Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Valproic acid and pubertas praecox

Introduction

Valproic acid (Depakine® and generics) is an antiepileptic drug and is indicated for *the treatment of primary generalized epilepsy and partial epilepsy, with or without secondary generalization [1].*

Precocious puberty refers to the appearance of physical and hormonal signs of pubertal development at an earlier age than is considered normal. In girls, the telltale signs of precocious puberty include any of the following symptoms before 7 or 8 years of age: breast development, pubic or underarm hair development, rapid height growth - a growth "spurt", onset of menstruation, acne and "mature" body odour. For boys, onset of puberty before age 9 years is considered precocious.

Precocious puberty can be divided into two distinct categories: central precocious puberty (CPP) and precocious pseudopuberty. CPP, which is gonadotropin-dependent, is caused by early maturation of the entire hypothalamic-pituitary-gonadal axis, with the full spectrum of physical and hormonal changes of puberty. Precocious pseudopuberty is much less common and refers to conditions in which increased production of sex steroids is independent of pituitary gonadotropin release. Causes of precocious pseudopuberty include congenital adrenal hyperplasia; tumours that secrete human chorionic gonadotropin; tumours of the adrenal gland, ovary, or testis; male-limited precocious puberty; McCune-Albright syndrome; aromatase excess syndromes; and exposure to exogenous sex steroid hormones.

Central nervous system (CNS) abnormalities associated with precocious puberty include the following: congenital anomalies, intra cranial tumours and acquired CNS injury caused by inflammation, surgery, trauma, radiation therapy, or abscess.

Reports

Until 12 December 2006, the Netherlands Pharmacovigilance Centre Lareb received four reports of precocious puberty associated with the use of valproic acid. The time to onset varies from seven months to four years. The drug was withdrawn in one case. All cases concerned girls.

Report A concerns a 7-year old female who experienced development of the genitals after a latency of four years. Valproic acid had been used for three months in a dosage which was reported to be too high for the age/weight. First symptoms were noted one year after valproic acid had been withdrawn.

Report B concerns a 7-year old Negroid female who experienced growth of underarm hair and pubic hair with a latency of 1.5 years. Concomitant medication was not reported

Report C, reported by a consumer, concerns an 8-year old female who experienced growth the mammae with a latency of 7 months. The mother noticed a change in body odour. Concomitant medication was not reported.

Report D concerns an 8-month old female old who was born by emergency caesarean at gestational age 35+3 weeks because a comatose state of the mother following epileptic seizures. Intra-uterine exposure to antiepileptics was not documented. The newborn was diagnosed with epilepsy resulting from severe CNS damage (thalamus, nucleus lentiformis). At the age of eight months she experienced growth of pubic hair on the labia majora (Tanner stadium 2) with an unknown latency. Concomitant medication: lamotrigine, clonazepam, lactulose and amoxicilline/clavulanic acid. The reporter considered clonazepam the suspect medication based on a case report [2].

Other sources of information

SPC

The SPC of Depakine® states in section 4.5.3 “other interactions” that valproic acid commonly does not induce enzymes and that therefore no reduction in effectiveness of oestrogen-progestagen oral contraceptives is to be expected. In section 4.8 of the SPC “adverse reactions – endocrinological system” irregular menstruation is reported to occur frequently and amenorrhoea is reported to occur rarely [1]. The occurrence of precocious puberty is not mentioned in the SPC.

Literature

Literature reports on precocious puberty associated with the use of valproic acid could not be retrieved from an exhaustive Medline search. However, studies have been published that show effects of valproic acid on sex steroids but an abnormal pubertal development could not be demonstrated:

Twenty-three girls and 15 boys (aged 8-16 years old) who were undergoing valproate treatment for epilepsy were compared with 15 control girls and 10 control boys of the same age range. Valproate did not affect pubertal development in the study group. No hirsutism or polycystic ovaries were found. Increases in weight and body mass index were observed in the group undergoing valproate treatment, but no statistically significant differences compared with the control group were found. Plasma testosterone was higher in valproate-treated girls (0.71±0.51 ng/ml) than in control girls (0.35±0.15 ng/ml) (p 0.001). This finding was an early adverse effect and independent of valproate dose and treatment duration. No changes in normal pubertal development or physical repercussions were found in epileptic patients [3].

Hyperandrogenism has been reported in girls taking valproic acid. Evaluation of testosterone levels in 41 girls, 8 to 18 years old, taking valproic acid revealed significantly higher serum testosterone levels compared to control subjects at the same pubertal stage. Of girls receiving valproic acid, 38% of prepubertal girls, 36% of pubertal girls, and 57% of postpubertal girls were hyper-androgenic [4].

In a case series all three patients developed hyperandrogenism and polycystic ovaries during treatment with valproate. It was associated with weight gain and menstrual disorders in two of the three women. Replacing valproate with

lamotrigine resulted in a decrease in serum testosterone concentrations in all three women. The polycystic changes disappeared from the ovaries in two of the women after valproate therapy was discontinued, and the two women who had gained weight and developed amenorrhea while being treated with valproate lost weight and resumed menstruating after the change in medication [5].

Databases

On 12 December 2006 the Lareb database contained 4 reports on precocious puberty associated with the use of valproic acid in girls, which is disproportional (ROR 450, 95% CI 46.7 - 4337). There are no other reports on precocious puberty in the Lareb database.

On 12 December 2006, the WHO Collaborating Centre had received 17 reports on precocious puberty associated with the use of valproic acid, which is disproportional (ROR 19.9, 95% CI 11.6- 34.0). Sixteen of these cases concerned girls, The total number of reports on precocious puberty in the WHO database is 86. The second most frequently medication associated with precocious puberty is carbamazepine with 12 reports.

Discussion

No reports on precocious puberty associated with the use of valproic acid could be retrieved from an exhaustive Medline search. But reports in the literature do indicate reproductive endocrine effects of valproic acid (and carbamazepine) as shown by clinical and/or laboratory evidence of hyperandrogenism and a high prevalence of polycystic ovary syndrome in female patients [5,6].
Nevertheless, both Lareb and WHO databases show a disproportional high number of reports, with all Lareb reports and all but one WHO report concerning females.
Since precocious puberty can be secondary to central nervous system abnormalities and injuries confounding by indication should be considered, Patient D could be an example of this confounding.

Conclusion

Both Lareb and WHO databases show a disproportional high number of reports on precocious puberty associated with the use of valproic acid. This potential signal from spontaneous reporting systems requires confirmation from other sources.

1. SPC Depakine. version date July 7 2006 at www.cbg-meb.nl/nl/prodinfo (accessed 18-12-2006)
2. Choonara IA, Rosenbloom L, Smith CS. Clonazepam and sexual precocity. New Eng J Med. 1985; 312(3): 185
3. Balaguer Martinez JV, Lopez Garcia MJ, Andres Celma M, Contell Villagrasa A, Castello Pomares ML.. Efectos del ácido valproico sobre el desarrollo sexual. An Pediatr (Barc). 2003 58(5):443-8
4. Vainionpaa LK, Rattya J, Knip M, Tapanainen JS, Pakarinen AJ, Lanning P, Tekay A, Myllyla VV, Isojarvi JI. Valproate-induced hyperandrogenism during pubertal maturation in girls with epilepsy. Ann Neurol. 1999 Apr;45(4):444-50.
5. Isojarvi JI, Tapanainen JS. Valproate, hyperandrogenism, and polycystic ovaries: a report of 3 cases. Arch Neurol. 2000 Jul;57(7):1064-8.
6. Isojarvi JI, Tauboll E, Pakarinen AJ, van Parys J et al. Altered ovarian function and cardiovascular risk factors in valproate-treated women. Am J Med. 2001;111(4):290-6.