LIT.001.0354

The Lancet · Saturday 23 April 1977

1-DEAMINO-8-D-ARGININE VASOPRESSIN: A NEW PHARMACOLOGICAL APPROACH TO THE MANAGEMENT OF HAEMOPHILIA AND VON WILLEBRAND'S DISEASE

P. M. MANNUCCI Z. M. RUGGERI
F. I. PARETI ANNA CAPITANIO

Third University Department of Clinical Medicine, Hæmophilia and Thrombosis Centre Angelo Bianchi Bonomi, Milan, Italy

Summary 1-Deamino-8-D-arginine vasopressin (D.D.A.V.P.) infusion causes a marked increase in factor-VIII (antihæmophilic-factor)-related properties in patients with moderate and mild hæmophilia and von Willebrand's disease (vWd). The possibility was therefore evaluated that such an autologous factor-VIII response might be hæmostatically effective, allowing patients to undergo surgery without plasma concentrates. 0·3 μg/kg of D.D.A.V.P. given before dental surgery and repeated in the early postoperative period was followed by a two to three fold rise in factor-VIII coagulant activity (VIII C.A.) in four patients with moderate and mild hæmophilia. In two, there was no abnormal bleeding after dental extraction, whereas plasma concentrates were necessary to control oozing from the sockets in the remaining two patients. A higher D.D.A.V.P. dosage (0·4–0·5 μg/kg) in patients with higher starting VIII C.A. (9% or more) was followed by a more marked response (four to six fold). VIII C.A. levels up to 100% of average normal were achieved and dental extractions and major surgery (such as cholecystectomy, thoracotomy, and two tonsillectomies) were carried out successfully in six patients with mild hæmophilia and in two with vWd. The mean half-life of autologous VIII C.A. was 9·4 h (range 7·5–11·6). Plasma and urine osmolality showed no consistent variation after drug administration. Thus D.D.A.V.P. appears a promising pharmacological alternative to plasma concentrates in the management of some patients with hæmophilia and vWd.

Introduction

IN patients with congenital coagulation disorders, plasma concentrates of clotting factors have to be used when surgery is undertaken. Patients with moderate and mild hæmophilia and von Willebrand's disease (vWd), who have little exposure to blood products, carry a higher risk of developing hepatitis after introduction of factor VIII (F VIII) (antihæmophilic factor) concentrates.[1] Hence, an alternative to plasma derivatives would be a substantial advance in their management. Several drugs (such as catecholamines, vasopressin derivatives, and insulin) are known to increase F VIII,[2–4] but unpleasant side-effects limit potential clinical application. 1-deamino-8-D-arginine vasopressin (D.D.A.V.P.), a synthetic analogue of the antidiuretic hormone 8-arginine vasopressin, is well tolerated when infused intravenously in normal volunteers and produces a marked, transient increase in plasma F VIII procoagulant activity (VIII C.A.), F VIII-related antigen (VIII Ag) and of the factor needed for aggregation of washed platelets by the antibiotic ristocetin (VIII R.A.F.).[4,5] Such an increase is also observed in patients with von Willebrand's disease (vWd)[5] and hæmophilia A[6] characterised by measurable plasma concentrations of F VIII-related properties, whereas the drug is ineffective in patients with severe hæmophilia and vWd.[5,6]

The rise in VIII C.A., VIII Ag and VIII R.A.F. induced by D.D.A.V.P. appears so rapidly that increased synthesis is unlikely to account for it, and endogenous release of autologous F VIII from storage sites (possibly the endothelial cells[7]) appears more likely. The present investigation shows that such F VIII is functionally active in hæmostasis, so that surgery can be safely carried out without plasma concentrates in patients with mild hæmophilia and vWd.

Patients and Methods

Patients

Two patients with moderate hæmophilia (VIII C.A. between 2 and 5%), eight patients with mild hæmophilia (VIII C.A. higher than 5%) and two patients with vWd undergoing dental extractions or other surgical procedures gave informed consent to a therapeutic trial with D.D.A.V.P. Their main laboratory values and the surgical procedures are shown in table I. All patients had a life-long history of excessive and prolonged bleeding after surgical challenge and dental extractions.

Drug Administration

D.D.A.V.P. (Ferring AB, Malmo, Sweden) was added to 30 ml of isotonic saline and administered shortly before operation by constant intravenous infusion over 5 min. Additional doses were usually given postoperatively. There was no consistent side-effect; occasionally, a few patients experienced mild and short-lasting facial flushing.

Tranexamic acid (1 g orally three times a day) was started 2 h before the operations and continued until healing was complete. Plasma derivatives were withheld from all patients unless bleeding occurred. The ethical justification for this was based upon the fact that bleeding after dental extraction is

8017 © The Lancet Ltd 1977

LIT.001.0355

MAIN LABORATORY MEASUREMENTS IN 12 PATIENTS

Patient no.	Age	Sex	VIII C.A. %	VIII Ag %	VIII R.A.F. %	Bleeding time (min)	Surgical procedures
1	32	M	2	115	..	..	Extraction 1 tooth
2	21	M	7	81	..	..	Extraction 2 teeth
3	51	M	5	116	..	..	Extraction 2 teeth
4	26	M	9	89	..	..	Extraction 1 tooth
5	16	M	12	71	..	..	Extraction 2 teeth
6	54	M	10	96	..	..	Extraction 2 teeth
7	41	M	9	127	..	..	Extraction 1 tooth
8	36	M	14	106	..	..	Extraction 1 tooth
9	38	M	16	95	..	..	Lymph-node biopsy, thoracotomy, and lung biopsy
10	19	M	18	81	..	..	Tonsillectomy
11 vWd	28	F	35	14	18	6	Tonsillectomy
12 vWd	42	M	44	22	<5	>20	Cholecystectomy
Normal range			56–148	49–145	45–141	1·55–6·15	

readily detectable and easily controlled by specific replacement therapy. In the second phase of the trial involving patients submitted to major surgical procedures, the use of D.D.A.V.P. was felt justified by the favourable experience gained with dental extractions.

Blood-sampling and Methods

Citrated venous blood for coagulation tests and heparinised samples for plasma osmolality were taken from the patients at various time intervals after D.D.A.V.P. administration. Urine samples were also collected and their osmolality measured. VIII C.A. (one stage assay), VIII Ag (immunoradiometric assay), VIII R.A.F. (washed platelet assay), and template bleeding time were done as described elsewhere.[8] All assays of the F VIII-related properties are expressed as percentage of average normal plasma.

Results

Dental extractions

In the first four patients undergoing extraction of one or two teeth, D.D.A.V.P. 0·3 μg/kg was administered. Since the post-transfusion rise in VIII C.A. was transient, the same dose of D.D.A.V.P. was repeated usually at 12 h intervals after extraction. In patient 1, who had a basal VIII C.A. of 2% and a maximum response of 5% after D.D.A.V.P., cryoprecipitate infusion was necessary to control early postoperative bleeding (fig. 1). Higher levels of VIII C.A. were attained after infusion in patients 2 (from 7 to 22%) and 3 (from 5 to 14%). The increase was transient but a new response was elicited when the same dose of D.D.A.V.P. was repeated at 12 h intervals; no bleeding occurred after extraction (fig. 1). In patient 4 an immediate two-fold rise in VIII C.A. (from 9 to 21%) was accompanied by early hæmostasis: oozing from the sockets, however, occurred 22 h after the extraction and required cryoprecipitate administration (fig. 1).

After this initial experience, subsequent therapeutic trials were done in patients with higher basal VIII C.A. concentrations (9% or more), a higher D.D.A.V.P. dosage (0.4 μg/kg) being repeated twice at 12 h intervals in the first 24 h after extraction. In this series (patients 5–8), the VIII C.A. increase after the first D.D.A.V.P. infusion was greater (from four to six fold) and there was no bleeding complication (fig. 2).

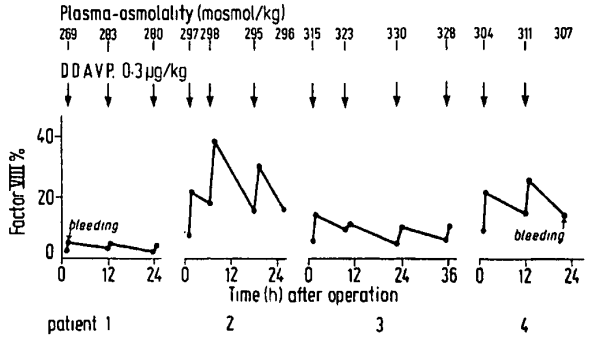

Fig. 1—Antihæmophilic factor (F VIII) procoagulant activity, and plasma osmolality after D.D.A.V.P. infusions (vertical arrows) in patients 1–4 with mild or moderate hæmophilia, undergoing dental extractions.

The plasma levels of VIII C.A. (●———●) assayed before and 15 min after each D.D.A.V.P. infusion are shown on the vertical axis and expressed as % of average normal plasma (frozen plasma pooled from 20 normal individuals). Plasma osmolality (indicated by vertical bars) was tested before each D.D.A.V.P. infusion.

Other Surgical Procedures

Patient 9, with a typical history of mild hæmophilia, showed bilateral enlargement of the hilar lymph-nodes on X-ray and also symmetrical nodular lung lesions. Biopsy of an enlarged cervical lymph-node was carried out after a single D.D.A.V.P. infusion (0·4 μg/kg) which raised VIII C.A. from 15 to 71%. There was no hæmatoma formation or oozing, and the wound healed normally. Since the biopsy was not informative, the patient underwent thoracotomy and lung biopsy (which gave histological evidence of sarcoidosis). After D.D.A.V.P. (0·5 μg/kg.), VIII C.A. rose from 16 to 94% and the procedure was carried out with no abnormal bleeding. After

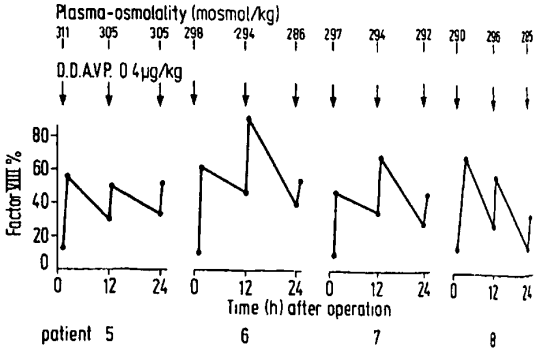

Fig. 2—VIII C.A. (●———●) after D.D.A.V.P. infusion in patients 5–8 with mild hæmophilia undergoing dental extractions.

LIT.001.0356

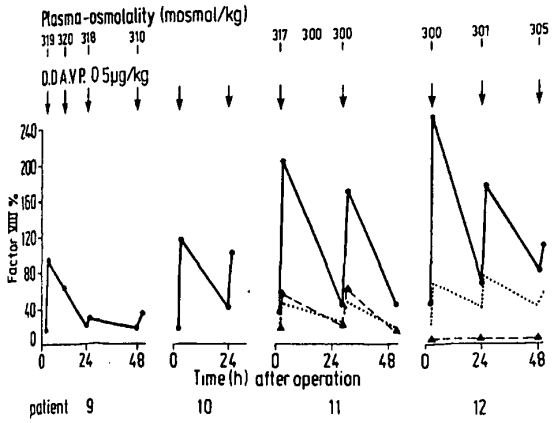

Fig. 3—VIII C.A. (●———●), VIII Ag (.....) and (VIII R.A.F. ▲— — —▲) in patients 9–12 undergoing major surgical procedures.

In patients 9 and 10 with mild hæmophilia the operations were thoracotomy and tonsillectomy respectively; in patients 11 and 12 with vWd, tonsillectomy and cholecystectomy. In patient 11 the bleeding time was normal (6 min) before the infusion was not repeated thereafter; in patient 12, it was recorded as >20 min before D.D.A.V.P. and throughout the observation period.

12 h VIII C.A. had fallen to 66%, and a further dose of D.D.A.V.P. was not followed by a measurable response; subsequently, two additional doses gave minimal VIII C.A. responses (from 20 to 26 and from ffl8 to 34%). These levels, however, were sufficient to maintain hæmostasis, and the postoperative course was uneventful (fig. 3).

In patient 10 with mild hæmophilia, tonsillectomy was carried out after a postoperative infusion of D.D.A.V.P. (0·5 μg/kg) which raised VIII C.A. from 19 to 113%. The same dose was repeated after 24 h, and VIII C.A. increased from 40 to 101%. The surgical wound healed without further treatment (fig. 3).

Patients 11 and 12 with vWd, undergoing tonsillectomy and cholecystectomy respectively, were treated with D.D.A.V.P. (0·5 μg/kg) before surgery and at 24 h intervals postoperatively. In both there was a greater increase in VIII C.A. than in VIII Ag; this magnified the discrepancy between the two measurements already present before D.D.A.V.P. infusion. VIII R.A.F. rose threefold in patient 11 (who had a normal bleeding time before D.D.A.V.P.), whereas it remained unmeasurable (less than 5%) in patient 12 (whose prolonged bleeding time was unchanged after treatment (fig. 3).

Kinetic Studies

Disappearance curves of plasma VIII C.A. after D.D.A.V.P. were obtained by taking multiple blood-samples after the start of infusion in the eight patients with mild hæmophilia. VIII C.A. values obtained by substracting the basal values from each observation after D.D.A.V.P. were plotted on a log scale against time on a linear scale. Most of the curves were monophasic, but a few showed an additional rapid component, which is likely to represent equilibration between the intravascular and extravascular pools. The half-life was calculated from the best fitted line of the prolonged component of the curve, which represents the true half-life due to biological degradation. The mean half-life was 9·4 h (range 7·5–11·6).

Metabolic Studies

There was no restriction of water intake in the patients and intravenous fluids were given as usual during anæsthesia and postoperatively. Plasma osmolality, which was monitored at frequent intervals when D.D.A.V.P. was administered, showed no consistent variation (figs 1–3). There was also no striking change in urine osmolality

Discussion

In patients with moderate and mild hæmophilia and vWd, D.D.A.V.P. induces a marked rise in autologous F VIII which is hæmostatically effective providing that adequate plasma concentrations are attained. Criteria for therapeutic adoption of D.D.A.V.P. depend on the starting level of VIII C.A. in patients and on the concentrations which must be achieved to meet a given surgical challenge. Since the average rise to be expected with a single preoperative dose (0·4–0·5 μg/kg) is four to six times the starting level, we suggest that basal concentrations of 8–10% are the lower limits to undertake dental extractions, whereas concentrations up to 100% can be achieved in patients with 10–20% or more, thereby allowing major surgery. The response is transient, but the disappearance time of endogenous F VIII does not seem to be much shorter than that of exogenous F VIII introduced with cryoprecipitate or other plasma concentrates.[9–10] In at least two patients undergoing major surgery (nos. 9 and 12), the pronounced increase observed after the preoperative infusion was definitely followed by a decline of the response when repeated doses of D.D.A.V.P. were administered. Although these observations need confirmation in larger series, it appears either that stores of F VIII are being depleted or that perhaps the mechanism of release has been impaired by surgery. This, however, did not seem to be a major drawback in the management of patients with mild hæmophilia and vWd.

We suggest that, once hæmostasis has been firmly established at the time of surgery by D.D.A.V.P. administration, the natural concentration of F VIII and the non-specific increase induced by surgery[11] are likely to be sufficient to maintain hæmostasis, as shown in the present series. Even though tranexamic acid may have helped to reduce F VIII requirements after dental extractions,[12] such a synthetic antifibrinolytic compound is unlikely to account for the successful management of major operations such as tonsillectomy, thoracotomy, and cholecystectomy. Tranexamic acid may have also been useful to counteract the enhancement of fibrinolysis which follows the administration of D.D.A.V.P.[13] In the present series, any brief fibrinolytic response which occurred did not appear to have an adverse effect on hæmostasis.

D.D.A.V.P. is almost devoid of the vasoactive and gastrointestinal unpleasant side-effects of the other vasopressin derivatives but shows a powerful antidiuretic action in patients with cranial diabetes insipidus.[14–16] Since its plasma half-life is very short,[16] it is not surprising that large doses spaced at intervals of 12 h or more do not produce water overload in patients with normal water metabolism despite unrestricted intake. However, removal of the antidiuretic effect with maintenance of the F VIII response appears desirable for extensive therapeutic application of the drug. The relative simplicity of its octapeptide structure and independence of the F VIII

LIT.001.0357

effect from the antidiuretic activity* suggest that vasopressin analogues may soon become available with a powerful and specific potential for increasing F VIII in plasma.

We thank Prof. G. I. C. Ingram for continuous encouragement and stimulation and for his help in the preparation of the manuscript; and Dr Jan Mülder who made available D.D.A.V.P.

Requests for reprints should be addressed to P.M.M., III University Department of Clinical Medicine, Hæmophilia and Thrombosis Centre, Via Pace 15, 20122 Milan, Italy.

REFERENCES

1. Kasper, C. K., Kipnis, S. A. *J. Am. med. Ass.* 1972, **221**, 510.
2. Ingram, G. I. C. *J. Physiol.* 1961, **156**, 217.
3. Mannucci, P. M., Gagnatelli, G., D'Alonzo, R. *Thromb. Diath. hæmorrh.* 1972, **51**, 105.
4. Mannucci, P. M., Aberg, M., Nilsson, I. M., Robertson, B. *Br. J. Hæmat.* 1975, **30**, 81.
5. Mannucci, P. M., Pareti, F. I., Holmberg, L., Nilsson, I. M., Ruggeri, Z. M. *J. Lab. clin. Med.* 1976, **88**, 662.
6. Mannucci, P. M. Unpublished.
7. Bloom, A. L., Giddings, J. C., Wilks, C. J. *Nature New Biol.* 1973, **241**, 217.
8. Ruggeri, Z. M., Mannucci, P. M., Jeffcoate, S. L., Ingram, G. I. C. *Br. J. Hæmat.* 1976, **33**, 221.
9. MacMillan, C. W., Diamond, K. L., Surgenor, D. M. *New Engl. J. Med.* 1961, **265**, 224.
10. Nilsson, I. M., Blombäck, M., Ramgren, O., Francken, I. *Acta med. scand.* 1962, suppl. 379, 61.
11. Egeberg, O., *ibid.* 1962, **171**, 679.
12. Walsh, P. N., Rizza, C. R., Matthews, J. M., Eipe, J., Kernoff, P. B. A., Coles, M. D., Bloom, A. L., Kaufman, B. M., Beck, P., Manan, C. M., Biggs, R. *Br. J. Hæmat.* 1971, **20**, 463.
13. Gader, A. M. A., Da Costa, J., Cash, J. D. *Lancet*, 1973, ii, 1417.
14. Vavra, I., Machova, A., Hdocek, V., Cort, J. H., Zaoral, M., Sorm, F. *Lancet*, 1968, i, 948.
15. Andersson, K. E., Arner, B. *Acta med. scand.* 1972, **192**, 21.
16. Edwards, C. R. W., Kitau, M. J., Chard, T., Besser, G. M. *Br. med. J.* 1973, iii, 375.

ULTRASONOGRAPHY IN THE MANAGEMENT OF HÆMOPHILIA

B. A. McVERRY JENNIFER VOKE
F. R. VICARY KATHARINE M. DORMANDY

Department of Hæmatology, University College Hospital, London, and Hæmophilia Centre, Department of Hæmatology, Royal Free Hospital, London

Summary Ultrasonography was used to demonstrate retroperitoneal hæmorrhages and an intramuscular hæmatoma in three patients with antibodies to factor VIII and one with von Willebrand's disease in whom major bleeding episodes occurred. Scans were useful in demonstrating the presence, location, size, and regression of hæmorrhages.

Introduction

IN patients with severe coagulation defects peripheral hæmorrhages, especially into joints, often develop. The extent of these lesions and their regression can be estimated by clinical observation. However, bleeding into "hidden" areas such as the retroperitoneal space and the deep musculature of the body is not uncommon and objective evidence of the location and size of these bleeds is seldom obtained. We report on the usefulness of ultrasonography in four patients, of whom three had retroperitoneal hæmorrhages and one had an intramuscular hæmatoma.

Patients and Methods

Patients were scanned by means of a grey-scale adaptation of the Nuclear Enterprises Ultrasonic 4102 imager. High-frequency sound waves (ultrasound) were generated by a transducer. The transducer was passed across the skin of the abdomen or back, which had been coated with warm arachis oil to provide good ultrasonic contact. Parasagittal and transverse scans were performed while the patient was prone.

Case-reports

Patient 1.—A 42-year-old man with severe hæmophilia and antibody to factor VIII was admitted to hospital with acute, left-sided abdominal pain. There was abdominal distension with tenderness and guarding in the left iliac fossa and a small area of anæsthesia over the left groin. Ultrasonography demonstrated a large transonic area anterior to the left kidney and extending down into the pelvis (fig. 1). Massive doses of factor VIII were given 6-hourly. Severe symptoms persisted for several days after which there was clinical improvement. A repeat scan 6 weeks later showed a definite decrease in the size of the hæmatoma (fig. 2).

Patient 2.—A previously healthy 69-year-old woman presented with a 24 h history of acute abdominal pain, anuria, and right-sided femoral palsy. There was tenderness and guarding in the right lower quadrant. An intravenous pyelogram showed poor excretion of dye on both

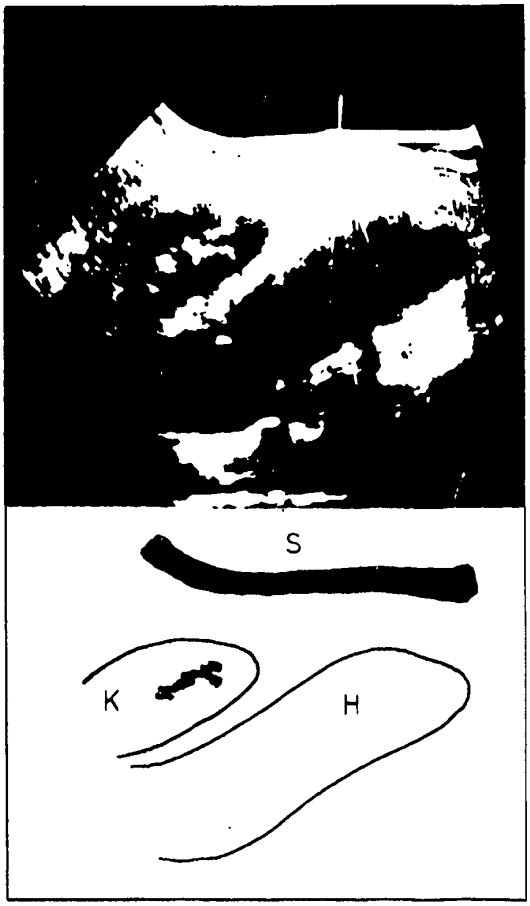

Fig. 1—Parasagittal scan showing skin (S), kidney (K) and hæmatoma (H) in patient 1.