Appetite and Weight Gain in Children:

A DOUBLE-BLIND TRIAL USING CYPROHEPTADINE AND METHANDROSTENOLONE*

BY

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Cyproheptadine is an antagonist of both histamine and serotonin and has been in clinical use for some eight years. In 1962, Lavenstein and co-workers described an interesting side-effect associated with the administration of this drug. While comparing the action of cyproheptadine and chlorpheniramine in children with hay fever and bronchial asthma, they noted a striking increase in weight and a lesser but significant increase in linear growth in those children taking cyproheptadine. This unexpected effect, apparently unique to cyproheptadine among the known compounds pharmacologically antagonistic to histamine or serotonin, has since been confirmed by others in both allergic and non-allergic subjects (Bergen, 1964; Drash *et al.*, 1966; Francini *et al.*, 1968), but has received scant attention in the paediatric literature.

The present study attempts to assess the action of cyproheptadine further by comparing the appetite, weight gain and linear growth in four groups of anorexic, underweight children.

METHODS

These children presented with poor appetite and physical under-development. All were below the fiftieth percentile for weight on the Stuart anthropometric charts. Physically they were otherwise normal and children with significant anaemia (haemoglobin below 11 gm. per cent.) were excluded. A normal erythrocyte sedimentation rate and a urine free of protein, sugar and formed elements were also required for admission to the study. Other investigations were performed, where indicated, but yielded uniformly negative results.

The experimental population comprised 96 subjects, whose ages ranged from 15 months to 13 years 5 months. There were 84 white children and 12 of mixed race. Each was allocated at random to one of four groups in a sequence not known to the author. The numbers in each group are indicated in Table I.

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Table I

Group	A	B	C	D
Male	14	13	10	12
Female	14	14	13	8
Total	28	27	23	20
Average age (years and months)	5.9	5.2	6.5	5.3
Average initial height (centimetres)	110.9	109.4	111.5	109.5
Average initial weight (kilograms)	17.58	17.72	17.39	17.40

Table II

Period and Drug	Per cent. of Initial Height	Per cent. of Last Height	Per cent. of Initial Weight	Per cent. of Last Weight
GROUP A:				
1. Cyproheptadine	—0.3	—0.3	4.9	4.9
2. Cyproheptadine	—2.3	—1.9	6.0	1.0
3. Placebo	—0.4	1.9	5.6	—0.4
4. Placebo	1.7	2.1	6.7	1.0
5. Nil	1.1	—0.6	4.1	—2.4
GROUP B:				
1. Placebo	0.1	0.1	0.8	0.8
2. Placebo	0.5	0.4	—0.7	—1.5
3. Cyproheptadine	2.1	1.6	3.0	3.7
4. Cyproheptadine	2.5	0.4	8.0	4.8
5. Nil	0.6	—1.8	3.2	—4.4
GROUP C:				
1. Cyproheptadine/ Methandrostenolone	0.5	0.5	7.7	7.7
2. Cyproheptadine/ Methandrostenolone	1.3	0.8	12.4	4.3
3. Placebo	1.9	0.6	9.7	—2.4
4. Placebo	1.8	0.1	8.9	—0.7
5. Nil	1.9	0.1	6.9	—1.8
GROUP D:				
1. Placebo/Methandrostenolone	0.5	0.5	3.7	3.7
2. Placebo/Methandrostenolone	0.9	0.5	5.8	2.0
3. Cyproheptadine	0.7	—0.2	6.7	0.9
4. Cyproheptadine	2.7	1.9	10.6	3.6
5. Nil	2.7	0.0	8.6	—1.8

Table III

Group	First Six Weeks		Second Six Weeks	
A	Cyproheptadine	6.0	Placebo	0.6
B	Placebo	—0.7	Cyproheptadine	8.8
C	Cyproheptadine/Methandrostenolone	12.4	Placebo	—3.1
D	Placebo/Methandrostenolone	5.8	Cyproheptadine	4.6

Group A received cyproheptadine 4 mgm. twice a day before meals for six weeks, followed by a placebo for the next six weeks.

Group B received the placebo for the first six weeks, followed by cyproheptadine 4 mgm. twice a day for six weeks.

Group C received methandrostenolone .04 mgm. per kilo in a single morning dose, together with cyproheptadine 4 mgm. twice a day, both for the first six weeks, followed by a placebo for the following six weeks.

Group D received methandrostenolone .04 mgm. per kilo in a single morning dose, together with a placebo for six weeks, followed by cyproheptadine 4 mgm. twice a day for the following six weeks.

The cyproheptadine and placebo tablets were identical in appearance and their nature was unknown to the author or subject during the trial.

Weight and height were measured at the commencement and thereafter at three-weekly intervals for the 12 weeks of the trial, with a final measurement three weeks after completion—that is, 15 weeks after the initial assessment.

At each interview details of intercurrent illness and unusual symptoms were noted. A rough subjective assessment of the child's appetite by the parent or guardian was also made, using a grading system from 0 to 3 (0=as at onset or worse, 1=slight improvement, 2=great improvement, 3=excessive).

Advice was given initially and reinforced at each subsequent interview regarding food values and feeding, and generally present faults in mealtime practice on the part of the parents were discussed (Rothney, 1968).

After completion of the study the actual and percentage increases in weight and height were calculated for each three-week period in each case and averaged for the whole group, using an electronic computer. The percentages of weight and height gained were calculated over both the initial levels and over each preceding level.

Finally, the bone ages in five children selected at random from each group were estimated at the commencement of the study and 15 weeks thereafter.

Results

The percentage increases in height and weight are indicated in Table II.

A statistical analysis of the data was carried out by Professor J. E. Kerrich, of the University of Witwatersrand, Johannesburg.

Weight Data

All three "active" treatments gave significantly better results than the placebo. The cyproheptadine/methandrostenolone combination was significantly better than cyproheptadine or methandrostenolone alone. There was no significant difference between the latter two preparations.

Height Data

Here the statistical evidence was less clear cut and most of the differences examined were not significant. Slight but significant increase in height occurred in Groups C and D at 15 weeks as compared with Groups A and B.

Appetite Scores

When tested at the 5 per cent. level, results over the first three weeks of treatment showed the mean score for cyproheptadine (1.5) to be better than that for either the combination (1.3) or the placebo (0.7) and methandrostenolone (1.9) to be better than the placebo. After the first three-week period none of the differences were statistically significant.

Percentage Gains Over "Normal"

Observed increases in weight and height 12 weeks after the onset of treatment were compared with normal expected increases. These were calculated in each case by referring to the appropriate percentile line on the Stuart anthropometric charts. The gain in per cent. of normal was obtained by dividing the observed increase by the expected increase and multiplying by 100. The results were then averaged for each group.

There was no significant departure from normal with regard to linear growth in any group. However, the differences in weight gain were striking:

Group	Percentage of "Normal Gain"
A	169
B	244
C	360
D	315

Bone Age

In no case was abnormal acceleration of epiphyseal development noted in those studied radiologically.

Comments

The respective gains in weight in the four groups are summarised in Table III.

There can be no doubt from the results reported in this study that cyproheptadine induces an increase in appetite, increased food intake and weight gain, thus confirming in non-allergic underweight children the findings reported by Lavenstein *et al.* (1962) and Bergen (1964) in asthmatic subjects, and more recently by Francini *et al.* (1968). The study provides no new evidence as to its mode of action. The children showed no bodily changes suggestive of adrenal cortical over-activity, virilisation or hypothyroidism, nor

were there symptoms of hypoglycaemia. Cyproheptadine appears to increase body weight primarily by stimulating appetite and hence increasing food intake (Lavenstein *et al.*, 1962). Drash *et al.* (1966), investigating normal adults receiving cyproheptadine, documented a small but statistically significant depression of the fasting blood glucose, and suggested that the increase in appetite might result from this. They tentatively concluded that decrease in blood sugar in their subjects was not insulin mediated and that the action of cyproheptadine may be on the cell membrane, causing an increased permeability to glucose. Appetite stimulation is apparently unique to the human and cannot be reproduced experimentally (Stone *et al.*, 1961; Lavenstein *et al.*, 1962).

No significant side-effect could be attributed to cyproheptadine. In five children only was drowsiness noted, and this passed off within a few days. A further six children taking cyproheptadine were reported to "sleep better at night."

Appetite enhancement occurred even though cyproheptadine was given only twice a day and not four times daily as in other studies (Lavenstein *et al.*, 1962; Bergen, 1964). Cannon (1968) has noted that cyproheptadine has perhaps the longest duration of action of any antihistaminic —up to 48 hours. If this is so, then the problem of drowsiness as a side-effect might be obviated altogether by giving the cyproheptadine only at night. This aspect is being investigated further.

Two children who had had methandrostenolone for six weeks showed slight hypertrophy of breast tissue with minimal alveolar pigmentation. This side-effect of methandrostenolone is well recognised. Signs of virilisation or other untoward effects were not noted.

Enhanced weight gain was not maintained in any group on stopping the "active" treatment. It is for this reason that the gain in weight at 12 weeks as a percentage of "normal gain" was only 169 per cent. in Group A compared with 244 per cent. in Group B. The children in Group A had been off cyproheptadine a full six weeks, whereas those in Group B had just completed their course.

No increased rate of linear growth was noted in the two groups on cyproheptadine alone. Lavenstein *et al.* (1962), who administered the cyproheptadine continuously for six months, described a small acceleration of growth in their series. They concluded that this resulted purely from the increased intake of food, as seen in normal children with "exogenous" obesity (Talbot and Sobel, 1947).

Functional feeding problems in children stem largely from parental misconceptions, from failure to respect the normal developmental aspects of infant feeding or, more seriously, from disturbed mother/child relationships. Advice, guidance and, if necessary, psychiatric help are patently fundamental in such problems, and the common practice of fobbing the child and mother off with a "tonic" or multivitamin mixture must be deprecated. In the author's opinion the appetite stimulating properties of cyproheptadine could be utilised with advantage in selected cases of anorexia in children. The risks of premature epiphyseal closure are not present, as is the case with the anabolic steroids, and no other significant side-effects have been reported. In severe appetite disturbances and in grossly debilitated subjects the combined use of cyproheptadine and methandrostenolone also merits further trial.

Summary

Ninety-eight anorexic, underweight but otherwise normal children were investigated in a double-blind trial utilising cyproheptadine, a placebo and methandrostenolone. The appetite stimulating properties of cyproheptadine and the concomitant effect on weight gain were clearly demonstrated. A group of children taking both cyproheptadine and methandrostenolone together showed by far the greatest increase in weight.

It is suggested that this effect of cyproheptadine could be utilised clinically.

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