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COMMENTARY

Factor VIII and von Willebrand factor are wavering proteins: the basis for the therapeutic development of desmopressin

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Concentrations of coagulation factors are stable in human plasma, with the notable exception of fibrinogen, which is an acute phase reactant to stimuli such as tissue damage and inflammation. The rise of plasma fibrinogen and its subsequent fall occurs over a period of 3 to 4 days needed for an increased synthesis and ceases when the triggers are no longer present, as is typical for acute-phase reactants. The same pattern of changes occurs for factor (F)VIII and its companion von Willebrand factor (VWF), also acute phase reactants. At variance, these hemostasis proteins have the rather peculiar feature of short-term rises that occur within minutes after the stimulus and subside equally rapidly.

It has been known for centuries that human blood clots more rapidly after stressful stimuli, but it was only in the 1960s that pioneer studies of Ingram [1] and Rizza [2] showed that hypercoagulability was due to the short-term increase of FVIII after adrenaline infusion and bouts of strenuous muscular exercise: in normal individuals as well as in patients with partial deficiencies of FVIII and VWF as nonsevere hemophilia A and type 1 von Willebrand disease (VWD), but not in cases with severe deficiency. This observation led to the mechanistic view that the short-term increase of these proteins was due to their release from body stores that are empty in severe deficiencies.

Since their pioneer studies, both Ingram [1] and Rizza [2] considered the possibility of exploiting therapeutically this peculiar feature of FVIII and VWF in persons with nonsevere hemophilia and VWD. Obviously, this was made impossible by the fact that neither adrenaline infusion nor strenuous muscular exercise were a feasible clinical alternative to factor replacement therapy. However, this potential approach raised my attention when I was a mentee of both Ingram [1] and Rizza [2] in the late 1960s in London and Oxford. The jumpy behavior of a few hemostasis factors also attracted the attention of John Cash, who in Edinburgh, being specifically interested in fibrinolysis, studied the short-term increase of plasminogen activator [3].

In the 1960s, there were still unmet needs for the treatment of the 2 main inherited bleeding disorders. The only weapon available for both was cryoprecipitate after the seminal work of Judith Pool. In the 1970s, more concentrated products manufactured from pooled human plasma became available and were the success story of the decade. However, they were expensive and not available in many settings, and the fact that they caused viral hepatitis began to emerge. This risk was particularly gloomy and unacceptable in persons with nonsevere hemophilia and VWD, who seldom needed treatment at the time of surgery or after trauma. With this unmet need, both the Edinburgh and Milan teams attempted to identify pharmacological approaches other than adrenaline and exercise. The quest was long and uncertain until we both identified the possibility of using desmopressin [4,5], a synthetic peptide originally developed to mimic the activity of the antidiuretic hormone vasopressin.

It remained to be demonstrated that the FVIII and VWF increases attained in plasma after the administration of desmopressin were as hemostatically competent as the naturally occurring proteins or those substituted by means of plasma-derived products. My colleagues and I in Milan thought to tackle this uncertainty by using desmopressin for dental extractions, with the caveat that any undue bleeding could be seen and controlled with local measures. Reassured by the favorable clinical experience in oral surgery, we chose to move to major surgical operations and reported the results in 1977 [6].

The favorable experience with desmopressin gained in Milan in nonsevere hemophilia and VWD was replicated in other hemophilia centers in Italy. Other countries did also approve the drug for this new

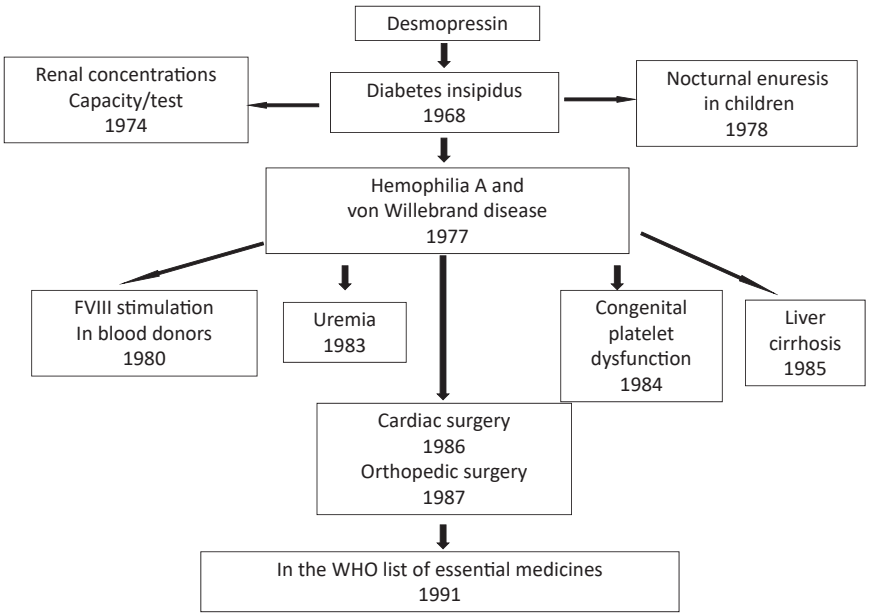

FIGURE Steps in the therapeutic development of desmopressin. FVIII, factor VIII; WHO, World Health Organization.

therapeutic use but only in the mid-1980s and had continued meanwhile to use pooled plasma products in nonsevere hemophilia. Because in the early 1980s HIV infection was being transmitted by these products to patients with congenital coagulation disorders, we chose to compare retrospectively the prevalence of HIV positivity in persons with mild hemophilia who in Italy used desmopressin earlier than in the USA, where the drug started to become available and was used when the HIV outbreak had already hit; the seroprevalence of HIV was much lower in Italy than in the USA [7]. We also used for comparison Italian persons with mild hemophilia B who, being unresponsive to desmopressin, had continued to use plasma-derived FIX [7]. Finding a higher HIV prevalence in these people than in persons with mild hemophilia A led us to conclude with admittedly indirect evidence that in the late 1970s and early 1980s, the early use of desmopressin in Italy helped to avoid HIV transmission by plasma products in a substantial number of persons with nonsevere hemophilia A.

Another important step for the early development of desmopressin as a therapeutic agent was the 1991 decision of the World Health Organization (WHO) to include it in the list of drugs considered essential for human use (Figure). It is likely that this WHO decision was prompted by the fact that desmopressin is much less expensive than plasma products and more easily accessible to resource-limited countries.

The 1980s and 1990s were decades of consolidation of the therapeutic use of desmopressin in the pivotal indications of nonsevere hemophilia A and VWD [8,9]. However, it was also explored as a general hemostatic agent in surgical operations characterized by excessive blood loss such as cardiac, orthopedic, and spinal surgery; in medical conditions associated with a bleeding tendency such as uremia and liver cirrhosis, to enrich with FVIII blood donations; and in inherited disorders of platelet function (Figure). For the time being, none of these indications has accrued unequivocal evidence, and desmopressin is not largely employed beyond the original goal to achieve a short-term increase of FVIII and VWF in nonsevere hemophilia A and type 1 VWD [8,9]. A number of reports helped to strengthen this indication. Rodeghiero et al. [10] showed in 1989 that the factor rise after desmopressin was reproducible over time in the same individual, leading to the still current recommendation to carry out in potential beneficiaries a test of desmopressin administration prior to surgery or invasive procedures. However, limitations of use became apparent, such as the fact that, at variance with the intra-individual consistency of the biological response, there was a high degree of between-individual variability [11]. Moreover, repeated administrations of desmopressin within a short time period led to progressively lower responses [12]. This phenomenon of tachyphylaxis drove the most recent recommendation contained in the World Federation of Hemophilia guidelines of using in each treated case no more than 2 daily doses for a maximal period of 3 consecutive days.

This implies in many instances the need to use beside desmopressin products containing FVIII when invasive procedures demand long-term increases of plasma FVIII and VWF. The issues of tachyphylaxis and the need for supplementary FVIII have been recently tackled by a group of Dutch hemophilia centers that chose to randomize persons with nonsevere hemophilia undergoing oral surgery to intravenous desmopressin for 3 daily doses followed on day 4 by recombinant FVIII (rFVIII) [13]. Combined desmopressin/rFVIII was randomly compared with rFVIII only [14]. Safety and hemostatic efficacy of the combined regimen were equal to those of cases treated with rFVIII only, but with a significant reduction of factor use and related cost reductions. In a brief report published in this issue of *Research and Practice in Thrombosis and Haemostasis*, Romano et al. [15] also addressed afresh the burden of tachyphylaxis, confirming in 26 cases who underwent invasive procedures that the early posttreatment response to desmopressin was very similar to that obtained before surgery in the context of the so-called desmopressin test [10]. However, responses after the second and third postoperative dose were on average between 36% and 45% lower than after the first. The main comment by the authors is that the decrease of the FVIII

response after repeated desmopressin doses was more marked than in the early study that showed the occurrence of tachyphylaxis [15]. Within the limitations of an indirect comparison, this report reinforces the concept that it is necessary to monitor plasma FVIII levels in nonsevere hemophilia A and those of VWF in VWD in order to assure adequate hemostasis in the postoperative period. On the whole, these recent studies from the Netherlands are revamping the suboptimal use of this essential WHO drug in nonsevere hemophilia [16] and substantiate the World Federation of Hemophilia recommendations of administering it for no more than 2 to 3 days in the postoperative period, followed by the use of FVIII or VWF products as needed.

Perhaps the suboptimal use is also explained by a shortage of this WHO essential drug, at least in North America, and for the intranasal formulation. The latter is preferably used in the USA and Canada, particularly by pediatricians, whereas the intravenous and subcutaneous formulation more largely employed in Europe. The shortage is due to the recall in August 2020 by the manufacturer and distributor of the intranasal spray formulation (Ferring Pharmaceutical and CSL Behring) [17]. The only alternative to STIMATE (Ferring Pharmaceuticals) was the formulation employed for diabetes insipidus and enuresis, which is much less concentrated than that for bleeding disorders (10 mcg vs 150 mg) and thus needs many fastidiously repeated nasal sprays in order to obtain a therapeutic response [17]. With the prospect of shortage extending into 2023, advocacy patient organizations petitioned the US Food and Drug Administration to add desmopressin to the National Drug Shortage list [17]. Accordingly, the Food and Drug Administration has newly asked STAQ Pharma to source a new desmopressin nasal spray to meet patients' needs. Apparently, the STAQ product is already available in at least 31 states in the USA and should soon become more widely available [17].

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Both the authors wrote, read, and approved the commentary.

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE AND ARTIFICIAL INTELLIGENCE–ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors declare that they have not used generative artificial intelligence and artificial intelligence–assisted technologies in the writing process.

RELATIONSHIP DISCLOSURE

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