DDAVP Infusion in Five Patients With Type Ia Glycogen Storage Disease and Associated Correction of Prolonged Bleeding Times

By Gerald E. Marti, Margaret E. Rick, James Sidbury, and Harvey R. Gralnick

Five patients with glycogen storage disease type I (GSD-I) were evaluated for a bleeding diathesis and subsequently were given an infusion of 1-deamino-8-D-arginine vasopressin (DDAVP). Although platelet counts were normal or slightly elevated, the baseline template bleeding times were prolonged in four of the patients. Prothrombin times and activated partial thromboplastin times were normal, while ADP- and epinephrine-induced platelet aggregations were absent in the three patients tested. Ristocetin- and collagen-induced platelet aggregations were abnormal. Laurell and immunoradiometric determinations of the factor VIII-related antigen (vWF antigen) were decreased. Glyoxyl agarose gel electrophoresis of the patients’ plasma revealed abnormal multimer patterns in four of the five patients. After the DDAVP infusion the platelet aggregation abnormalities persisted; however, the bleeding time and the von Willebrand antigen and activity corrected. We conclude that GSD-Ia patients may have a metabolically acquired form of von Willebrand’s syndrome as well as an acquired intrinsic platelet defect, and that DDAVP may be useful in the management of bleeding in these patients.

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Glycogen storage disease, Type I (GSD-Ia), formerly known as von Gierkie’s disease, is an autosomal recessive disease with a deficiency of glucose-6-phosphatase in the liver, kidney, and intestine. It is characterized by hepatomegaly, hypoglycemia, lactic acidosis, hyperlipidemia, hyperuricemia, and a bleeding diathesis. The bleeding diathesis is associated with a prolonged bleeding time and a qualitative platelet defect, while clinically it is manifested by epistaxis and bleeding after invasive procedures or trauma. We have studied the effects of an infusion of 1-deamino-8-D-arginine vasopressin (DDAVP) in five patients with GSD-Ia and show that DDAVP consistently normalizes the prolonged bleeding time and corrects the abnormal values of the factor VIII complex and vWF activities.

Table 1. Clinical Summary of GSD, Type I Patients Receiving DDAVP

<table>
<thead>
<tr>
<th>Patient (age/sex)</th>
<th>Bleeding History</th>
<th>Simple Bleeding Time (min)</th>
<th>Platelet Count (x 10^9/µL)</th>
<th>Aggregation Studies</th>
<th>PT (sec)</th>
<th>aPTT (sec)</th>
<th>TT (sec)</th>
<th>Fibrinogen (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRT (22/m)</td>
<td>Severe epistaxis in childhood</td>
<td>18</td>
<td>318</td>
<td>abnormal*</td>
<td>12.2</td>
<td>36.5</td>
<td>30.4</td>
<td>502</td>
</tr>
<tr>
<td>RSB (26/m)</td>
<td>epistaxis</td>
<td>10.5</td>
<td>384</td>
<td>abnormal*</td>
<td>12.7</td>
<td>36.3</td>
<td>37.2</td>
<td>1,072</td>
</tr>
<tr>
<td>MPS (20/m)</td>
<td>epistaxis</td>
<td>15</td>
<td>365</td>
<td>abnormal*</td>
<td>13.2</td>
<td>31.4</td>
<td>32.4</td>
<td>570</td>
</tr>
<tr>
<td>DS (26/m)</td>
<td>bleeding with loss of deciduous teeth</td>
<td>18</td>
<td>330</td>
<td>ND</td>
<td>11.4</td>
<td>31.7</td>
<td>28.4</td>
<td>544</td>
</tr>
<tr>
<td>JMK (3.5/m)</td>
<td>epistaxis</td>
<td>9</td>
<td>570</td>
<td>ND</td>
<td>13.5</td>
<td>38.0</td>
<td>30.5</td>
<td>390</td>
</tr>
<tr>
<td>Normal ranges</td>
<td></td>
<td>2.3–9.5</td>
<td>145–364</td>
<td>10.8–13.2</td>
<td>26.8–38.8</td>
<td>26–35</td>
<td>165–385</td>
<td></td>
</tr>
</tbody>
</table>

*See text for specific abnormalities of ADP, epinephrine, collagen- and ristocetin-mediated platelet aggregation.
DDAVP infusion. A single dose of DDAVP (0.3 μg/kg) was infused over 30 minutes in 50 mL of normal saline. A preinfusion baseline bleeding time and citrated blood sample were obtained from a distal site through an indwelling butterfly needle after discarding the initial 3 to 5 mL of blood. The bleeding time was performed and blood samples were again obtained at 30 minutes, one hour, two hours, and four hours following the infusion. Body weight, serum sodium, hematocrit, and platelet count were determined within 24 hours of completing the infusion. Consent was obtained from patients and/or parents after they were informed of the real and potential risks of this study.

RESULTS

The five patients evaluated in this report all had clinical histories, physical findings, and laboratory values consistent with GSD-Ia and the diagnosis had been confirmed by liver biopsy and enzyme analysis. All five patients had histories of abnormal bleeding which was usually recognized by the age of 2 years and was most often reported as easy bruising and frequent severe nosebleeds. These symptoms became less pronounced by the time the patients became adolescents. Platelet counts were normal or slightly elevated in all patients, but four of five had prolonged template bleeding times (Table 1). The patients were in good metabolic control on multiple cornstarch feedings.

Initial coagulation parameters (PT, aPTT, TT) were normal in all patients except for elevations of fibrinogen. In patient RSB this had been noted five years previously and had been evaluated on numerous occasions by immunologic, biochemical, and chronometric methods; the results were concordant in all three assays. Of interest, this patient has a filling defect on a liver-spleen scan that is thought to be compatible with a benign adenoma.

All three patients tested had abnormal platelet aggregation with ADP and epinephrine. Little or no aggregation was noted with epinephrine while the secondary wave was absent with ADP. Two of the three patients (MPS, RSB) showed no response to low concentrations of ristocetin and had a decreased initial slope at all concentrations of ristocetin and collagen. Aggregation studies repeated after the DDAVP infusion showed no change. Figure 1 is a representative platelet aggregation study.

The responses in the bleeding times of four of five patients to DDAVP are shown in Fig 2. Of the five patients tested, all except one (JMK) showed a decrease in the baseline preinfusion bleeding time to normal. JMK’s baseline bleeding time was nine minutes, and a one-hour post-DDAVP infusion bleeding time was eight minutes. By four hours post-DDAVP infusion, the bleeding time had returned to preinfusion values in all five patients. The effects of DDAVP upon VIII:C, VIII R:Ag, and vWF parameters are summarized in Tables 2 and 3. In general, there is a 2- to 4-fold increase in
Table 2. Summary of Percent VIII:C (Coagulant Activity) and VIII:CAg (U/mL) Before and After DDAVP*

<table>
<thead>
<tr>
<th>Patient</th>
<th>LRT</th>
<th>RSB</th>
<th>MPS</th>
<th>DS</th>
<th>JMK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VIII:C (%)</td>
<td>VIII:CAg (%)</td>
<td>VIII:C (%)</td>
<td>VIII:CAg (%)</td>
<td>VIII:C (%)</td>
</tr>
<tr>
<td>Baseline (pre)</td>
<td>94</td>
<td>72</td>
<td>104</td>
<td>155</td>
<td>72</td>
</tr>
<tr>
<td>30'</td>
<td>232</td>
<td>213</td>
<td>316</td>
<td>462</td>
<td>280‡</td>
</tr>
<tr>
<td>1 hour</td>
<td>119</td>
<td>104</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2 hours</td>
<td>113</td>
<td>85</td>
<td>—</td>
<td>—</td>
<td>141</td>
</tr>
<tr>
<td>4 hours</td>
<td>97</td>
<td>85</td>
<td>175</td>
<td>342</td>
<td>103</td>
</tr>
</tbody>
</table>

*VIII:C = VIII coagulant activity; VIII:CAg = VIII coagulant antigen.
† not done.
‡ Sample obtained at 45’.

all parameters evaluated. As was seen with the bleeding times, measurements of VIII:C and VIII R:Ag remained slightly elevated or had returned to baseline within the four hours following the DDAVP infusion.

Baseline vWF activity and VIII R:Ag were abnormal in three patients (LRT, DS, JMK; Table 3). In addition, plasma vWF multimeric patterns on glyoxyl agarose gel electrophoresis showed an abnormal pattern in four of the five patients. The patterns were characterized by a diffuse decrease of all multimers (JMK, moderate; DS, mild), or an apparent decrease in only the larger multimers (RSB, MPS). All five patients showed an apparent increase of the larger forms in their multimeric patterns following the DDAVP infusion, and on occasion a doublet was noted (seen best in the fastest migrating multimer). A composite autoradiogram is shown in Fig 3.

**DDAVP side-effects.** During the DDAVP infusion four of the five patients showed facial flushing which they were unaware of, and one patient complained of vague abdominal cramping. No other side-effects were noted. There was no change in weight, hematocrit, or platelet count.

### DISCUSSION

The occurrence of a bleeding tendency has been widely recognized in patients with GSD-Ia. It is usually recognized in early infancy and is characterized by easy bruising, severe nosebleeds, and prolonged bleeding following minor trauma, surgical or dental procedures. However, bleeding with liver biopsy is unusual. Most investigators report a prolongation of the bleeding time despite normal platelet counts. Lelong et al first demonstrated a qualitative platelet defect, and documented decreased prothrombin consumption and a retardation of platelet thromboplastin generation. Although it was initially thought that platelets from patients with GSD-I had higher levels of glycogen and a deficiency of glucose-6-phosphatase, this observation has not been confirmed.

We have studied five patients with type GSD-Ia. We found abnormal platelet aggregation, prolonged bleeding times, reduced VIII:R:Ag and vWF activity, and abnormal vWF multimer plasma patterns. In the present study, the VIII:C activity was normal in all individuals tested (Table 2). The ristocetin cofactor activity and VIII R:Ag levels were abnormally low in three of the patients (LRT, DS, JMK). The abnormalities in the multimer patterns showed either a diffuse decrease (DS, JMK) or an additional decrease in the largest multimers (RSB, MPS). These data indicate that some patients with GSD-Ia may have an acquired von Willebrand syndrome or a syndrome that mimics vWD.

Our five patients with GSD-Ia were given DDAVP intravenously. During the ensuing four hours after infusion, we observed an increase to normal levels of VIIIIR:Ag in all patients and a correction of the bleeding time in four of five patients. The multimer patterns of plasma vWF showed an increase in all multimers and the appearance of larger multimers in those plasmas that were previously deficient.
DDAVP presumably causes the release of vWF multimers including high molecular weight multimers from endothelium and/or other storage sites. In patients with type I and type IIa vWD this is associated with a transient shortening or normalization of the bleeding time, and in vitro perfusion studies have shown increased platelet adherence and platelet aggregate formation. The five patients examined in this report all responded to DDAVP in a manner similar to that seen in patients with vWD, hemophilia A, uremia, and dysfunctional platelet syndromes.

In vitro platelet function studies have demonstrated the absence of a secondary wave in ADP- and epinephrine-induced platelet aggregation, while with collagen and ristocetin the response is diminished. Platelet adenine nucleotide levels may be normal or reduced and the defective release of ADP remains to be confirmed. Reports of mixing experiments involving GSD-I plasma and its effect upon normal platelet aggregate are contradictory. Early attempts to characterize the mechanism of the platelet dysfunction examined the relationship between the prolonged bleeding times and metabolic abnormalities: hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia. Several investigators have shown that infusions of glucose, intravenous hyperalimentation, and total parenteral hyperalimentation can lead to correction of the bleeding times and in vitro platelet function. However, it would appear that several days (10 to 12) of this therapy are required before normalization occurs. Portacaval shunting can result in the long-term correction of these abnormalities.

Kao et al reported impaired ristocetin-induced platelet aggregation in six children with GSD-Ia. Studies with washed platelets indicated a plasma abnormality rather than an intrinsic platelet defect, and binding studies revealed a normal number of VIII:RAg receptor sites on GSD-Ia platelets. Further studies suggested that the fibrinogen from GSD-Ia plasma was inhibiting ristocetin-induced agglutination in these patients. A posttranslational modification of the carbohydrate in fibrinogen could occur in plasma of GSD-Ia patients which might account for this phenomenon; further analysis of our patients’ fibrinogens is being carried out.

The present study confirms previous reports of abnormal platelet aggregation in conjunction with prolonged bleeding times in patients with GSD-Ia. The data also indicate a probable high incidence of decreased vWF levels and activity in these patients. Regardless of the nature of the defect(s), our data demonstrate that GSD-Ia patients responded to DDAVP in a predictable manner, and suggest that DDAVP may be efficacious in the treatment of bleeding episodes or treatment prior to minor surgical procedures in these patients.

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REFERENCES

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