1.1. Valproic acid and hair texture changes

Introduction
Valproic acid (Depakine®) is an anti-epileptic drug which is indicated for the treatment of primary generalized epilepsy, partial epilepsy with focal and psychomototic symptoms and secondary forms of generalized epilepsy. The most commonly reported adverse reactions of valproic acid are gastrointestinal symptoms like nausea, vomiting and diarrhoea. In the SmPC of valproic acid alopecia and a change in hair color are mentioned as adverse effect, hair structure changes are not described [1]. This report describes hair texture changes associated with the use of valproic acid.

Reports
On February 1, 2009 the database of the Netherlands Pharmacovigilance Centre Lareb contained seven reports of hair structure changes associated with the use of valproic acid. One patient got brittle hair after she started to use valproic acid and six patients got curly hair after they started to use valproic acid. In some cases hair loss or hair color changes were reported as well. The time to onset of hair changes varied from two weeks to six months. In most cases, valproic acid was continued and the hair texture changes persisted. Valproic acid was withdrawn in one case, the hair texture normalized approximately one year after cessation of the therapy. All reports of curly hair concerned women between 28 and 37 years old.

Table 1. Reports of hair structure changes associated with the use of valproic acid.

<table>
<thead>
<tr>
<th>Patient, Sex, Age</th>
<th>Drug, Indication for use</th>
<th>Concomitant medication</th>
<th>Suspected adverse drug reaction</th>
<th>Time to onset, Action with drug outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, 79319 F, 37</td>
<td>valproic acid Mood swings</td>
<td>lithium, fluoxetine, aripiprazole</td>
<td>from straight to curly hair</td>
<td>within 2 years, unknown</td>
</tr>
<tr>
<td>B, 77945 F, 36</td>
<td>valproic acid 500mg 3dd, prophylaxis after surgical removal of meningioma</td>
<td>not reported</td>
<td>from straight to curly hair</td>
<td>6 months, curling of the hair persisted during treatment</td>
</tr>
<tr>
<td>C, 43755 F, 28</td>
<td>valproic acid 500mg 5dd, bipolar affective disorder</td>
<td>no concomitant medication</td>
<td>curling and darkening of the hair</td>
<td>unknown, medication was continued, curling of the hair persisted</td>
</tr>
<tr>
<td>D, 43472 F, 36</td>
<td>valproic acid 500mg 2dd, bipolar disorder</td>
<td>quetiapine lorazepam salbutamol</td>
<td>alopecia and tight curls</td>
<td>2 weeks, medication was continued, curling of the hair persisted</td>
</tr>
<tr>
<td>E, 26357 F, 36</td>
<td>valproic acid 500mg 3dd bipolar affective disorder</td>
<td>olanzapine, candesartan</td>
<td>curly hair, previously she had no curls</td>
<td>5 months, medication was continued, unknown</td>
</tr>
<tr>
<td>F, 12387 F, 35</td>
<td>valproic acid 300mg not reported</td>
<td>from straight hair to curly hair</td>
<td>1 month, unknown</td>
<td></td>
</tr>
<tr>
<td>G, 15334 F, 9</td>
<td>valproic acid 300mg 2dd, epilepsy</td>
<td>Not reported</td>
<td>brittle hair and hair loss</td>
<td>several months, recovered 1 year after discontinuation</td>
</tr>
</tbody>
</table>
Other sources of information

Literature

The association between valproic acid and hair structure changes was mentioned in several case reports [2-7]. In some of the cases the hair changes disappeared after withdrawal of valproic acid [3] or seemed dose dependent [4]. Hair loss and hair discoloration were also seen in some patients with hair structure changes [3,5]. It has been suggested valproic acid might induce kinky hair syndrome [5]. Characteristic hair abnormalities are seen in patients with kinky hair syndrome, including kinky, dry, brittle and lusterless hair with pili torti. Under light microscopy the hair shafts are flattened and twisted [5,8].

In some of the cases in the Lareb database, patients experienced curling of the hair in combination with brittle hair, hair loss or hair color changes. These hair changes also resemble the hair abnormalities seen with kinky hair syndrome.

Other databases

The WHO database of the Uppsala monitoring centre contained 60 reports of abnormal hair texture in association with valproic acid. This ADR is more often associated with valproic acid compared to other drugs, which supports a causal relationship (ROR = 7.7; 95% CI 5.9-9.9). On February 2 2009, the Eudravigilance did not contain any reports of changes in hair texture. In the Eudravigilance database, the majority of reports is of a ‘serious nature’. For this reason it is possible that this ADR is underrepresented compared to the national databases.

Mechanism

The mechanism by which valproic acid changes the hair texture is not clear. Possibly the chelating properties of valproic acid can explain the effects on the hair structure. Several metals are essential to hair growth and keratinisation [4]. Decreased copper, zinc and magnesium concentrations were found in subjects treated with valproate [9]. Furthermore, a resemblance was seen between the hair changes seen with valproate and the hair texture seen in Menkes Kinky hair syndrome [5]. Low copper plasma levels are one of the characteristics of this syndrome [8]. This could support this hypothesis. However, the cases reported to Lareb did not mention changed concentrations in plasma metal levels, hence our cases cannot support nor question this proposed mechanism.
Conclusion

Lareb received seven reports of hair structure changes in association with valproic acid, including six reports of curly hair. Several case reports were described in the literature and support the association between valproic acid and hair structure changes. An underlying mechanism of action is not found yet.

References


This signal has been raised on April 2009. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).