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Cyproterone acetate and osteoporosis

Introduction

Cyproterone acetate (Androcur®) is an antiandrogen with progestogenic activity and was granted a marketing authorisation for the Dutch market in 1973. According to the Dutch SPC cyproterone acetate is indicated: *in males for the treatment of advanced prostatic carcinoma, hypersexual behaviour disorders and hot flushes associated with orchiectomy or LHRH agonist therapy in males and for the treatment of idiopathic hirsutism and androgenic induced acne and alopecia in females* [1]. Adverse effects of cyproterone acetate include impotence, inhibition of spermatogenesis, headache, lassitude, menstrual irregularities, gynecomastia, galactorrhea, weight gain, lipid abnormalities, gastrointestinal disturbances, and anemia; several cases of hepatotoxicity (some fatal) have been reported in the literature.
Long-term treatment with androgen-depleting drugs is associated with osteoporosis. Hypogonadism, chronic alcoholism and chronic glucocorticoid therapy are the major cause of osteoporosis in men and account for approximately one-half of all cases of male osteoporosis [2]. Osteoporosis in men seems to occur rarely.

Reports

The Netherlands Pharmacovigilance Centre Lareb received two reports of osteoporosis in men taking cyproteron acetate (table 1).

- Patient A, a male aged 39, was reported to have osteoporosis 18 months after start of cyproterone acetate to treat exhibitionism. The therapy was successful but caused gynaecomastia and symptoms of cyproterone acetate induced hypogonadism: reduced frequency of erections, loss of ejaculation and diminished beard growth.
  A control duplex radiographic absorptiometry (DXA) scan showed a significant reduction of bone mineral density (BMD) at the lumbar region of the spine (L2-L4 T-score –3.3, Z-score -4.0; femoral neck T-score –1.6, Z-score –0.9) indicating osteoporosis [3]. The patient however did not experience any musculosceletal complaints. Physical examination revealed a normal male hair pattern, adiposity (133kg weight and 1.89m height). Both testicles were normal on palpation.
  Laboratory results: testosterone 4.1 [normal range 14 – 42 nmol/L] was reduced. All other laboratory results (SHBG, TSH, FreeT4, LH, FSH, cortisol, Hb, glucose, kreatinine, calcium, phosphate, AF) were within the normal range indicating absence of hormonal disturbances. Treatment of osteoporosis with risedronate (Actonel®) and calcium suppletion was initiated.
- Patient B, a man aged 52, had been treated for a sexual deviation with cyproterone acetate for ten years. Then, osteoporosis was diagnosed (BMD: T-score –3.4 and Z-score –2.8) [4].

Table 1. Lareb reports of osteoporosis or fractures in males associated with the use of cyproterone acetate (patient B also published as a case report [4])

Patient, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset
A, 39	cyproterone acetate tabl 1 dd 50mg Sexual deviation	none reported	osteoporosis	18 months after start
B, 52	cyproterone acetate injection 300 mg every 2 weeks Sexual deviation	captopril, hydrochlothiazide	osteoporosis, hip fracture	10 years after start

Other sources of information

Literature

Gooren *et al.* presented patient B as a case-report in the Lancet [4].

Vasireddy and Swinson published another case report concerning a 58 year-old male with a sexual deviation who had been treated with cyproterone acetate from 1976 –1979. After complaints of pain in the back he was diagnosed to have osteoporotic wedge fractures of dorsal vertebrae in 1987. A DXA-scan in 1992 confirmed a significant reduction in BMD at the spine (L2-L4 T-score –2.46, Z-score –1.96) [5].

Databases

In February 2003 the Lareb database contained a grand total of 4 ADR reports with event code osteoporosis. Apart from patient A and patient B listed in the table, osteoporosis was also reported in a female aged 35 - suspected drug oxcarbazepine and in a male aged 51 - suspected drug gosereline. At the end of the 4th quarter of 2002 the WHO combination database contained 6 reports, ROR 19.2 (8.6-42.9) of osteoporosis in association with cyproterone acetate.

Mechanism

The underlying mechanism of osteoporosis is the same in men and women: an absolute or relative (to bone formation) increase in osteoclast mediated bone resorption leading to progressive bone loss [5].
Estrogen playes a major role in regulating male bone metabolism: both estrogen and testosterone are important in maintaining bone formation and estrogen regulates bone resorption partly through its action on estrogen-receptor alpha.
In the male estrogen is produced by conversion of androgen precursors, mediated by the enzyme aromatase [5]. Therapy with anti-androgens influences bone homeostasis because it interferes with this conversion of androgens into estrogens [5].

Conclusion

The Netherlands Pharmacovigilance Centre Lareb received two reports of osteoporosis in men taking cyproteron acetate for a period of months to years for treatment of sexual deviant behaviour. This association is supported by data from the database of the WHO and the literature. Pharmacological plausibility also supports this association.

References

1. Dutch Summary of Product Characteristics of Androcur® (version 20-07-1991) http://www.cbg-meb.nl
2. Smith MR. Osteoporosis and other adverse bodycomposition changes during androgen deprivation therapy for prostate cancer. Cancer Met Rev 2002; 21: 159–66.
3. How does it work? Bone mineral density scans. BMJ 2002; 325: 31
4. Gooren LJG, Lips P, Gijs L. Osteoporosis and androgen-depleting drugs in sexoffenders. Lancet 2001;357:1208-09.
5. Vasireddy S, Swinson DR. Male osteoporosis associated with longterm cyproterone treatment. J. Rheumatology 2001;28:1702-03.