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Effects on Weight Reduction and Safety of Short-Term Phentermine Administration in Korean Obese People

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The phentermine, an appetite suppressant, has been widely applied in Korea since 2004. However, there have been relatively few reports about the efficacy and the safety of phentermine in Korea. The aim of this study is to verify the effect of phentermine on weight reduction and the safety in Korean patients. This randomized, double-blind, placebo-controlled study had been performed between February and July, 2005, in Seoul on 68 relatively healthy obese adults whose body mass index was 25 kg/m^2 or greater. They received phentermine-HCl 37.5 mg or placebo once daily with behavioral therapy for obesity. The primary endpoints were the changes of body weight and waist circumference from the baseline in the intention-to-treat population. Mean decrease of both body weight and waist circumference in phentermine-treated subjects were significantly greater than that of placebo group (weight: -6.7 ± 2.5 kg, $p < 0.001$; waist circumference: -6.2 ± 3.5 cm, $p < 0.001$). Significant number of subjects in phentermine group accomplished weight reduction of 5% or greater from the baseline and 10% or more ($p < 0.001$). There were no significant differences in systolic and diastolic blood pressure between the groups ($p = 0.122$ for systolic BP; $p = 0.219$ for diastolic BP). Dry mouth and insomnia were the only statistically significant adverse events that occurred more frequently in phentermine group. Most side effects of phentermine were mild to moderate in intensity. Short-term phentermine administration induced significant weight reduction and reduction of waist circumference without clinically problematic adverse events on relatively healthy Korean obese people.

Key Words: Obesity, phentermine, treatment outcome

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INTRODUCTION

Obesity, characterized by the excess accumulation of fat in body, is a chronic disease which is induced by many causes and needs long-term management. Obesity prevails all over the world. Moreover, obesity leads to the increase of several co-morbidities and all-cause mortality, and produces extreme economic losses for management of the obesity-related diseases.[1-4] The situation is same in Korea. The obese population [body mass index (BMI) $\geq$ 25 kg/m^2] rate of Korea has soared by 12.6%, from 23.3% in 1992 to 35.9% in 2000.[5]

Several methods have been tried in order to prevent and treat the increasing rate of obesity and its related disorders. One of such attempt is the application of appetite-suppressing drugs, which is used in many countries for reducing the energy intake. Among these drugs, phentermine (Ionamin®) is the drug which had been approved for short-term use as treatment of obesity by US FDA in 1959, and has been used steadily until present. Phentermine, classified as a β-phenethylamine drug, stimulates the secretion of noradrenalin in central nervous system, and noradrenalin, in turn, suppresses appetite by stimulating the β-adrenergic receptors.[6,7]

One of the reasons why phentermine is still prescribed in the era of appearance of several new anti-obesity drugs is that it has been administered safely without serious side effects for the past 40 years in US. However, because of the fact that phentermine is a sympathomimetic amine, we should keep in mind the possible side effects of the drug of this class in using phentermine.

Although the combination of fenfluramin and phentermine have been demonstrating a remarkable weight reduction effect, US FDA has removed fenfluramin from the market in September 1997, due to the successive reports about the serious side effects of valvular heart disease and primary pulmonary hypertension. There have been scarce reports about serious side effects for the single use of phentermine; however, there is a researcher who argued that 15 of 1000 phentermine administered patients might experience serious side effects.[4]

Another reason for wide distribution of phentermine prescription is its low economic burden for use in contrast to the new drugs. Comparing the cost-effectiveness of sibutramine and phentermine, in US, 103.8 $ per month for sibutramine 10 mg daily induces 4.45 kg weight reduction in 12 months. On the other hand, 39.59 $ per month for phentermine resin 30 mg daily induces 3.6 kg weight reduction in 6 months.[8] Such data regarding this cost-effectiveness might be the important criteria for the selection of which drug to use.

Phentermine has been introduced in Korea since 2004, and have been prescribed widely. The reports of the randomized controlled studies of phentermine had been published from 1975 to 1999, and there have been no further clinical trials on the phentermine usage since 1999.[9] Moreover, there are few reports about the effect and safety profile of phentermine in Korean. Therefore, we performed a double-blind placebo-controlled trial of phentermine in order to reaffirm the effect of phentermine on weight reduction and to verify the safety in Korean obese patients.

MATERIALS AND METHODS

Subjects

The study was conducted in men and women aged 20 years or older who were obese without any other documented health problems except hypertension and dyslipidemia. BMI of individual subjects were 25 kg/m^2 or higher, which is used as a cutoff point for obesity in the Asia-Pacific region.[10,11] The recruitment had been done between January and February, 2005, in Seoul, and the target number of the recruitment was 80.

With respect to hypertension, those subjects, whose systolic blood pressure was controlled under 140 mmHg and diastolic pressure was controlled under 90 mmHg by taking anti-hypertensive drugs except MAO inhibitors and whose prescription of anti-hypertensives had not been changed in the last two months, were included. For dyslipidemia, only the subjects who do not take any lipid lowering drug were included. Furthermore, subjects who had not been diagnosed as diabetes mellitus and whose fasting plasma glucose was less than 126 mg/dL without any diabetic care were included. In addition to the medication currently under the study, aspirin for the prevention of cerebrovascular disease and anti-hypertensives, except MAO inhibitors, were the only permitted medication during the study period.

Those subjects who have experienced weight change by more than 5% of baseline body weight in several months before the recruitment were excluded. Pregnant women and breast-feeding mothers were also excluded. Subjects taking any type of medication or receiving any kind of medical treatment during the previous 1 month prior to enrolment into the study were excluded, as well. Also excluded were the subjects who had any other active acute or chronic illnesses, except hypertension and dyslipidemia, subjects with the past history of malignancy or eating disorder in the last five years, subjects who had undergone a bariatric operation, and subjects who were regarded as high risk person by researchers' judgment. Also contraindicated were the subjects with a history of significant cardiovascular disease, liver disease, renal disease, drug abuse, psychiatric conditions, or cataract. Subjects with an abnormal hematological profile, creatinine levels and/or thyroid function test were excluded, too.

Methods

All subjects were briefed on the research procedures, and a written consent for participation was obtained from each subject. The Severance Hospital Institutional Review Board approved this

study.

The study had been performed between February and July, 2005. The study was a randomized, double-blind, placebo-controlled study with the initial screening period and the 14 weeks of treatment period including 2-week single-blind placebo run-in period.

During the screening period, subjects who were determined to their minds to participate in the study were measured for body weight and height, and were interviewed to confirm whether they were appropriate for the study participation. And then, they visited the researchers with an empty stomach for more accurate anthropometric measurement and screening laboratory test. According to the screening test results, final decision whether the applicant shall be included was made. Subjects who had been permitted for the study participation were randomized to treatment with phentermine HCl 37.5 mg once daily or placebo at Baseline. The ratio for phentermine and placebo was 1 : 1.

After 2-week placebo run-in period, all subjects were required to visit the hospital every 4 weeks to receive behavioral therapy for obesity based on the LEARN program developed by Brownell.[12] Under the program, subjects were counseled on how to modify their behavior and diet (based on a 1500 kcal/day allowance) and how to increase their overall exercise. Compliance with the guidelines was assessed at each of these visits. Any side effects that subjects had felt during medication were to be reported to the researchers at every visit.

Body weight, waist circumference, and blood pressure were measured at the outset and at every subsequent visit. Height was determined prior to commencing study medication. Height was measured to the nearest to 0.1 cm, and weight to the nearest to 0.1 kg with the subjects wearing light clothing and with an empty stomach. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Waist size was measured to the nearest to 0.5 cm by the same person following the instructions suggested by NIH.[13] Concentration of total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride in serum, fasting plasma glucose, high-sensitive CRP and uric acid levels were determined prior to commencing study medication and at endpoint.

The most valuable consideration in evaluating the efficacy is the change in body weight and waist circumference before and after the treatment in the intention-to-treat (ITT) population. Another weight-related criterion was the proportion of patients who lost 5% or more weight and 10% or more weight than the baseline weight. Changes in the level of cholesterol, triglycerides, HDL and LDL, high-sensitive CRP, uric acid and blood pressure were assessed as secondary variables.

In addition, for safety assessment, chest X-ray and ECG of each subject were taken, and thyroid stimulation hormone level was determined prior to commencing study medication, and standard laboratory tests (hematology, blood chemistry) were done prior to the commencement of study medication, and at endpoint.

Statistical analysis

All statistical analyses used statistical analysis system (SAS) for Window (version 8.01).

For the change of anthropometric measurement values and blood pressure, analysis was made in the ITT population using the last observation carried forward method. T-test was performed to test a statistical significance of mean differences in this analysis.

For the laboratory test results, analysis was done in the completer population. Because the sample size was too small for normal distribution, nonparametric methods were used. Wilcoxon's rank sum test was used to compare characteristics between phentermine group and placebo group. Wilcoxon's signed rank test was used to assess changes in variables in subjects after the treatment.

For the difference of the occurrence rate of adverse events between the two groups, only those symptoms which had occurred in at least more than 5% of subjects in any group among all abnormal reported symptoms were analyzed. However, adverse events complained in initial run-in period were removed from the analysis. All other complaints in ITT population were included in adverse event analysis. In addition, one subject who reported that she wishes to discontinue the study participation on the 4th week of medication

due to the side effect was included in adverse event analysis. For the analysis of side effects, chi-square test was used in principle. In the case of very small number of cell count, Fisher's exact test was used. All statistical tests were two-sided at the 5% significance level.

RESULTS

In total, 94 men and women have displayed intention to participate in the study. 15 of them were eliminated as they violated the initial instruction during screening period, and 11 were eliminated as they fell in with the exclusion criteria. Actual number of participation subjects was 68, and 13 men and 55 women were randomly assigned to double-blind treatment. 35 were randomized to phentermine group, and 33 to placebo group. 36 of 68 (52.9%) had completed the 14-week treatment course. 24 of 35 phentermine group (68.6%), and 12 of 33 (36.4%) had completed the study.

At baseline, there was no significant difference

Table 1. Baseline Characteristics

	Phentermine (n = 35)	Placebo (n = 33)
Age (yrs)*	34.74 ± 8.54	31.97 ± 8.05
Female (%)†	28 (80.0%)	27 (81.8%)
Weight (kg)*	76.42 ± 10.25	77.41 ± 10.40
Body mass index (kg/m^2)*	29.29 ± 3.05	29.42 ± 2.91
Waist (cm)*	92.79 ± 6.39	92.29 ± 8.01
Systolic BP (mmHg)*	125.37 ± 11.36	125.85 ± 13.26
Diastolic BP (mmHg)*	79.70 ± 9.17	82.45 ± 10.02
Smoking (current smokers)†	10 (28.6%)	6 (18.2%)

*Data are mean ± SD.
† Data are number (%).

Table 2. Changes in Body Weight, Waist Circumference, and Blood Pressure in Intention-To-Treat Population

		Phentermine (n = 28)	Placebo (n = 24)	*p* value
Weight (kg)	Baseline	77.7 ± 11.0	77.8 ± 11.5	
	14th week	70.5 ± 11.1	75.9 ± 12.1	
	Change	-7.2 ± 2.7	-1.9 ± 2.7	< 0.001*
Waist (cm)	Baseline	93.0 ± 6.4	91.9 ± 8.4	
	14th week	85.8 ± 7.6	89.9 ± 8.7	
	Change	-7.2 ± 3.1	-2.0 ± 4.0	< 0.001*
SBP (mmHg)	Baseline	126.3 ± 11.4	123.4 ± 13.7	
	14th week	124.3 ± 12.6	127.3 ± 10.0	
	Change	-2.0 ± 12.0	3.9 ± 11.8	0.081*
DBP (mmHg)	Baseline	79.6 ± 8.5	78.1 ± 8.1	
	14th week	83.3 ± 11.0	84.4 ± 9.7	
	Change	3.7 ± 9.3	6.3 ± 8.1	0.296*

*Student's t-test.

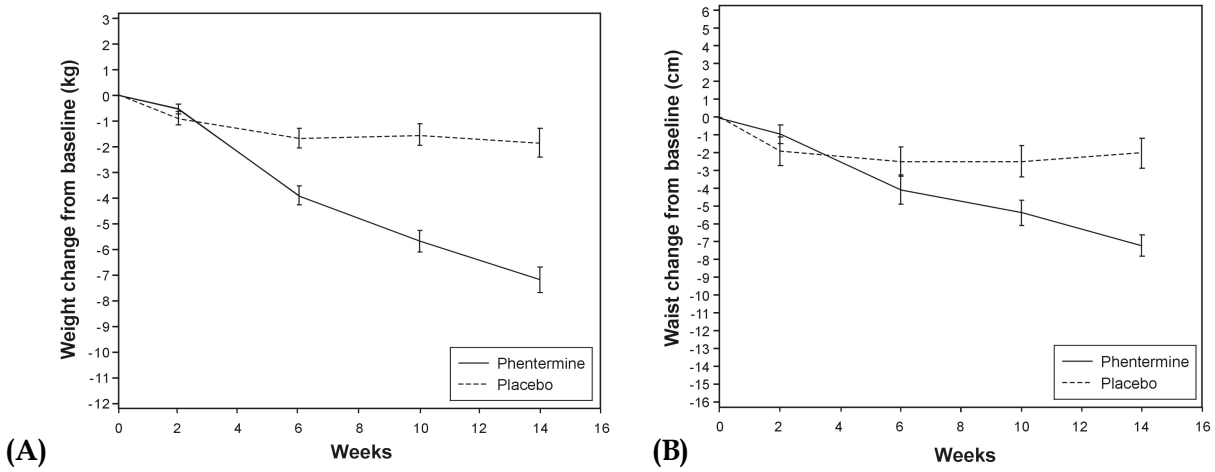

Fig. 1. Change from baseline in body weight (A) and waist circumference (B). Data are mean (SE) values for the full intention-to-treat population with the last observations carried forward. $p < 0.001$ for phentermine vs. placebo in body weight and waist circumference.

between the groups in terms of age, sex, weight, waist, blood pressure, and smoking rate (Table 1).

During the two-week run-in period, the mean decrease in weight was 0.58 (SD 1.18) kg, and that of BMI was 0.22 (SD 0.46) kg/m^2, with the associated reduction of 1.20 (SD 3.19) cm in waist circumferences across both groups.

In the analysis of the ITT population, there was a statistically significantly greater mean reduction in both body weight and waist circumference in phentermine- treated subjects to subjects in placebo group (p <0.001) (Fig. 1, Table 2). There was no significant difference in blood pressure change between the two groups after the treatment.

Table 3 shows the result in completers. In the analysis of completers, there was also a statistically significantly greater mean reduction in both body weight and waist circumference in phentermine-treated subjects to subjects in placebo group ($p < 0.001$) (Table 3). Including the weight reduction of the run-in period, placebo group shows about 2 - 3 kg of weight reduction and phentermine group shows about 7 kg of weight reduction (Table 2, 3). Run-in period subtracted analysis showed that phentermine HCl 37.5 mg was associated with significant weight reduction (-7.1 [SD 2.4] kg for completers and -6.7 [SD 2.5] kg for ITT) and shortening of waist circumference (-6.9 [SD 3.3] cm for completers and -6.2 [SD 3.5] cm for ITT; data not shown in table; all $p < 0.001$).

In the analysis of both ITT and completers, a significantly greater proportion of patients in the phentermine group achieved weight reduction of 5% or greater from the baseline compared with the placebo group, and it was same for the subjects who lost 10% or more weight from baseline (Fig. 2).

In completers, the changes of blood pressure, lipid levels, fasting plasma glucose, high-sensitive CRP and uric acid from baseline to endpoints are shown in Table 3. There was no statistically significant difference between the groups in these variables except total cholesterol. After the treatment, the mean change of total cholesterol in phentermine group was -7.8 (SD 28.5) mg/dL, compared to 10.7 (SD 20.2) mg/dL in placebo group. The changes from baseline to endpoints in each group were not significantly different from zero. However, the difference between groups was significant ($p = 0.048$, Table 3).

In addition, the change of non-HDL-cholesterol between groups was also significant (data not shown in table, $p = 0.023$ by Wilcoxon rank sum test). The mean change of non-HDL-cholesterol in phentermine group was -9.7 (SD 24.8) mg/dL, while the mean change in placebo group was 7.8 (SD 24.8) mg/dL. However, the changes in each group were not significant, same as total cholesterol.

The proportion of patients who had reported

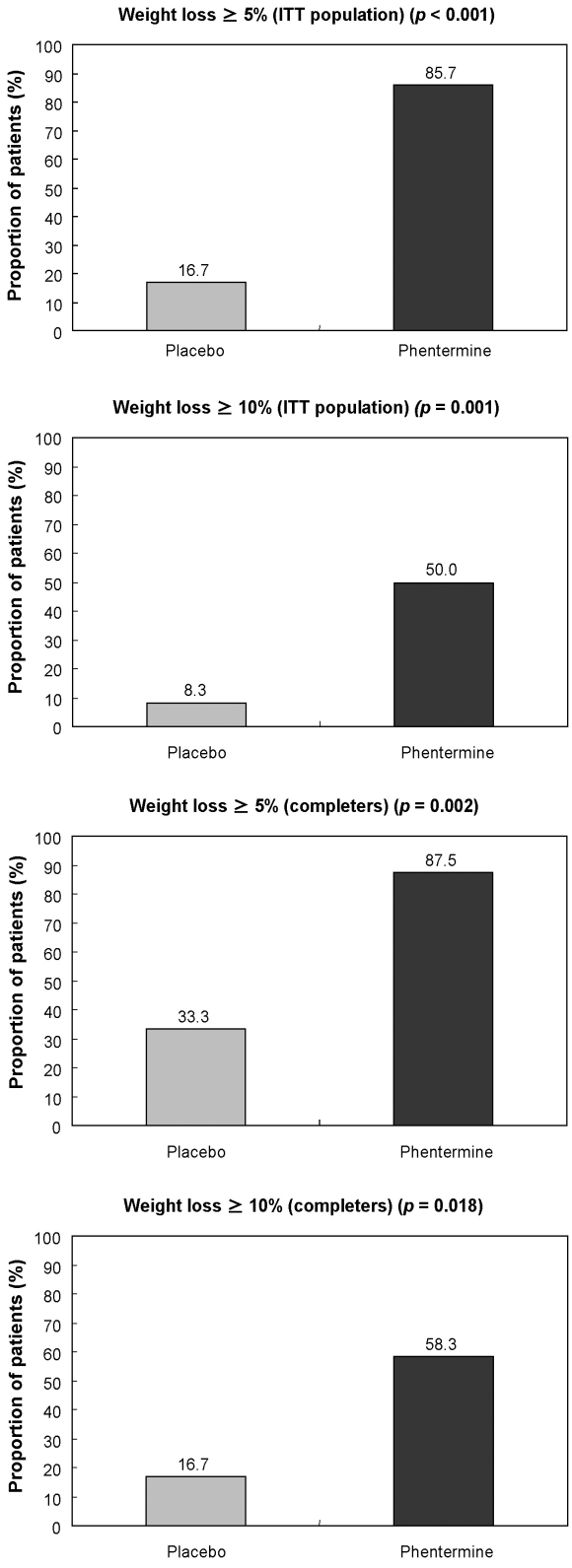

Fig. 2. Proportion of patients who lost ≥ 5% and ≥ 10% of baseline weight at 14th week. ITT, intention-to-treat.

any side effect was higher than that of patients who had not reported. Table 4 provides an analysis of all the adverse events occurred in at least 5% of patients in any group. The adverse events in Table 4 are listed in the frequency order of phentermine group. The number of subjects who had reported any adverse events in phentermine group was significantly larger than that in placebo group. However, the reported rate of adverse events in placebo group was even with 75% (18/24). Among all reported adverse events, dry mouth and insomnia are the events which occurred significantly more frequently in phentermine group. The occurrence rates of the other adverse events were not significantly different between the groups. For the most part, these events were mild to moderate in intensity, and only a few cases needed to reduce the dosage.

There were two subjects who withdrew due to adverse events. One of them withdrew because of dry mouth and foreign body sensation in throat. The other withdrew due to nausea and headache. Another two subjects complained severe adverse symptoms. One complained of severe headache, and the other, of severe headache and nausea. However, after reducing dosage by half, their symptoms had improved much or totally removed, and both of them had succeeded in completing the study. All four were included in phentermine group.

The discontinuation rate was significantly higher in placebo group ($p = 0.008$), and there was significant difference in the mean duration of study participation between two groups, 11.0 (SD 4.9) weeks for phentermine group vs. 8.2 (SD 5.3) weeks for placebo group ($p = 0.030$). In phentermine group, 11 of 35 (31.4%) withdrew after run-in period. Seven of them discontinued study participation without any clear reason, and two of them discontinued because of adverse events. One subject withdrew due to no weight losing effect of the drug. There was one subject who discontinued due to the difficulty in following the behavioral guideline. In placebo group, 21 of 33 (63.6%) withdrew after run-in period. 15 of them discontinued study participation without any clear reason. There was nobody who withdrew because of adverse events. Five was due to

Table 3. Changes in Anthropometric Values and Cardiovascular Risk Factors in Patients Who Completed 14 Weeks Follow-up

		Phentermine (n = 24)	Placebo (n = 12)	*p* value
Weight (kg)	Baseline	78.0 ± 11.5	77.4 ± 9.4	
	14th week	70.5 ± 11.8	74.3 ± 10.5	
	Change	-7.5 ± 2.7	-3.1 ± 3.2	< 0.001†
Waist (cm)	Baseline	93.1 ± 6.8	91.1 ± 8.0	
	14th week	85.8 ± 8.1	87.8 ± 7.3	
	Change	-7.3 ± 3.3	-3.3 ± 4.7	< 0.001†
SBP (mmHg)	Baseline	126.9 ± 12.1	129.0 ± 13.0	
	14th week	123.8 ± 13.5	131.2 ± 9.5	
	Change	-3.1 ± 12.5	2.2 ± 8.5	0.122*
DBP (mmHg)	Baseline	79.4 ± 7.8	80.5 ± 6.4	
	14th week	83.5 ± 11.7	87.8 ± 9.9	
	Change	4.1 ± 9.0	7.3 ± 8.1	0.219*
Fasting glucose (mg/dL)	Baseline	89.2 ± 9.9	92.3 ± 7.7	
	14th week	88.0 ± 9.8	87.1 ± 7.6	
	Change	-1.2 ± 10.1	-5.2 ± 5.7	0.163*
Total-C (mg/dL)	Baseline	183.0 ± 32.1	166.8 ± 18.9	
	14th week	175.2 ± 32.7	177.4 ± 25.9	
	Change	-7.8 ± 28.5	10.7 ± 20.2	0.048*
TG (mg/dL)	Baseline	120.3 ± 54.6	148.7 ± 96.5	
	14th week	89.3 ± 41.1	164.4 ± 293.0	
	Change	-31.0 ± 45.2	15.8 ± 239.1	0.907*
HDL-C (mg/dL)	Baseline	52.0 ± 14.2	52.9 ± 14.4	
	14th week	53.9 ± 12.5	55.8 ± 15.1	
	Change	1.9 ± 7.8	2.9 ± 8.8	0.840*
LDL-C (mg/dL)	Baseline	116.5 ± 31.9	92.8 ± 12.7	
	14th week	115.7 ± 30.4	107.2 ± 22.0	
	Change	-0.8 ± 28.5	14.4 ± 22.2	0.058*
hsCRP (mg/dL)‡	Baseline	2.18 ± 2.76	0.59 ± 0.44	
	14th week	1.38 ± 1.79	0.95 ± 1.17	
	Change	-0.79 ± 3.14	0.36 ± 1.35	0.203*
Uric acid (mg/dL)	Baseline	5.01 ± 1.65	4.78 ± 1.29	
	14th week	4.89 ± 1.59	5.31 ± 1.94	
	Change	-0.13 ± 0.74	0.53 ± 1.11	0.062*

*By Wilcoxon rank sum test.
† By Student's t-test.
‡ Number of phentermine group = 21.

Table 4. Patients Reporting Adverse Events (≥5% in Any Treatment Group)

	Phentermine (n = 29)*	Placebo (n = 24)	*p* value
Any adverse event	28 (96.6)	18 (75.0)	0.021†
Dry mouth	16 (55.2)	4 (16.7)	0.004†
Insomnia	10 (34.5)	0 (0.0)	0.001†
Headache	8 (27.6)	3 (12.5)	0.178†
Dizziness	8 (27.6)	3 (12.5)	0.178†
Fatigue	7 (24.1)	3 (12.5)	0.281†
Palpitation	6 (20.7)	2 (8.3)	0.211†
Nausea	5 (17.2)	6 (25.0)	0.488†
Flushing	4 (13.8)	0 (0.0)	0.117‡
Constipation	4 (13.8)	2 (8.3)	0.678‡
Indigestion	4 (13.8)	3 (12.5)	1.000‡
Back pain	3 (10.3)	0 (0.0)	0.242‡
Epigastric pain	3 (10.3)	0 (0.0)	0.242‡
Chest discomfortness	3 (10.3)	1 (4.2)	0.617‡
Mood change	3 (10.3)	2 (8.3)	1.000‡
Skin problem	2 (6.9)	0 (0.0)	0.495‡
Sweating	2 (6.9)	0 (0.0)	0.495‡
Foreign body sensation of throat	2 (6.9)	0 (0.0)	0.495‡
Anxiety	2 (6.9)	2 (8.3)	1.000‡

*A patient who had been withdrawn due to adverse events without clinic visit is included.
† By Chi-square test.
‡ By Fisher's exact test.

personal schedule, and one due to no weight losing effect of the drug. Among 114 reports of total adverse events in subjects who were treated for more than 6 weeks, only 31 (27.2%) had newly occurred after the 6th week of treatment, and 24 (21.1%) symptoms had prolonged for more than 4 weeks. In phentermine group, 13 of 29 had reported the occurrence of adverse events after the 6th week of treatment, and in placebo group, 4 of 24 had reported after the 6th week.

In completers, there was no significant difference of change of level from baseline to endpoints in RBC, WBC, and platelet counts, hemoglobin, hematocrit, BUN, creatinine, total bilirubin, AST and ALT levels.

DISCUSSION

Generally, currently recommended obesity treatment method is the improvement of life style, the essentially featuring reduction of calorie intake and increasing physical activity. However, the outcome of such method have shown to be disappointing. Therefore, several drugs have been developed for weight reduction, and a few of them had been approved for obesity treatment. Phentermine is one of these drugs. It is a drug which had been approved by US FDA in 1959 with a brand name of Ionamin®, and more than 50 million prescriptions of which have been written out since 1960. Despite its wide usage, few clinical trials of phentermine for the weight

reducing effect and safety have been performed in Korea. Phentermine is produced in two major forms. One is phentermine resin (eg. Ionamin®) and the other is phentermine-HCl (eg. Adipex®), where the latter is released more rapidly.

Cost is an important factor in the pharmacologic therapy of obesity. The difference of cost-effectiveness between sibutramine and phentermine in US has already been described in introduction, which is guite the same in Korea. Moreover, obesity treatment is not covered by medical insurance in Korea until present in 2006. Therefore, total drug purchasing expense for obesity treatment is burdened to patients. Until 2006, Reductil® and Xenical® are the only drugs approved for long-term treatment of obesity in Korea. Both of these drugs are expensive. Purchasing cost for 1 month as initial recommended dosage is over 100,000 won in 2006. However, the price for the use of phentermines is around one fourth of the price for using Reductil® or Xenical®. Relatively lower cost of phentermine maybe of assistance for those patients who have difficulty in purchasing highly priced obesity drugs.

In this study, 2 weeks run-in period and 12 weeks administration of phentermine-HCl 37.5 mg had induced clinically significant weight reduction, shortening of waist circumference, and reduction of total cholesterol and non-HDL-cholesterol level. This result would reduce the risk of cardiovascular disease in the ultimate. Moreover, over 80% of subjects of phentermine group lost 5% or more of initial weight and more than half subjects lost 10% or more. This shows us that most of obese patients can obtain the conventional goal of obesity treatment by short-term use of phentermine.

There have been many reports about the weight reduction effect of phentermine until today. In 1968, Munro et al.[14] performed long-term double blind placebo-controlled study on 108 obese women with phentermine resin. They compared three groups of placebo, continuous phentermine therapy and intermittent phentermine therapy (administration of phentermine and placebo every 4 weeks, alternatively) for 36 weeks, and reported that both continuous therapy (mean weight loss 12.2 kg) and intermittent therapy (13.0 kg) resulted in significant weight reduction than placebo (4.8 kg, $p < 0.001$). In this study, they reported that phentermine had held the effect of gradual loss in weight even after the 6 months of drug administration, which is different to other weight-losing drugs Langlois et al.[15] performed placebo-controlled study on 59 patients with phentermine hydrochloride for 22 weeks (the duration of drug administration was 14 weeks) in 1968. In this study, phentermine group (mean weight loss 16.1 kg) showed significantly more weight loss than placebo (3.9 kg, $p < 0.001$). In both studies, experiments reported that side effects were not serious. Weintraub et al.[7] reported the result of placebo controlled study in which they compared the effect of phentermine resin 30 mg, fenfluramine hydrochloride 60 mg and phen-fen (phentermine resin 15 mg + fenfluramine hydrochloride 30 mg) on 81 subjects for 24 weeks in 1984. In this result, phentermine group (mean weight loss 10.0 kg), fenfluramine group (7.5 kg), and phen-fen group (8.4 kg) showed significantly superior weight reduction effect than placebo. However, phentermine only group induced more side effects than phen-fen combination therapy or placebo. In addition to these studies, there had been several other small sized clinical trials using phentermine, however, all of them showed similar weight reduction effect, and reported similar side effect profiles which could be mimicked with by subjects in general.

Desirably, the process of weight reduction should be taken gradually and continue for a long time. However, this is difficult. Therefore, the intentional weight losing process should be divided into two periods, initial weight reduction period and sustaining reduced weight period. The guideline of US National Institutes of Health[16] recommends that the target weight which is 10% or more less than initial weight should be gained over 6 months, and then the patient should attempt to maintain it. It is because, after certain amount of weight reduction, it becomes very difficult to lose more weight due to several adaptation processes to reduced weight such as decreased basal metabolic rate. In our study, phentermine group gained 7.2 kg of weight loss on average for 14 weeks, and this amount of reduced weight is 9.3% of initial weight. The result of our study shows that phentermine can

induce initial target weight, even though the clinical trial of long-term usage of phentermine is needed.

Phentermine is classified as sympathetic amine, which shows its effect by the secretion of norepinephrine at nerve terminal. However, the exact appetite suppressing mechanism of phentermine is not fully understood. Several studies on this topic suggest that phentermine may suppress appetite on hypothalamus by the increase of the concentration of norepinephrine,[17] dopamine[18,19] and serotonin[20] in CNS. Phentermine usually induce tachycardia and increase blood pressure because of its sympathomimetic effect. In this study, pulse rate had not regularly checked on every visit. However, in adverse events analysis, only 6 of 29 (20.7%) phentermine group subjects complaint on their palpitation, and this number is not significantly more than placebo group. Similarly, blood pressure had not increased after treatment period in phentermine group, and there had been no significant difference between both groups. Not only the blood pressure of endpoints but also the blood pressure of 4 weeks administration of phentermine is not significantly different between two groups. Not shown in the results, the analysis of blood pressure at 6th week, i.e. after 4 weeks administration of phentermine, the mean systolic pressure was 127.4 (SD 10.2) mmHg and the mean diastolic pressure was 85.1 (SD 8.4) mmHg in phentermine group (n = 28), compared to systolic 127.3 (SD 12.7) mmHg and diastolic 83.5 (SD 10.4) mmHg in placebo group (n = 24). Therefore, we can suggest that the administration of phentermine would not induce any serious cardiovascular effect at least for the patients whose risk of cardiovascular disease is not high.

In our study, the administration of phentermine caused just a few serious adverse events. In completers, no subjects showed abnormal result on standard laboratory test. Although the number of subjects who had reported adverse events was much larger than that of subjects without adverse events, and more subjects in phentermine group complained on side effects than subjects in placebo group, dry mouth and insomnia were the only adverse events that occurred significantly more frequently in phentermine group. Moreover, these events were not so serious as to prevent the subjects from participating in the study. Drinking plenty of water could reduce dry mouth symptom and in most cases, it resolved of itself. 5 of 28 phentermine completers reported that they had experience dry mouth during the whole period of phentermine administration. There was nobody who reported that their insomnia prolonged over 4 weeks. In many cases of insomnia, by switching the administration time to the morning the symptom could be improved.

According to the direction of Gate pharmaceuticals which is one of drug companies producing phentermine drugs, known adverse effects of phentermine are primary pulmonary hypertension, valvular heart disease, palpitation, tachycardia, elevated blood pressure, hypersensitivity, dizziness, insomnia, mood change, tremor, headache, driness of the mouth, unpleasant taste, diarrhea, urticaria, impotence, and changes in libido, etc.[21] At the initial briefing on the research procedure to the subjects, the possibility and symptoms of primary pulmonary hypertension and valvular heart disease were informed and the subjects had been instructed to notify to the researchers immediately if they had felt related symptoms. However, there had been no report of symptoms related to these two serious adverse events in the study period. The majority of other known adverse effects had been reported in the study. For taste change, there was one report in placebo group and the symptom was minimal and self-limited. There was no report of taste change in phentermine group. There was no report of tremor and diarrhea in both groups. There had been no definite report of urticaria. However, one subject reported minimal temporary itching sensation at the 10th week in phentermine group, and another reported temporary skin lesion on face at the 6th week which could not been identified by researchers because of complete recovery on the subsequent clinical visit. There had been no report on impotence and change of sexual desire, and this might be due to the self report method of side effects whichever they felt during study participation, not the selection method on side effects list.

There had been seven reports about epigastric pain and chest discomfort. After detailed history taking and physical examination, all of these reports had been considered to be not related to

cardiac problems, and therefore no further diagnostic study had been performed. In the study, the subjects were relatively healthy obese people; the age of the subjects was not high and there had been no subjects with hypertension and diabetes mellitus, both of which are strong risk factors of cardiovascular disease. Only 23.5% of subjects were smokers, and the rate was relatively lower than known average smoking rate amongst Korean. It might be due to the female abundance of the subjects. Therefore, the possibility of cardiovascular disease in this study group might be much lower than that of average Korean obese population. In real practice of obese patient with administration of phentermine, the health provider should pay attention to the symptoms of epigastric pain or chest discomfort especially with the high risk patients with cardiovascular disease. Then, again, further evaluation on the cardiac related symptoms could be performed even though for the case of non cardiac disease. Such aspect of phentermine administration might be the limitation of usage on the obese patients with high age, diabetes mellitus, or past medical history of cardiovascular disease.

Phentermine is classified by US Drug Enforcement Agency (DEA) as schedule IV drug.[22] The completers had been requested to visit the researchers at the 18th week for the check up of withdrawal symptoms or other unexpected adverse events, at where they were provided with laboratory results. 12 of 24 (50%) phentermine completers and 6 of 12 (50%) placebo completers visited researchers. There had been nobody who complained withdrawal symptoms or other adverse events.

Phentermine hydrochloride is indicated by US FDA as a short-term (a few weeks) adjusted in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial BMI $\geq 30\,kg/m^2$, or $\geq 27\,kg/m^2$ in the presence of other risk factors (e.g., hypertension, diabetes, and hyperlipidemia). A short-term is generally accepted as around three months. Some experts insist that if the initial three month effect on weight reduction is acceptable good, the prolonged administration of phentermine will be appropriate.[23] This study is for the evaluation of the effect and the safety of short-term usage of phentermine. The clinical trials for long-term effect and safety are also necessary.

Conclusively, we can suggest that short-term phentermine administration can induce significant weight reduction and the shortening of waist circumference without clinically problematic adverse events on relatively healthy obese people, by this study.

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