0021-7557/07/83-05-Suppl/S172
Jornal de Pediatria

REVIEW ARTICLE

Pharmacological management of children with short stature: the role of aromatase inhibitors

Durval Damiani,[1] Daniel Damiani[2]

Abstract

Objective: To review the use of aromatase inhibitors, a novel treatment strategy for patients with short stature, which aims at delaying bone age advancement. Skeletal maturation is estrogen-dependent even in male children.

Sources: We performed a MEDLINE search of studies published in the last 10 years, including aromatase, short stature, and early puberty as keywords. The most informative articles on indications, dosages, treatment schedules, and side effects of aromatase inhibitors were included in the review.

Summary of the findings: It has become increasingly clear that bone age advancement depends on the production of estrogen and its effect on the growth plate. In boys, testosterone is converted to estradiol by the cytochrome P450 enzyme aromatase. The use of aromatase inhibitors has been shown to be effective in prolonging the length of the growth phase in children with idiopathic short stature, constitutional growth delay, delayed puberty, as well as in children with growth hormone deficiency, in which bone age advancement jeopardizes the results of hormonal replacement therapy with growth hormones. As yet, significant adverse effects have not been reported, and results are encouraging in terms of effective increase in height, whenever the indication for the drug is appropriate.

Conclusions: Among the pharmacological treatments for short stature, aromatase inhibitors are indicated in cases in which bone age advancement may constitute an obstacle for reaching a final height that is in keeping with the family's target height.

J Pediatr (Rio J). 2007;83(5 Suppl):S172-177: Short stature, aromatase inhibitors, bone age, estrogens, androgens, puberty.

Introduction

Concerns about short stature, especially among boys, have become an obsession and, generally, a misleading idea that parents can "choose" the final height of their children is given. It is always important to remember that height has a genetic basis and that the hereditary growth potential must be respected. The role of pediatricians and pediatric endocrinologists is to allow for the full expression of individual growth potentials.

The unlimited availability of recombinant growth hormone (GH), produced by genetic engineering techniques, created a pressure for its use as a medication to increase the final height of children. From an originally very strict indication as a hormonal replacement therapy for children with GH deficiency, new indications were introduced. Studies showed that many patients could benefit from its use and reach a substantially higher final height, despite not having a "classic" GH deficiency, as demonstrated by conventional tests. Thus, Turner syndrome, Prader-Willi syndrome, intrauterine growth restriction, renal failure, and idiopathic short stature were included in the list of GH indications.

Whenever statural growth and final height are considered, it is important to keep in mind that the effector organ is the bone and that the potential to continue to increase stature depends on the stage of growth plate maturation. The first description of an inactivating mutation of the estradiol receptor involved a 28 year-old male, who presented with tall stature (204 cm) and bone age of 15 years. This case led

1. Professor livre-docente. Chefe, Unidade de Endocrinologia Pediátrica, Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (USP), São Paulo, SP, Brazil.
2. Biomédico. Aluno de iniciação científica, Faculdade de Medicina, Universidade Nove de Julho, São Paulo, SP, Brazil.

Suggested citation: Damiani D, Damiani D. Pharmacological management of children with short stature: the role of aromatase inhibitors. J Pediatr (Rio J). 2007;83(5 Suppl):S172-177.

doi 10.2223/JPED.1699

researchers to reconsider what exactly makes growth plates reach their complete maturation, ceasing any possibility of further growth.[1] Since then, researchers began to consider the hypothesis that estrogen was responsible for bone maturation, promoting the complete ossification of the growth cartilage and limiting linear growth. Shortly after, two other cases of male subjects with a similar phenotype, but with normal estrogen receptor, were described. A mutation was identified in the gene that codes for the enzyme aromatase P450, located on chromosome 15, which is responsible for the conversion androgens to estrogens, thus reinforcing the concept that estrogen is the major responsible the advancement of skeletal maturation. Unlike the first patient described, whose mutation affected an estrogen receptor (and therefore, would not benefit from the use of estrogen to promote bone maturation), these two other patients did benefit from estrogen therapy, which closed growth plates after 6 and 9 months of treatment, ceasing any further increase in stature.[2,3] In situations in which there is an early estrogen production (precocious puberty or sex hormone producing tumors), early closure of the growth plate is observed; on the other hand, in cases in which estrogen production is delayed or inexistent (late puberty, hypogonadism), delayed bone age and extended growth period are seen. Such natural experiments highlight the fact that the genetic potential of an individual may be modified, under certain conditions, to reach a height that is higher than expected based on parental height. This requires the blocking of the process that leads to skeletal maturation. This concept has, in fact, been applied in the treatment of precocious puberty, in which, to preserve the final height, puberty is blocked as a means of avoiding bone age advancement.

Aromatase inhibitors

Aromatase is an enzyme of the cytochrome P450 (CYP19), which promotes the conversion of androgens (C_{19}) to estrogens (C_{18}). It is located on chromosome 15 and is expressed in various tissues, including ovarian luteal and granulosa cells, Sertoli and Leydig cells of the testis, brain, fat cells, muscles, hair follicles, and bones. Aromatase is locally produced in several sites, justifying the higher local concentration of estrogens compared to serum levels. This can be seen, for example, in breast tissue.

Aromatase inhibitors (AI) have been used for over two decades as a therapeutic option in the treatment of breast cancer. However, the introduction of third generation nonsteroidal AI (anastrozole and letrozole), as well as the third generation steroidal type (exemestane), represented a hallmark. These are extremely efficient AI, causing >98% aromatase inhibition, with minimal side effects.[4] AI are substances that block the conversion of androgens to estrogens, therefore blocking the pathways that convert testosterone to estradiol, androstenedione to estrone, and 16OH androstenedione to estriol. Several compounds, with different chemical structures (Table 1), have been identified as potential AI. These may be grouped as follows: 1) steroidal analogues to androst-4-ene-3,17-dione, the natural substrate of aromatase; 2) analogues of aminoglutethimide; 3) azole heterocyclic compounds, such as fadrozole hydrochloride, a potent nonsteroidal inhibitor.[5]

Among inhibitory steroids, some of the most important are the following:

- Formestane.
- Exemestane (a third generation non-competitive, selective and irreversible aromatase inhibitor): a pharmacokinetic study with healthy eugonadal men (aged 14-26 years) showed suppression of plasma estradiol levels both with the 25 mg/day and the 50 mg/day doses, and a reciprocal increase in the concentration of testosterone. With the 25 mg/day dose, time to maximum concentration is 1 hour, indicating rapid absorption. Half-life is 8.9 hours, and maximal estradiol suppression (62±14%) was observed at 12 hours. The drug is well tolerated.[6]

These are some of the available nonsteroidal AI:

- Aminoglutethimide: it was the first AI (first generation). Due to the lack of specificity, low potency and selectivity (blocking the activity of other P450 enzymes), aminoglutethimide is not recommended for clinical practice.
- Anastrozole [1,3- benzenediacetonitrile, $\alpha, \alpha, \alpha', \alpha'$, tetramethyl -5-(1H-1,2,4 triazol-1- ylmethyl]: third generation competitive aromatase inhibitor. It is metabolized in the liver, with elimination half-life of 50 hours and total elimination half-life of approximately 2 days. Plasma levels reach a steady state in 7 days, when patients are treated with daily doses, orally administered. Currently, the drug is approved by the Food and Drug Administration (FDA) for the treatment of breast cancer.[7]
- Letrozole: third generation competitive aromatase inhibitor.

Comparisons of the potency of several AI in breast tissue reveals that, while the concentrations of aminoglutethimide required to reach half maximal inhibitory concentration (IC_{50}) are in the µM range, new drugs can have the same effect with concentrations in the nM range. Approximate IC_{50} values for aminoglutethimide are 20 µM; for letrozole, 2 nM; for anastrozole, 8 nM; for exemestane, 15 nM; and for formestane, 30 nM.[10]

Metabolic effects of estrogen suppression in males

A preliminary question when considering the use of AI in males concerns the estrogen-dependent activities that will be blocked in these patients. Estrogens have a wide range of effects, anabolic and cardiovascular, in bone tissue and in the intragonadal environment.

Table 1 - Classification of aromatase inhibitors (Smith,[8] Freedman[9])

Generation	Type 1 (steroidal inhibitor)	Type 2 (nonsteroidal inhibitor)
First	None	Aminoglutethimide
Second	Formestane	FadrozoleRogletimide
Third	Exemestane	AnastrozoleLetrozoleVorozole

Studies carried out with male prepubertal and young adults show that both aromatizing and non-aromatizing androgens significantly increase total protein synthesis and muscle protein synthesis.[11,12] Pituitary GH production occurs predominantly through the aromatization of androgens.

Analyzing the consequences of an inactivating mutation on estrogen receptors or on the enzyme itself, both of which compromise estrogen function, we can conclude that, even in males, estrogens are involved in the closure of epiphyseal plates.[2,3,8]

In a study aimed at assessing the action of anastrozole in male adolescents, a 50% reduction in estrogen levels was observed as soon as the second day of treatment, with 0.5 and 1 mg/day doses.

Testosterone levels increased by 41% in the first day and by 61% in the second. Significant changes in IGF-I were not observed, and dehydroepiandrosterone sulfate levels rose by 10% after the second day of treatment, but did not remain increased after 10 weeks. Neither basal nor induced levels of GH showed significant changes. However, LH and FSH levels increased in the first day of treatment, with a 1 mg/day dose, reinforcing the idea that, even in males, estrogen is a major regulator in gonadotropin feedback.[13,14]

Levels of osteocalcin and alkaline phosphatase, markers of bone formation,[7] and sex hormone binding globulin (SHBG), did not change. The administration of anastrazole for 10 weeks did not affect liver function, blood glucose and insulin levels, LDL and HDL. Also, anastrazole did not increase catabolic effects in protein metabolism or in the intermediate metabolism of substrates, and did not cause any change in body composition, muscle strength or in calcium metabolism. On the other hand, the effects of AI differed from those obtained with gonadotropin releasing hormone analogue (GnRHa). After 10 weeks of GnRHa, patients presented an increase in adiposity levels, a decrease of protein synthesis rate and lipid oxidation, a reduction in muscle strength, and a substantial loss of urinary calcium. In these patients, estradiol suppression was more pronounced than in those using AI.[11,15]

Potential clinical applications of aromatase inhibitors

The main indication for the use of AI has been breast cancer, as estrogen stimulates the growth of these tumor cells. However, based on the concept that bone maturation is the major limiting factor in linear growth, AI have been tested in different contexts in which height is an issue of concern.

Constitutional delay of puberty

In cases of constitutional delay of growth and puberty, it was believed that a greater final height could be reached with the use of AI associated with androgen stimulation. From a group of 38 patients with delayed puberty, short stature or both, treated at the University of Helsinki, Finland, 33 joined a study. Ten of these patients decided to wait for spontaneous progression of puberty without treatment, while the other 23 were enrolled for treatment. From these 23 boys, 12 received intramuscular testosterone enanthate (1 mg/kg, every 4 weeks) and oral placebo for 12 months. The remaining 11 boys received testosterone enanthate and an AI (letrozole). Predicted adult height did not change significantly in the untreated group and in the placebo group, whereas in the group treated with letrozole the mean increase was 5.1 cm. An aspect that reinforces the role of estrogen in bone maturation is the fact that the group treated with AI, despite having higher testosterone levels, had slower bone age advancement. Another interesting data is that the slowing in bone maturation persisted even after treatment, bringing additional benefits towards a greater final height.[16] In a more recent study, a group of 17 patients was treated for 2 years, following the same protocol of the previous study. Again, predicted adult height increased after treatment (175.8 in the treatment group *versus* 169.1 in the placebo group). When considering the target height, final height of the treated group did not differ from their target (175.6 *versus* 177.1), whereas the mean final height in the placebo group was lower than their target height (169.1 *versus* 173.9).[17]

Idiopathic short stature

A group of 28 boys with idiopathic short stature, aged from 9 to 14.5 years, was randomly treated with letrozole or placebo for 2 years. The predicted final height increased 5.9 cm in the group receiving letrozole. Bone mineral density (BMD), measured at the lumbar spine and femoral neck using emission X-ray absorptiometry (DEXA), revealed an equal increase in both groups.[18]

Growth hormone deficiency

Twenty adolescents with GH deficiency were enrolled in a study by Mauras et al. Mean age was 14.5±0.5. Out of the 20

subjects, 10 were included in the control group and 10 received GH and anastrozole for 12 months. After this period, the concentration of estradiol in the group treated decreased from 1.8±0.5 to 0.7±0.3 pg/mL, and the levels of testosterone increased from 304±31 to 626±64 ng/dL, representing a 117% increase. In the control group, testosterone increased by only 47% (from 274±89 to 398±51 ng/dL). IGF-I levels increased by 42% in the control group, but did not change in the treated group. No changes were observed in bone markers, plasma lipids, insulin, glucose and liver function tests. After 12 months, there were no chances in growth rate, height SDS, bone age advancement, predicted adult height or testicular volume. In conclusion, despite reducing estrogen levels, with normal virilization and without negative effects on body composition, lipid levels, bone metabolism, or in the rate of pubertal maturation, the 12 month treatment did not increase the predicted adult height. It remains unclear whether a longer treatment would lead to higher final heights in comparison to the untreated group.[19] In studies that promoted changes in the predicted final height of adolescents with GH deficiency, using high doses of GH or the association of GH and GnRHa, changes in height only became significant after the third year of therapy.[20,21]

It called our attention that, in this study, IGF-I levels did not increase in the group treated with GH and anastrozole, whereas it increased by 45% in the group that received only GH. These data suggest that the endogenous effect of estradiol affects IGF-I levels through a mechanism that is independent of GH, possibly through the modulation of hepatic transcription to IGF-I.

McCune Albright syndrome

In McCune Albright syndrome, activating somatic mutations of the G protein cause ovarian estrogen production, independent of gonadotropins. Typically, the clinical manifestations include bone changes (polyostotic fibrous dysplasia) and café au lait spots, with notably irregular borders. As in any other case of precocious puberty, stature is at stake, and estrogen-blocking treatment, currently done with tamoxifen, has shown positive results. The use of AI in female patients, with the goal of preventing bone age advancement, must be weighted against the risks of virilization.

Testotoxicosis

A constitutive activation of the LH receptor causes boys with testoxicosis to start puberty early. Testoxicosis is a form of gonadotropin-independent precocious puberty. As part of the treatment (which includes inhibitors of testosterone synthesis, such as ketoconazole, and androgen receptor blockers), AI help to prevent bone age advancement.

Congenital adrenal hyperplasia

One of the consequences of the treatment of congenital adrenal hyperplasia is short stature. Limited treatment compliance is one of the causes, but a direct effect of the disorder on linear growth can not be ruled out. Treatment strategies based on lower doses of glucocorticoids and mineralocorticoid, associated with androgen receptor blocker and AI, aim at preserving bone age, thus promoting linear growth.

Side effects

The use of AI has not been accompanied by significant side effects, and the drugs have been well tolerated. In a study of 23 adolescents using AI for 1 year, no side effects requiring treatment discontinuation were reported. Nevertheless, it is important to monitor BMD and lipid metabolism.[22] In regard to the potential role of estrogen suppression on spermatogenesis, *in vitro* studies showed that estradiol acts as a germ cell survival factor;[23] patients with a mutation in the gene for the estrogen receptor alpha (Erα) have normal testicular volume, normal sperm density, but reduced sperm viability (18% *versus* > 50%). A patient with aromatase deficiency presented subthreshold testicular volume (8 mL) and reduced sperm count, with 100% immotile sperm. Nevertheless, this seminal variation in men with aromatase deficiency may not be related to estrogen activity, once azoospermia and infertility were also reported in the brother of this patient, whose aromatase gene was normal. Moreover, results of semen analysis did not change during treatment with transdermal estradiol, suggesting that the problem in the spermatogenesis was not related to estrogen. After one year of letrozole treatment, male adolescents did not exhibit alterations of spermatogenesis.

In regard to bone density, after a period of 1 year of treatment, there was no evidence of decreased BMD. As patients with androgen insensitivity present a reduced BMD even before reaching the peak bone mass, endogenous androgens are important for the acquisition of bone mass. The use of AI causes the elevation of testosterone levels, which can compensate for the lack of estrogen in the bones, thus preventing losses of BMD.[24]

AI have some effect on HDL levels. In a group of adolescents treated with letrozole, after 5 months of treatment, HDL levels decreased, but then remained stable despite the continuation of treatment.[22] In a group of 31 adolescents treated for 2 years, HDL cholesterol and relative fat mass also decreased, without affecting insulin sensitivity.[25] The levels of LDL-cholesterol and triglycerides do not seem to be affected by AI.[26] Nevertheless, it is important to monitor the lipid profile of patients undergoing treatment with AI.

AI do not seem to interfere with insulin sensitivity. During treatment with AI, a reduction in blood insulin levels has been observed, with patients showing improved insulin sensitivity, and not the contrary.

It has been suggested that a negative feedback exists between estradiol and LH in the beginning and in the middle of puberty.[27] Thus, with aromatase inhibition, an elevation of

gonadotropins (LH and FSH) is observed, despite androgen increase.

Conclusions

Short stature has become a prominent problem in the practice of pediatric endocrinology, as stature is incorrectly considered to be linked with success. In searching for better results in terms of final height, several treatments have been proposed, not always leading to effective results. The use of AI in boys with idiopathic short stature, in an attempt to avoid bone age advancement, has shown to be effective, and side effects have not led to discontinuation of therapy. Patients with GH deficiency in whom treatment is delayed, constitutional delay of puberty and testotoxicosis are some of other potential indications for AI treatment. Thus, if well-prescribed, AI can be incorporated in the treatment plan of patients with short stature and may represent a therapeutic alternative; in some cases, AI may be the only treatment option for increasing final height. The safe use of these drugs requires periodic monitoring of the lipid profile, especially HDL-cholesterol, liver function and gonadotropin levels.

References

1. Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med. 1994;331:1056-61.
2. Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. J Clin Endocrinol Metab. 1995;80:3689-98.
3. Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J, et al. Effect of testosterone and estradiol in a man with aromatase deficiency. N Engl J Med. 1997;337:91-5.
4. Lenning PE, Geisler J, Krag LE, Erikstein B, Bremnes Y, Hagen AI, et al. Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. J Clin Oncol. 2005;23:5126-37.
5. Furet P, Batzl C, Bhatnagar A, Francotte E, Rihs G, Lang M. Aromatase inhibitors: synthesis, biological activity, and binding mode of azole-type compounds. J Med Chem. 1993;36:1393-400.
6. Mauras N, Lima J, Patel D, Rini A, di Salle E, Kwok A, et al. Pharmacokinetics and dose finding of a potent aromatase inhibitor, aromasin (exemestane), in young males. J Clin Endocrinol Metab. 2003;88:5951-6.
7. Mauras N, O'Brien KO, Klein KO, Hayes V. Estrogen suppression in males: metabolic effects. J Clin Endocrinol Metab. 2000; 85:2370-7.
8. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med. 2003;348:2431-42.
9. Freedman OC, Verma S, Clemons MJ. Pre menopausal breast cancer in aromatase inhibitors: treating a new generation of women. Breast Cancer Res Treat. 2006;99:241-7.
10. Miller WR. Biology of aromatase inhibitors: pharmacology/ endocrinology within the breast. Endocr Relat Cancer. 1999; 6:187-195.
11. Mauras N, Hayes V, Welch S, Rini A, Helgeson K, Dokler M, et al. Testosterone deficiency in young men:marked alterations in whole body protein kinetics, strength and adiposity. J Clin Endocrinol Metab. 1998;83:1886-92.
12. Sheffield-Moore M, Urban RJ, Wolf SE, Jiang J, Catlin DH, Herndon DN, et al. Short-term oxandrolone administration stimulates net muscle protein synthesis in young men. J Clin Endocrinol Metab. 1999;84:2705-11.
13. Finkelstein JS, O'Dea LS, Whitcomb RW, Crowley WF. Sex steroid control of gonadotropin secretion in the human male. II. Effects of estradiol administration in normal and gonadotropin-releasing hormone-deficient men. J Clin Endocrinol Metab. 1991; 73:621-8.
14. Bagatell CJ, Dahl KD, Bremner WJ. The direct pituitary effect of testosterone to inhibit gonadotropin secretion in men is partially mediated by aromatization to estradiol. J Androl. 1994;15:15-21.
15. Mauras N, Hayes VY, Vieira NE, Yergey AL, O'Brien KO. Profound hypogonadism has significant negative effects on calcium balance in males: a calcium kinetic study. J Bone Miner Res. 1999;14:577-82.
16. Wickman S, Sipilä I, Ankarberg-Lindgren C, Norjavaara E, Dunkel L. A specific aromatase inhibitor and potential increase in adult height in boys with delayed puberty: a randomized controlled trial. Lancet. 2001;357:1743-8.
17. Hero M, Wickman S, Dunkel L. Treatment with the aromatase inhibitor letrozole during adolescence increases near-final height in boys with constitutional delay of puberty. Clin Endocrinol (Oxf). 2006;64:510-3.
18. Hero M, Norjavaara E, Dunkel L. Inhibition of estrogen biosynthesis with a potent aromatase inhibitor increases predicted adult height in boys with idiopathic short stature: a randomized controlled trial. J Clin Endocrinol Metab. 2005; 90:6396-402.
19. Mauras N, Welch S, Rini A, Klein KO. An open label 12-month pilot trial on the effects of the aromatase inhibitor anastrozole in growth hormone (GH)-treated GH deficient adolescent boys. J Pediatr Endocrinol Metab. 2004;17:1597-606.
20. Mauras N, Attie KM, Reiter EO, Saenger P, Baptista J. High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. J Clin Endocrinol Metab. 2000; 85:3653-60.
21. Mericq MV, Eggers M, Avila A, Cutler GB, Cassorla F. Near final height in pubertal growth hormone (GH)-deficient patients treated with GH alone or in combination with luteinizing hormone-releasing hormone analog: results of a prostpective, randomized trial. J Clin Endocrinol Metab. 2000;85:569-73.
22. Dunkel L, Wickman S. Novel treatment of short stature with aromatase inhibitors. J Steroid Biochem Mol Biol. 2003;86:345-56.
23. Pentikäinen V, Erkkilä K, Suomalainen L, Parvinen M, Dunkel L. Estradiol act as a germ cell survival factor in the human testis in vitro. J Clin Endocrinol Metab. 2000;85:2057-67.

24. Wickman S, Kajantie E, Dunkel L. Effects of suppression of estrogen action by the p450 aromatase inhibitor letrozole on bone mineral density and bone turnover in pubertal boys. J Clin Endocrinol Metab. 2003;88:3785-93.

25. Hero M, Ankarberg-Lindgren C, Taskinen MR, Dunkel L. Blockade of oestrogen biosynthesis in peripubertal boys: effects on lipid metabolism, insulin sensitivity, and body composition. Eur J Endocrinol. 2006;155:453-60.

26. Wickman S, Saukkonen T, Dunkel L. The role of sex steroids in the regulation of insulin sensitivity and serum lipid concentrations during male puberty: a prospective study with a P450-aromatase inhibitor. Eur J Endocrinol. 2002;146:339-46.

27. Wickman S, Dunkel L. Inhibition of P450 aromatase enhances gonadotropin secretion in early and midpubertal boys: evidence for a pituitary site of action of endogenous E. J Clin Endocrinol Metab. 2001;86:4887-94.

Correspondence:
Durval Damiani
Rua Bela Cintra 2117/9, C. César
CEP 01415-002 – São Paulo, SP – Brazil
Tel.: +55 (11) 3082.6651
Fax: +55 (11) 3064.0012
E-mail: durvald@iconet.com.br