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Safety and Efficacy of a Combination of Cyproheptadine and Tricholine Citrate: Phase IV Study.

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ABSTRACT

Background: Undernutrition or anorexia is very common in infants and children in developing countries like India. An FDC of Cyproheptadine and Tricholine Citrate, an appetite and growth stimulant is popular in the treatment of undernutrition or anorexia. The phase IV clinical study was conducted for evaluating the efficacy and safety of combination of Cyproheptadine and Tricholine Citrate in the treatment of undernutrition or anorexia in infants and children. **Methods:** Out of 322 patients, 279 patients completed the study. Safety assessment was made by inspecting the adverse events during trial. Efficacy assessment was made by analysis the increase in appetite and meal frequency. Safety assessment was made by analysing the adverse events during the clinical trial. **Result:** Average increase in meal frequency and change in meal quantity (very low/low/moderate/high/very high) was analysed at all three visit. As compared to baseline visit, it was found that in conclusion visit the patients with very low and low appetite shifted to moderate and high appetite and some patients were found with very high appetite. The average meal frequency as compared to baseline visit was found out to be increased in conclusion visit. **Conclusion:** The combination of Cyproheptadine and Tricholine Citrate is safe and effective for the treatment of undernutrition or anorexia in infants and children.

Keywords: Cyproheptadine, Tricholine Citrate, Undernutrition, Anorexia, Meal Frequency and Meal Quantity.

INTRODUCTION

The common health problem in developing countries is undernutrition. There are multi-dimensional factors that cause undernutrition in childhood are inadequate food intake, lack of exclusive breast feeding, intrauterine growth retardation, inappropriate complementary feeding, repeated attacks of infectious illnesses, and micronutrient deficiencies.[1,2] Inadequate food intake may leads to lack of appetite and/or diet scarcity which leads to undesirable effect on mental and physical health in children.[3] The rates of prevalence in undernutrition children below 5 years is around 20-32% in low and middle income countries whereas sometimes it is comparatively higher among the highest income countries.[1,2]

Lack of appetite or anorexia is type of eating disorder that perpetuate the biochemical changes marked by an inability to maintain a normal healthy body weight, often dropping below 85% of ideal body weight (IBW), ketosis and starvation illness.[4,5] It is one of the important reason for inadequate food intake leading to undernutrition.

It is important to find a safe and effective medical treatment for increasing appetite in children with undernutrition because the long term anorexia can have impact on children's cognitive and future growth.[1,2]

The intake of food is controlled by the centre in the hypothalamus, lateral hypothalamic area and another centre ventromedial hypothalamus called satiety centre. Serotonin is a neurotransmitter carries the message to satiety centre which stimulates the loss of appetite and satiety centre. In case of anorexia, serotonin level is very high. This leads to activation of satiety centre which results in the suppression of appetite centre and weight loss.[6-8]

Cyproheptadine, an anti-histaminic drug with anti-serotonergic activity first invented as the drug for the treatment of pruritis and other allied conditions and later on it was recognised as an appetite and growth stimulant. The simulation of appetite effect of Cyproheptadine is probably due to serotonin antagonism which antagonizes the satiety stimulation effect of serotonin on satiety center. Cyproheptadine intake finds clinical application in children with increased growth, weight gain and regulation of the secretion growth hormone.[9-11]

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Tricholine citrate is a lipotropic agent that helps to deplete accumulation of fat in liver. Thus it is a hepatoprotective agent. Tricholine citrate also increases appetite and spares methionine for muscle enhancing. Tricholine citrate increases hepatobiliary flow that results in greater availability of bile in GI tract. It also increases emulsification, transport and utilisation of fat.[12]

The combination of Cyproheptadine and Tricholine Citrate help increases appetite due to its synergistic effect. Such combination are readily available in the market and are very popular for its use in anorexia and undernutrition. However there is lack of clinical data available for this combination hence Post-Marketing study (PMS) or Phase IV was conducted to document the safety and efficacy of the combination of Cyproheptadine and Tricholine Citrate in the treatment of anorexia in infants and children.

MATERIALS AND METHODS

This phase IV clinical study was conducted at 24 paediatrics speciality centres all across India from January 2017 to May 2017. A total of 322 patients were recruited for the study, out of which 279 patients completed the study and 63 patients were lost to follow-up.

Inclusion and exclusion criteria

Patients with confirmed diagnosis of undernutrition or anorexia were enrolled in the study. Patients with both genders (male as well as female) having age of up to 12 years and having weight of below 85 percentile of the normal weight for age were recruited in the study. The patients and guardians who could strictly adhere to the protocol and sign the inform consent form were recruited for the study. Patients with hypersensitivity to the individual study drug or to any of its ingredients were excluded from the study. Patients having angle- closure glaucoma, peptic ulcer, bladder neck obstruction and pyloroduodenal obstruction were also excluded from this study.

Study intervention

Study drug- Drops containing FDC of Cyproheptadine 1.5 mg, Tricholine Citrate 55 mg in a flavoured syrupy base per ml for infants, Syrup containing FDC of Cyproheptadine 2 mg, Tricholine Citrate 275 mg and sorbitol (70%) 3 gm. per 5 ml for children over 1 year. Two 10 ml bottles of drops and 100 ml syrup study medication provided to patients at free of cost for infants and children respectively. All the samples were dispensed by the investigator to the patient. Study dosage and administration- Patients were advised to take study drug medication as mentioned in the table no. 1 for drops and [Table 2] for Syrup.

Table 1: Study dosage for Drops.

Drops	
Age	**Dose**
Up to 6 months	0.5 ml bid
6 to 12 months	1 ml bid

Table 2: Study dosage for Syrup.

SYRUP	
Age	**Dose**
1- 3 years	2.5- 5 ml
3 years and above	5 ml

Study procedure

The study duration for drops and syrup was kept 5 days. Patients of anorexia or undernutrition who met with the decided inclusion and exclusion criteria were recruited for the clinical study.

A detailed medical history was obtained from each patient and physical examination was conducted by the investigators. The paediatrician were involved as an investigator for conducting this study. Patients whose weight is below 85 percentile of normal weight for age were dispensed with two 10 ml bottles of drops as study drug medication by investigators and asked to consume in the dose of 0.5 ml twice a day for up to 6 months of infants and 1 ml twice a day for 1 to 3 years of infants for a study period of 5 days. Patients whose weight is below 85 percentile of normal weight for age were dispensed with 100 ml bottles of syrup as study drug medication by investigators and asked to consume in the dose of 2.5 - 5 ml twice a day for 1 to 3 years of children and 5 ml twice a day for 3 years and above children for a study period of 5 days. Patient's guardians were asked to maintain a diary to record any adverse events occurring during the study duration.

Three visits were planned for all the patients recruited in this study-the first visit was baseline visit (V1) on day 1 before treating patient with the study drug combination, the second visit was revaluation visit (V2) on day 3 and third visit was conclusion visit (V3) on day 5. Adverse events occurring and total symptom score were noted during each visit along with medical history and physical examination. Investigators were asked to discontinue the study drug in case of severe adverse event and with discretion, clinical experience in case of mild or moderate adverse events.

Concomitant therapy

No Pharmacological, Non- pharmacological interventions and medications were allowed during the study period of 5 days.

Efficacy Assessment

The efficacy assessment was done by analysing the increase in appetite i.e. meal quantity (very low/low/moderate/high/very high) and meal frequency per day. In visit 1 (baseline) meal quantity

and meal frequency was recorded. In visit 2 (day 5) and visit 3 (day 10) change in appetite i.e. meal quantity and meal frequency was recorded.

Safety assessment

Throughout the clinical study patients were questioned by investigator about any adverse event at each visit and if present were noted in the case report form (CRF) during each visit. The adverse events were classified into 2 categories as serious or non-serious adverse events. After thorough investigation adverse effects observed in patient is recorded in case report form. Adverse events observed were followed up and treated if necessary by the investigators till the symptoms subside.

Regulatory matters

In India, the said combination is available and classified under schedule 'H' drug, therefore it should it should be sold in the presence of prescription of a registered medical practitioner only. All the patients participated in the study have read and signed the ICF. The combination for drops containing FDC of Cyproheptadine 1.5 mg, Tricholine Citrate 55 mg in a flavoured syrupy base per ml and syrup containing FDC of Cyproheptadine 2 mg, Tricholine Citrate 275 mg and sorbitol (70%) 3 gm per 5 ml, is approved by DCGI office (Drug Controller General of India), Central Drugs Standard Control Organization (CDSCO).

RESULTS

A total number 322 patients were recruited at 24 paediatrics speciality center across India. 279 patients completed the study and were analysed.

Efficacy analysis

Average increase in meal frequency and change in meal quantity (very low/low/moderate/high/very high) was analysed at all three visit. In baseline visit (V1), 63 patients were found out to be with very low appetite, 179 patients were with low appetite. On visit (V2) on day 3, 4 patients were found with very low appetite, 50 patients with low appetite, 195 with moderate appetite and 30 patients with high appetite. Here in re-evaluation visit (V2), after medication it was found that number of patients with very low and low appetite were decreased and there was increase in patients with moderate appetite and some patients were found with high appetite.

On conclusion visit (V3) on day 5, 0 patients were found with very low appetite, 8 patients with low appetite, 105 with moderate appetite, and 160 patients with high appetite and 6 patients with very high appetite. Here as compared to visit (V1), it was found that number of patients with very low appetite, low appetite and moderate appetite were decreased and there was increase in patients with high appetite and some patients were also found with very high appetite.

Table 3: Change in meal quantity at visit 1, 2 and 3 for all the patients.

Change In Meal Quantity	Number Of Patients		
	V1 (Day 0) (Baseline Visit)	V2 (Day 3) (Re-Evaluation Visit)	V3 (Day 5) (Conclusion Visit)
Very Low	63	4	0
Low	179	50	8
Moderate	37	195	105
High	0	30	160
Very High	0	0	6

The average meal frequency in baseline visit (V1) was found out to be 5.34. In visit 2 (V3) the average meal frequency was increased to 7.41 and further in visit 3 (V3) it was increased to 9.24. Therefore it was found that through medication there was change in appetite and average meal frequency.

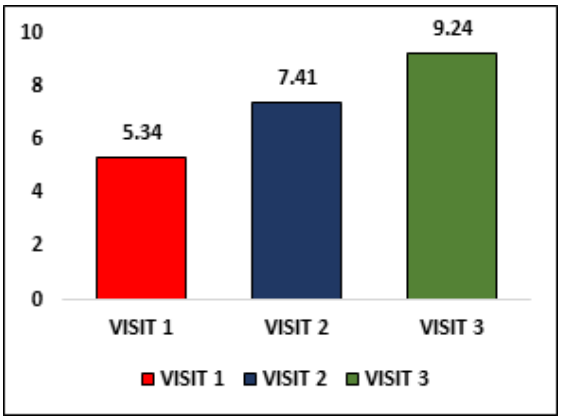

Figure 1: Average meal frequency at visit 1, 2 and 3 for all the patients.

Safety analysis

The overall incidences of reported study drug related adverse events were 38 seen in 24 patients. The list of adverse events with the number of episodes is mentioned in [Table 3]

Table 4: Adverse events, no. of episodes, no. of patients and percentage of patients experience from total population.

Adverse event	No. of episodes	No. of patient	Percentage of patients
Drowsiness	8	8	2.86
Dry mouth	13	12	4.30
Dizziness	17	22	7.88
Total	38	24	8.60

DISCUSSION

In authors knowledge, this was the first clinical study for the combination of Cyproheptadine and Tricholine Citrate in Indian patients i.e. Infants and children suffering from undernutrition or anorexia. A strength of this study is both the parameter of appetite stimulation i.e. Meal Quantity and Frequency were studied over a period of study duration.

In baseline visit (V1), it was found that 63 (22.58%) patients were with very low appetite, 179 (64.15%) with low appetite and 37 (13.26%) with moderate appetite. After medication on revaluation visit 2 (V2), patients with very low appetite and low appetite was found to be decreased from 63 (22.58%) to 4 (1.13%) and from 179 (64.15%) to 50 (17.92%) respectively with increase in number of patients with moderate appetite from 37 (13.26%) to 195 (69.89%) and 30 (10.75%) were also found with high appetite. On conclusion visit (V3) as compared to revaluation visit (V2), it was found that there was no patient with very low appetite, patients with low appetite and moderate appetite was decreased from 50 (17.92%) to 8 (2.86%) and from 195 (69.89%) to 105 (37.63%) respectively, however there was an increased in patients with high appetite from 30 (10.75%) to 160 (57.34%) and 6 (2.15%) patients were also found with very high appetite. Therefore from the overall change in appetite study it was observed that at Visit 2 (V2) patients with very low and low appetite were shifted to moderate appetite and some in high appetite. In visit (V3), some patients were found with low appetite however patients with moderate appetite were shifted to high and very high appetite.

At baseline visit (V1) the average meal frequency was found out to be 5.34. In visit 2 (V2) and visit (V3) the average meal frequency was increased by 38.76% and then by 73.03% respectively as compared to baseline meal frequency.

A total of 38 adverse events were related to study drug. Drowsiness/Dry mouth/Dizziness was most documented adverse event affecting 8.60% of study population.

Kardinal et al.[13] conducted a placebo-controlled, randomised, double-blind clinical trial for Cyprohepatadine, 8 mg orally three times a day to test the efficacy and safety. The study was conducted on 295 patients in which 145 patients were treated with Cyproheptadine and 150 were treated with Placebo. The average weight gain for Cyproheptadine was and placebo was found out to be 0.9 ponds and 0.5 pounds respectively. 55% patient's appetite was improved with Cyproheptadine. The effect of study medication on food intake was found out to be more in patients with Cyproheptadine (53%) as compared to placebo (36%). Patients assigned to Cyproheptadine lost an average weight of 4.5 pounds per month compared to 4.9 pounds per month for patients assigned to placebo (P =0.72).

Epifanio M et al.[14] conducted a double-blind, placebo-controlled trial at two centres to test the efficacy of cyproheptadine to induce weight gain in patients of cystic fibrosis with the age between 5 to 18 years. The patient were randomised into two groups to receive either cyproheptadine 4 mg thrice a day or placebo thrice a day for study period of 84 days (12 weeks). The average weight gain in patients who had taken placebo was 0.67 kg whereas 1.16 kg who have taken cyproheptadine (p=0.03). BMI was decreased by 0.07kg/m2 in the placebo group whereas the BMI increase by 0.46kg/m2 in the cyproheptadine group (p=0.003). The BMI score decrease by 0.19 in the placebo group and increase by 0.2 in the cyproheptadine group (p=0.003). So Epifanio M et al had concluded that cyproheptadine ids efficient in patients of cystic for the significant weight gain.

Marisa Couluris, D.O. et al.[15] conducted a clinical study to test the efficacy of cyproheptadine in children suffering with concern associated cachexia to prevent further weight loss. The study was conducted for four weeks on 66 patients. Out of 66 patients 50 demonstrated a response to cyproheptadine and their average weight gain was found out to be 2.6 kg whereas other receive megestrol acetate and their average weight gain was found out to be 2.5 kg. So therefore it was concluded that cyproheptadine is a safe and effective way to promote weight gain in children with cancer/treatment- related cachexia.

Madani S. et al.[16] conducted a study to evaluate clinical improvement, safety and efficacy with use of cyproheptadine in functional gastrointestinal disorders (FGIDs) in children. Among 151 patients, 58% were girls, ages 1 to 18 years, 72.8% (110) reported complete symptom improvement; 27.2% (41) reported partial or no improvement. A total of 68% (102/151) were reported with no adverse effects. Adverse effects shown were as weight gain in 15/151 (10%) and sleepiness in (13%) 19/151.Patients in smaller numbers had significant improvement in 10/10 (100%) IBS, 13/18 (72%) abdominal migraine and 6/8 (75%) cyclic vomiting syndrome. A 1 unit increase in body mass index (BMI) with cyproheptadine use increased the odds of clinical improvement by P¼=0.01.Hence Cyproheptadine in a relatively larger number of patients was found to be effective in improving symptoms of functional abdominal pain, functional dyspepsia.

CONCLUSION

The combination of Cyproheptadine and Tricholine Citrate was found to be efficacious as well as safe to increase the appetite in infants and children suffering from undernutrition or anorexia.

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Disclosure

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