

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 psychomotoric 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 Valproic acid was withdrawn in one case, the hair texture normalized approximately one year after cessation of the therapy.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.

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

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

1. Dutch SMPC Depakine enteric®. (version date November 2007) <http://db.cbg-meb.nl/IB-teksten/h07476.pdf>
2. Fischer-Steenvoorden MGJ, Stravens LCM. Verandering van haar bij gebruik van valproïnezuur. Pharmaceutisch Weekblad 1996; 26: 744.
3. Flaig MJ, Rupec RA. Valproate-induced change in hair color. J Am Acad Dermatol. 2008 58(2 Suppl):S63-4.
4. Wilting I, van Laarhoven JH, de Koning-Verest IF, Egberts AC. Valproic acid-induced hair-texture changes in a white woman. Epilepsia. 2007;48:400-1.
5. Caneppele S, Mazereeuw-Hautier J, Bonafé JL. Cheveux crépus acquis induits par le valproate de sodium. Ann Dermatol Venereol. 2001 Feb;128:134-5.
6. Jeavons PM, Clark JE, Harding GF. Valproate and curly hair. Lancet. 1977 1(8007):359.
7. Gupta AK.'Perming' effects associated with chronic valproate therapy. : Br J Clin Pract. 1988; 42(2):75-7.
8. Stratigos AJ, Baden HP. Unraveling the molecular mechanisms of hair and nail Genodermatoses Arch dermatol 2001; 137: 1465-71.
9. Suzuki T, Koizumi J, Moroji T, Shiraishi H, Hori T, Baba A, Kawai N, Tada K. Effects of long-term anticonvulsant therapy on copper, zinc, and magnesium in hair and serum of epileptics. Biol Psychiatry. 1992 Mar 15;31(6):571-81.

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).