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GnRH agonists leuprorelin, buserelin or triptorelin and epiphysiolysis

Introduction

Leuprorelin (Lucrin®) buserelin (Suprefact®, Suprecur®) or triptorelin (Decapaptyl®) belong to the group of gonadotropin-releasing hormone analogues and is a synthetic nonapeptide analogue of the hypothalamic peptide gonadorelin. Leuprorelin has granted a marketing authorisation for the Dutch market in 1989 for the *treatment of moderate to severe forms of endometriosis, prostate carcinoma with metastases, when suppression of testosterone production is needed. Finally, it can be used for the treatment of idiopathic central precocious puberty* [1].
Adverse events are often a consequence of its induction of a prolonged hypoestrogenic state or low levels of testosterone. They include bone loss as well as menopausal-like symptoms (irritability, nervousness, anxiety insomnia, hot flushes, amenorrhoea, and reduction in bone density).

Reports

Lareb received one report by a general practitioner concerning an 11-year-old girl who had been using leuprorelin 3.75mg once a month for precocious puberty. Five years after the start of leuprorelin and 7 months after the last injection bilateral epiphysiolysis of both capital femoral epiphyses occurred. Epiphysiolysis is a disease in which the epiphysis in a growing child slowly separates from the metaphysis. She had received a total amount of 37 injections of leuprorelin in 4 years. She fully recovered after surgery.

Other sources of information

Literature

Kempers and Noordam reported a relationship between epiphysiolysis of the capital femoral epiphysis and the GnRH agonists buserelin and triptorelin treatment in four patients during or shortly after discontinuation of treatment with the GnRH agonists [2]. One patient treated with triptorelin developed sequential epiphysiolysis of both hips.
In the five patients of epiphysiolysis reported in the literature or to Lareb, one case of epiphysiolysis occurred during GnRH agonist treatment and four shortly after treatment was stopped.

Database

The WHO database contains 5790, 443 and 96 reports on leuprorelin, buserelin and triptorelin respectively. No cases of epiphysiolysis have been reported to the WHO yet.

Mechanism

Slipped capital femoral epiphysis mainly occurs in pubertal children and is associated with delayed skeletal maturation, obesity, high growth velocity and tall stature [2]. None of the patients described in literature or the patient reported to Lareb met these typical risk factors.
Epiphysiolysis often coincides with endocrine disorders. Probably the hormonal changes during and shortly after treatment with GnRH agonists make the epiphysis more prone to slip. Kempers et al hypothesise that during GnRH agonist therapy, low oestrogen levels and a reduced growth velocity decrease epiphyseal activity and weaken the epiphyseal plate. Near the end of GnRH agonist therapy bone turnover is low and bone maturation is extremely slow. When growth is stable this weakening has no immediate consequence. However, when treatment is stopped, there is an increase in growth velocity, which reduces the shearing force, which may enable the displacement of the epiphysis [2].

Conclusion

Lareb has received one case report of bilateral epiphysiolysis on leuprorelin in an 11-year-old girl. The pharmacological plausibility and one publication of epiphysiolysis in four children, who had

been using buserelin or triptorelin, support the association.

References
1. Dutch summary of Product Characteristics of Lucrinl®. 1-07-1999.
2. Kempers MJE, Noordam C, Rouwe CW, Oten BJ. Can GnRH-agonist treatment cause slipped capital femoral epiphysis? J Ped Endocrinol Metab. 2001;14:729-34.
3. Dutch summary of Product Characteristics of Suprefact®. 3-10-1997.
4. Dutch summary of Product Characteristics of Suprecur®. 3-10-1997.
5. Dutch summary of Product Characteristics of Decapaptyl®. 1-10-2002