Drugs of the Future 2006, 31(8): 713-718
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CCC: 0377-8282/2006
DOI: 10.1358/dof.2006.031.08.1009736

Peripheral precocious puberty

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CONTENTS

Abstract

Precocious puberty, or premature sexual maturation, can be either gonadotropin-dependent (central; CPP) or -independent (peripheral; PPP). Gonadotropin-releasing hormone (GnRH) analogues effectively control CPP and treatment advancements are now focusing on extended-release therapies. In contrast, GnRH analogues play no role in PPP, and this condition is difficult to treat due to the many underlying syndromes, etiologies and different therapeutic targets. This article will focus on new advances in the clinical management of the two main disorders described within PPP: testotoxicosis in boys and McCune-Albright syndrome (MAS) in girls.

Introduction

When premature sexual maturation occurs before the age of 8 years in a girl or 9.5 years in a boy, it is termed precocious puberty (PP). PP can be either gonadotropin-dependent (central; known as 'idiopathic' or 'complete' in earlier literature) or -independent (peripheral; known as 'incomplete' or 'partial' in earlier literature). In central PP (CPP), the pattern of normal puberty is maintained, with the exception that it occurs at an earlier age; however, in children with peripheral precocious puberty (PPP) this harmony is lost.

CPP, the most common form of PP, can be caused by lesions or, less commonly, tumors of the CNS, and involves early maturation of the entire hypothalamic-pituitary-gonadal (HPG) axis, with the full spectrum of physical and hormonal changes of puberty (1). Thus, high-amplitude pulses of gonadotropin-releasing hormone (GnRH) cause pulsatile increases in the pituitary gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Increased LH levels stimulate the production of androgens or estrogens by testicular Leydig cells or ovarian granulosa cells, respectively. These hormonal changes induce the physical changes and growth spurts associated with puberty, eventually promoting follicular maturation in girls and spermatogenesis in boys.

GnRH analogues are considered to be the treatment of choice for CPP. They suppress gonadotropin pulsatility and secretion by providing a constant GnRH stimulus, whereas the pituitary gland only responds to pulsatile GnRH stimulation. In general, GnRH analogues effectively control premature sexual maturation and growth velocity in CPP, causing a reversible reduction in gonadotropin and gonadal steroid concentrations. However, therapy (such as daily injections) can often be unpleasant for young patients, and recent pharmacological advances have focused on improving formulations for currently marketed GnRH analogues. Novel advanced therapies include 3-month extended-released injections for leuprolide (2) and triptorelin (3) and a once-yearly subcutaneous implant for histrelin (4). In those subjects who experience marked growth deceleration during GnRH treatment, combination therapies involving oxandrolone in girls and tamoxifen in boys have recently been described (5, 6).

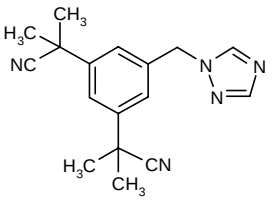
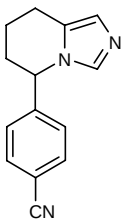
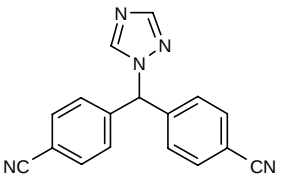
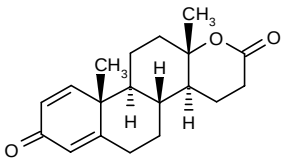
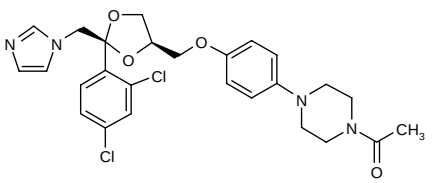
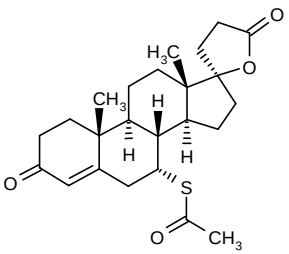
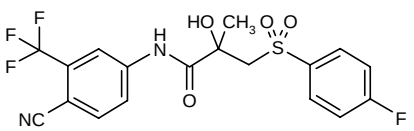
In contrast, GnRH analogues play no role in gonadotropin-independent PP, as PPP does not involve activation of the HPG axis. Thus, although the incidence of this condition is approximately one-fifth that of CPP, it is difficult to treat due to the many underlying syndromes, etiologies and different therapeutic targets involved. These include congenital adrenal hyperplasia (CAH), tumors that secrete human chorionic gonadotropin (hCG), tumors of the adrenal gland, ovary or testis, testotoxicosis, McCune-Albright syndrome (MAS), aromatase excess syndromes and exposure to exogenous sex steroid hormones. This article will focus on the two main disorders described within PPP: testotoxicosis in boys and McCune-Albright syndrome. Table I summarizes the therapeutic candidates for these syndromes.

Peripheral precocious puberty

Testotoxicosis

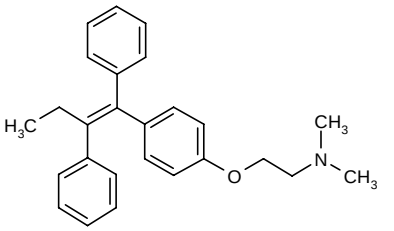
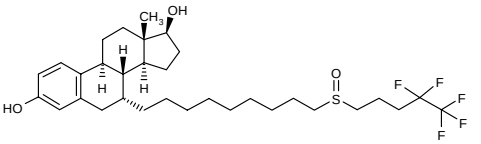
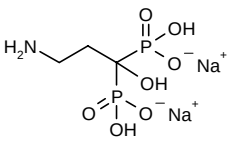
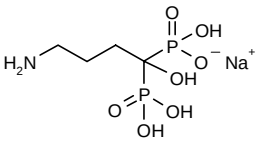
Testotoxicosis (also known as familial male precocious puberty) is a rare form of PPP that involves early onset and progression of puberty in boys. Accelerated growth and early development of secondary sexual characteristics occur as a direct result of maturation of the testes, independent of the hypothalamus or pituitary

Table I: Therapeutic candidates for testotoxicosis (Tx) and McCune-Albright syndrome (MAS).

Drug class	Drug name	Structure	Syndrome	Ref.
Aromatase inhibitors	Anastrozole		Tx MAS	15, 16 24, 25
	Fadrozole		MAS	21
	Letrozole		MAS	26
	Testolactone		Tx MAS	11-14 22, 23
Antiandrogens	Ketoconazole		Tx	9, 10
	Spironolactone		Tx	11-14
	Bicalutamide		Tx	15, 16

continuation

Table I (cont.): Therapeutic candidates for testotoxicosis (Tx) and McCune-Albright syndrome (MAS).

Drug class	Drug name	Structure	Syndrome	Ref.
Estrogen receptor modulators	Tamoxifen		MAS	27, 28
	Fulvestrant		MAS	29
Growth hormone receptor antagonists	Pegvisomant	—	MAS	32, 33
Bisphosphonates	Pamidronate		MAS	38-41
	Alendronate		MAS	42

gland. Reports considering age of onset vary among publications, although puberty generally becomes evident between the ages of 1 and 4 years. It is generally characterized as a hereditary (autosomal dominant) disorder involving a heterozygous mutation of the LH receptor gene (7), although constitutive mutations have been reported to arise sporadically to cause testotoxicosis (8). This mutation induces the formation of an activated receptor conformation on Leydig cells, even in the absence of LH binding, which autonomously stimulates the production of testosterone. If left untreated, testotoxicosis can lead to behavioral disturbances and reduced adult height, due to early epiphyseal maturation.

Therapies for testotoxicosis are targeted to inhibiting the synthesis and activity of sex steroids. The antifungal agent ketoconazole acts as a potent inhibitor of steroid synthesis in humans. A recent study in 5 patients demonstrated that this treatment is well tolerated over the long term (mean dose = 16.2 mg/kg/day; median treatment time = 6.2 years) and effectively and continuously suppresses testosterone production to achieve normal adult height (9). However, despite treatment efficacy, previous reports have shown that secondary activation of the gonadotropic axis can occur, consequently causing CPP and thus necessitating additional therapy with GnRH agonists (10).

As the changes seen in testotoxicosis are mediated by both androgens and estrogens (promotion of epiphyseal fusion), other potential therapeutic strategies target both hormones by combining antiandrogens and inhibitors of the enzyme aromatase, which converts androgens to estrogens. Earlier studies utilized spironolactone and testolactone as combined antiandrogen and aromatase inhibitor therapy, respectively (11, 12). A more recent clinical investigation has assessed how these agents, along with the LHRH agonist deslorelin (given upon the onset of secondary CPP), affected growth and development in 10 boys diagnosed with testotoxicosis over a period of at least 6 years. This therapeutic regimen restored growth velocity and bone maturation to prepubertal levels during the first year of therapy, effects that were sustained for the duration of treatment, and progressively improved predicted height (13). The National Institutes of Health (NIH) continued to assess this combined therapy in phase II clinical trials in approximately 80 patients (14). This study was completed in January 2004, although the results of this larger patient cohort have yet to be published.

Current studies are focusing on more potent and specific antiandrogens and aromatase inhibitors: principally bicalutamide and anastrozole, respectively. A case report involving a 3-year-old boy with testotoxicosis described an effective reduction in secondary sexual characteristics and sustained preservation of adult height potential within 4 months of treatment, and decreased skeletal maturation after 13 months of once-daily dosing (15). AstraZeneca is currently conducting and recruiting for an open-label, uncontrolled, multicenter phase II study of bicalutamide in combination with anastrozole for testotoxicosis, which is expected to enroll a total of 12 patients (16).

McCune-Albright syndrome

McCune-Albright syndrome (MAS), a genetic (but not hereditary) disorder, is caused by sporadic postzygotic activating point mutations in the gene encoding for the α subunit of the stimulatory G-protein (Gsα) (17, 18), predominantly localized at the Arg201 position (19). This results in constitutive activation of hormone receptors and hormone overproduction, in the absence of hormone stimulation. MAS is characterized by a classic triad of physical signs: polyostotic fibrous dysplasia, café-au-lait skin pigmentation and PPP and/or other endocrinopathies such as Cushing's syndrome.

Irregular, flat areas of hyperpigmentation of the basal epidermal layer are called 'cafe-au-lait' spots because in children with light complexions they resemble the color of coffee with milk. These melanotic macules are usually present from birth, although they rarely spread and do not exhibit abnormal pathology; thus they are not associated with medical problems and do not require therapeutic interventions. However, treatments for PPP and polyostotic fibrous dysplasia (PFD) in MAS are symptomatic and supportive, targeting specific characteristics of the disease.

The hallmark of McCune-Albright syndrome is PPP, which can appear in girls as young as 4 months of age. Early sexual development may also occur in boys, but this is not as common (20). Menstruation can begin in early childhood, long before the appearance of breasts or pubic hair, which normally develop first. PPP in MAC girls is caused by estrogens that are secreted into the bloodstream by ovarian cysts, which develop and enlarge independent of stimulation by gonadotropins. In addition, excess estrogen exposure often stimulates increased growth velocity and can result in a marked advancement of skeletal maturity.

Investigational forms of treatment have included agents to block estrogen synthesis. First-generation aromatase inhibitors such as fadrozole, however, do not appear to effectively block estrogen synthesis or PPP in the majority of girls with MAC (21). Furthermore, clinical observations published to date suggest that testolactone only partially prevents secondary sexual characteristics (22), although data from a large-scale phase II study conducted by the National Institute of Child Health and Human Development (NICHD) have yet to be presented (23). A recent case study has reported on the safe and effective use of a specific aromatase inhibitor, anastrozole (Arimidex®; AstraZeneca). Oral anastrozole therapy (0.5 mg daily) in a girl aged 3.5 years halted vaginal bleeding, reduced estradiol levels, decreased corpus/cervix length and facilitated a decline in the size of an ovarian cyst, the ovaries and the uterus, with complete eradication of the cyst after 8 months (24). AstraZeneca recently completed a phase II clinical trial in the U.S. and Europe to evaluate the safety and efficacy of anastrozole (1 mg p.o. once daily) as a treatment for PPP in girls with MAS (25). Further clinical trials involving an alternative aromatase inhibitor are currently ongoing and recruiting at the National Institute of Dental and Craniofacial Research (NIDCR). This study will examine whether letrozole (Femara®; Novartis) can lower estrogen in girls with MAS and arrest puberty (26).

An additional promising therapeutic strategy involves modulation of the estrogen receptor. Accordingly, a 12-month, prospective, open-label, multicenter study in the U.S. has reported on the use of tamoxifen in 25 girls aged under 10 years and diagnosed with MAS. Tamoxifen treatment (20 mg daily) was well tolerated and reduced vaginal bleeding, with significant improvements in growth velocity and rate of skeletal maturation (27). A recent case series report involving 5 MAS patients at hospital facilities in China has also reported efficacy for tamoxifen as a treatment for associated PPP, eliminating vaginal bleeding within 1 month and slowing bone maturation within 4 months (28). The efficacy and safety of the estrogen receptor antagonist fulvestrant (Faslodex™) are also currently under phase II clinical investigation by AstraZeneca in the U.S. (29).

PFD in MAS is characterized by bone abnormalities due to ineffective growth of multiple bones, which, on X-ray, are seen as patchy areas of osteoporosis and areas of bone thickening. This fibrous dysplasia usually progresses throughout childhood and the weakened bones cause pain and increase the patients' risk of bone fractures and bone deformities (30). Although rare, thickening of the skull bone can compress cranial nerves, causing vision and hearing deficits if untreated.

Screening of MAS patients has revealed that a significant proportion exhibit excess serum levels of growth hormone (GH), which plays a central role in skeletal development and maintenance both directly and indirectly (via insulin-like growth factor-I [IGF-I]). Thus, normalization of surplus GH is postulated to be important to prevent loss of vision or hearing associated with PFD (31). Correspondingly, researchers from the NIDCR recently completed a phase III study to examine the effect of pegvisomant (Somavert®; Pfizer), a GH receptor antagonist, on GH excess in PFD patients (32). Data from 5 patients recruited in this study were recently published in the literature. While pegvisomant effectively controlled GH excess in these MAS patients, significantly normalizing IGF-I and a specific IGF-I-binding protein (IGFBP-3), it did not improve PFD symptoms (bone pain or bone metabolism) (33).

PFD is also associated with inappropriate proliferation and differentiation of osteoblasts, resulting in the formation of a fibrotic bone matrix, which is thought to occur due to overproduction of the proinflammatory cytokine IL-6 in response to increased cAMP synthesis upon Gsα mutation (34). Studies have shown that bisphosphonates inhibit IL-6 (35) and osteoclast activity (36). Incidentally, additional studies have also hypothesized that bisphosphonates may target humoral factors, which are thought to underlie hypophosphatemia, another clinical feature of MAS. FGF-23 has been postulated as the principal candidate humoral factor, which, when released from bone lesions, inhibits phosphate transport (37). Subsequent studies have thus utilized agents such as pamidronate and alendronate to investigate how these bisphosphonates may be beneficial for PFD. While recent clinical evaluations have demonstrated that pamidronate treatment is safe in children with PFD and controls associated bone pain, it does not appear to have a beneficial effect on bone lesions to prevent disease progression (38-40). More promising data for this therapy have recently been published from a 1.9-9-year follow-up study. Results pooled from a group of patients receiving long-term pamidronate indicated eradication of bone pain, a significant reduction in bone fractures and bone mass density, and lesion healing (mainly thickening of the cortical bone) in approximately 36% of patients (41). Researchers from the NIDCR recently completed a phase II study to evaluate the effectiveness of alendronate to treat bone abnormalities in PFD and MAS (42).

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