

Valproic acid and gingival disorders

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 mechanism of action of valproic acid has not yet been established, the activity may be related to increased brain concentrations of gamma-aminobutyric acid (GABA). Furthermore valproic acid may act on the GABA receptor itself. The most commonly reported adverse drug reactions of valproic acid are gastrointestinal symptoms like nausea, vomiting and diarrhoea. In the SmPC of valproic acid, stomatitis is mentioned as adverse effect. Adverse effects on the gingival tissue are not described [1].

The current observation describes the association between valproic acid and gingival disorders.

Reports

On the 1st of June 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained seven reports of gingival disorders associated with the use of valproic acid, including four reports of gingivitis, two reports of gingival recession and one report of gingival hyperplasia. The time to onset of the gingival disorders varied from one week to several years. Patient D was recovering after valproic acid was withdrawn; the outcome was not reported in any of the other cases. Patient F also used amlodipine, a frequent cause of gingival hyperplasia. Not only children were affected: five reports concerned gingival disorders in adults.

Table 1. Reports of gingival disorders 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
6454, A M,23	valproic acid 300, epilepsy	carbamazepin	gingivitis	2 weeks, continued, not reported,
8498, B M,8	valproic acid 150, not reported	not reported	gingival recession	2 years continued, not reported,
20815,C F,28	valproic acid 500, epilepsy	carbamazepin 200 *	gingivitis	not reported**, continued, not reported,
32910,D F,49	valproic acid 500, not reported	omeprazole, oxazepam, famotidin dexamethason	gingival recession	1 week, withdrawn, recovering
47177,E F,60	valproic acid 450; bipolar disorder	mesalazin, amlodipin, calcium/colecalciferol, flurazepam, atenolol, lithium acamprosate	gingivitis	creams not reported, continued, not reported,
51547, F F,16	valproic acid 500, epilepsy	creams	gingivitis	not reported, continued, not reported,
70544,G F, 37	valproic acid 300, bipolar disorder	paroxetine	gingival hyperplasia	10 years, withdrawn, unknown

* Also reported as suspected medication.

** Time to diagnosis was 9 years.

Other sources of information

Literature

The association between valproic acid and gingival hyperplasia has been published in only a few case reports [2-5]. All reports concerned children. The gingival disorder appeared with a latency of 1-18 months [2-4]. The progression of gingival overgrowth stopped when the patient switched to carbamazepine in the case reported by Gulati [5]. Regression of gingival hyperplasia was seen after discontinuation of valproic acid in the case reported by Benhari [2]. The symptoms were dose dependent in the case reported by Syrjänen [4]. Other common causes of gingival overgrowth were excluded and concomitant use of phenytoin, a well known cause of gingival hyperplasia, was also excluded [2-4]. In the case reported by Syrjänen biopsy of the gingival tissue revealed a considerable number of mast cells, suggestive for a stimulatory effect of valproic acid on the tissue mast cells [4]. A study on periodontal problems in children showed that epileptic children on valproate are at risk for the development of gingival enlargement. The study was conducted to determine the occurrence, severity, and risk factors of gingival enlargement in children treated with valproate and other non-valproate antiepileptic drugs. In the study 68 epileptic children were compared with 50 controls. The gingival condition was evaluated by the gingival index, dental plaque index, probing depth and gingival enlargement. The periodontal condition was significantly lower in the children with epilepsy (48 with valproate and 22 non-valproate) than in the children in the control group. The children on valproate, the duration of the treatment with valproate had a significant effect on gingival enlargement. These children had a poorer periodontal health compared to the children in the non-valproate group, despite similar gingival index values and better oral hygiene [6].

Databases

The Lareb database contains seven reports of gingival disorders associated with the use of valproic acid and the WHO database of the Uppsala monitoring centre contained 53 reports of gingival hyperplasia in association with valproic acid.

Table 2. Reports of gingival disorders in association with valproic acid in the Lareb and WHO database.

	Adverse drug reaction	reports	ROR (95% CI)
Lareb database	Gingival disorders	7	6.0 (2.8 - 12.8)
WHO database	Gum hyperplasia	53	3.0 (2.3 - 4.0)

On June 8 2008, the Eudravigilance database contained 17 reports of gingival disorders associated with valproic acid/valproate. In one patient gingival bleeding was reported in relation to pancytopenia. Nine patients were children younger than twelve years, once a foetal valproic syndrome was mentioned explicitly. Valproic acid was three times reported to be the sole medication used. Four times, three or less concomitantly used drugs were reported, twice this was phenytoin.

Mechanism

Several drugs, including some anti-epileptics (phenytoin, phenobarbital and vigabatrin) are associated with gingival enlargement [6]. But the pathogenesis of drug induced gingival disorders is still uncertain. Possibly an interaction between drugs and/ or metabolites with the gingival fibroblasts may be an explanation [7]. But other factors like age, gender, genetic predisposition, plaque-induced inflammatory and immunological changes and activation of growth factors also play a role in development of gingival disorders [7,8]. Furthermore antiepileptic drugs may cause depletion of folic acid, which may have an effect on the enlargement of gingival tissue [9]. What mechanism plays a role in valproate induced gingival enlargement is unclear [6].

Conclusion

Lareb received seven reports of gingival diseases in association with valproic acid, including five case reports in adults. Although gingival disorders have multifactorial causes and can occur spontaneously, the reported cases suggest a causal relationship. Several case reports have been described in the literature and a study on periodontal problems in children with epilepsy, suggest an association between valproic acid and gingival disorders. Gingival disorders should be mentioned in the SmPC of valproic acid.

References

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This signal has been raised on July 2008. 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).