1.1. Dutasteride and testicular pain

Introduction

Dutasteride (Avodart® and Combodart®) has been registered internationally since 2002. It is indicated for *moderate to severe symptoms of benign prostatic hyperplasia*. Dutasteride is a selective testosterone-5-alpha-reductase inhibitor, which reduces the free circulating dihydrotestosterone (DHT) concentration by inhibiting both type I and II iso-enzymes of 5-alpha reductase. DHT itself is a strong androgen that stimulates the prostatic gland to hyperplasia. Inhibiting the synthesis of DHT reduces prostatic hyperplasia and improves urinary voiding [1-3].

Testicular pain can be caused by several conditions, such as testicular torsion, appendiceal torsion, and epididymitis. Other causes could be trauma, inguinal hernia, Henoch-Schönlein purpura, post-vasectomy, a complication of mumps, Fournier's gangrene and referred pain [4].

In this report the association between dutasteride and testicular pain will be discussed in more detail.

Reports

On July 29, 2011 the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports concerning testicular pain with the use of dutasteride.

Table 1. Reports of testicular pain associated with the use of dutasteride

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 86896 M, 61 – 70 years General Practitioner	dutasteride 0,5mg Prostatism		testicular pain	2 days unknown not recovered
B 117664 M, 71 years and older Patient	dutasteride 0,5mg Benign prostatic hyperplasia	carbasalate calcium	testicular pain	3 days continued not recovered
C 119680 M, 61 – 70 Pharmacist	dutasteride 0,5mg	enalapril, zopiclon, alfuzosin retard, flecainide acetate, atorvastatin	pain in testis	1 day discontinued recovered

Patient A, a male aged 61-70 years, his medical history mentions an inguinal hernia in 1991 (report is from 2009). Patient is diagnosed with prostatism in August 2009 and was initially treated with alfuzosin without result. After two days of treatment with dutasteride the testicular pain appeared. The action taken for the drug is unknown, but the patient has not recovered. Patient has a medical history of hernia inguinalis in 1991, but this is unlikely to have influenced his current complaints.

Patient B, a male aged 71 years and older, experienced testicular pain three days after start of dutasteride. The patient continued taking dutasteride but had not recovered. The reporter mentioned the absence of testicular pain as an ADR in the product information leaflet, although the urologist and the hospital pharmacist warned for testicular pain as a possible adverse drug reaction in their own patient's brochure.

Patient C, a male aged 61-70 years, experienced testicular pain after one day of treatment with dutasteride. He recovered from these symptoms after discontinuation.

All latencies in these reports are quite similar, one to three days, and for one patient it is known that the symptoms diminished after cessation of the drug.

Other sources of information

SmPC

Testicular pain is not mentioned in the SmPC's of dutasteride containing products [1,2]. However, testicular pain is mentioned in the Dutch SmPC of Proscar®, a finasteride containing product, which is also a 5-alpha-reductase inhibitor, which was reported during post-marketing experience [5].

Literature

A Pubmed search revealed no publications on the possible association between dutasteride and testicular pain.

Databases

On July 29, 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained three cases of testicular pain in association with dutasteride, which was reported disproportionally (ROR = 254.8, 95% CI: 71.4 - 909.0).
The WHO database of the Uppsala Monitoring Centre contained 17 reports of testicular pain associated with the use of dutasteride, and this also was reported disproportionally (ROR = 35.0, 95% CI: 21.6 - 56.6).
The Eudravigilance database, consisting predominantly of serious ADR reports, contained four reports of testicular pain associated with the use of dutasteride, which was reported disproportionally as well (ROR 43.6, 95% CI 16.2-117.4).

Prescription data

The number of patients using dutasteride and finasteride in the Netherlands is shown in table 2 [6]. Dutasteride and finasteride are both testosterone-5-alpha-reductase inhibitors which are used for moderate to severe symptoms of benign prostatic hyperplasia in the Netherlands.

Table 2. Number of patients using finasteride or dutasteride containing products in the Netherlands between 2005 and 2009.

Drug	2005	2006	2007	2008	2009
Finasteride	27,189	34,578	33,597	32,281	31,873
Dutasteride	12,423	20,772	27,931	34,910	41,007

Mechanism

The mechanism explaining how dutasteride can cause testicular pain is unknown. Testosterone-5-alpha-reductase inhibitors reduce the transformation of testosterone into dihydrotestosterone, especially in the male external genitalia. This inhibition may result in a rise of testosterone and estradiol levels. Estradiol is formed by the conversion of testosterone by the enzyme complex aromatase. These disturbances in the local testicular hormonal balance could possibly attribute to the observed complaints.

Discussion

There are three reports of testicular pain associated with the use of dutasteride, all with latencies of one to three days. In one case a positive dechallenge is described.
For finasteride, another testosterone-5-alpha-reductase inhibitor, testicular pain is noted in the SmPC as a known adverse drug reaction, which has been discovered during post-marketing surveillance.
Although we cannot explain these symptoms pharmacologically, it is assumable that due to changes in androgen and estrogen concentration in male external genitalia physical disturbances can result in testicular pain.
Since finasteride has been registered on the market since 1992 and dutasteride since 2002, it is plausible that testicular pain has not been detected before with the use of dutasteride.

Conclusion

Three Lareb reports of testicular pain, and one report with a positive dechallenge, support the association with dutasteride. Disproportionate statistics from other databases also support the association. Although there is no conclusive pharmacological explanation for this association, it is a known adverse drug reaction in association to another 5-alpha-reductase inhibitor finasteride. It should be considered to mention testicular pain in the SmPC of dutasteride.

- New signal of dutasteride associated with testicular pain.

References
1. Dutch SmPC Avodart® . (version date: 7-3-2011, access date: 29-7-2011) http://db.cbg-meb.nl/IB-teksten/h28317.pdf.
2. Dutch SmPC Combodart®. (version date: 3-5-2010, access date: 29-7-2011) http://db.cbg-meb.nl/IB-teksten/h104130.pdf.
3. KNMP Kennisbank. KNMP Kennisbank. (version date: 2011, access date: 29-7-2011) .
4. Up to Date, search term testicular pain. (version date: 2011, access date: 29-7-2011) http://www.uptodate.com/contents/evaluation-of-the-acute-scrotum-in-adult-men?source=search_result&selectedTitle=1%7E26.
5. Dutch SmPC Proscar®. (version date: 3-11-2010, access date: 29-7-2011) http://db.cbg-meb.nl/IB-teksten/h15482.pdf.
6. GIP Databank. (version date: 2011, access date: 29-7-2011) http://www.gipdatabank.nl/.

This signal has been raised on November 2011. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).