Brief Communication

Aromatase inhibitors in male sex

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ABSTRACT

Aromatase inhibitors (AI) have been used in males in idiopathic short stature, constitutional delay of puberty, precocious puberty, gynecomastia, oligospermia, hypogonadism related to obesity and ageing. This retrospective study echoed the benefit of AI in Indian males in varied conditions.

Key words: Aromatase inhibitors, constitutional delay of puberty, hypogonadism

Introduction

Aromatase inhibitors (AI) have been used in the treatment of idiopathic short stature (ISS), constitutional delay of puberty (CDP) and precocious puberty in boys to increase adult height. Moreover, it has been used in the management of gynecomastia, oligospermia and male hypogonadism related to obesity and ageing.[1-3] This retrospective study was carried out to assess the efficacy of letrozole, an AI, in varied conditions in Indian males.

Case Reports

Case A

A 15-year-old male presented with macromastia. He had delayed puberty.

Wt - 62.7 kg; Ht - 155 cm; Sexual Maturation Rate (SMR) - G1P1, testes - 3 ml, stretched penile length (SPL) - 5 cm.

LH - 6.3 IU/L, follicle-stimulating hormone (FSH) - 2.9 IU/L, prolactin (PRL) - 5.1 ng/ml, normal thyroid-stimulating hormone (TSH) and T4.

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Testosterone (T) - 43.8 ng/dl and estradiol (E2) - 9.79 pg/ml. T/E2 = 4.4:1. He was prescribed letrozole 2.5 mg - 3 times/week.

After 6 months of AI therapy:
Wt - 68.8 kg; Ht - 158.5 cm; SMR - G3P3, testes 10 ml, SPL - 6 cm. There was insignificant change in breast enlargement.

T - 331.62 ng/dl; E2-8.05 pg/ml. T/E2 = 41.2.

There was 650% increase in T and 17.9% decrease in E2.

Case B

A 14-year-old male was referred for obesity. He had delayed puberty.

Wt - 66.6 kg; Ht - 158 cm; SMR - G1P1, SPL - 4 cm.

LH - 3.59 IU/L; FSH - 2.48 IU/L; PRL - 13.8 ng/ml, normal TSH and T4.

T - 25.81 ng/dl; E2 - 141.3 pg/ml; T/E2 = 0.18:1.

He was prescribed injection T - 100 mg monthly and letrozole 2.5 mg - 3 times/week for 4 months. After 3 weeks of last dose of injection T and 3 days of last dose of letrozlole: Wt - 68.9 kg; Ht - 159.5 cm; SMR-G2P2, SPL ~5 cm.

T - 310.6 ng/dl; E2 - 13.15 pg/ml; T/E2 = 23.6:1.

There was ~1100% increase in T and 90% decrease in E2.

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Case C

A 23-year-old male was referred for management of hypogonadism.

Wt - 55.9 kg; Ht - 161 cm; body mass index - 21.6; no anosmia; SMR - G1P1, SPL - 4 cm. LH <0.07 IU/L, FSH - 0.032 IU/L, PRL - 4.93 ng/ml, T - 13 ng/dl.

He was prescribed injection T - 100 mg every 3 weeks along with letrozole 2.5 mg - 2 times/week. After 3 weeks of last (4th) injection T and 3 days of last letrozole dose: T - 74 ng/dl.

There was 469% increase in T.

Case D

A 27-year-old male was referred for poor semen quality. His total functional sperm fraction (TFSF), denoted by sperm count ($\times 10^6$) by normal morphology (%) by normal motility (%), was 70×10^6/ml $\times$ 30% $\times$ 30% =6.3.

T - 257.9 ng/dl; E2 - 35.8 pg/ml; T/E2 = 7.2:1.

He was prescribed letrozole - 2.5 mg - 2 times/week.

After 1 month of therapy: T - 754.9 ng/dl; E2 - 28.5 pg/ml; T/E2 = 26.5:1.

There was 200% increase in T and 20% decrease in E2.

TFSF - 80 $\times$ 106 $\times$ 70% $\times$ 30% =16.8.

Discussion

AI have been used in boys with ISS and CDP to increase adult height.[1,4,5] Boys with ISS with a mean age of 11 years were treated with letrozole 2.5 mg once daily or placebo for 2 years. There was a gain of 5.9 cm in predicted adult height in the letrozole treated group.[4] A significant increase in predicted adult height has also been observed in boys with CDP who were treated with a combination of T and letrozole.[5] AI slow down epiphyseal maturation by lowering E2 levels. This approach proved successful in other conditions, too, viz. aromatase excess syndrome, sertoli cell tumors and testotoxicosis (along with antiandrogen).[1] AI have limited efficacy in the treatment of gynecomastia; hence, they are not recommended as a first line treatment for gynecomastia.[1] Significant improvement in SMR was observed in CDP cases (Case A and B). There was marked improvement in SMR in case A with "sole" therapy with letrozole, but insignificant response in gynecomastia. Case B was treated with a "combination" of T and letrozole.

AI therapy is associated with a sustained increase in FSH and a positive effect on sperm concentration and motility.[1] Case D (T <300 ng/dl; T/E <10:1) showed improvement in semen quantity and quality with letrozole even though sperm count was normal. Some men with severe oligospermia (<5 $\times$ 10^6/ml), low T levels (<300 ng/dl), T (ng/dl) to E2 (pg/ml) ratio <10 and normal gonadotropins concentration may have a treatable endocrinopathy. AI have been successfully used in this subset of patients.[1,3,6] 2.5 mg/d letrozole for 6 months has been shown to improve seminal parameters (denoted by TFSF).[3]

AI have been used in the treatment of hypogonadism related with obesity and ageing. Letrozole 2.5 mg once a week produced sustained normalization of serum total T in males with obesity related hypogonadism; however, free T rose to supraphysiological levels emphasizing the need for estimation of free T during AI treatment.[2]

It has been suggested that aromatase is less suppressed in the testis compared with adipocytes and muscle tissue. It is questionable whether AI are able to stimulate T production sufficiently in men with truly low T levels.[1] There was a marked increase in T with combination treatment with T and letrozole in CDP (Case B) as compared with Idiopathic Hypogonadotropic Hypogonadism (IHH) (Case C) where there was lesser response with the same combination therapy. The marked increased in T with letrozole in CDP as compared to lesser response in IHH can aid in distinguishing the two conditions with the use of AI.

Most of the recent studies with AI in boys and adult men do not show a major detrimental effects (including bone).[1] The harmful effects are unlikely if the dose is carefully adjusted (even weekly) based on T and E2 levels.[3]

This retrospective study in Indian males showed insignificant effect of AI in gynecomastia and IHH, significant effect in CDP and some benefit in improving seminal parameters. Moreover, this study highlights the importance of estimating E2 (along with T and gonadotropins) in various endocrinopathies, which can be benefitted by reducing E2 by AI.

Further prospective, randomized, blinded, placebo-controlled, long-term studies are needed to clarify the role of AI in the management of growth impairment, male infertility and hypogonadism.

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