



Effect of Ketotifen and Cyproheptadine on Appetite and Weight Changes in Mice

Mahboob Nemati^{a,b,c,*}, Bohlool Habibi Asl^d, Kamran Sharifi^a

^aDepartment of Pharmacognosy and Food Sciences, Faculty of Pharmacy

^bFood Sciences and Nutraceuticals Laboratory, Drug Applied Research Center

^cNutritional Research Center

^dDepartment of Pharmacology, Faculty of Pharmacy

Tabriz University of Medical Sciences, Tabriz, Iran

Abstract

Ketotifen is a potent, safe and long acting antihistamine that is effective in treatment of asthma and its use is believed to causes weight gain and drowsiness. Cyproheptadine, an antihistamine, has anticholinergic and antiserotonergic effects, and causes increases of the appetite and weight gain. In this study the effects of different doses of ketotifen and/or cyproheptadine on the appetite and weight changes in mice is evaluated. Sixty four male mice were divided in 8 groups and received the following drug regimens for 45 days. Control group, normal saline (10 ml/kg, s.c.), three groups of cyproheptadine (5, 10, 20 mg/kg, s.c.), three groups of ketotifen (8, 16, 32 mg/kg, s.c.), and one group cyproheptadine (5 mg/kg, s.c.) combined with ketotifen (8 mg/kg, s.c.). Weight changes caused by above drug regimens were recorded every 2 days and average of food intake was recorded every day for 45 days. The results showed that the high dose of ketotifen (32 mg/kg, s.c.) increased weight, significantly, but its low dose (8 mg/kg, s.c.) decreased weight significantly. Cyproheptadine (5 mg/kg, s.c.) caused significant increase in weight gain and stimulated appetite, but its high dose of (20 mg/kg, s.c.), decreased the appetite and weight. Co-administration of cyproheptadine and ketotifen decreased the appetite, significantly. The results showed that different doses of cyproheptadine and ketotifen have different effects on the appetite and weight gain in mice, and possibly different mechanisms of action.

Keywords: Appetite; Cyproheptadine; Ketotifen; Weight change.

Received: February 14, 2006; **Accepted:** April 1, 2006

1. Introduction

Obesity and the resulted adverse effects

such as cardiovascular diseases and increased rate of morbidity and mortality are problems resulting from changes in life habits and industrialization, however, weight variations as obesity or leanness sometimes are signs of a serious disease and need serious attention,

*Corresponding author: Mahboob Nemati, Department of Pharmacognosy and Food Sciences, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.
Tel (+98)411-3392580, Fax (+98)411-3344798
E-mail address: nematim@tbzmed.ac.ir

too. Wasting can result from certain cancers such as pancreas and other gastrointestinal malignancies [1, 2]. Many factors in human body are involved in weight regulation. Neuropeptide Y, serotonin, glucagon like peptide 1, tumor necrosing factor- α (TNF- α) and some hormones like insulin and leptin are some of these regulators [3, 4]. TNF- α induces weight loss by increasing catabolism of adipose and muscle cells, loss of appetite and inhibition of synthesis of lipoprotein lipase. Lipoprotein lipase is essential to release of fatty acids from lipoproteins circulating in blood flow to be used by tissues [5].

Some medicines such as histamine receptor (H_1) blockers can affect weight regulation mechanisms and cause weight changes. Cyproheptadine is one of the most administered drugs for appetite increase and weight gain in people who suffer from strong weight loss [6]. Recently, cyproheptadine has been accepted as an appetite stimulator in catexia [7, 8].

Ketotifen is a potent, safe and long acting antihistamine that is effective in treatment of asthma and taking this drug causes weight gain and drowsiness in human beings [9]. Some studies suggest that ketotifen inhibits the release of TNF- α from mono nuclear cells of peripheral blood stream. Administration of ktotifen to patients with acquired immune deficiency syndrome (AIDS) who have elevated levels of TNF- α causes improvement of their disease, reduction (14%) of TNF- α level, and weight gain about 11-12 Lb in less than 4 weeks [10, 11].

Antihistamines (H_1 -blockers) are administered for their antihistaminic effects to control allergic reactions, but in some cases their side effects such as appetite increase and weight gain are the aim of their administration. In the present study, we investigated the effect of different doses of ketotifen on the appetite and weight changes in mice and compared it with the effect of cyproheptadine, a well recognized drug with

similar effects.

2. Materials and methods

2.1. Drugs

Pure powders of ketotifen and cyproheptadine were obtained from Hakim and Darupaksh Pharmaceutical Companies, Tehran, Iran, respectively. The powders were dissolved in sodium chloride solution and the determined doses of them were injected subcutaneously to the mice.

2.2 Animals and treatment

Male mice (body weight 20-23 g) were used for this study. They were allowed access to water and food ad libitum. The animals were divided into eight groups of eight mice each and received the following treatments for 45 days. Group I was control group and received normal saline (s.c.) during study. Three groups (II-IV) received three different doses of ketotifen (8, 16 and 32 mg/kg, s.c.). Three other groups (V-VII) treated with three doses of cyproheptadine (5, 10 and 20 mg/kg, s.c.). The eighth group (VIII) received ketotifen (8 mg/kg) and cyproheptidine (5 mg/kg) simultaneously by one s.c. injection. Diet intake was measured daily and body weight (BW) was recorded every 2 days.

2.3. Statistical analysis

The data were expressed as the mean \pm SE of eight mice in each group and statistical comparisons were made with the Student's t-test, and $p < 0.05$ were considered significant.

3. Results

3.1. Effect of different doses of cyproheptadine on the weight and appetite of mice

Cyproheptadine at the lowest dose used (5 mg/kg) caused a weight gain, but higher doses did not. The 10 mg/kg dose did not cause a significant weight gain, and the 20 mg/kg dose even caused a weight loss compared to the control group ($p < 0.01$) (Figure 1). Effect of cyproheptadine on appetite of mice is

represented as the amount of consumed diet in Figure 2. The results show that the low dose of cyproheptadine (5 mg/kg) caused a significant increase in food intake in mice ($p<.001$), but the 10 mg/kg dose of it did not significantly affect the food intake, and the 20 mg/kg dose resulted in a significant decrease in food intake ($p<0.05$).

3.2. Effect of different doses of ketotifen on weight and appetite of mice

Ketotifen caused a significant weight gain in mice and this increase in weight was dose dependent (Figure 3). Day to day comparison of the weight change in mice during 45 days of administration shows that injection of ketotifen with a dose of 16 mg/kg does not significantly change the weight of mice compared to the control group, but with a dose of 32 mg/kg significantly increased weight, especially during days 20 to 45 of the experiment (Figure 3). As shown in Figure 4, only the highest dose of ketotifen used (32 mg/kg) caused a significant increase in food intake ($p<0.01$).

3.3. Effect of co-administration of ketotifen and cyproheptadine on weight and appetite of mice

Results presented in Figure 5 suggest that co-administration (s.c.) of ketotifen (8 mg/kg)

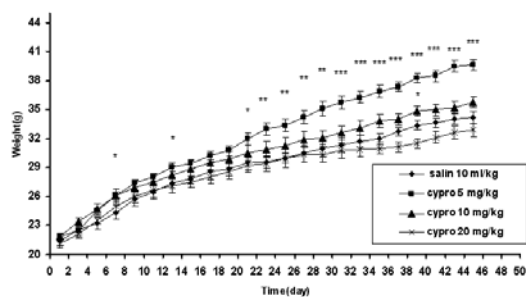


Figure 1. Weight change caused by different doses of cyproheptadine administered (s.c.) in mice for 45 days. Values represent the Mean \pm SE of 8 animals per group. Significantly different from the control group; * $p<0.05$, ** $p<0.01$, *** $p<0.005$.

and cyproheptadine (5 mg/kg) causes less weight gain than either of the two administered alone ($p<0.01$). The mean of food intake during 45 days of study in mice received co-administration of ketotifen and cyproheptadine was significantly higher than in mice received ketotifen alone ($p<0.01$) and lower than in mice received cyproheptadine alone ($p<0.01$) in similar doses (Figure 6).

4. Discussion

Ketotifen is a safe antihistamine administered extensively to the patients, however, appetite stimulation and weight gain are its common side effects in human [12, 13].

Ketotifen inhibits release of TNF- α from mononuclear cells in blood [11]. TNF- α causes weight loss through increasing catabolism of fat and muscular cells. It is believed that anorexia created by TNF- α is the main cause of weight loss. Also, TNF- α inhibits the synthesis of lipoprotein lipase [14].

Cellular infection associated by HIV causes secretion of many cytokines that create different signs of AIDS. TNF- α is one of the most important cytokines which cause spreading of viruses and contamination of T-

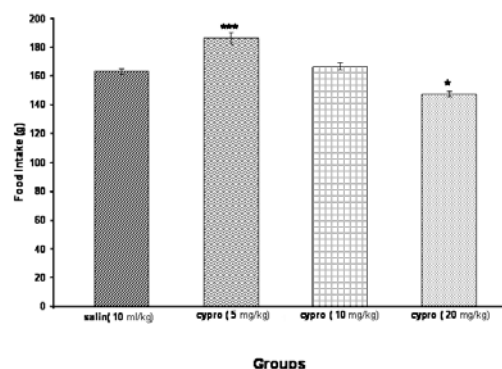


Figure 2. Changes in food intake caused by different doses of cyproheptadine administered (s.c.) in mice for 45 days. Values represent the Mean \pm SE of 8 animals for per group. Significantly different from the control group; * $p<0.05$, *** $p<0.005$.

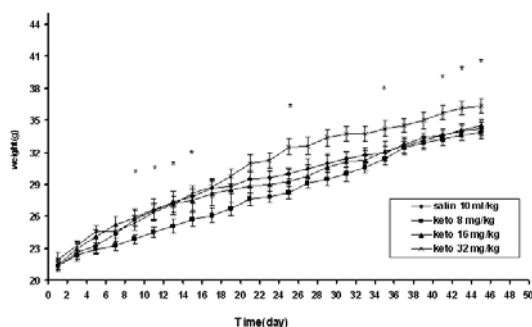


Figure 3. Weight change caused by different doses of ketotifen administered (s.c.) in mice for 45 days. Values represent the Mean±SE of 8 animals per group. Significantly different from the control group; * $p < 0.05$.

cells and lymphatic glands. It seems that TNF- α is in correlation with wasting acquired in AIDS [11]. Inhibition of release of TNF- α from mononuclear cells in blood by ketotifen probably helps in treating the malnutrition resulted from HIV.

As shown in some studies, administration of ketotifen to patients with AIDS who had higher levels of TNF- α resulted in improvement of the disease process, 14% reduction in TNF- α levels and 11-12 pound weight gain during less than 4 weeks [11, 15]. Ketotifen also has been reported to cause a significant weight gain in children with asthma during treatment of their disease [16]. In the present study, however, injection of different doses of ketotifen showed different results in mice, and the high doses of ketotifen caused a significant weight gain, compared to the control group, while the low doses resulted in a significant weight loss. These results suggest that different doses of ketotifen may act through different mechanisms and may show different results in different patients. However, mechanisms may be different in human and mice, as well.

Cyproheptadine is an antihistamine with strong anticholinergic and antiserotonergic effects [17, 18]. It has been used for the treatment of anorexia and weight loss associated with cystic fibrosis and has shown

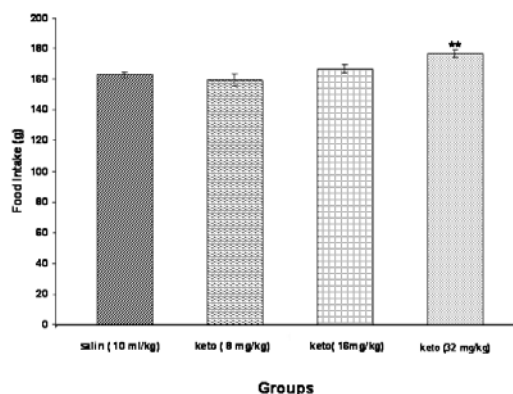


Figure 4. Changes in food intake caused by different doses of ketotifen administered (s.c.) in mice for 45 days. Values represent the Mean±SE of 8 animals per group. Significantly different from the control group; ** $p < 0.05$.

stimulation of appetite [19]. Also cyproheptadine is used successfully in treatment of serotonin syndrome and caused an increase in appetite and weight gain [6].

The possible reasons for appetite stimulation and weight gain by cyproheptadine are: 1) inhibition of 5-HT_{2A} receptors, 2) reduction in gastrointestinal tract motility and subsequently increasing transit time of food, due to anticholinergic effects of the drug, and 3) drowsiness and hypoactivity and storage of excess calories [20].

The results obtained by different doses of cyproheptadine (5, 10 and 15 mg/kg) in mice in the present study showed a significant weight gain by low dose while high dose of cyproheptadine caused a significant weight loss. The weight gain caused by low dose of cyproheptadine shows that this drug increases the appetite and feeding at low doses. Medium dose of cyproheptadine used in this study (10 mg/kg) resulted in weight gain without a significant increase in feeding. The probable reason for this result is anticholinergic, tranquilizer and sedative effects of cyproheptadine. On the other word, at this dose, drug does not stimulate appetite strongly, but reduces GI motility and animal activity and increases transit time of food. High dose of cyproheptadine (20 mg/kg) caused weight loss without a significant reduction in feeding in animals. The different results by variable

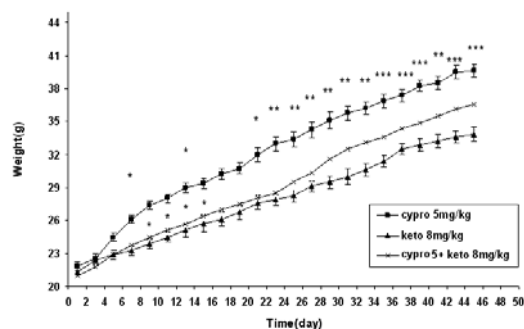


Figure 5. Weight change caused by cyproheptadine, ketotifen and their co-administration (s.c.) in mice for 45 days. Values represent the Mean \pm SE of 8 animals per group. Significantly different from co-administration group; * p <0.05, ** p <0.01, *** p <0.005.

doses of cyproheptadine suggest different mechanisms of action with different doses.

Administration of ketotifen (8 mg/kg) and cyproheptadine (5 mg/kg) simultaneously in one injection compromises the effects of these drugs when administered separately. That is, in this position the weight gain is greater than ketotifen and less than cyproheptadine, when given alone. This is to say that in long term use, weight gain by cyproheptadine has been overcome to weight loss caused by ketotifen. Finally, it can be concluded from this study that probably appetite stimulating effects of ketotifen appears to be dose dependent and appears with delay. Probably administration of these two drugs at the same time can help to overcome the appetite stimulating effects of cyproheptadine where this effect is unpleasant. Of course, more studies are needed to confirm this result.

References

- [1] Pyeritz R. Metabolic Disease. In: Anderoli TH, (editor). *Cecil essentials medicine*, 6th edition. Philadelphia: Saunders Company, 2004; pp. 549-53.
- [2] Prelipcean MS, O'Neil PJ, Bell DS. Hyperinsulinemic hypoglycemia precipitated by weight loss. *South Med J* 2005; 98: 726-8.
- [3] Crowley VE, Spiegelman BM. Obesity therapy: Altering the energy intake and expenditure balance sheet. *Nat Rev Drug Disc* 2002; 1: 276-81.
- [4] Flier JS, Maratos-Flier E. Obesity. In: Kasper

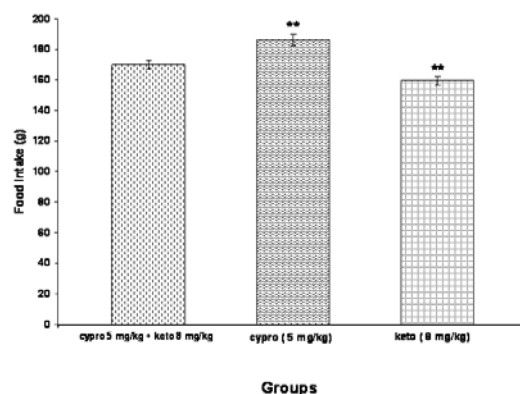


Figure 6. Changes in food intake caused by cyproheptadine, ketotifen and their co-administration (s.c.) in mice for 45 days. Values represent the Mean \pm SE of 8 animals per group. Significantly different from co-administration group; ** p <0.01.

DL et al, (editors). *Harrison's principles of internal medicine*. 16th ed. New York McGraw-Hill, 2005; pp. 422-9.

- [5] Guyton AC, Hall JF. *Medical physiology*, 10th ed. Philadelphia: Saunders Company, 2000; pp. 755-7.
- [6] McDaniel WW. Serotonin syndrome: Early management with cyproheptadine. *Ann Pharmacother* 2001; 35: 870-3.
- [7] Herfindal ET, Gourley DR *Textbook of therapeutics drug and disease management*, 7th ed. New York: Lippincott Williams and Wilkins, 2000; pp. 1277-80.
- [8] Ferriols LF, Tordera BM. Wasting syndrome in cancer patients: Pathophysiology, manifestations and drug therapy. *Farm Hosp* 2003; 27: 308-16.
- [9] Schwartz G, Bassler D, Mitra A, Duchame FM, Forster J. Ketotifen alone or as additional medication for longterm control of asthma and wheeze in children. *Cochrane Database Syst Rev* 2004; CD001384.
- [10] Nevzorova VA, Prosekova EV, Gel'ster BI, Lukianov PA, Shestoskaia Iu V, Arzamastseva AI. Changes in biochemical inflammation markers in evaluation of the effectiveness of basic chemotherapy in bronchial asthma. *Ter Arkh* 2001; 73: 24-7.
- [11] Ockenga J, Rohde F, Suttman U, Herbarth L, Ballmaier M, Schedel I. Ketotifen in HIV infected patients: Effects on body weight and release of TNF- α . *Eur Clin Pharmacol* 1996; 50: 167-70.
- [12] Katzung BG. Histamine, serotonin and the ergot alkaloids. In: Katzung BG, (editor). *Basic and clinical pharmacology*, 9th ed. New York: McGraw Hill, 2004; pp. 259-68.
- [13] Martin UL, Romer D. The pharmacological

- properties of a new orally active antianaphylactic compound: Ketotifen a benzocycloheptatiophen. *Drug Res* 1993; 28: 770-82.
- [14] Kern PA, Sghizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB. The expression of tumor necrosis factor α in human adipose tissue, regulation by obesity, weight loss and relationship to lipoprotein lipase. *J Clin Invest* 1995; 95: 2111-5.
- [15] Grundfeld G, Feingold KR. Metabolic disturbances and wasting in the acquired immunodeficiency syndrome. *New Engl J Med* 1992; 327: 329-37.
- [16] Caps LP. Immunologic and therapeutic aspects of ketotifen. *Allergy* 1991; 11: 189-91.
- [17] Joel F. Lehrer cyproheptadine's antiserotonin effects are responsible for its antimigraine activity headache. *J Head Face Pain* 2004; 44: 935.
- [18] Xin HB, Zhang BH. Scavenging effects of cyproheptadine on oxygen free radicals. *Yao Zue Xue Bao* 1993; 28: 161-5.
- [19] Homnick DN, Marks JH, Hare KL, Bonnema SK. Long-term trial of cyproheptadine as appetite stimulant in cystic fibrosis. *Pediatr Pulmol* 2005; 40: 251-6.
- [20] Daviss WB, Scott J. A chart review of cyproheptadine for stimulant-induced weight loss. *J Child Adolesc Psychopharmacol* 2004; 14: 65-73.