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A Single Histrelin Implant Is Effective for 2 Years for Treatment of Central Precocious Puberty

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Abstract

We investigated whether a “yearly” histrelin implant would provide pubertal suppression when left in place for 2 years. Equivalent suppression was observed when comparing 12 and 24 months in 33 children with central precocious puberty. A single implant for 2 years reduces cost and number of implant procedures.

The 50 mg histrelin implant provides continuous release of the potent gonadotropin releasing hormone analog (GnRHa) histrelin for the treatment of central precocious puberty (CPP).[1] Because histrelin is released at ~65 mcg per day,[2] a single implant of a “yearly” device theo-retically would last 2 years. However, whether this would actually be the case in the clinical setting is unknown. The objective of this study was to investigate whether a single implant would provide hypothalamic-pituitary-gonadal (HPG) axis suppression when left in place for 2 years.

Methods

Following institutional review board approval, girls 2-10 years and boys 2-11 years receiving a histrelin implant (Supprelin LA; Endo Pharmaceuticals, Westbury, New York) for CPP were recruited. CPP was defined biochemically as a peak stimulated luteinizing hormone (LH) >6 IU/L or random ultrasensitive (US) LH >0.3 IU/L as well as an advanced bone age (≥1 year) and breast Tanner stage ≥ II in girls and testicular volume ≥ 4 mL in boys. Informed consent was obtained from parents or legal guardians. All implant procedures were performed by a single pediatric surgeon under local anesthesia with the exception of 1 subject in whom general anesthesia was used.

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A history and physical examination were performed every 6 months. Bone age radiographs were obtained at baseline, 12 months, and 24 months and interpreted by each child's endocrinologist. At 6 and 18 months an US LH was measured by immunochemiluminometric assay or electrochemiluminescent (Esoterix, Calabasas Hills, California or Quest Diagnostics, Auburn Hills, Michigan), both of which have a prepubertal reference range of <0.3 IU/L. At 12 and 24 months, a GnRHa stimulation test was performed. Leuprolide acetate 20 mcg/kg was given subcutaneously and LH and follicle-stimulating hormone were drawn at 0, 30, and 60 minutes and sent to the institutions lab (Clarian Pathology Lab, Indianapolis, Indiana). Estradiol (girls) or testosterone (boys) was measured at time 0. Skeletal advancement was defined as the ratio of bone age to chronologic age. Patients with an US LH >1 IU/L at 6 or 18 months underwent a leuprolide stimulation test shortly thereafter due to concerns about insufficient suppression. Suppression was defined as peak LH ≤ 4 IU/L.[3]

Statistical Analyses

Continuous variables were summarized using descriptive statistics. Discrete variables were summarized by frequency and percentages. Comparisons of continuous variables were made using 2-sided *t* test and comparisons of categorical variables were made using Fisher exact test. SD scores and predicted adult height were calculated using the Children's Hospital Boston Growth Calculator 2.01.[4]

Results

Thirty-three children (26 girls) aged 7.2±2.5 years treated with a histrelin implant for CPP were enrolled, of whom 20 were naïive to GnRHa therapy. Baseline characteristics are summarized in Table I.

Of 33 initial subjects, 1 child withdrew within the first 6 months because of insurance issues, and 2 subjects terminated the study early at 18 and 22 months, respectively, because of concerns about pubertal progression. One patient had the implant in place for 24 months but was lost to follow-up. Thus, 29 subjects completed the study. Peak LH at 12 and 24 months was equivalent (0.89 IU/L 0.51, range 0.2-2.2 vs 0.89 ± 0.54, range 0.2-2; $P = .44$) indicating suppression at both time points in all cases. As we previously reported,[5] a significant number of patients had a pubertal US LH at 6 months (n = 17, 59%), 18 months (n = 14, 48%), or both (n = 11, 41%). Complete HPG axis suppression was found in all cases in which a GnRHa stimulation test was performed early (n = 4). Estradiol was detectable in 6 girls, (range 22-30 pg/mL). Testosterone was <30 ng/dL at all measured time points in boys.

The degree of skeletal maturation (ratio of bone age to chronologic age) significantly declined during the 24 months of the study and the body mass index z-score remained stable (Table II). The predicted adult height z-score increased from −1.50 ±1.23 at baseline to −1.03 ±1.33 at 24 months ($P = .02$) in the group as a whole, and an improvement in this measure from year 1 to year 2 was also seen in treatment naïive patients. Tanner staging improved or stabilized in the vast majority of patients. However, implants were removed early (at 18 and 22 months) in 2 girls because of clinical concerns including breast

enlargement and linear growth acceleration in association with rapid weight gain. GnRHa stimulation tests performed just prior to explantation revealed complete HPG axis suppression in both (peak LH 0.3 IU/L and 0.6 IU/L).

All but 1 patient had implantation performed under local anesthesia. One patient had an infection at the incision site 4 months after implantation and required surgical re-incision with irrigation and an antibiotic course. The implant was left in place and the patient completed the 2-year study. Explantation was performed under local anesthesia in 27 children (94%) and under general anesthesia in 2 (6%). Difficulty with implant removal occurred in 12 cases (39%) and included need for a small perpendicular incision (n = 8), implant breakage (n = 6), and implant migration (n = 1).

Discussion

The subcutaneous histrelin implant is an established modality for the treatment of CPP. However, its high cost and need for surgical procedures present barriers to its use. In addition, many centers use conscious sedation or general anesthesia, which increases both the cost and risk of each procedure. Although the histrelin implant is labeled for 12-month use, a small pilot study reported continued suppression for up to 15 months.[6] This, combined with the known diffusion rate of 65 mcg of histrelin per day led us to hypothesize that a single implant would provide HPG axis suppression for 2 years, which would be particularly advantageous for the many children who are only treated for this length of time.

Strengths of our study include its prospective nature and the ability to observe nearly 30 patients for 2 years in the context of routine clinical care. Limitations include that Tan-ner staging and bone age interpretations were performed by each child's pediatric endocrinologist and that there was not a control group having implants replaced annually. However, consecutive years of therapy demonstrating ongoing and comparable degrees of suppression with annual replacement of the implant have already been reported.[2,7] An unantici-pated finding from our study is that US LH often does not revert to a prepubertal range in many children during treatment for CPP despite evidence of complete HPG axis suppression,[5] indicating that the use of US LH to monitor therapy in CPP is problematic.

Limited information is available regarding surgical outcomes related to the histrelin implant. Although difficulty occurred in 39% of our patients, this likely represents a best case scenario because our pediatric surgeon has extensive experience with placement and removal of the implant. Whether a higher complication rate causing one to refrain from leaving the implant in place for more than 1 year would occur in a less optimal surgical setting is unknown.

In conclusion, we demonstrated continued HPG axis suppression and excellent clinical response in a diverse group of children with a single histrelin implant left in place for 2 years. This approach would reduce cost and numbers of procedures for children who require at least 2 years of therapy for CPP.

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Glossary

CPP	Central precocious puberty
GnRHa	Gonadotropin releasing hormone analog
HPG	Hypothalamic-pituitary-gonadal
LH	Luteinizing hormone
US	Ultrasensitive

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Table I

Baseline patient characteristics

Patients N (%)	Age at implant, y Mean (range)	Ethnicity N (%)	CNS* abnormality N (%)	Previous GnRHa treatment N (%)	Pubertal staging
All	7.2 ± 2.5 (2.2-10.8)	White-24 (73)	4 (12)	13 (39)	
33		Black-5 (15)			
		Biracial-2 (6)			
		Hispanic-1 (3)			
		East Indian-1 (3)			
Girls	7.13 ± 3.2 (2.2-10.5)	White-20 (77)	3 (12)	12 (46)	Breast Tanner stage, %
26 (79)		Black-5 (19)			II-4, III-73, IV-23
		Hispanic-1 (4)			Menarche, N (%)
					2 (8)
Boys	7.5 ± 3.2 (2.5-10.8)	White-4 (57)	1 (14)	1 (14)	Testicular volume, mL
7 (21)		Biracial-2 (29)			4, 4-5, 8-10, 10,10-12, 12, 12-15
		East Indian-1 (14)			

CNS, central nervous system.

*Hypothalamic hamartoma (n = 2), neurofibromatosis-1 with optic glioma (n = 1), and hypothalamic glioma (n = 1).

Table II
Growth data from baseline, 12 months, and 24 months

Variable	Baseline	12 mo	24 mo	*P* value
All patients (n = 29)				
BA/CA	1.32 ± 0.24	1.25 ± 0.23	1.19 ± 0.25	$P = .02^{*}$
	N = 28	N = 26	N = 28	$P = .23^{\dagger}$
				$P = .01^{\ddagger}$
Height SDS	0.71 ± 1.38	0.55 ± 1.63	0.32 ± 1.46	$P = .85^{*}$
	N = 26	N = 29	N = 29	$P = .03^{\dagger}$
				$P = .01^{\ddagger}$
Weight SDS	1.68 ± 2.25	2.01 ± 3.04	1.75 ± 2.78	$P = .11^{*}$
	N = 28	N = 28	N = 28	$P = .10^{\dagger}$
				$P = .66^{\ddagger}$
BMI	18.53 ± 4.00	19.57 ± 5.26	20.01 ± 5.68	$P = .003^{*}$
	N = 27	N = 29	N = 29	$P = .08^{\dagger}$
				$P \leq .01^{\ddagger}$
BMI SDS	0.93 ± 1.56	0.91 ± 1.53	0.62 ± 1.60	$P = .33^{*}$
	N = 19	N = 22	N = 23	$P = .91^{\dagger}$
				$P = .63^{\ddagger}$
PAH	158.35 ± 11.94	161.15± 11.83	160.67 ± 12.47	$P = .01^{*}$
	N = 18	N = 21	N = 25	$P = .35^{\dagger}$
				$P = .02^{\ddagger}$
PAH SDS	−1.50 ± 1.23	−1.11 ± 1.24	−1.03 ± 1.33	$P = .01^{*}$
	N = 18	N = 22	N = 25	$P = .37^{\dagger}$
				$P = .02^{\ddagger}$
Treatment naïve patients (n = 17)				
PAH	158.09 ± 13.92	161.51 ± 13.51	163.82 ± 13.90	$P = .07^{*}$
	N = 12	N = 14	N = 14	$P = .02^{\dagger}$
				$P = .009^{\ddagger}$
PAH SDS	−1.66 ± 1.47	−1.23 ± 1.41	−0.76 ± 1.49	$P = .07^{*}$
	N = 12	N = 15	N = 14	$P = .02^{\dagger}$
				$P = .009^{\ddagger}$

BA/CA, ratio of bone age to chronologic age; *BMI*, body mass index; *PAH*, predicted adult height.

*Baseline to 12 months.

†12-24 months.

‡Baseline to 24 months.