressin (0.3–0.4 μg/kg), indicating an improved platelet status and function (Table 1) [28]. This improvement was equal for both patients with VWD and those with platelet functional defects without known aetiology.