1.1. Tamoxifen and hirsutism

Introduction

Tamoxifen is a non-steroid triphenylethylenderivate with estrogen antagonist- and agonist effects in different tissues. It was approved for the Dutch market in 1975. It is indicated for the treatment of hormone sensitive tumors such as mamma carcinomas. [1]
Hirsutism is a condition observed in women and children when there is excess coarse body hair of an adult male distribution pattern, such as facial and chest areas. It is the result of elevated androgens from the ovaries, the adrenal glands, or exogenous sources. The concept does not include hypertrichosis, which is an androgen-independent excessive hair growth. [2]

The SmPC of tamoxifen (Nolvadex®) does not mention hirsutism as possible ADR.[3] In this report, the association between the use of tamoxifen and hirsutism was analysed.

Reports

On the 1st of August, 2008 the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports concerning hirsutism during tamoxifen use.

Patient A (61078) is a 58-year-old woman After finishing a FEC (Fluorouracil, Epirubicine Cyclophosphamide) treatment for breast cancer, she received tamoxifen 20 mg once daily. 15 days after start of tamoxifen the patient developed hirsutism. No information about further drug use was reported. At the time of notification, the patient had not yet recovered.

Patient B (77003) is a 47 year old woman. She was treated with chemotherapy for breast cancer. Thereafter treatment with tamoxifen 20 mg once daily was initiated. 3 weeks after start the patient developed increased hair growth in her face, which was interpreted as hirsutism by the reporter. She also experienced hair discoloration. Tamoxifen dose was not changed, the patient had not recovered 4 months after the event.

Other sources of information

Literature

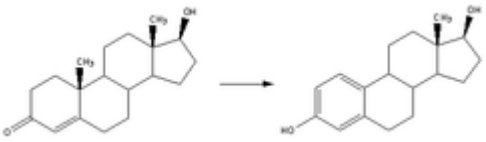
In Meyler's side effects of drugs hirsutism is mentioned as and ADR occuring during tamoxifen use.[4] The Farmacotherapeutisch Kompas also mentions hirsutism as an ADR. A Medline search using "Tamoxifen"[Mesh] AND "Hirsutism"[Mesh] did not yield any result.

Databases

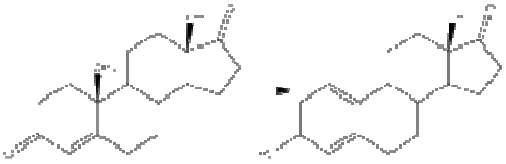
The number of two reports in the Dutch databank is too low to calculate a reliable ROR. On August 1st, 2008 the database of the WHO contained 77 reports of tamoxifen and hypertrichosis (the WHO-ART term corresponding to the MedDRA term hirsutism) with a ROR of 9.1 CI (7.2-77.4). The Eudravigilance database does not contain any serious reports of alopecia related to the use of tamoxifen

Mechanism

Estradiol, estriol, and estrone, the three naturally occurring estrogens, are all synthesized from the androgens testosterone and androstenedione. The conversion of the androgens to estrogens are catalysed by the enzyme aromatase.[5]



Aromatase converts testosterone to estradiol



Aromatase converts androstenedione to estrone

Hirsutism is caused by and an elevation of androgens.[6]It is possible that tamoxifen, due to its binding to the estrogen receptor can change the equilibrium in the estrogen synthesis and shifting it to the right, increasing the level of androgens.

Discussion

Testosterone and its active metabolite, dihydrotestosterone can affect hair growth both positively (hirsutism) and negatively (alopecia). Alopecia as an ADR related to the use of tamoxifen has been reported in literature. Hirsutism is also being described as and ADR associated with aminogluthemide use (aromatase inhibitor).

Conclusion

The Netherlands Pharmacovigilance Centre Lareb has received two reports of hirsutisme with a latency of 2-3 weeks. This association is described in international as well as national reference books. Data from the WHO databank also supports this association. A possible mechanism is that tamoxifen alters the androgen-estrogen balance in the body.

References

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This signal has been raised on December 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).