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A Retrospective Study of Body Weight Changes in Patients Receiving Cyproheptadine in A Hospital-Based Outpatient Setting in Thailand

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ABSTRACT

The use of cyproheptadine as an appetite stimulant is off label in Thailand which depends on professional discretion. This study aimed to determine the potential of weight gain effect of cyproheptadine in Thai patients. A retrospective study was conducted in adult patients receiving cyproheptadine as an off-labelled use for appetite stimulant, having body weight records at 2 times consecutively during 12-month period at the medical outpatient department, the Police General Hospital, Thailand. Of 125 participants, 69.6% were females and the mean age was 78.38 (SD ± 11.68) years. Hypertension, dyslipidemia and diabetes mellitus were the most common underlying conditions. The mean body mass index (BMI) at 1st visit was 21.16 (SD ± 3.64) kg/m^2. The mean body weight at 1st and 2nd visit were 52.46 (SD ± 11.11) kg, and 52.61 (SD ± 10.98) kg, respectively. Overall, there was no significant change in body weight between two visits. In underweight patients (BMI < 18.5 kg/m^2), the mean BMI decreased significantly in the 2nd visit compared to 1st visit ($p = 0.044$). At the 2nd visit, older age and high-density lipoprotein cholesterol levels were negatively associated with body weight ($p < 0.05$). The polypharmacy (odds ratio (OR), 0.778; 95% confidence interval (CI), 0.616 – 0.982), the presence of hypertension (OR, 0.022; 95%. CI, 0.001 – 0.390) and low-density lipoprotein cholesterol levels (OR, 0.969; 95% CI, 0.942 – 0.996) were also negatively associated with abnormal BMI. In conclusion, cyproheptadine might not improve body weight at 4 mg per day. The factors associated with lower body weight in this study may be helpful in further research.

Keywords: Appetite, Body weight, Cyproheptadine, Outpatients, Weight change

INTRODUCTION

Nutritional requirements are diverse in patients with various clinical conditions including chronic and metabolic diseases. Patients with anorexia due to underlying diseases or drug treatments may experience loss of appetite and body weight. There were medicatons used to stimulate appetite; one of the common conventional appetite stimulants was cyproheptadine (Roeland *et al.*, 2020). Cyproheptadine is a first-generation antihistamine which has both antihistamine and anti-serotonin properties. Activation of serotonin (5-HT) receptor plays an important role in the inhibition of food intake (Blundell, 1984). Cyproheptadine appears to stimulate appetite by interfering serotonin effect (5-HT antagonism) on a satiety control area located in the hypothalamus (Scholar, 2007). Inhibition of serotonin makes the subject necessary for more energy, which increases appetite (Hall, 2011; Voigt & Fink, 2015). According to the literatures, cyproheptadine was a well-tolerated appetite stimulant with favorable side effects in both normal and underweight populations (Harrison *et al.*, 2019). It was suggested that the use of cyproheptadine could be a short-term strategy for patients who require nutritional support (Epifanio *et al.*, 2012).

The effect of cyproheptadine was firstly recognized in the clinical study on asthmatic

children where participants showed a significant increase in appetite and body weight (Lavenstein *et al.*, 1962). Later on, the weight enhancing effect of cyproheptadine was noted in patients with various clinical conditions (Epifanio *et al.*, 2012; Najib *et al.*, 2014; Summerbell *et al.*, 1992). Over the past century, it was prone to be effective stimulant for appetite and weight gain in underweight population (Noble, 1969). In the study group, both appetite and body weight increased significantly after receiving cyproheptadine at day 14, 28, 42 and 56. Likewise, the weigh gaining property of cyproheptadine was noted in human immunodeficiency virus (HIV) infected people with wasting (Summerbell *et al.*, 1992). However, the inconsistencies on the weigh gaining effect of cyproheptadine were noted in the previous literature reporting that cyproheptadine was not effective in increasing body weight of patients with anorexia (Vigersky, 1977).

There are still discrepancies among studies on weight enhancing effect of this "old" drug in different populations. The effects of this medication on weight changes in adults and elderly are also unclear. The National List of Essential Medications of Thailand currently specify the indications of cyproheptadine as drugs used in the prophylaxis of migraine and the management of acute serotonin syndrome; however, the use of cyproheptadine as an appetite stimulant is off label which depends on professional discretion. Over the past years, studies on the outcomes of cyproheptadine use in Asian population; including Thailand, are limited. Thus, this study aimed to determine whether cyproheptadine use influenced on body weight over a year, and potential associated factors of body weight in Thai patients.

MATERIAL AND METHODS

Study design and participants

This retrospective longitudinal study collected data from the clinical and laboratory records of the adult patients receiving cyproheptadine at the outpatient medical department, the Police General Hospital, Bangkok, Thailand from January 2019 to December 2021. The Police General Hospital is currently a fully-fledged state-run tertiary-care hospital with approximately 900 beds. The study was approved by the Institutional Review Board of the Police General Hospital (the number of approval was 133/2564) in accordance with the Declaration of Helsinki ethical principles for medical research involving human subjects. A requirement for informed consent was exempted due to the retrospective nature of the study and anonymous reported data.

Inclusion and exclusion criteria

The study included Thai patients receiving cyproheptadine as an off-labelled use for appetite stimulant, aged 18 years and above, whose body weights were recorded at 2 time periods within a year follow-up at the medical outpatients. Patients with incomplete body weight records, pregnancy, or lactating women were excluded. Patients who were diagnosed with migraine or acute serotonin syndrome were also excluded. We calculated sample size using the G*Power (v 3.1.9.4) software. We selected the statistical test as the means: the difference between two dependent means (matched pairs) with the effect size 0.25, alpha criterion 0.05, and the desired power as 0.8. After assumed 15% missing data was applied, the estimated required sample size was equal to 120 participants.

Data collection

Body weight data of the participants were carefully collected at two-time periods: 1st visit and 2nd visit between 2019 and 2021. In addition to body weights, height (for BMI calculation), age, gender, reimbursement status and clinical conditions including underlying medical conditions at the 1st visit were collected through the review of patients' medical records. Dosage regimen of cyproheptadine, and the number of concurrent medications were also recorded to assess the polypharmacy status (5 or more medications) (Junius-Walker *et al.*, 2007).

Laboratory data including fasting blood glucose, hemoglobin A1C, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN) and serum creatinine (sCr) were collected to analyze the effect of cyproheptadine on their changes at hospital visits.

According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline (Cederholm *et al.*, 2017), BMI < 18.5 kg/m^2 was classified as malnutrition. Participants in this study were classified as: underweight (< 18.5 kg/m^2), normal weight (18.5 - 23 kg/m^2) and overweight (> 23 kg/m^2) for Asian population.

Table I. Characteristics of participants included in the study.

Characteristics (N = 125)	N (%) / mean ± SD			P-value[a]
	Total	Male (N = 38)	Female (N = 87)	
Age (years)	78.38±11.68	74.92±13.90	79.88±10.29	0.028
Aged ≥ 60 years	115 (92)	32 (84.2)	83 (95.4)	0.043
Aged < 60 years	10 (8)	6 (15.8)	4 (4.6)	
Height (cm)	157.2±9.54	168.10±6.57	152.44±6.10	<0.001
Body weight (kg)	52.61±10.99	59.29±11.49	49.68±9.42	<0.001
BMI (kg/m^2)	21.24±3.64	20.92±3.45	21.37±3.73	0.523
Underweight (BMI < 18.5 kg/m^2)	29 (23.2)	9 (23.7)	20 (23)	0.551
Overweight (BMI > 23 kg/m^2)	37 (29.6)	7 (18.4)	30 (43.5)	0.053
Duration between 2-time points of weight record (months)	6.49±2.39	6.26±2.27	6.58±2.45	0.491
No. of medications	9.27±4.00	9.39±4.40	9.22±3.84	0.086
Polypharmacy at 1st visit	107 (85.6)	29 (76.3)	78 (89.7)	0.051
Polypharmacy at 2nd visit	109 (87.2)	32 (84.2)	77 (88.5)	0.508
No. of complications	1.93±0.89	1.78±0.84	1.98±0.91	0.252
Hypertension	76 (60.8)	16 (42.1)	60 (69.0)	0.005
Dyslipidemia	56 (44.8)	17 (44.7)	39 (44.8)	0.993
Diabetes mellitus	33 (26.4)	8 (21.1)	25 (28.7)	0.252
Cardiovascular disease	25 (20)	9 (23.7)	16 (18.4)	0.326
Reimbursement status				0.127
Self-paid	16 (12.8)	3 (7.9)	13 (15)	
Supported by the Comptroller General's Department	75 (60)	28 (73.7)	47 (54)	
Social security	12 (9.6)	4 (10.5)	8 (9.2)	
Universal health insurance	22 (17.6)	3 (7.9)	19 (21.8)	

Note. N, number; %, percentage; SD, standard deviation; BMI, body mass index; [a]Independent t-test or Chi-square test comparing between gender.

Table II. Overall mean difference in body weight and body mass index (N=125).

Characteristics	Mean	SD	Mean difference	P-value[a]
Body weight (kg) at 2nd visit	52.61	10.98	0.15	0.684
Body weight (kg) at 1st visit	52.46	11.11		
BMI (kg/m^2) at 2nd visit	21.24	3.64	0.08	0.595
BMI (kg/m^2) at 1st visit	21.16	3.64		

Note. SD, standard deviation; BMI, body mass index; [a]Paired t-test comparing the means between hospital visits.

Statistical analysis

Data were analyzed by IBM SPSS (version 22.0, Chicago, IL, USA). Demographic characteristics were presented as descriptive statistics. Categorical data were presented as numbers and percentages. Continuous data were presented as mean and standard deviation (SD). Paired t-test and independent t-test were used to analyze the mean differences and between-group differences, respectively. Multiple logistic regression and multiple linear regression were used to evaluate the potential association of body weight with factors such as age, gender, medications. P-value of < 0.05 was set up as a significance.

RESULTS AND DISCUSSION

A total of 125 patients were included. Eighty-seven participants were female, and mean age of the participants was 78.38 (SD ± 11.68) years. Majority (92%) were aged ≥ 60 years. The mean BMI at 1st visit was 21.16 (SD ± 3.64) kg/m^2 (Table I). The common medical conditions of the participants were hypertension, dyslipidemia, and diabetes mellitus. The off-labelled indication of cyproheptadine was appetite stimulant for anticipated weight improvement. In this population, the mean number of medications use including cyproheptadine and other concurrent drugs was substantially high. Polypharmacy was found in 109 (87.2%) of the participants. The interval duration between the visits was 2 to 12 months with the mean as 6 months.

All participants in this study received cyproheptadine 4 mg per day: before bedtime or after dinner due to its sedative effect. The mean body weight of the participants were 52.46 (SD ± 11.11) kg and 52.61 (SD± 10.98) kg at 1st and 2nd visits, respectively. There were no statistical differences in body weights between the two visits (p = 0.684). Likewise, BMI showed no significant differences between the two hospital visits (p=0.595) (Table II). Among 84 participants who had the 6 to 12-month visit time interval, the mean body weight were 51.46 (SD ± 10.87) kg and 52.32 (SD± 10.86) kg at 1st and 2nd visits, respectively. Again, no significant differences inbody weights and BMI between the two hospital visits. By dividing participants into three groups: underweight (< 18.5 kg/m^2), normal weight (18.5 - 23 kg/m^2) and overweight (> 23 kg/m^2), the mean differences in body weight between hospital visits were analyzed. The mean BMI in the underweight participants significantly declined over time showing a mean difference of -1.47. However, no significant differences in body weight were found between two visits in normal and overweight patients. Compared to the 1st visit, the prescribed medications in overweight patients became higher at the 2nd visit (Table III). By stratifying age into two groups: aged < 60 years and ≥ 60 years, the mean values were compared between hospital visits. However, mean body weight changes were negligible in both group (Table IV).

The changes in laboratory parameters after the administration of cyproheptadine in our patients are also analyzed. Although there were no significant changes among the hospital visits, most laboratory values were lower at 2nd visit compared to 1st visit. Using the Pearson's correlation analysis, we observed some factors correlated with body weight variation in this population. Factors including age, HDL and serum creatinine levels had clinically significant negative correlation with the body weight (data not shown). Multiple linear regression showed the associated factors of body weight variation in patients with different clinical underlying conditions. The increased HDL levels and older age were significantly associated with low body weight (Table V). By adjusting age and gender, the potential factors in association with normal body weight and abnormal body weight groups were analyzed by binary logistic regression. It was observed that participants with normal body weight had low number of prescribed medications, low prevalence of hypertension and low LDL levels (Table VI).

This study did not find the clinically significant weight change in medical outpatients after the administration of 4 mg cyproheptadine during two hospital visits with the mean interval of 6 months. The common underlying medical conditions of the patients were hypertension, hyperlipidemia, and diabetes mellitus. Majority of participants were elderly (aged ≥ 60 years) with polypharmacy in more than 80% of population. It is interesting to document that cyproheptadine appears to have no significant effect on the body weight in advance aged population. The finding was in accordance with the clinical trial of Kardinal *et al.*,(Kardinal *et a l.*, 1990) in which the mean age of the population was 65 years. The administration of 8 mg cyproheptadine three times a day did not show any significant enhancement in the body weight of cancer patients with anorexia and/or cachexia despite its mild appetite stimulation. A recent systematic review on the use of cyproheptadine as an appetite stimulant by Harrison *et al.*,(Harrison *et al.*, 2019) included 46 studies in 21 different populations. The overall effect of cyproheptadine seemed to increase body weight; however, there were only minimal effects or no benefit in patients with cancers or HIV infection.

We analyzed mean body weight changes over period in patients with different medical conditions such as hypertension, diabetes mellitus, dyslipidemia and cardiovascular disease by subgroup analysis. There were no significant weight changes in our patients between 1st and 2nd visits. However, we found that older age and high HDL levels were correlated with lower body weight.

Table III. Mean differences in laboratory data classified by BMI criteria (N=125)

Characteristics	Underweight (N=29)				Normal weight (N=59)				Overweight (N=37)			
	1st visit	2nd visit	Mean difference	P-value[a]	1st visit	2nd visit	Mean difference	P-value[a]	1st visit	2nd visit	Mean difference	P-value[a]
Body weight (kg)	42.81	41.33	-1.47	0.061	51.58	52.10	0.52	0.218	61.41	62.23	0.82	0.314
BMI (kg/m^2)	17.20	16.61	-0.59	**0.044**	20.55	20.78	0.23	0.164	25.23	25.58	0.35	0.305
No. of medications	8.06	8.51	0.45	0.441	8.59	9.00	0.41	0.239	9.19	10.29	1.10	**0.020**
FBG (mg/dL)	96.14	99.43	3.29	0.400	120.24	106.18	-14.06	0.203	123.09	113.45	-9.64	0.065
HbA1C (%)	5.94	5.84	-0.1	0.156	6.17	5.74	-0.43	0.331	6.75	6.16	-0.59	0.076
Total cholesterol (mg/dL)	159.33	162.67	3.34	0.678	159.46	172.46	13.00	0.087	173.00	179.08	6.08	0.591
Triglyceride (mg/dL)	92.43	87.43	-5.00	0.691	111.53	99.07	-12.46	0.074	117.69	114.46	-3.23	0.763
HDL (mg/dL)	59.14	61.57	2.43	0.373	58.80	62.93	4.13	0.082	52.43	49.89	-2.54	0.481
LDL (mg/dL)	79.55	86.91	7.36	0.299	84.29	88.52	4.23	0.369	99.38	97.14	-2.24	0.796
AST (mg/dL)	23.58	26.67	3.09	0.320	34.56	33.75	-0.81	0.775	45.21	26.07	-19.14	0.216
ALT (mg/dL)	15.28	16.79	1.51	0.429	22.69	23.96	1.27	0.446	31.63	19.21	-12.42	0.099
BUN (mg/dL)	15.36	16.25	0.89	0.756	17.61	16.74	-0.87	0.424	16.49	18.18	1.69	0.419
sCr (mg/dL)	0.89	0.85	-0.04	0.373	1.19	1.16	-0.03	0.327	1.42	1.39	-0.03	0.678

Table IV. Mean differences in laboratory data classified by age.

Characteristics	Aged < 60 years (N=10)					Aged ≥ 60 years (N=115)				
	Number of participants	1st visit	2nd visit	Mean difference	P-value[a]	Number of participants	1st visit	2nd visit	Mean difference	P- value[a]
Body weight (kg)	10	58.03	59.56	1.50	0.093	115	51.97	52.00	0.03	0.943
BMI (kg/m^2)	10	21.34	21.92	0.58	0.101	115	21.14	21.17	0.03	0.828
No. of medications	10	6.90	7.70	0.80	0.290	115	8.80	9.41	0.61	**0.022**
FBG (mg/dL)	3	179.00	123.33	-55.67	0.467	66	113.41	106.39	-7.02	0.171
HbA1C (%)	1	12.10	6.30	-	-	32	6.12	5.88	-0.24	0.126
Total cholesterol (mg/dL)	1	226.00	180.00	-	-	31	162.97	173.10	10.13	0.063
Triglyceride (mg/dL)	1	160.00	185.00	-	-	34	108.53	100.03	-8.50	0.118
HDL (mg/dL)	1	78.00	49.00	-	-	35	55.77	57.84	2.07	0.196
LDL (mg/dL)	1	154.00	108.00	-	-	50	87.58	91.05	3.47	0.376
AST (mg/dL)	6	28.50	28.83	0.33	0.945	36	36.05	29.22	-6.83	0.262
ALT (mg/dL)	7	30.71	28.43	-2.28	0.692	49	22.89	19.43	-3.46	0.246
BUN (mg/dL)	6	12.42	12.95	0.53	0.796	56	17.41	17.58	0.17	0.866
sCr (mg/dL)	9	0.80	0.84	0.04	0.228	85	1.23	1.19	-0.04	0.150

Note. BMI, body mass index; FBG, fasting blood glucose; HbA1C, hemoglobin A1C; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol. AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; sCr, serum creatinine; [a]Paired t-test

Table V. Factors associated with body weight by linear regression.

	Unstandardized coefficient		Standardized coefficient	t	P-value	95% confidence interval	
	B	Std. Error				Lower bound	Upper bound
Model 1							
Constant	63.150	5.381		11.736	0.000	52.337	73.963
HDL (mg/dL)	-0.186	0.091	-0.280	-2.039	0.047	-0.370	-0.003
Model 2							
Constant	88.543	12.680		6.983	0.000	63.049	114.037
HDL (mg/dL)	-0.242	0.092	-0.363	-2.642	0.011	-0.426	-0.058
Age (years)	-0.284	0.129	-0.302	-2.194	0.033	-0.544	-0.024

Note. B, beta coefficient; t, t-statistics; HDL, high-density lipoprotein cholesterol

Table VI. Association of variables with normal weight status (BMI 18.5 – 23 kg/m^2).

	B	S.E.	Wald statistics	Odds ratio	95% confidence interval	P-value[a]
Gender						
Female (Ref)						
Male	1.564	1.049	2.223	4.779	0.611– 37.364	0.136
Age (years)	0.048	0.048	1.014	1.049	0.956 – 1.152	0.314
No. of concurrent medications	-0.251	0.119	4.449	0.778	0.616 – 0.982	**0.035**
No. of complications	1.205	0.782	2.373	3.336	0.720 – 15.452	0.123
Hypertension	-3.836	1.476	6.751	0.022	0.001 – 0.390	**0.009**
Diabetes mellitus	1.167	1.105	1.116	3.212	0.368 – 28.011	0.291
Dyslipidemia	0.506	0.836	0.366	1.658	0.322 – 8.542	0.545
HDL (mg/dL)	0.052	0.027	3.776	1.053	1.000 – 1.110	0.052
LDL (mg/dL)	-0.032	0.014	4.934	0.969	0.942 – 0.996	**0.026**
sCr (mg/dL)	0.272	0.347	0.613	1.312	0.665 – 2.591	0.434
Constant	-3.475	4.614	0.567	0.031		0.451

Note. B, beta coefficient; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; sCr, serum creatinine; [a]Multiple logistic regression

Moreover, interestingly, patients with abnormal body weight seemed to have a high number of medications, hypertension and high LDL levels in this study.

In the previous clinical study on the effect of cyproheptadine, young adults received 4 mg cyproheptadine three times per day for a month. Compared to the placebo group, participants receiving the study drug significantly gained body weight (Silverstone & Schuyler, 1975). Of interest, the weight gaining effect of cyproheptadine was likely due to its stimulation of hunger which suggested the central serotonergic mechanism of drug. The recent double-blind, placebo-controlled randomized trial by Kim et al.,(Kim *et al.*, 2021) included healthy adults with poor appetite. The study reported that there were significant increases in body weight and BMI after the 8-week administration of 3 mg cyproheptadine. Our study, however, did not support the previous findings, perhaps due to variation in appetite status and underlying disease status.

There are some limitations in our study. A retrospective study limited the causal relation of cyproheptadine and body weight. The assessment of medication adherence was beyond our records. We were unable to record side effects from the medication, assessment of nutritional status, appetite measurement, lifestyle factors and socioeconomical factors. The use of cyproheptadine in older population should be aware of the possible side effects such as orthostatic hypotension, tremor, dry mouth, drowsiness, irregular heartbeat, or difficulty

urinating; however, limited data were recorded in the medical charts. There were also variations in underlying medical conditions which might influence our results. Moreover, due to the spread of corona virus and nationwide lock-down in the first pandemic period, the number of participants recruited for this study was limited in the medical records. The study did not collect first weight data of participants who had used cyproheptadine earlier than our study confined 1st visit. Thus, the use of medication over a long period may not effectively change the body weight. There was no control group to analyze the effects of cyproheptadine. Since the study was based on a previously recorded electronic database, there might have registry bias in retrieved data.

The results of this study might be influenced by several factors such as different medical conditions, physical activity, different types of diet and lifestyle behaviors of the participants. Of note, it is crucial to consider the drug interactions of cyproheptadine with other concurrent medications as most of our participants had polypharmacy. In this study, the majority of the participants were well-nourished, and we did not find any improvement in body weight in underweight patients as well. Overall, it could be assumed that cyproheptadine did not change the body weight of patients with normal nutritional status; possibly because the amount of food intake varies in relation to nutrient requirements or energy expenditure. Additionally, the nutritional counseling should be considered in certain malnourished individuals to achieve the clinical improvement.

CONCLUSION

The administration of 4 mg cyproheptadine did not result in significant weight gain in medical outpatients with various chronic diseases. Several factors such as age, HDL, LDL, concurrent medications, hypertension were necessary to note as they may potentially influence the body weight of participants receiving cyproheptadine. Over-prescription of cyproheptadine should be aware that it may not produce any beneficial effect in patients normal body weight. The information of this study will be useful for health care practitioners for considering medications to patients with various chronic diseases. Further prospective studies on the effect of cyproheptadine in malnourished patients with chronic diseases are highly warranted.

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