1904

A NEW DDAVP-PREPARATION FOR IMPROVEMENT OF SUBCUTANEOUS (S.C.) INJECTION. M.Köhler, P.Hellstern, A.Harris, M.Hammer, E.Wenzel. Dept.of Clinical Haemostaseology and Transfusion Medicine, Homburg,FRG.

The s.c. administration of DDAVP was currently limited by the large volumes, which had to be injected. Thus, a new preparation containing 40 µg DDAVP per ml was investigated using a standard dose of 0.4 µg/kg body weight by s.c. injection. The pharmacokinetics of s.c. DDAVP and the resulting effects on the haemostatic system were assessed in 10 healthy male subjects in a placebo-controlled study. Peak levels of DDAVP, ranging from 480 to 638 pg/ml (median 505 pg/ml) were found one hour after injection. DDAVP declined with a median (m) half-life of 3.1 h (range: 2.9- 3.6 h). Maximum FVIII levels were measured 1 or 2 h after DDAVP, the m increases were 2.7 and 3.0× basal levels for FVIII:C and FVIII:Ag, respectively. A 2.1-fold increase of t-PA antigen was observed. The number of leucocytes significantly increased (absulute mean increment of 3.3×10^9/l granulocytes) 4 h after DDAVP. These results were confirmed in plasmapheresis donors (N=13). Two bags of plasma were obtained after s.c. DDAVP with a mean content of 1.7 U/ml FVIII:C and 1.9 U/ml ristocetin cofactor. The effect of s.c. DDAVP was was tested in 10 haemophilia A patients and 2 carriers of hemophilia A (m FVIII:C: 0.17 U/ml). The mean increase of FVIII:C was 2.3-fold (FVIII:Ag 2.5-fold) 1 h post injection. Eight bleeding episodes or operations were successfully treated with s.c. DDAVP, in one case postoperative haematoma occurred. In eight patients with uraemic bleeding the influence of s.c. DDAVP was investigated in the steady state. Bleeding time (BT) significantly shortened in 7 patients (before m BT: >15 min; 90 min after DDAVP BT: 6 min). Additionally, platelet count decreased while platelet retention increased.

DDAVP, s.c. injected, was shown to be a safe and effective measure in bleeding disorders and may become a useful tool for conditioning of plasma or granulocyte donors.

1905

A NEW DELIVERY SYSTEM FOR DDAVP: CLINICAL EXPERIENCE OF DDAVP SPRAY PUMP IN MILD HAEMOPHILIA A AND vWD TYPE I. S. Lethagen,+ A.S. Harris,* I.M. Nilsson.+ Dept of Coagulation Disorders+, Malmö Allmänna Sjukhus, Malmö, and Biomedicum*, Uppsala, Sweden

Until recently, the reliability and predectibility of the intranasal route of administration of DDAVP has been too poor to recommend it in routine practice.

With the development of a new delivery system in the form of a spray pump we have previously shown that absorption and biological effect of DDAVP in volunteers is enhanced(1).

In this patient study we compared intranasal administration of 300 µg DDAVP using a newly developed pre-compression spray pump with intravenous administration of 0.3 - 0.4 µg/kg. We studied 24 patients with mild haemophilia A, 23 with mild vWD Type IA and 8 with Type IB. We measured VIII:C (one-stage assay), vW:Ag (IRMA) and bleeding time (Simplate II) before and 30 - 60 min and 1 hour post treatment after i.v. and i.n. administration respectively.

Results.

	% of initial activity (Mean ± S.D.)					Bleeding Time (sec)	
	VIII:C			vW:Ag			
	Haem. A	vWD Type IA	vWD Type IB	vWD Type IA	vWD Type IB	vWD Type IA	vWD Type IB
i.v.	308 ± 97	367 ± 179	458 ± 179	309 ± 110	345 ± 144	620 ± 236	480 ± 85
i.n.	243 ± 84	398 ± 337	436 ± 283	295 ± 248	303 ± 177	651 ± 56	593 ± 84

The spray resulted in a 2 to 4 times increase in basal levels of VIII:C and vW:Ag and was comparable in effect to intravenous administration. Moreover, bleeding time was significantly reduced to within the normal range in most patients. Several patients reported good clinical effects of the spray after tooth extraction, menorrhagia and epistaxis.

We conclude that the DDAVP spray is a clear improvement over previous attempts at intranasal administration. The spray deposits well controlled and reproducible doses in the nasal cavity resulting in a clear enhancement in absorption with a magnitude and reliability of its biological effect which is comparable to the intravenous delivery. Furthermore, the spray offers a convenient and practical means of self-treatment to haemophilia patients without delay.

1. Harris A.S., Nilsson I.M., Wagner Z.-G., Alkner U. Intranasal Administration of Peptides: Nasal Deposition, Biological Response, and Absorption of Desmopressin. J Pharm Sci (in press, December 1986).

1906

COMPARISON OF THE BIOLOGICAL EFFECT, PHARMACOKINETICS AND REPRODUCIBILITY OF INTRANASAL AND INTRAVENOUS ADMINISTRATION OF DDAVP S. Lethagen,+ A.S. Harris,* I.M. Nilsson+. Dept of Coagulation Disorders+, Malmö Allmänna Sjukhus, Malmö, and Biomedicum*, Uppsala, Sweden

DDAVP has previously mostly been given by the parenteral route but the development of intranasal delivery has made it possible for the patients to treat themselves at home without delay. The effect of intranasal administration of DDAVP as drops using a rhinyle catheter or a pipette has been unpredictable. The development of a spray has improved the intranasal administration of DDAVP with well controlled doses and better absorption.

In this study we compared intranasal administration of 300 µg DDAVP by spray, with intravenous administration of 0.2, 0.3 and 0.4 µg DDAVP/kg in 10 healthy volunteers. We measured the effect on VIII:C, VIII:Ag and vW:Ag and also followed plasma levels of DDAVP before and 10', 30', 45', 60', 90', 2 h, 4 h, 6 h and 8 h after administration.

We also studied the reproducibility of the spray effect. 10 healthy volunteers were tested before and 1 h after the administration of 300 µg DDAVP intranasally by spray on 5 different occasions with an interval of at least 1 week between the tests.

DDAVP Dose	Max concentration (% of initial activity) VIII:C	VIII:Ag	vW:Ag
0.2 µg/kg i.v.	295 ± 88	449 ± 271	235 ± 32
0.3 µg/kg i.v.	366 ± 79	604 ± 280	269 ± 23
0.4 µg/kg i.v.	326 ± 113	429 ± 108	225 ± 26
Spray 300 µg	269 ± 58	329 ± 13	191 ± 16

The highest response was obtained after 0.3 µg/kg i.v. The response to 0.4 µg/kg i.v. was less than 0.3 µg/kg indicating that maximum stimulation was reached with 0.3 µg/kg. The effect of spray approximates the 0.2 µg/kg response.

The reproducibility of the effect of the spray dose on VIII:C was 25% (coefficient of variation) and 33% for the intra-individual and inter-individual variation respectively. This compares favourably with the inter-individual variation after intravenous administration of 0.2 µg/kg (30%), 0.3 µg/kg (22%) and 0.4 µg/kg (35%). It was of interest to note that the intra- and inter-individual variation of pre-treatment basal levels of VIII:C was 14% and 17% respectively.

Intranasal DDAVP (300 µg) is as effective as 0.2 µg/kg intravenously and provides an accurate, reproducible and convenient alternative to parenteral administration.

1907

SUBCUTANEOUS AND INTRAVENOUS ADMINISTRATION OF DESMOPRESSIN (DDAVP) TO HEMOPHILIACS: PLASMA PHARMACOKINETICS AND FACTOR VIII (VIII:C) RESPONSES P.M. Mannucci, V. Vicente, I. Alberca, E. Sacchi, A.S. Harris, A. Lindqvist. A. Bianchi Bonomi Hemophilia & Thrombosis Center, Univ. Milano, Italy, Hematology Dept, Univ. Salamanca, Spain, Clinical Research Dept, Ferring AB, Malmö, Sweden.

Reported studies dealing with the clinical use of DDAVP in mild and moderate hemophilia A patients show a very large between-patient variability for the maximum increase of VIII:C after the drug given intravenously (i.v.) or subcutaneously (s.c.). By measuring DDAVP plasma levels with a sensitive and specific RIA method, we elected to evaluate whether or not between-patient response variability was related to the variability of DDAVP levels achieved in their plasma. To this purpose 14 moderate or mild hemophilic volunteers (baseline VIII:C 4 to 31 U/dL) were randomly given 0.3 µg/Kg of i.v. or s.c. DDAVP with a between-treatment interval of 15 - 30 days. Plasma DDAVP pharmacokinetics in relation to the routes of administration are shown in the table.

	AUC (pg/mL×hr)	C_{max} (pg/mL)	t_{max} (min)	$t_{\frac{1}{2}}$ (hr)
i.v. DDAVP	3854 ± 1854	2363 ± 2368	18 ± 10	4.4 ± 1.1
coefficient of variation (c.v.)	48%	100%	56%	25%
s.c. DDAVP	3030 ± 822	582 ± 158	63 ± 26	4.7 ± 1.6
coefficient of variation (c.v.)	27%	27%	41%	34%

Pack levels (C_{max}) were higher after i.v. DDAVP ($p < 0.02$). Time to peak levels (t_{max}) was shorter for i.v. DDAVP ($p < 0.001$). There was no difference between i.v. and s.c. DDAVP for plasma time curve (AUC) and half-life ($t_{\frac{1}{2}}$).

The bioavailability of the s.c. route relative to the i.v. route was 85 ± 32%. Of further interest, was the greater variability of the i.v. pharmacokinetics compared to the s.c. data. These differences were reflected in the VIII:C response. Maximum VIII:C increase over baseline levels was 3.2 ± 2.4 fold (i.v.) and 3.2 ± 1.3 fold (s.c.) (n.s.).

Thus the i.v. route gave a marginally greater response but the effect was more variable than the s.c. route. Finally, no significant correlation was found between the VIII:C response and plasma DDAVP levels for either route of administration (i.v. route r = 0.03, s.c. route r = 0.23).

These findings establish the subcutaneous route to be bioequivalent in effect to the intravenous route with less variation. This study also demonstrates that the VIII:C response to DDAVP is neither a function of the rate of absorption of the compound into the body nor the magnitude of the plasma concentration.