Desmopressin testing in haemophilia A patients and carriers

Results of a multi centre survey

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Keywords
Haemophilia A, desmopressin testing, DDAVP

Summary

Introduction: Desmopressin (DDAVP) testing (DT) in patients (pts) with haemophilia A (HA) and carriers (CHA) is up to now not standard-ized. This prompted us to evaluate results of DT carried out between 1996 and 2011 in centres of the Competence Network Haemor-rhagic Diatheses East. Patients and method: An increase of the factor VIII activity (FVIII) above 50% or at least the two fold of initial values within 120 min after DDAVP was defined as complete response (CR). Data from 80 patients (31 children, 49 adults) of whom 64 suffered from HA (sub-HA: n = 48, mild: n = 14; moderate: n = 2) and 16 patients CHA were evaluated. Results: In 34 patients DDAVP was given i.v. (dose range: 0.26–0.6 μg/kg body weight, mean: 0.33), in 31 intra- nasally (i.n. 300–600 μg) and in 15 s.c. (15–40 μg). The maximal FVIII increase was reached 60 min after DDAVP. For i.v. application the mean FVIII increase was 3.1-fold, for i.n. 2.1-fold and for s.c. 2.4-fold. A CR was detected in 71 patients, a non-response in 9. Mild side effects such as flush, headaches or nausea were observed in 11 patients (14%). Conclusion: For desmopressin testing in patients with haemophilia A and carriers i. v. application at 0.3 μg/kg body weight and the determination of FVIII before and 60 min after desmopressin infusion is recommended.

Zusammenfassung

Einleitung: Der Desmopressin(DDAVP)-Test (DT) bei Patienten mit Hämophilie A und Konduktoren (KHA) ist nicht standardi-siert. Das veranlasste uns, die Desmopressintests der Zentren des Kompetenznetzwerks Hämorrhagische Diathesen Ost von 1996 bis 2011 zu analysieren. Patienten, Methode: Ein Faktor-VIII-Aktivitätsanstieg (FVIII) auf über 50% oder um mindestens das Doppelte der Initialwerte innerhalb von 120 min nach DDAVP wurde als komplette Response (KR) gewertet. Daten von 80 Patienten (31 Kinder, 49 Erwachsene), davon 64 mit HA (Sub: n = 48; leicht: n = 14; mittelschwer: n = 2) und 16 KHA wurden evaluiert. Ergebnisse: Bei 34 Patienten wurde DDAVP i. v. gegeben (Be-reich: 0,26–0,6 μg/kg Körpergewicht, Mittel: 0,33), bei 31 intranasal (i. n.; 300–600 μg) und bei 15 s. c. (15–40 μg). Der maximale FVIII-Anstieg wurde 60 min nach DDAVP erreicht. Nach i.v.-Gabe war der mittlere FVIII-Anstieg 3,1-fach, nach i.n.-Applikation 2,1-fach und nach s.c.-Gabe 2,4-fach. Ein KR lag bei 71 Pa-tienten und ein Non-Response bei 9 vor. Leich-te unerwünschte Arzneimittelwirkungen wie Flush, Kopfschmerzen oder Übelkeit tratten bei 11 Patienten (14%) auf. Schlussfolgerung: Bei Patienten mit Hämophilie A und Konduktorin- nen wird zur Testung i.v. DDAVP 0,3 μg/kg Körpergewicht mit FVIII-Bestimmung vor und 60 min nach Infusion empfohlen.


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Patients with severe and moderate forms of haemophilia A (HA) receive plasma-derived or recombinant factor VIII concentrates for treatment and prophylaxis of bleeding epi-sodes. However, those with mild haemophili-a A and carriers of haemophilia A can be managed by stimulating the release of endo- genous factor VIII from storage sites using desmopressin (DDAVP) (1, 2). Despite the relatively easy availability of factor VIII con-centrates in the industrial nations, their high cost is still a major reason to use DDAVP in patients with a factor VIII activity (FVIII:C) above 5% who show a positive response to the administration of DDAVP.

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DDAVP testing is recommended in
- haemophilia A patients with FVIII:C above 5%,
- haemophilia A carriers with a FVIII:C less than 50% before they undergo an elective invasive procedure (2).

Only few published data exist about DDAVP response testing in children with haemophilia and the test procedure itself is not standardized. Moreover, some authors report a considerable number of patients, particularly adults, suffering from DDAVP-induced side effects (3). This prompted us to conduct a survey on DDAVP testing in haemophilia A patients and carriers for HA by evaluating the procedures and results of tests carried out in the centres participating in the Competence Network Haemorrhagic Diatheses East between 1996 to 2011.

Patients, material, methods

Patients

Data from 64 haemophilia A patients and 16 haemophilia A carriers with DDAVP testing performed in the centres between 1996 to 2011 were collected from patient records by personal centre visits of trained staff using a standardized protocol (Tab. 1).

Diagnostic criteria for haemophilia A:
- FVIII activity below the reference range and
- exclusion of other congenital bleeding disorders such as von Willebrand disease including a VWF multimeric analysis or
- genetically proven diagnosis of haemophilia A or a carrier status.

All patients gave their informed consent to data collection in accordance with the Ethical Review Board approval of the University Hospital Dresden.

The response to DDAVP was evaluated by determination of factor VIII activity (FVIII : C) before and after DDAVP administration.

Definition of DDAVP response

Laboratory criteria were defined to categorize patients as
- complete responders (CR) and
- non-responders (NR).

A complete response was defined as an increase in FVIII : C levels between 50–150% or an increase of FVIII : C by at least up to two fold of the pre-test value within 120 min after DDAVP administration. Non-responders reached none of these criteria.

Statistical analysis

Due to the small number of patients, data were analyzed using the non-parametric Friedman-rank test. If this test indicated significance, the Wilcoxon signed-rank test with Holm adjustment of the p-values were used to analyze significance between time points. The Qui-square-test according to Fisher or Mann-Whitney-U-Test was used for testing the influence of sex, age and route of administration on FVIII : C response. Statistical analyses were performed using SPSS for Windows software, version 17.0.0 (SPSS Inc., Chicago, IL, USA).

<table>
<thead>
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<th>patients</th>
<th>paediatric (&lt;18 years)</th>
<th>adult (≥ 18 years)</th>
<th>total</th>
</tr>
</thead>
<tbody>
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<td>49</td>
<td>80</td>
</tr>
<tr>
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<td>8.9</td>
<td>39.9</td>
<td>27.9</td>
</tr>
<tr>
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<td>2.2 – 17.6</td>
<td>18.0 – 65.5</td>
<td>2.2 – 65.5</td>
</tr>
<tr>
<td>female (n)</td>
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<td>12</td>
<td>16</td>
</tr>
<tr>
<td>male (n)</td>
<td>27</td>
<td>37</td>
<td>64</td>
</tr>
<tr>
<td>moderate HA (n)</td>
<td>1</td>
<td>16.7</td>
<td>2.5</td>
</tr>
<tr>
<td>mean age*</td>
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<td>35.2</td>
<td>14.2</td>
</tr>
<tr>
<td>age range*</td>
<td>2.6 – 14.2</td>
<td>30.3 – 40.5</td>
<td>2.6 – 40.5</td>
</tr>
<tr>
<td>mild HA (n)</td>
<td>7</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>mean age*</td>
<td>8.3</td>
<td>19.2</td>
<td>29.0</td>
</tr>
<tr>
<td>age range*</td>
<td>2.2 – 17.1</td>
<td>18.0 – 65.5</td>
<td>2.2 – 65.5</td>
</tr>
<tr>
<td>sub-HA (n)</td>
<td>19</td>
<td>29</td>
<td>48</td>
</tr>
<tr>
<td>mean age*</td>
<td>8.3</td>
<td>19.2</td>
<td>29.0</td>
</tr>
<tr>
<td>age range*</td>
<td>2.2 – 17.1</td>
<td>18.0 – 65.5</td>
<td>2.2 – 65.5</td>
</tr>
<tr>
<td>carriers (n)</td>
<td>4</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>mean age*</td>
<td>10.8</td>
<td>35.6</td>
<td>29.4</td>
</tr>
<tr>
<td>age range*</td>
<td>4.3 – 17.6</td>
<td>19.2 – 55.3</td>
<td>4.3 – 55.3</td>
</tr>
</tbody>
</table>

* in years

Tab. 1

Patients enrolled in this study

Fig. 1

Proportion of patients undergoing determination of coagulation parameters at time points before and after DDAVP administration.
Results

Parameters and time points

FVIII:C was determined at different time points after i.v. and intranasal DDAVP administration ranging from 15 min to 4 hours. In patients with s.c. application, FVIII:C was measured up to 60 min after DDAVP injection. As depicted in Figure 1, the majority of samples were obtained before and 60 min after DDAVP administration.

DDAVP application

DDAVP was administered (Tab. 2)
- intravenously (Minirin® parenteral, Ferring Pharmaceuticals, Kiel, Germany) in 34 patients (42%),
- intranasally (Octostim® Nasenspray, Ferring Pharmaceuticals, Kiel, Germany) in 31 patients (39%) and
- subcutaneously (Minirin parenteral or Octostim 15 μg/ml, Ferring Pharmaceuticals, Vienna, Austria) in 15 patients (19%).

After DDAVP application i.v. FVIII:C showed a significant increase until 240 min (Fig. 2a). The significant increase of FVIII:C after intranasal administration was maintained only over 120 min (Fig. 2b). The maximum values for FVIII:C were reached 60 min after DDAVP administration in all routes of application. The FVIII:C increased up to 3.1-fold depending on the route of application (Tab. 3).

Responders and non-responders

A complete response revealed 71 patients (89%) and 9 patients (11%) (8 adults, 1 child) were non-responders (Tab. 4). As can be depicted from Table 5, a non-response was observed mainly in the group with intranasal DDAVP administration (8 of 23 patients), while only one patient in the s.c. group and no patient in the i.v. group showed a non-response. These differences are statistically significant.
Clinical application

In 11 patients (14%) side effects such as discomfort, nausea, headaches and flush were observed during DDAVP testing.

DDAVP was successfully administered in 41 patients for prophylaxis against bleeding complications before invasive procedures mostly surgery or dental extractions (n = 22) to avoid bleeding complications and in 19 to stop acute bleedings such as epistaxis, menorrhagia, extended haematomas and postoperative bleedings.

Discussion

Our study demonstrates the heterogeneous ways of DDAVP testing in haemophilia A patients in German haemophilia treatment centres due to the lack of an accepted standardized test procedure, similar to the different test procedures reported in the literature (2, 4-7). Differences between centres were observed concerning the route of DDAVP administration and time points of blood sampling.

For the i. v. DDAVP administration, a dose of 0.3 μg/kg body weight (b. w.) given as short infusion over 30 to 60 min is recommended by the manufacturer. This was confirmed by the results of our study where 34 patients received DDAVP i. v. at a mean dose of 0.33 μg/kg b. w. According to literature, the magnitude of response of FVIII : C after i. v. application may vary from two- to six-fold increase over baseline, peak levels occur mostly at the end of infusion or 30 min later and show a long-lasting effect with a factor VIII : C half life of 5 to 8 hours (2). In line with these results, we observed that patients treated by i. v. route exhibited a 3.1-fold mean increase ranging from 1.3 to 9.1 with a FVIII : C peak 30 to 60 min after DDAVP infusion. FVIII : C values were significantly increased until 240 min after DDAVP administration compared to the initial values.

According to the manufacturer, the recommended dose for intranasal application is 300 μg in adults and 150 μg in children between 4 and 12 years. Castaman et al. recommend the lower dose of 150 μg in patients with a body weight of 50 kg or less (2). This route of application requires a 20-fold greater amount of DDAVP because of its poor absorption (8, 9). In our study, mainly doses of 300 μg were preferred, except for one centre that used a much higher dose of 600 μg. The mean increase in FVIII : C was only 2.1-fold ranging from 1- to maximal 3.7-fold, which was much lower compared to the i. v. route. Moreover, statistical analysis revealed that FVIII : C activity 240 min after DDAVP application was not significantly different from the initial value.

The s. c. administration of DDAVP is not licensed in Germany and can be used in patients with bleeding disorders only on an off-label base. This is why data from only 15 patients were available for evaluation. Patients in this group showed a 2.4-fold mean increase in FVIII : C, with a peak reached 30 min after DDAVP injection. The magnitude of response seems to be similar to what is observed with the i. v. route. This might be due to the similar half life of DDAVP after s. c. and i. v. application of about 4.5 hours (10).

We defined the complete DDAVP response as FVIII : C levels of at least 50% or as an increase of FVIII : C at least up to two fold of the initial values within 120 min after DDAVP administration. This is in part in accordance with already published reports where patients with FVIII : C values above 50% were classified as complete responders (5, 8, 11, 12). The complete response rate of 89% in our patients confirms the data of the literature reporting high response rates between 60 to 90% (6, 7, 13, 14). Data about the DDAVP responsiveness in children with haemophilia A are limited. Published data show that a young age and a low pre-test FVIII : C are predictors of a poor response (6, 7). Because only one out of

<table>
<thead>
<tr>
<th>response</th>
<th>complete</th>
<th>none</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/n</td>
<td>%</td>
<td>n/n</td>
</tr>
<tr>
<td>n/n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>moderate HA</td>
<td>2/2</td>
<td>100</td>
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<tr>
<td>mild HA</td>
<td>11/14</td>
<td>79</td>
</tr>
<tr>
<td>sub-HA</td>
<td>44/48</td>
<td>92</td>
</tr>
<tr>
<td>carriers</td>
<td>14/16</td>
<td>88</td>
</tr>
<tr>
<td>total</td>
<td>71/80</td>
<td>89</td>
</tr>
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</table>

Tab. 4 Response of patients with respect to the severity of haemophilia

<table>
<thead>
<tr>
<th>route of DDAVP administration</th>
<th>mean (range)</th>
<th>median (range)</th>
<th>mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. v.</td>
<td>28.8 (1.7 – 68)</td>
<td>37 (11 – 82)</td>
<td>40.4 (3.5 – 68)</td>
</tr>
<tr>
<td>intranasal</td>
<td></td>
<td>41.6 (11.4)</td>
<td></td>
</tr>
<tr>
<td>s.c.</td>
<td></td>
<td>43.4 (4.9)</td>
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</tr>
</tbody>
</table>

Tab. 3 Basal and maximum levels of FVIII : C according to the route of DDAVP administration

<table>
<thead>
<tr>
<th>response</th>
<th>complete</th>
<th>none</th>
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<tbody>
<tr>
<td>n</td>
<td>71</td>
<td>9</td>
</tr>
<tr>
<td>sex (m/f)</td>
<td>56/15</td>
<td>7/2</td>
</tr>
<tr>
<td>median age [years] (range)</td>
<td>23.4 (2.6 – 65.5)</td>
<td>39.9 (2.2 – 64.9)</td>
</tr>
<tr>
<td>DDAVP administration</td>
<td>i. v.</td>
<td>i. n.</td>
</tr>
<tr>
<td>before DDAVP administration</td>
<td>FVIII : C [%] median (inter-quartile range)</td>
<td>37 (34)</td>
</tr>
<tr>
<td>aPTT [s] median (inter-quartile range)</td>
<td>41.6 (11.4)</td>
<td>43.4 (4.9)</td>
</tr>
</tbody>
</table>

Tab. 5 Characteristics of complete and non-responders
of nine patients with a non-response was a child and the initial values of FVIII:C in respondents and non-responders were not significantly different, this was not confirmed by our results. Predictors for the DDAVP response in the individual patient are not well studied. Nevertheless, the results suggest that the underlying genetic defect seems to have a more important influence on the response (11, 15, 16).

DDAVP can induce self-limiting side effects in about 30% of the patients (17) such as

- facial flush,
- headache and
- an increase in heart rate.

However, DDAVP associated occurrence of arterial thrombotic episodes was also reported (18–21), although very rarely in haemophilia (22). In our study, only 14% of the patients suffered from mild, self-limited side effects. Although DDAVP hardly exerts any antidiuretic effect, hyponatraemia and seizures have been observed, particularly in children younger than two years (23–27).

Therefore, DDAVP should not be used in infants and only with caution in toddlers, but is well tolerated and effective in older children and adolescents (28).

Conclusion

DDAVP is well-tolerated and effective in children and adults with mild haemophilia A and haemophilia A carriers. For a standardized test, the i.v. DDAVP administration at a dose of 0.3 μg/kg body weight and the determination of FVIII:C immediately before and 60 min after DDAVP infusion can be recommended.

Acknowledgement

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Conflict of interest

The authors declare, that they have no conflict of interest.

References