Valproic Acid and Augmentation of Fetal Hemoglobin in Individuals With and Without Sickle Cell Disease

To the Editor:

Increased synthesis of fetal hemoglobin may ameliorate the clinical severity of sickle cell disease; both chemotherapeutic and non-chemotherapeutic agents have been shown to augment fetal hemoglobin synthesis in selected populations of affected patients. Some studies have suggested that the fatty acid analogue valproic acid (n-propylacetic acid) may increase the synthesis of fetal hemoglobin. A study of 36 patients with epilepsy treated with valproic acid (10 to 46 mg/kg body weight per day) reported that the percentage of red blood cells containing fetal hemoglobin (F cells) was significantly higher in these individuals than in 293 patients not receiving this therapy; parallel changes in fetal hemoglobin were not reported. A study of four adults with sickle cell disease treated with valproic acid (15 to 40 mg/kg/d) reported a threefold increase in fetal hemoglobin in three patients, with no corresponding decrease in the frequency of vaso-occlusive crises, over 2 to 13 weeks. Finally, a study in which 10 patients with sickle cell disease received treatment with hydroxyurea followed by valproic acid (20 mg/kg/d) reported no difference in the concentrations of fetal hemoglobin, frequency of vaso-occlusive crises, or adverse drug effects in patients treated with either agent.

We examined the changes in fetal hemoglobin synthesis in individuals without sickle cell disease and receiving valproic acid for epilepsy to determine whether previously reported valproic acid-induced changes in F-cells are associated with measurable increases in fetal hemoglobin. In parallel, we evaluated laboratory and clinical responses associated with valproic acid therapy in seven patients with sickle cell disease.

One hundred and six consecutive patients attending the Neurology Clinic at The Hospital for Sick Children, Toronto, with a diagnosis of seizure disorder, none of whom had sickle cell disease or trait, were studied. Fifty-seven patients, aged (mean ± SD) 9.3 ± 4.4 years, were receiving therapy with carbamazepine (Tegretol), whereas 49 patients, aged 9.9 ± 5.2 years, had been treated with valproic acid (15 to 50 mg/kg/d) for 4.0 ± 0.5 years. Although a significant mean increase in mean red blood cell volume (from 84 ± 5 fl before treatment with valproic acid to 90 ± 5 fl; P < 0.01) had been observed in the latter group, the percentage of fetal hemoglobin (mean ± SEM, 0.9% ± 0.1%) in patients with therapeutic serum drug concentrations of valproic acid did not differ significantly from that of the carbamazepine-treated patients (0.8% ± 0.1%; P = NS).

In parallel, seven patients, aged 16.5 ± 10 years, with severe sickle cell disease, defined as three or more hospitalizations in the year before treatment, were offered valproic acid at 15 ± 3 (range, 9 to 20) mg/kg/d. Complete blood counts were obtained twice monthly. Patients were reviewed by a physician twice a month and questioned regarding adverse effects of treatment, sickle cell disease-related pain, admissions to hospital, and compliance with therapy. Annual rates of vaso-occlusive crises were calculated as previously described by dividing the number of crises by the number of years of therapy (for example, 2 crises in 6 months = 4 crises per year). The number of days spent in hospital and the number of red blood cell transfusions administered were calculated in a similar manner. Compliance with valproic acid was monitored by the Medication Event Monitoring System, a bottle with a computer chip in the lid that determines the timing and frequency of bottle openings, and by determinations of concentrations of serum valproic acid obtained at clinic visits.

The changes observed during therapy with valproic acid over 5.8 ± 0.9 (3.2 to 9.0) months are shown in Table 1. Data are presented as the mean ± standard deviation.

Compliance with valproic acid was 93% ± 7% drug taken of that prescribed. Mean trough serum levels (561 ± 115 μmol/L) were within the therapeutic range (350 to 750 μmol/L; 50 to 100 μg/mL). No changes in liver function tests were observed; in one patient, the platelet count decreased to 98 × 10^9/L, prompting discontinuation of valproic acid. Review of this patient’s medical records showed that he had chronic low-grade thrombocytopenia before the initiation of valproic acid; this finding has persisted after withdrawal of valproic acid. Bone marrow aspiration showed abundant megakaryocytes. The relationship between thrombocytopenia in this patient and valproate therapy, acknowledged to induce thrombocytopenia in 21% to 60% of treated patients who have serum concentrations exceeding 100 to 140 μg/mL, is unclear.

Because of the lack of clinical improvement and frequent hospital admissions during valproic acid, one patient requested discontinuation of therapy. The changes observed during therapy with valproic acid in this patient are shown in Table 1. The number of days spent in hospital and the number of red blood cell transfusions administered were calculated in a similar manner.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-Valproic Acid</th>
<th>Post-Valproic Acid</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8.3 ± 0.9</td>
<td>9.3 ± 1.2</td>
<td>.05</td>
</tr>
<tr>
<td>Hemoglobin F (%)</td>
<td>6.4 ± 2.6</td>
<td>8.4 ± 4.3</td>
<td>.05</td>
</tr>
<tr>
<td>Hemoglobin F (g/dL)</td>
<td>5.4 ± 2.2</td>
<td>7.9 ± 4.5</td>
<td>.05</td>
</tr>
<tr>
<td>Mean cell volume (fl)</td>
<td>83 ± 8.0</td>
<td>86 ± 7.0</td>
<td>NS</td>
</tr>
<tr>
<td>Annual rate of Vaso-occlusive crises</td>
<td>3.1 ± 3.1</td>
<td>5.8 ± 9.0</td>
<td>NS</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>1.1 ± 3.0</td>
<td>0.3 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>In-patient hospital days</td>
<td>31 ± 28</td>
<td>37 ± 53</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data obtained at evaluation before beginning valproic acid were compared with those at the completion of the study using the Student’s t-test for paired data. All tests were two-tailed; a significance level of .05 was used to indicate statistical significance.

REFERENCE

Fig 1. Shown are concentrations of fetal hemoglobin in a patient with sickle cell disease treated initially with valproic acid over 5 months and subsequently with oral hydroxyurea at an initial dose of 11 mg/kg/d (arrows). Fetal hemoglobin at the start of valproic acid therapy was 8%, increasing to 9% during treatment. The patient discontinued valproic acid and began hydroxyurea. During the subsequent 11 months of hydroxyurea therapy, a steady increase in fetal hemoglobin was noted; the present value of fetal hemoglobin, during therapy with 16.2 mg of hydroxyurea per kilogram body weight per day, is 23.7%.

...tion of this therapy and initiation of hydroxyurea. In this patient, the percentage of fetal hemoglobin increased from a value of 9% immediately after 5 months of therapy with valproic acid to 24% after 11 months of treatment with hydroxyurea (Fig 1); after the initiation of hydroxyurea, this patient required no further admissions to hospital.

These data show that, during valproic acid therapy in patients without sickle cell disease, previously reported increases in F-cells are not reflected by measurable changes in the synthesis of fetal hemoglobin. During valproic acid therapy in patients with sickle cell disease, a modest mean increase in fetal hemoglobin concentration over 6 months was not paralleled by changes in crisis rate, number of transfusions required, or total days of hospitalization. The lack of clinical effect in these patients stands in contrast to that observed in a group of patients of comparable age treated with hydroxyurea. Also of striking contrast to the modest hematologic responses of these patients during treatment with valproic acid are the changes in clinical status and fetal hemoglobin concentration observed in one patient during subsequent hydroxyurea therapy, which induced a near tripling of fetal hemoglobin from the values attained during valproate therapy.

Although all of these patients had serum concentrations of valproic acid within the therapeutic range for antiseizure effect, they received slightly lower daily doses of valproic acid than that prescribed in previous studies. Although higher daily doses of valproic acid may more substantially increase fetal hemoglobin synthesis in patients with sickle cell disease, heightened risks of hematologic or hepatic toxicity may accompany more intensive dosing regimens of this agent.

ACKNOWLEDGMENT

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Prevalence of Selective IgA Deficiency in Spain: More Than We Thought

To the Editor:

Selective IgA deficiency (sIgA-ID) is the most common well-defined primary immunodeficiency disorder, with a frequency reported to range between 1:328 in American blood donors and 1:18,500 in Japanese blood donors. We report here an epidemiologic study with a frequency of 0.61% (1:163), which is the highest prevalence of selective IgA deficiency reported in a healthy population.

In 1993, demographic information and serum samples were collected for an epidemiologic study of infectious diseases and cardiovascular risk factors among scholars of Cáceres province (Western Spain). One of the variables determined was the concentration of IgG, IgA, and IgM. Of a population of 80,745 individuals, 1,956 samples had undetectable IgA (0.61%; 95% confidence interval, 0.26 to 0.95). No isolated absence of IgG or IgM was found. All participants were volunteers responding to an application in the schools and informed consent was obtained. Full classrooms were selected. The study was completed with 100 adult blood donors (50 women and 50 men). IgA were quantified by rate nephelometry (Array 360; Beckman Instruments, Inc, Brea, CA). The limit of detection of serum IgA is 0.0667 g/L. The Beckman IgA Test is standardized to the International Federation of Clinical Chemistry (IFCC) International Reference Preparation for Plasma Proteins. No detectable IgA was confirmed by radial immunodiffusion (Kallestad Endoplate; Sano Diagnostics Pasteur, Chaska, MN). Twelve of 1,956 samples had undetectable IgA (0.61%; 95% confidence interval, 0.26 to 0.95). No isolated absence of IgG or IgM was found. No differences were found in age, sex, or geographical area. IgA-deficient sera showed IgG levels much higher than those of the normal population (Table 1). The data could indicate a compensation for the IgA deficiency by serum IgG but not serum IgM.

Our results suggest that the prevalence of sIgA-ID is underestimated in the Caucasian population. It could be due to the bias in prevalence studies with volunteer blood donors because of pathology associated to sIgA-ID: infections in the respiratory and gastrointestinal tracts or autoimmune and atopic diseases. On the other hand, sIgA-ID could be almost asymptomatic in a lot of cases and underdiagnosed in the general population. This study was performed using a pediatric sample and a transient sIgA-ID could be possible (although normally this is described in children less than 2 years of age). These data could be of interest in the prevention of anaphylactic reactions after intravenous administration of blood products containing IgA and in the avoidance of complications of this disease. Lack of awareness of the real prevalence of patients with sIgA-ID has resulted in underdiagnosis and diagnostic delay and inadequate management of their complications.

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Table 1. IgA Deficiency: Sex and Age Distribution, Levels of IgG and IgM

<table>
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<tr>
<th>Case No.</th>
<th>Sex/Age (yr)</th>
<th>IgG (mg/dL)</th>
<th>IgA (mg/dL)</th>
<th>IgM (mg/dL)</th>
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<tbody>
<tr>
<td>1</td>
<td>F/4</td>
<td>883</td>
<td>&lt;6.6</td>
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<tr>
<td>2</td>
<td>M/4</td>
<td>1,440</td>
<td>&lt;6.6</td>
<td>85.6</td>
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<tr>
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<td>1,130</td>
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<td>945</td>
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<tr>
<td>6</td>
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<td>1,190</td>
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<tr>
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<td>2,090</td>
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<tr>
<td>8</td>
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<td>12</td>
<td>F/18</td>
<td>1,670</td>
<td>&lt;6.6</td>
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</table>

REFERENCES
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