Growth hormone inhibition causes increased selenium levels in Duchenne muscular dystrophy: a possible new approach to therapy*

P J COLLIPP, J KELEMEN, S Y CHEN, M CASTRO-MAGANA, M ANGULO, AND A DERENONCOURT

From the Departments of Pediatrics and Medicine, Nassau County Medical Center, East Meadow, New York, USA.

SUMMARY Nine children with Duchenne muscular dystrophy were given Sanorex (mazindol), a growth hormone inhibitor, daily for 6 months. There was no significant change in their muscle function, but there was a significant reduction in weight gain and in levels of growth hormone, somatomedin C, hair zinc, serum zinc, and serum LDH. Selenium and glutathione peroxidase in the serum increased significantly. Thirteen other children with growth hormone deficiency had a significant reduction in hair selenium following growth hormone administration.

These results show a significant relationship between growth hormone and selenium nutritional status and confirm our previous reports indicating an effect of growth hormone on zinc nutritional status. It is possible that prolonged therapy with a growth hormone inhibitor would attenuate the course and improve the longevity of patients with muscular dystrophy.

In a recent report of a family with Duchenne muscular dystrophy, an affected brother with growth hormone deficiency was substantially less disabled than his younger sibs.¹ Based on this observation, we decided to evaluate the effect of administering a growth hormone inhibitor to nine children with Duchenne muscular dystrophy.

Methods

The nine children studied had been followed for 1 to 9 years in our Muscular Dystrophy Clinic. Their diagnosis had been confirmed by the typical clinical course, characteristic physical findings, which included pelvifemoral weakness and calf pseudo-hypertrophy, family history, raised serum levels of creatinine kinase (CK), lactate dehydrogenase (LDH), and serum glutamate oxaloacetate transaminase (SGOT), and abnormal findings on muscle biopsy and electromyography. The ages of these nine children at the time of entry into the study were 5, 6, 7, 7, 8, 10, 12, 12, and 14 years.

After a group discussion with all the parents, and individual discussions, a written informed consent

was obtained for each child. The study was approved by our institutional research committee (IRB).

Each child received Sanorex® (mazindol) at a dose of 2 mg daily for 6 months. Careful manual muscle testing and peak flow during forced expiration were done for each child at the beginning of the study and at 3 and 6 months by one of us (JK), and accurate measurements of height and weight were done by at least two of us at each examination. Laboratory tests were also performed at the beginning of the study and at 3 and 6 months. Human growth hormone was assayed in serum obtained before and 90 minutes after the oral administration of clonidine (0.1 to 0.2 mg). Selenium was assayed in serum and hair by the fluorometric method.² Glutathione peroxidase, CK, LDH, and SGOT were assayed by standard methods. Hair and serum zinc were assayed by atomic absorption spectrophotometry. Somatomedin C was assayed by radioimmunoassay. Parents were instructed in the method of collecting 24 hour urine specimens and creatinine was assayed in aliquots of these specimens.

Thirteen additional children (aged 2 to 16 years) with isolated growth hormone deficiency were studied. Six of them were given human growth hormone injections (two units three times a week

*Supported in part by a grant from the Muscular Dystrophy Association, Nassau Chapter.

Received for publication 21 October 1983.

Accepted for publication 17 November 1983.

intramuscularly) and hair selenium was measured after 3 months of growth hormone therapy. These 13 children were 3 to 5 SD below the mean in height and had retarded bone ages. After insulin induced hypoglycaemia and intravenous arginine administration the peak serum growth hormone was below 5 ng/ml in all of them. The results of other trace element assays in these children will be reported separately.

Results

No significant change in muscle strength or peak expiratory flow was found in these nine children

TABLE 1 Muscular function* during Sanorex administration in children with muscular dystrophy.

Tests of muscular function	Time at which test was done		
	0	3 months	6 months
Neck flexion	3.04	2.93	2.65
Quadriceps	3.10	3.29	3.11
Shoulder abduction	3.52	3.62	3.44
Foot dorsiflexion	3.45	3.81	3.77
Hip flexion	2.89	2.93	2.86
Peak expiratory flow (l/min)	241	246	232

*Mean values presented: 0=no contraction, 1.0=palpable contraction without joint movement, 2.0=joint movement with gravity eliminated, 3.0=overcomes gravity but no more, 4.0=greater than gravity but less than normal, and 5.0=normal strength. Normal peak expiratory flow at this age is 200 to 400 l/min. Because of great range in strength, especially between grade points 3 and 5, 0.25 of a grade was added or subtracted for strengths that varied slightly from the above values. Thus, strength minimally greater than gravity = 3.25, strength nearly but not fully normal = 4.75, etc.

TABLE 2 Effects of Sanorex (2 mg daily) administration to nine children with muscular dystrophy.

Growth parameter	Control (6 months)	Sanorex (6 months)	p value
Height (cm)	+3.3	+2.5	NS
Weight (kg)	+1.43	+0.22	0.05

during 6 months of Sanorex administration (table 1). This lack of change applied equally to both younger and older participants.

Administration of Sanorex resulted in a significant reduction in weight gain in the nine children with muscular dystrophy. The slight slowing in their growth rate was not significant (table 2). Baseline growth hormone levels were not affected, but there was a reduction in the level of growth hormone after clonidine stimulation. Somatomedin C levels were also reduced. Hair and serum zinc levels were reduced following Sanorex administration (table 3) and the serum LDH level was decreased from 1140 to 789 U/l.

Selenium and glutathione peroxidase in the serum were both significantly increased during Sanorex administration. When 13 growth hormone deficient children were started on growth hormone therapy this year, we found a significant reduction in hair selenium concentration after 3 months of therapy in six of them (table 4).

TABLE 4 Selenium and glutathione peroxidase in children after administration of growth hormone and Sanorex.

	Time when test was done		
	0	3 months	6 months
Growth hormone administration to three growth hormone deficient children			
Hair selenium ($\mu\text{g/g}$)	0.5 ± 0.2178 (7 children)	0.2 ± 0.09 $p < 0.01$ (6 children)	
Sanorex administration to nine children with Duchenne muscular dystrophy			
Plasma selenium (ng/ml)	0.105 ± 0.009	0.130 ± 0.010	0.148 ± 0.026 $p < 0.01$
Blood glutathione peroxidase ($\mu\text{g/g Hb}$)	80 ± 10	98 ± 13	130 ± 19 $p < 0.01$

TABLE 3 Changes in biochemical studies during 6 months' Sanorex (2 mg daily) administration to nine children with muscular dystrophy.

Biochemical parameters	Time when test was done			p value comparing 0 and 6 months
	0	3 months	6 months	
Growth hormone (ng/ml)				
Baseline	1.6	2.4	3.9	NS
Clonidine peak	8.6	8.4	5.9	0.05
Somatomedin C ($\mu\text{U/ml}$)	1.1	0.7	0.8	0.05
Hair zinc ($\mu\text{g/g}$)	138	—	104	0.01
Serum zinc ($\mu\text{g/ml}$)	104	108	95	NS
Urinary creatinine (g/day)	0.33	0.30	0.30	NS
LDH (U/l)	1140	907	789	0.05
CK (U/l)	3425	—	2092	NS
SGOT (U/l)	272	248	95	NS

Discussion

This preliminary study of the effects of a growth hormone inhibitor on children with muscular dystrophy was undertaken because of the report of a child who had a less severe clinical course and was also growth hormone deficient. The prevailing hypothesis in the aetiology of Duchenne muscular dystrophy indicates that the muscle membrane is the site of the primary defect.³ We previously observed that both growth hormone deficiency and zinc deficiency also had effects on membrane lipid composition and membrane function.⁴⁻⁷ We had also previously observed effects of both zinc administration on growth hormone levels, and effects of growth hormone administration on zinc levels.^{8,9} Thus, we wondered if the drug would lower zinc levels, decrease membrane fluidity, and, therefore, result in improved muscle membrane function, lower serum enzyme levels, and increased strength in these children.

In 1976 we reported that Sanorex administration resulted in slowed growth rate with concomitant growth hormone reduction in 17 children.¹⁰ Since that time we have used Sanorex successfully to slow the growth rate of 12 tall girls who were emotionally disturbed by the fact that their predicted height was greater than 183 cm. Sanorex has been widely prescribed as an appetite suppressant^{11,12} for obese patients and it did result in a reduction in the rate of weight gain in these children.

While selenium deficiency is known to cause white muscle disease in cattle, it has not been found to be deficient in children with muscular dystrophy. The levels in these children were all within the normal range we have reported for children on Long Island.² However, it is interesting that a growth hormone inhibitor significantly increased both the serum selenium level and the glutathione peroxidase activity (a selenium dependent enzyme) in these children. Also, we have found that growth hormone administration to growth hormone deficient children lowered the hair selenium significantly. There is very little reported concerning the relationship between selenium and growth hormone concentration. Selenium deficient rats have been reported to have reduced growth rates as well as reduced pituitary growth hormone content.¹³

Sanorex administration failed to improve muscular function in these children with Duchenne muscular dystrophy during 6 months of therapy.

However, it is not possible to determine from this study whether the rate of progression was affected by the drug. A longer controlled therapeutic trial would be needed to define fully the effect of growth hormone inhibition on Duchenne muscular dystrophy.

References

- 1 Zatz M, Betti RTB, Levy JA. Benign Duchenne muscular dystrophy in a patient with growth hormone deficiency. *Am J Med Genet* 1981;**10**:301-4.
- 2 Chen SY, Collipp PJ, Boasi LH, et al. Fluorometry of selenium in human hair, urine and blood; a single tube process for submicrogram determination of selenium. *Ann Nutr Metab* 1982;**26**:186-90.
- 3 Mohri B, Engel AG. Duchenne dystrophy; electron microscopic findings pointing to a basic early abnormality in the plasma membrane of the muscle fiber. *Neurology (Minneapolis)* 1975;**25**:1111-20.
- 4 Clejan S, Maddaiah VT, Castro-Magana M, Collipp PJ. Zinc-deficient induced changes in the composition of microsomal membranes and in the enzymatic regulation of glycerolipid synthesis. *Lipids* 1981;**16**:454-60.
- 5 Clejan S, Castro-Magana M, Collipp PJ, et al. Effects of zinc deficiency and castration on fatty acid composition and desaturation in rats. *Lipids* 1982;**17**:129-35.
- 6 Clejan S, Collipp PJ, Maddaiah VT. Hormones and liver mitochondria influence of growth hormone, thyroxine, testosterone, and insulin on thermotropic effects of respiration and fatty acid composition of membranes. *Arch Biochem Biophys* 1980;**203**:744-52.
- 7 Maddaiah VT, Clejan S, Palekar AG, Collipp PJ. Effect of growth hormone and thyroxine on respiration, fluorescence of 1-anilino-8-naphthalene sulfonate, and enzyme activity of complex I and complex II of sub-mitochondrial particles. *Arch Biochem Biophys* 1981;**210**:666-77.
- 8 Collipp PJ, Castro-Magana M, Petrovic M, et al. Improvement in growth and growth hormone levels with oral zinc therapy. *Ann Nutr Metab* 1982;**26**:287-90.
- 9 Cheruvanky T, Castro-Magana M, Chen SY, et al. Effect of growth hormone on hair, serum and urine zinc in growth hormone deficient children. *Am J Clin Nutr* 1982;**35**:668-70.
- 10 Collipp PJ, Gupta KB, Amin A, et al. Effects of mazindol on growth and growth hormone. *Pediatr Res* 1977;**11**:379A.
- 11 Sharma RK, Collipp PJ, Rezvani I, et al. Clinical evaluation of the anorexic activity and safety of 42-548 in children. *Clin Pediatr* 1973;**12**:145-9.
- 12 Bray GA. Treatment of obesity with drugs and invasive procedures. In: Bray GA, ed. *Obesity in America*. Washington DC: HEW 79-359, 1979:179-93.
- 13 Ewan RC. Effect of selenium on rat growth, growth hormone and diet utilization. *J Nutr* 1976;**106**:702-9.

Correspondence and requests for reprints to Professor P J Collipp, Department of Pediatrics, Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554, USA.