Effect of cyproterone acetate on adrenocortical function in children with precocious puberty

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SUMMARY Seven children with precocious puberty were treated with cyproterone acetate and their adrenal function studied. In each child the drug caused significant adrenal hypofunction which was secondary to adrenocorticotrophic hormone suppression. None of these children had clinical evidence of adrenal hypofunction and it is assumed that the drug has glucocorticoid-like properties. Children receiving cyproterone acetate should carry information to warn doctors of this effect since they may require steroid cover during illness.

The medical treatment of precocious puberty is not entirely satisfactory. The commonly used drugs medroxyprogesterone acetate (Provera), and danazol (17 α -pregna-2, 4-dien-20-yno [2, 3-*d*] isoxazol-17-ol) slow the progress of sexual maturation but do not arrest bone age advancement, and therefore do not prevent short stature. A newer treatment is with the synthetic steroid hormone cyproterone acetate (17 α -acetoxy-6-chloro-1 α , 2 α -methylenepregna-4, 6-dien-3, 20-dione). This steroid is both an anti-androgen, competing with testosterone for target organ receptor sites, and a potent progestogen, suppressing gonadotrophin synthesis and release. In this way it modifies some of the manifestations of precocious puberty. However the hormone also has a suppressive effect on adrenal function and this aspect of the drug in 7 children treated for precocious puberty was studied.

Patients and methods

Details of the 7 children studied are given in Table 1. The children were seen in the endocrine clinic at 3-monthly intervals, and were treated with cypro-

terone acetate 50 mg three times daily. Their responses to treatment were evaluated by physical examination, height velocity, x-ray films of the left hand and wrist for bone age, and plasma hormone estimations.

Adrenocorticotrophic function was assessed before treatment and monitored every 3 to 6 months during the first year of treatment, but at longer intervals later. It was examined by measurement of 24-hour urine excretion of adrenocortical metabolites, the plasma adrenocorticotrophic hormone (ACTH), and cortisol responses to insulin hypoglycaemia, and the plasma cortisol response to intravenous tetracosactrin (Synacthen). Adrenocortical metabolites were measured in 24-hour urine specimens collected in plain containers and kept at -20°C until extraction. Assay was by gas-liquid chromatography estimating adrenocortical cortisol derivatives and androgens separately.

During insulin-induced hypoglycaemia (0.1 unit insulin per kg/body weight) plasma cortisol was measured at 0 and 60 minutes, and serum growth hormone and plasma ACTH at 0, 30, 60, 90, and 120 minutes. Plasma cortisol was also measured at

Table 1 *Clinical details of children with precocious puberty*

Case	Sex	Age treatment started (years)	Pubertal status*	Diagnosis	Dose cyproterone acetate (mg/kg a day)	Duration of treatment (years)
1	M	3.8	P ₄ G ₄	Hypothalamic hamartoma	5.3-3.7	3.6
2	F	3.7	P ₃ G ₃	Hypothalamic hamartoma	6.8-3.5	3.2
3	F	7.0	P ₄ G ₄	Hydrocephalus	4.4-2.2	3.6
4	F	4.5	P ₂ G ₂	Hydrocephalus	9.6-5.4	2.9
5	F	5.1	P ₃ G ₃	Idiopathic	6.4-5.1	2.7
6	F	6.7	P ₁ G ₄	Hydrocephalus	8.4-6.8	2.7
7	F	8.5	P ₄ G ₅	Idiopathic	3.5-3	2.0

*Using Tanner's assessment.²⁴

Table 2 Cortisol derivatives (mg/24 h)* in urine samples of children treated with cyproterone acetate

Case	Before treatment	Treatment (months)					
		6	12	18	24	30	36
1	15.2 (0.5)	4.1 (0.1)	5.9 (0.2)		3.7 (0.1)		4.4 (0.1)
2	11.9 (0.5)	8.5 (0.3)	0.4 (0.1)		2.7 (<0.1)		2.9 (<0.1)
3	20.9 (0.6)	22.6 (0.6)	9.5 (0.2)	10.4 (0.2)		10.4 (0.2)	
4	10.8 (0.7)	1.9 (<0.1)	0.7 (<0.1)	2.1 (<0.1)			
5	17.4 (0.7)	4.8 (0.2)	1.9 (<0.1)	2.5 (<0.1)		0.9 (<0.1)	
6	Incontinent						
7	39.3 (0.9)	6.9 (0.2)	7.4 (0.2)		1.8 (<0.1)		

*SI conversions (in $\mu\text{g/kg}$) are shown in brackets. Normal values 0.25–0.75 $\mu\text{g/kg}$.

0, 30, and 60 minutes after 250 μg intravenous tetracosactrin. All steroid and protein hormones were assayed by radioimmunoassay.

Results

Adrenocortical metabolites. The levels of the cortisol derivatives in urine samples are given in Table 2. In 6 children they decreased greatly with treatment to levels seen in hypoadrenocortical states.

The excretion of the adrenal androgens decreased with treatment (Table 3). However in 4 children the values rose during the second year of treatment; in only one child (Case 3) was this associated with a reduced dose of cyproterone acetate.

Plasma cortisol. After treatment the morning basal plasma cortisol levels were below the lower limit of the normal range—280–700 nmol/l (10–25.4 $\mu\text{g}/100\text{ ml}$) in all the children except one (Case 7). Many of the values were barely within the sensitivity of the assay system. The cortisol response to hypoglycaemia was poor or absent in 6 of the 7 children (Figure) and normal in only 1 child out of 5 children after stimulation with tetracosactrin (Table 4).

Plasma adrenocorticotrophic hormone. Plasma ACTH during insulin-induced hypoglycaemia was measured in 5 children, and on 2 occasions in one child (Case 1). In all of them except Case 7 the basal plasma ACTH was low when related to the subnormal basal

cortisol value. Two children (Cases 4 and 6) had no ACTH response and this was associated with no cortisol response to either hypoglycaemia or tetracosactrin. Case 2 had a late peak of ACTH but all the cortisol levels were in the normal hypoadrenocortical range. Case 1 had a normal plasma ACTH response at 1 and 2 years after the start of treatment, but all the cortisol levels were clearly abnormal. In Case 7 the response of ACTH was poor and was associated with normal cortisol values (Table 4).

Growth hormone. Growth hormone levels were measured in all the children during insulin-induced hypoglycaemia. Peaks greater than 8 mU/l are regarded as normal¹ and were present in all the children except Case 3 in whom obesity was probably the reason for the poor response to growth hormone.

Figure Basal plasma cortisol level and peak cortisol response to insulin hypoglycaemia before and during treatment with cyproterone acetate.

Table 3 Adrenal androgens ($\mu\text{mol}/24\text{ h}$) in urine samples of children treated with cyproterone acetate

Case	Before treatment	Treatment (months)					
		6	12	18	24	30	36
1	3.5	0.5	1.8		3.4		2.6
2	1.9	1.0	0.4		1.3		0.8
3	4.4	1.0	0.8	3.0		3.1	
4	0.7	0.2	0.3	3.4			
5	3.9	5.7	1.6	0.5		0.3	
6	Incontinent						
7	3.8	1.9	2.4		2.7		

Table 4 *ACTH, cortisol, and growth hormone response to sequential insulin hypoglycaemia and stimulation with tetracosactrin*

	<i>Insulin hypoglycaemia (0.1 U/kg)</i>					<i>Tetracosactrin stimulation (250 µg intravenously)</i>		
	<i>Time (minutes)</i>					<i>Time (minutes)</i>		
	0	30	60	90	120	0	30	60
Case 1 (1st)								
Glucose (mmol/l)	3.0	0.9	1.5	2.3	2.5			
Cortisol (nmol/l)	40		40			50	60	85
ACTH (ng/l)	33	196	251	133	187			
Growth hormone (mU/l)	9.3	7.3	13.1	16.6	12.5			
Case 2								
Glucose	3.2	0.9	1.9	2.7	3.2			
Cortisol	210		190			140	225	175
ACTH	<10	59	50	56	372			
Growth hormone	5.4	10.7	10.8	8.5	4.8			
Case 4								
Glucose	3.3	1.9	3.3	3.3	3.3			
Cortisol	<20		<20			<20	<20	25
ACTH	<12	<31	<39	<38	50			
Growth hormone	<2	31.5	56.5	33.5	6.3			
Case 7								
Glucose	3.4	2.0	2.8	2.5	3.2			
Cortisol	410		840			370	445	700
ACTH	<10	60	22	<10	<10			
Growth hormone	3.6	41.4	15.4	4.0	3.6			
Case 6								
Glucose	2.9	1.5	3.1	2.9	3.0			
Cortisol	35		40			45	50	60
ACTH	<5	<5	<5	<5	<5			
Growth hormone	13.4	8.7	3.1	5.1	7.3			
Case 1 (2nd)								
Glucose	4.2	3.1	Intravenous glucose 1.3*	7.9	39.0			
Cortisol	50		75			50	55	60
ACTH	43	75	135	112	331			
Growth hormone	<0.4	<0.4	10.4	10.4	39.0			

*Pronounced symptoms of hypoglycaemia.

Cyproterone acetate dosage and adrenocortical suppression. The dosage of cyproterone acetate was correlated with adrenocortical suppression. A dosage greater than 2 mg/kg per 24 hours always suppressed adrenocortical function.

Recovery of adrenocortical function after treatment. Treatment has been stopped in 2 children who are not included in this report. One child had been taking 6 mg/kg per 24 hours. The dose was reduced and the drug stopped over a 3-week period. Two weeks later the cortisol derivatives were normal at 0.52 µmol/kg compared with 0.09 µmol/kg some 5 weeks previously. The other child was receiving 4 mg/kg per day and had complete suppression of cortisol derivatives at 0.07 µmol/kg. These reverted to 0.28 µmol/kg within 3 weeks of stopping the drug and were normal at 0.54 µmol/kg when measured 3 months later.

Discussion

Cyproterone acetate suppresses the clinical signs of sexual maturation in precocious puberty.²⁻⁵ It is less

certain whether it has any effect on bone maturation or height velocity, and thus it is uncertain whether it prevents short adult stature.^{4,6}

Its effect is due to its anti-androgenic properties which block the peripheral action of testosterone, and to its central anti-gonadotrophic action which decreases the concentration of circulating gonadotrophins and thus reduces the release of gonadal steroids.⁷ This latter action of the drug is similar to that of medroxyprogesterone acetate which is used in the treatment of precocious puberty and which has an effect on other central pituitary hormones.⁸

In experimental animals cyproterone acetate decreases adrenal weight.⁹⁻¹⁰ It also reduces plasma cortisol levels¹¹ and the ability of the adrenal to respond to stress.¹² Adrenal atrophy induced by cyproterone acetate can be prevented by simultaneous ACTH administration.¹¹ Girard and Baumann¹³ found the drug lowered plasma corticosterone and ACTH concentrations significantly in albino rats compared with controls. Therefore its site of action is probably the hypothalamus or pituitary.

Cyproterone acetate appears to have a similar

effect in man. Patients receiving cyproterone acetate have a diminished excretion of adrenocortical metabolites¹³⁻¹⁴ and ACTH levels are depressed.^{13 15}

In none of these studies did the patients show any ill effects from this biochemical adrenocortical hypofunction. It has been supposed therefore that cyproterone acetate has inherent glucocorticoid properties.¹⁶ This not only suppresses ACTH production and causes secondary adrenal atrophy, but also protects the patients against the effect of cortisol deficiency.

Our study confirms that the hypoadrenocortical function is secondary to suppression of the hypothalamic pituitary axis. In all of our patients the adrenocortical metabolites in the urine decreased on treatment and in all (except Case 7) the plasma cortisol response to insulin-induced hypoglycaemia and intravenous tetracosactrin was abnormal. The responses of plasma ACTH to hypoglycaemia were unequivocally low in 3 children. Two children (Cases 1 and 2) had normal ACTH peak levels despite obvious adrenocortical hypofunction. This probably reflected the ability of severe stress, in this instance profound hypoglycaemia, to override the tonic negative feedback effect of this cortisol-like drug.

Initially the excretion of the adrenal androgens was as suppressed as that of the cortisol metabolites. However a rise of the adrenal androgens towards pretreatment levels was seen in 4 of the 6 children after the first year of treatment. Gupta reported similar results in 2 of 3 children who had been treated with cyproterone acetate for over 2 years.²³

The explanation is not clear. The reported adrenal androgen excretion may contain significant amounts of gonadal testosterone metabolites since in the adult man this may make up 30% of the total androgen excretion. In the only boy in this series plasma testosterone levels, after an initial fall, rose to pretreatment levels. This has been reported by others.^{3 17} In girls androgen secretion by the ovary is very limited and the rise in their cases was presumably of adrenal origin.

It is of interest that the timing of this increase in adrenal androgen excretion coincides with the escape of gonadotrophin suppression which has been supposed to occur during prolonged treatment with cyproterone acetate.¹⁸ We have reported this in these children in a longitudinal study examining the gonadotrophin response to luteinising hormone releasing hormone.¹⁹

The control of adrenal androgen secretion and in particular the cause of its increased production at puberty is not known. One suggestion has been that a gonadotrophin, possibly luteinising hormone, may be concerned, perhaps synergistically, with ACTH or another pituitary hormone.²⁰⁻²² The unequal effect of

cyproterone acetate on the secretion of cortisol and adrenal androgens and its possible association with the escape of luteinising hormone from suppression requires further study.

It is unlikely that this failure to maintain suppression of the adrenal androgens has any significant effect on bone maturation or height velocity since the anti-androgenic properties of cyproterone acetate will effectively block the peripheral action of these androgens.

We inform the parents and the general practitioners of the effect of the drug on the adrenal gland. All the children wear Medic-Alert bracelets and they know that the drug should not be stopped without consultation with the clinic. The general practitioners are advised that the children may require steroid cover if they are ill. In fact this has not proved necessary and all the normal childhood illnesses have been passed without problems. Steroid cover is given routinely if surgery is required. It is clear in the 2 children in whom the drug was stopped that normal basal adrenal function, as assessed by urinary adrenocortical steroid output, soon reappeared. However the response of the adrenal gland to chronic stress may not be adequate for some months and during the first year after the end of treatment particular care must be taken during illness.

Clinically cyproterone acetate is well tolerated and effectively suppresses the secondary sexual characteristics of precocious puberty. We have not been so impressed with its ability to slow the rapid growth that is associated with this disorder. Whether it has any advantages over other compounds used in the treatment of precocious puberty must depend on its potential to slow bone maturation and thus increase final height.

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