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REVIEW ARTICLES

Desmopressin: an historical introduction

P. M. MANNUCCI

Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and Department of Medicine and Medical Specialties, University of Milan, and the IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, Milan, Italy

Summary. This review summarizes the steps that led to the development of desmopressin as a hemostatic agent. This drug has broadened the panel of pharmacological agents that can be used to treat or prevent bleeding in patients with mild hemophilia and von Willebrand disease.

Keywords: desmopressin, haemophilia, von Willebrand disease

Pharmacological compounds that potentiate the haemostatic mechanisms have attracted the interest of many scientists for more than two centuries. The first relevant observation in this field was made in the middle of the eighteenth century by William Hewson [1], who noticed an acceleration of blood clotting after acute haemorrhage. This observation was revisited first in 1903 by Vosburgh and Richards [2], who reported a shortening of the clotting time in dogs after administration of adrenaline. It was followed in 1914 by the famous American physiologist Cannon *et al.* [3–5], who reported several detailed investigations on the effect on blood clotting of adrenaline and of various procedures (such as pain, emotional excitement, haemorrhage and splanchnic stimulation) that release adrenaline in dogs. The first real clue in understanding the mechanism underlying the acceleration of blood clotting induced by adrenaline was the discovery by Ingram [6] that the injection of adrenaline into healthy humans is followed by a short-term rise in the coagulant activity of factor VIII (FVIII:C), the factor deficient in classic haemophilia. Interestingly, adrenaline also raises FVIII:C in FVIII:C-deficient patients with mild haemophilia [6] and von Willebrand disease (VWD) [7]. Strenuous physical exercise produces a similar rise [8], both in normal persons and in mild haemophiliacs, and this rise is mediated by the release of endogenous adrenaline.

These observations stimulated further research, because it was obvious that pharmacologic compounds that circumvented the need for strenuous exercise and lacked the side-effects of adrenaline could be potentially useful to raise FVIII:C in the management of haemophilia and VWD. In particular, this therapy might decrease the need for the use of blood products, which transmitted hepatitis and other infections and were not largely available in the 1960s when these studies first appeared. Hence, a potential alternative to plasma-derived FVIII:C appeared at that time a substantial advance for the management of haemophilia and VWD. Other pharmacological compounds, such as vasopressin and its derivates and insulin, were subsequently found to induce a short-term rise of FVIII:C [9], but again severe side-effects made their clinical use unrealistic.

An important step forward was made in the early 1970s, with the independent observations by Cash *et al.* [10] and Mannucci *et al.* [11] that 1-deamino-8-D-arginine vasopressin (DDAVP, desmopressin), a synthetic analogue of the antidiuretic hormone L-arginine vasopressin (AVP), raises plasma FVIII:C levels when infused into healthy volunteers. The effects of desmopressin on the haemostatic system are not restricted to FVIII:C, because the compound, like other drugs that augment FVIII:C, also raises the plasma levels of the von Willebrand factor (VWF) [12] and plasminogen activator [13]. Unlike the natural antidiuretic hormone and the majority of its synthetic analogues, desmopressin has very little effect on the V1 vasopressin receptors of the smooth muscle cells, the ratio of its antidiuretic (mediated by

Correspondence: P. M. Mannucci, Via Pace 9, 20122 Milano, Italy.
Tel.: +39 0255035421; fax: +39 02 50320723;
e-mail: pmmannucci@libero.it

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V2 receptors) to its pressor V1 activity being approximately 2000–3000 times greater than that of the parent hormone [14]. Accordingly, it produces little or no constriction of the vessel and smooth muscle [14], as these effects are related to the stimulation of V1 receptors. These differences are the result of molecular manipulations of vasopressin involving deamination of homocysteine at position 1, which results in a more prolonged duration of action of the antidiuretic defect (2–6 h for vasopressin, 6–24 h for desmopressin), and substitution of the D-isomer of arginine for L-arginine at position 8, which leads to a diminished pressor activity [14].

In 1977, Mannucci *et al.* [15] were the first to use desmopressin for the prevention of bleeding during dental extraction and then during major surgical procedures carried out in 25 patients with moderate or mild haemophilia or VWD. Surgical procedures were safely performed without the administration of blood products, showing that autologous FVIII:C and VWF induced by administration of desmopressin in plasma could effectively replace homologous FVIII:C and VWF contained in blood products. The only side-effects were mild facial flushing, a 10–20% increase in pulse rate and minor falls in systolic and diastolic blood pressure. These results were subsequently confirmed by several investigators, and desmopressin has now an established place in the management of patients with mild haemophilia A and type 1 VWD [16].

Subsequently, its use was proposed with increasing frequency in the management of haemostatic disorders other than haemophilia and VWD, suggesting that the clinical indications for the compound might be even wider than hitherto appreciated (Fig. 1). In 1986, Salzman *et al.* [17] showed that desmopressin reduced by approximately 30% blood loss and transfusion requirements during operations of cardiac surgery. Subsequent attempts to reproduce these findings gave varied results, but the majority of them failed to confirm the marked benefits originally found [18–20]. A few meta-analyses indicated that although desmopressin does indeed reduce perioperative blood loss, the effect is too small to influence other more relevant clinical outcomes such as the need for transfusion and reoperation [21–23]. Desmopressin did not reduce blood loss nor transfusion requirements during elective partial hepatectomy, another operation often associated with major blood loss [24]. The initial finding that desmopressin reduced blood loss associated with posterior spinal surgery for idiopathic scoliosis [25] was not confirmed by subsequent studies [26–28]. The use of this drug to shorten the prolonged bleeding time in patients with uraemia [29] is no longer necessary after the widespread use of recombinant erythropoietin which makes this haemostasis abnormality much less frequent [30]. The use of desmopressin in some patients who bleed as a consequence of inherited and acquired defects of platelet function may be considered, although these indications are not supported by sound clinical evidence on relevant endpoints [31]. The most common adverse effects of desmopressin are usually mild (facial flushing, transient hyponatremia), although arterial thrombotic events have been reported [31].

The development and clinical use of desmopressin in clinical medicine is summarized in Fig. 1. In all, the availability of desmopressin has broadened the panel of pharmacological agents that can be

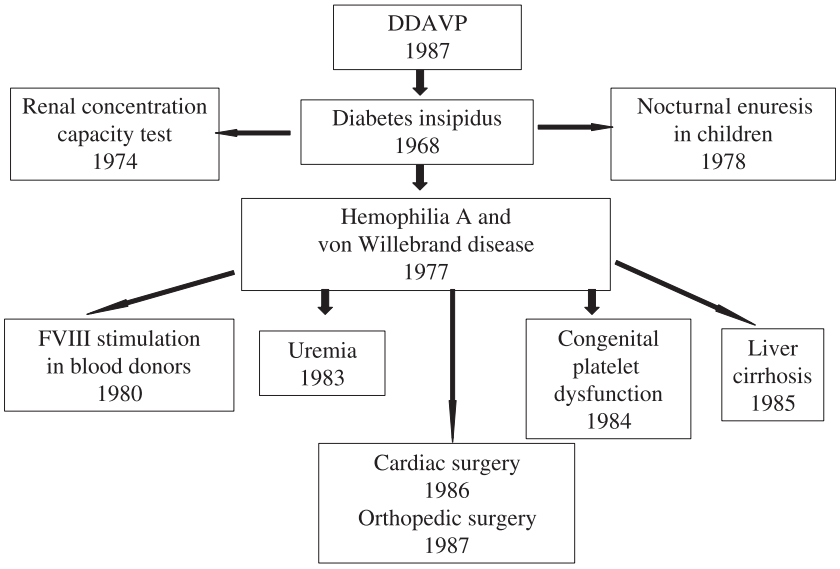

Fig. 1. Chronological development of clinical indications for desmopressin (DDAVP).

employed to treat acute haemorrhage or to prevent bleeding in patients with mild haemophilia and VWD. This drug is not a universal panacea good for all purposes but is relatively inexpensive and has little side-effects. We could demonstrate that its early use in Italy at the onset of the outbreak of acquired immunodeficiency syndrome (AIDS) reduced the number of patients with mild haemophilia A who became human immunodeficiency virus (HIV)-infected, in comparison with Italian patients with haemophilia B who could not use desmopressin because it does not raise factor IX [32]. One has to be cognizant that the use of any drug that potentiates haemostasis cannot be without the risk of thrombosis, particularly when they are used in elderly people and in those with other risk factors for thrombosis.

References

1 Hewson W. Some further observation on the coagulable lymph, and on the sudden changes produce upon it. In: Gulliver G, ed. *The Works of William Hewson*. London: 1984: 69.

2 Vosbourgh CM, Richards AN. An experimental study of the sugar content and extravascular coagulation of the blood after administration of adrenaline. *Am J Physiol* 1903; **9**: 36.

3 Cannon WB, Gray H. Factors affecting the coagulation time of blood. II. The hastening or retarding of coagulation by adrenaline injections. *Am J Physiol* 1914; **34**: 232.

4 Cannon WB, Mendenhall WL. Factors affecting the coagulation time of blood. III. The hastening of coagulability stimulating the splanchnic nerves. *Am J Physiol* 1914; **34**: 243.

5 Cannon WB, Mendenhall WL. Factors affecting the coagulation time of blood. IV. The hastening of coagulation in pain and emotional excitement. *Am J Physiol* 1914; **34**: 252.

6 Ingram GIC. Increase in antihaemophilic globulin activity following infusion of adrenaline. *J Physiol (London)* 1961; **156**: 217–224.

7 Egeberg O. Changes in the activity of antihemophilic A factor (F. VIII) and in the bleeding time associated with muscular exercise and adrenaline infusion. *Scand J Clin Lab Invest* 1963; **15**: 539–49.

8 Rizza CR. Effect of exercise on the level of antihaemophilic globulin in human blood. *J Physiol* 1961; **156**: 128–35.

9 Mannucci PM, Gagnatelli G, D'Alonzo R. Stress and blood coagulation. In: Brinkhous KM, Hinnon S, eds. *Thrombosis: Risk Factors and Diagnostic Approach*. Stuttgart: Schattauer Verlag, 1972: 105–10.

10 Cash JD, Gader AM, da Costa J. The release of plasminogen activator and factor VIII to lysine vasopressin, arginine vasopressin, I-desamino-8-D-arginine vasopressin, angiotensin and oxytocin in man. *Br J Haematol* 1974; **27**: 363–4.

11 Mannucci PM, Aberg M, Nilsson IM, Robertson B. Mechanism of plasminogen activator and factor VIII increase after vasoactive drugs. *Br J Haematol* 1975; **30**: 81–93.

12 Mannucci PM, Pareti FI, Holmberg L, Nilsson IM, Ruggeri ZM. Studies on the prolonged bleeding time in von Willebrand's disease. *J Lab Clin Med* 1976; **88**: 662–71.

13 Gader AM, da Costa J, Cash JD. A new vasopressin analogue and fibrinolysis. *Lancet* 1973; **2**: 1417–18.

14 Richardson DW, Robinson AG. Desmopressin. *Ann Intern Med* 1985; **103**: 228–39.

15 Mannucci PM, Ruggeri ZM, Pareti FI, Capitanio A. 1-deamino-8-D-arginine vasopressin: a new pharmacological approach to the management of haemophilia and von Willebrands' diseases. *Lancet* 1977; **1**: 869–72.

16 Kasper CK. Desmopressin acetate (DDAVP). Good news. *JAMA* 1984; **251**: 2564–5.

17 Salzman EW, Weinstein MJ, Weintraub RM *et al.* Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. A double-blind randomized trial. *N Engl J Med* 1986; **314**: 1402–6.

18 Rocha E, Llorens R, Paramo JA, Arcas R, Cuesta B, Trenor AM. Does desmopressin acetate reduce blood loss after surgery in patients on cardiopulmonary bypass? *Circulation* 1988; **77**: 1319–23.

19 Hackmann T, Gascoyne RD, Naiman SC *et al.* A trial of desmopressin (1-desamino-8-D-arginine vasopressin) to reduce blood loss in uncomplicated cardiac surgery. *N Engl J Med* 1989; **321**: 1437–43.

20 Ansell J, Klassen V, Lew R *et al.* Does desmopressin acetate prophylaxis reduce blood loss after valvular heart operations? A randomized, double-blind study. *J Thorac Cardiovasc Surg* 1992; **104**: 117–23.

21 Fremes SE, Wong BI, Lee E *et al.* Metaanalysis of prophylactic drug treatment in the prevention of postoperative bleeding. *Ann Thorac Surg* 1994; **58**: 1580–8.

22 Cattaneo M, Harris AS, Stromberg U, Mannucci PM. The effect of desmopressin on reducing blood loss in cardiac surgery – a meta-analysis of double-blind, placebo-controlled trials. *Thromb Haemost* 1995; **74**: 1064–70.

23 Henry DA, Moxey AJ, Carless PA *et al.* Desmopressin for minimizing perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2004; art. CD001884.

24 Wong AY, Irwin MG, Hui TW, Fung SK, Fan ST, Ma ES. Desmopressin does not decrease blood loss and transfusion requirements in patients undergoing hepatectomy. *Can J Anaesth* 2003; **50**: 14–20.

25 Kobrinsky NL, Letts RM, Patel LR *et al.* 1-desamino-8-D-arginine vasopressin (desmopressin) decreases operative blood loss in patients having Harrington rod spinal fusion surgery. A randomized, double-

blinded, controlled trial. *Ann Intern Med* 1987; **107**: 446–50.
26 Guay J, Reinberg C, Poitras B *et al.* A trial of desmopressin to reduce blood loss in patients undergoing spinal fusion for idiopathic scoliosis. *Anesth Analg* 1992; **75**: 405–10.
27 Theroux MC, Corddry DH, Tietz AE, Miller F, Peoples JD, Kettrick RG. A study of desmopressin and blood loss during spinal fusion for neuromuscular scoliosis: a randomized, controlled, double-blinded study. *Anesthesiology* 1997; **87**: 260–7.
28 Alanay A, Acaroglu E, Ozdemir O, Ercelen O, Bulutcu E, Surat A. Effects of deamino-8-D-arginin vasopressin on blood loss and coagulation factors in scoliosis surgery. A double-blind randomized clinical trial. *Spine* 1999; **24**: 877–82.
29 Mannucci PM, Remuzzi G, Pusineri F *et al.* Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 1983; **308**: 8–12.
30 Moia M, Mannucci PM, Vizzotto L, Casati S, Cattaneo M, Ponticelli C. Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin. *Lancet* 1987; **2**: 1227–1229.
31 Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997; **90**: 2515–21.
32 Mannucci PM, Ghirardini A. Desmopressin: twenty years after. *Thromb Haemost* 1997; **78**: 958.