Appetite stimulation and weight gain with cyproheptadine (periactin) in tuberculosis patients (double-blind clinical study)

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Appetite stimulation and weight gain properties of Cyproheptadine were first noted by Levenstein et al. (1962) in asthmatic children while this was primarily administered as an anti-allergic drug. Since then many clinical trials have been conducted on relationship of cyproheptadine with appetite stimulation and weight gain.

Cyproheptadine is an anti-histamine preparation with anti-allergic and anti-serotonin properties. Serotonin (5-Hydroxy tryptamine) is a normal constituent of grey matter of the brain, highest concentration being in the hypothelamus, mid-brain, limbic lobe and floor of the fourth ventricle. Appetite centre is in the hypothelamus and is said to be under the influence of serotonin, which is antogonized by Cyproheptadine, thus releasing the appetite centre free.

In pulmonary tuberculosis, patients underweight and lose of appetite are very important features. Anorexia is further aggravated when they are treated with P.A.S., thiacetazone, and ethionamide. In order to improve the appetite and weight gain as rapidly as possible it was thought that medical profession should have a drug for this disease with least side-effects. The past studies by other authors suggest that Cyproheptadine fulfils the above objective. One with this is view, our study was carried out on under-weight adult patients who had chronic pulmonary tuberculosis, at chest unit, Jinnah Post-Graduate Medical Centre, Karachi, Excluded from this study were patients in whom steroid, anabolics were contraindicated, e.g. impaired liver function, prostatic carcinoma, sodium retention. Also excluded were pregnant patients and those who were suffering from glaucoma or gave a history of urinary retention.

Material & Methods:

Double-blind control trial was conducted on 27 patients. Patients were given drug according to radom allocation numbers. All patients were admitted in the ward and kept for 12 to 16 weeks excepting three patients who did not complete their trials as they left hospital against advice and later did not turn up in out-patient department for follow-up. Another patient was excluded who was found to be pregnant 4 weeks after her inclusion. Thus study included 23 patients suffering from Pulmonary tuberculosis.

During their indoor stay each patient got convalescent diet which consisted of about 3000 calories per day on the average. Each patient was given 3 tablets of either active drug or placebo i.e. one tablet one hour before each meal for 12 weeks and each tablet of active drug contained 4 mgm of cyproheptadine. Total duration of

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study was 16 weeks. Each case was diagnosed on the basis of history, physical findings, X-ray chest, mantoux test, E.S.R. and sputum examination. All patients were given routine anti-tubercular treatment which consisted of:-

Inj. Streptomycin		1 G. daily
Tabs.	PAS	10 G. daily
Tab.	INH	300 mg. daily

Few cases who gave history of previous haphazard chemotherapy for a long duration and were of clinically resistant type given thiacetazone 150 mgm daily in place of PAS. None of the patients were confined to bed rather allowed to continue their normal activities in the ward. At the start of the study patient's height, weight, pulse, respiration, temperature, built and nutrition, were noted. Alongwith this following laboratory investigations were carried out; haemoglobin estimation, RBC and WBC count, serum albumin estimation, urine for sugar and albumen, stools for ova or cysts.

In subsequent period weekly recordings during the first month, forthnightly during the second and third month and finally at the end of the fourth month were made. All investigations of initial visit were repeated at above noted order. Along with this any voluntered untoward effects were noted down. Out of 23 patients who completed the trial 11 were on active drug while 12 are on placebo.

Age and Sex Distribution of the patients, and drug allocation with sex distribution are shown in Table I and II

TABLE I

Age & Sex Distribution

1. 15–29 years	– 12 patients	Male – 5	Female – 7
2. 30–44 years	– 10 patients	Male – 9	Female – 1
3. 45 years/above	– 1 patient	Male – 1 (50 years)	

TABLE II

Drug Allocation with sex Distribution

Periactin	Male – 8		Female – 3
Placebo	Male – 7		Female – 5
(Total:	Male – 15	+	Female – 8 = 23)

TABLE III
Weight gain (in pounds) on active drug

No.	Age (years)	Sex	Initial (lbs.)	4 weeks (lbs,)	8 weeks (lbs.)	12 weeks (lbs.)	16 weeks (lbs.)	Gain(+) or loss(−) at the end of the 16 weeks (lbs.)	
1.	24	M	102	110	110	111	112	+	10
2.	24	F	75	80	92	96	98	+	25
3.	25	F	80	82	82	86	86	+	6
4.	25	F	69	73	80	84	85	+	16
5.	28	M	110	112	118	118	120	+	10
6.	30	M	76	78	79	78	78	+	2
7.	35	M	88	96	101	106	105	+	17
8.	38	M	75	75	76	76	76	+	1
9.	42	M	74	75	76	78	78	+	4
10.	42	M	97	104	110	110	112	+	15
11.	50	M	105	108	113	115	117	+	12
					Total weight gain			+	116
		mean	86.45 lbs.				97.00 lbs.	+	10.55 lbs.

TABLE IV
Weight Gain (in pounds) on Placebo

No.	Age (years)	Sex	Initial (lbs.)	4 weeks (lbs.)	8 weeks (lbs.)	12 weeks (lbs.)	16 weeks (lbs.)	Gain(+) or loss(−) at the end of 16 weeks (lbs.)	
1.	16	F	67	65	62	65	66	−	1
2.	19	F	100	102	105	105	104	+	4
3.	20	F	80	80	80	85	85	+	5
4.	22	M	74	79	86	86	86	+	12
5.	24	M	85	86	86	86	86	+	1
6.	25	F	79	76	75	75	76	+	3
7.	25	M	98	101	102	104	105	+	7
8.	30	M	85	89	92	95	95	+	10
9.	34	M	85	88	90	90	89	+	4
10.	40	F	68	70	71	70	71	+	3
11.	40	M	116	120	120	120	120	+	4
12.	43	M	107	110	110	111	112	+	5
					Total weight gain			+	51
		mean	87 lbs.				91.25 lbs.	+	4.25 lbs.

Results:

These patients with active drug showed a mean increase of weight of 10.55 lbs (Table III). While those on placebo showed a mean increase of weight of 4.25 lbs (Table IV) after 12 weeks of treatment and follow-up of upto 16 weeks. This difference is significant. It is interesting to note that the mean initial weight was almost equal in both the groups i.e. 86.45 in active group and 87 lbs. in placebo group. The mean dinal weight after 16 weeks of medication shows a significant difference i.e. 97 lbs. in active drug group and 91.25 lbs. in placebo group. This means that the active drug clearly comes out to be superior for stimulating appetite and producing weight gain in tuberculosis patients.

Side Effects:

The main side effect noted was slight drowsiness in seven active cases of whom 5 had this complaint almost throughout the treatment period. On the other hand 4 placebo cases had slight drowsiness initially for 1-2 weeks.

An interesting feature noted was that of unexplained slight restlessness initially for 1-2 weeks in 2 active and placebo cases.

Laboratory results:

No deviation in laboratory reports noted either in active cases or in placebo cases. However, response to chemotherapy was noted by diminished E.S.R. X-ray, shadows and sputum results.

Comments and discussion

All the 23 cases who completed the trial come from very poor socio-economic community and all of them had chronic pulmonary tuberculosis for a long time and received standard anti-tubercular chemotherapy outside. The same chemotherapy was continued for 16 cases and the rest, i.e. seven cases likely to be resistent to one or more of standard chemotherapy were given thiacetazone in place of PAS.

Hospitalization of these patients was necessary for infectious status of their disease, severe clinical manifastations and complications like haemoptysis. All the patients were either young, adult or early middle-aged. Children were excluded for the reason that in a clinical trial like this growth and developmental factors may influence the result if observation is continued for a long time.

It has been observed that admitted patients with effective specific chemotherapy, gain weight very rapidly due to response to the treatment and high calorie diet. Those patient with non-effective chemotherapy i.e. treatment failure cases also show weight gain but slowly due to good diet. Adequate rest also contribute in weight gain which these patients rarely get when treated on domiciliary basis. Lack of appetite is one of the commonest clinical feature of active pulmonary tuberculosis. When these patients are treated with PAS or thiacetazone (which is invariably given with INH and or Streptomycin) their appetite, is further depressed. Gastric intolerance like nausea, lack of appetite, gastralgia, fullness of stomach, vomiting and diarrohea are most important side effects of PAS and thiacetazone, and lack of appetite is the commonest of all. It is, therefore, desirable to find a drug which not only counteract the effect of the disease itself but also prevents the depressing effect of PAS and thiacetazone medicaments. Thus the drug will enhance the appetite to a degree with when they will eat more thereby gain weight speedily so that tubercular patients can return; to their job quickly. With this in view, the clinical trial of Cyphoheptadine was conducted.

The Cyproheptadine has been studied by many authors for its appetite stimulating and growth promoting properties. It was used in patients of different ages, suffering from chronic diseases. It was also studied in otherwise normal person with poor appetite and underweight.

One of the frequently quoted observations of Lavanstein et al's double-blind trial of 28 patients conducted in Pediatric Clinic of John Hopkin School of Medicine showed the effect of Cyproheptadine on weight gain and liniar growth children suffering from bronchial asthma. In this study the comparison was made with chlorpheniramine for about 6 months and a significant weight gain wiht marked improvement in appetite was reported in patients receiving Cyproheptadine.

Another investigation was carried out by Chakrbarty et al to see the effect of Cyproheptadine on the electrical activity of the hypothalmic feeding centre and medial 'Satisty Centre' in cats. Increase hungar behaviour, increased food intake and weight gain was reported in all cats and occassional paroxysm of drowsiness was also recorded in addition.

Noble in his study of 12 healthy underweight adult out-patients for 56 days observed the mean

weight in PERIACTIN group was significantly higher statistically than corresponding placebo group.

Chowdhury et al reported the benefit of PERIACTIN for promoting weight gain in double-blind trial of 20 under-weight subjects who were otherwise normal. Seven out of ten cases active drug gained weight and only two placebo. The study period in this series was rather short as the subjects were given medicament and placebo for 4 weeks only. However, they are closely observed for 6-8 weeks after stoppage of therapy.

Shah has reported another clinical double-blind trial on 56 underweight tubercular patients and his findings of weight gain and improved appetite are in agreement with our result.

It will be seen from the observations that the findings of our trial is in agreement with the above noted investigations that Cyproheptadine is a useful drug in stimulating appetite and weight gain. The patients receiving active drug showed mean weight gain of 10.55 lbs. whereas placebo group gained 4.25 obs. The differents of 6.30 lbs. in 16 weeks of Cyproheptadine therapy and follow-up is highly significant. The drug is particularly found useful for tuberculosis patients receiving PAS and Thiacetazone-the appetite depressant drug. Cyproheptadine is also recommended for patients suffering from other diseases having lack of appetite or poor weight gain. Above studies have established the efficacy of this drug but the specific mode of action is not known, further study is needed to reveal its mode of action.

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