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The Use of Tamoxifen to Improve Height Potential in Short Pubertal Boys

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ABSTRACT. A retrospective chart review of 7 pubertal boys who were treated with tamoxifen was conducted to determine the effects of this therapy on skeletal maturation and predicted adult height. Tamoxifen significantly decreased the rate of skeletal maturation and increased the predicted adult height without negative effects on sexual maturation. Additional evaluation of this therapy is now required to determine if the increase in predicted adult height results in a clinically significant increase in final adult height. *Pediatrics* 2005;116:1513–1515; *growth, puberty.*

ABBREVIATIONS. SERM, selective estrogen receptor modulator; PAH, predicted adult height; TV, testicular volume; Δ BA, change in bone age; Δ CA, change in chronologic age; SDS, SD score.

For children with significant short stature, the preservation of growth potential is an important goal. This is particularly true of adolescents presenting late to the pediatric endocrine clinic, who are often well into puberty by the time that pharmacologic intervention is considered.

Historically, long-acting gonadotropin-releasing hormone analogs have been used in pubertal growth hormone deficient and non-growth hormone deficient patients as a way of delaying epiphyseal fusion and increasing adult height.¹ However, new discoveries highlighting the importance of estrogen in mediating closure of the growth plates has led to the evaluation of novel alternative therapies aimed at decreasing estrogen synthesis or blocking estrogen effects. These therapies have included the use of antiestrogens in the form of aromatase inhibitors and selective estrogen receptor modulators (SERMs) such as tamoxifen. In this study we retrospectively evaluated the effect of tamoxifen on the rate of skeletal maturation and predicted adult height (PAH) in pubertal boys with limited growth potential. To our knowledge, no reports of the use of tamoxifen for this purpose currently exist.

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METHODS

A retrospective chart review of pubertal boys treated with tamoxifen was conducted by searching a transcription database. Inclusion criteria included male patients who had a ≥ 4 -mL testicular volume (TV) at the initiation of tamoxifen therapy. Availability of bone-age radiographs to calculate the rate of skeletal maturation was also an inclusion criterion. The rate of skeletal maturation was defined as change in bone age (Δ BA) divided by change in chronologic age (Δ CA). Bone-age radiographs were read independently, using the standards of Greulich and Pyle,² by 2 pediatric endocrinologists who were unaware of the subjects' age or treatment status. If the bone-age reading was between 2 standards, the average of those 2 standards was used. These interpretations then were averaged with those of the treating physicians, and the PAH was calculated by using the Bayley-Pinneau method.³ The use of tamoxifen was off-label, and the dose was chosen on the basis of previous studies in children⁴ and individual physician preference. In general, patients were started on tamoxifen if their PAH was below the midparental height or there was a concern regarding loss of height potential as a result of pubertal status or pubertal tempo.

The retrospective chart review was approved by the institutional review boards of Indiana University (Indianapolis, IN) and St Joseph Regional Medical Center (South Bend, IN).

Data were analyzed by using the Statview program for Mac-Intosh computers (Abacus Concepts Inc, Berkeley, CA). Δ BA/ Δ CA and PAH were compared before and during tamoxifen therapy by using the paired Student's *t* test. A *P* value of $<.05$ was considered statistically significant.

RESULTS

Seven boys were identified for study inclusion, 6 of whom were concurrently on growth hormone therapy. At initiation of tamoxifen, the mean age was 14 years 11 months, and the average height SD score was -2.27 . The mean duration of tamoxifen therapy was 26 months (range: 6–48 months) (Table 1).

Tamoxifen therapy (10–20 mg twice daily) significantly decreased the rate of skeletal maturation, which decreased from 1.1 ± 0.19 before treatment to 0.44 ± 0.13 while on tamoxifen (*P* = .038). In addition, the average PAH increased from 167.74 ± 4.62 cm at baseline to 177.6 ± 4.09 cm during tamoxifen therapy (*P* = .01). These results are illustrated in Fig 1. Individual subjects' results are found in Table 2.

The average growth velocity was 6.6 ± 1.3 cm/year during tamoxifen treatment. All patients manifested normal progression of secondary sexual development. The average TV before therapy initiation was 8 mL, and the average TV at the last physical examination was 20 mL. On average, pubic hair was Tanner stage IV at the last evaluation.

Hepatic transaminases were routinely recorded for 6 of the 7 patients. In all cases, the alanine aminotransferase, aspartate aminotransferase, and gamma glutamyl transferase remained normal. No adverse effects of therapy were apparent. One patient complained of blurred vision after the initiation of ta-

TABLE 1. Patient Characteristics

Subject	Diagnosis	Age at Tamoxifen Initiation	Treatment Duration, mo	Maximum Tamoxifen Dose, mg bid
1	ISS	15 y 8 mo	24	15
2	GHD	14 y 7 mo	20	10
3	ISS	14 y 5 mo	38	10
4	CDGP	15 y 2 mo	12	10
5	NSGHD	14 y 3 mo	6	20
6	GHD	13 y 10 mo	32	10
7	ISS	16 y 4 mo	48	15

bid indicates twice daily; ISS, idiopathic short stature; GHD, growth hormone deficiency; CDGP, constitutional delay of growth and puberty; NSGHD, neurosecretory growth hormone deficiency.

Fig 1. Comparison of PAH and $\Delta BA/\Delta CA$ before and during tamoxifen therapy. A significant increase in the PAH (*) and a significant decrease in the $\Delta BA/\Delta CA$ (**) are demonstrated.

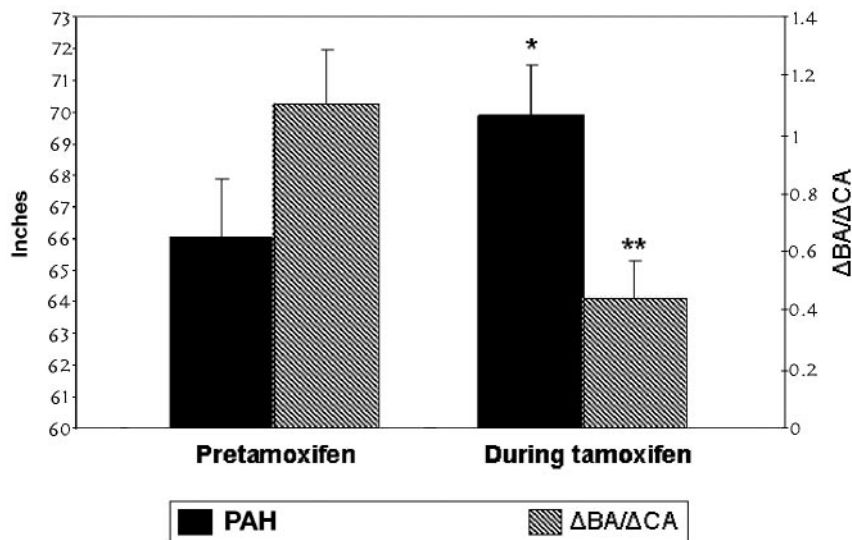


TABLE 2. Results

Subject	Midparental Height, SDS	Height at Tamoxifen Initiation, SDS	Height at Last Evaluation, SDS	PAH Before Tamoxifen, SDS	PAH at Last Evaluation, SDS	TV Before Tamoxifen, mL	TV at Last Evaluation, mL	Bone Age at Last Evaluation, y
1	0.36	-2.34	-1.30	0.97	1.41	6-8	20	13.75
2	1.19	-1.32	-0.12	-0.23	1.01	8	20-25	15.25
3	1.10	-3.11	-2.89	-2.87	-1.86	5	15	14.25
4	0.93	-1.01	-0.67	0.65	0.94	10	20	14
5	—*	-1.95	-1.28	-3.61	-0.80	8-10	15	14
6	0.78	-3.30	-2.8	-1.79	-1.66	4-6	25	14.5
7	-0.03	-2.84	-1.17	-0.68	0.69	8-10	25	14

* The information was not available because the subject was adopted.

moxifen. Tamoxifen was discontinued, and ophthalmologic examination revealed no abnormalities. After reinitiation of tamoxifen the patient had no recurrence of visual symptoms.

DISCUSSION

The phenotypic descriptions of human mutations in the estrogen receptor and the aromatase gene have increased our understanding of the role of estrogen in maturation and ultimate closure of the epiphyseal growth plates in males and females^{5,6}; this has led to the concept of specifically targeting estrogen as a potential therapeutic strategy for patients with limited height potential. Aromatase inhibitors block the conversion of androgens to estrogens, and SERMs have a different mechanism but ultimately lead to the same effect by decreasing estrogen exposure at

the tissue level. It has been shown that letrozole, an aromatase inhibitor, decreased the rate of skeletal maturation and increased PAH in boys with constitutional delay of puberty.⁷ Tamoxifen has been used in girls with McCune-Albright syndrome and precocious puberty and resulted in a significant decrease in skeletal maturation.⁴ However, the use of tamoxifen or other SERMs in boys with short stature has not been reported.

Although tamoxifen is only approved for use in children with McCune-Albright syndrome, it has been used in a variety of childhood disorders including nasopharyngeal fibromas,⁸ pubertal gynecomastia,^{9,10} and a variety of tumors including gliomas.¹¹ In these populations, adverse effects have been rare, and tamoxifen seems to have an excellent safety profile overall.

With our patients, the rationale for treatment was

based on a concern that continued pubertal progression would result in a deterioration of height potential to well below the genetic target (midparental height). Oral administration and the ability to allow puberty to continue at a physiologically appropriate time make tamoxifen an attractive option for delaying skeletal maturation and preserving height potential.

It is important to recognize that 6 of the 7 patients in this study were also on growth hormone therapy, yet the average growth velocity was low for pubertal boys. Whether tamoxifen attenuated the growth rate in our patients or whether tamoxifen alone would affect growth velocity during puberty remains unknown. Because none of the subjects had reached final adult height, it is impossible to know if the increase in PAH will translate into a clinically significant increase in final height. It is also difficult to determine the effects of growth hormone therapy alone on increasing the PAH. Because of the retrospective nature of the study, the length of time in which the patients received tamoxifen or growth hormone alone is variable, making specific analysis of the pure effect of tamoxifen on PAH difficult to assess. However, one would not expect growth hormone therapy alone to decrease the rate of skeletal maturation, thus suggesting that the increase in PAH was at least, in part, a result of tamoxifen use.

CONCLUSIONS

Our findings suggest that tamoxifen may be effective and safe in the treatment of pubertal boys with limited growth potential. Although the study was retrospective, uncontrolled, and had a small sample size, these preliminary data provide the foundation

for prospective clinical trials to further evaluate efficacy and other metabolic effects of tamoxifen in this patient population.

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Freudenheim M. *New York Times.* September 22, 2005

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