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POSSIBLE PERIPHERAL LIPOLYTIC EFFECT OF CLOBENZOREX HYDROCHLORIDE IN PATIENTS WITH OBESITY

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Summary

Introduction. It is well known that clobenzorex hydrochloride is an amine that inhibits appetite by its sympathomimetic action on the lateral hypothalamus. However, it has been reported that this drug also has a peripheral lipolytic effect, which has not been studied sufficiently. The aim of this study was to evaluate such lipolytic action in obese patients. Methods: A controlled clinical trial was conducted with male and female patients having class I and II obesity and an age range of 30-60 years (n=33). Patients were randomized into two groups: the experimental group (n=16) received a single oral dose of 90 mg clobenzorex, and the control group (n=17) a placebo. Blood samples were taken at 0, 60, 120, 180 and 240 min post-administration to determine serum levels of free fatty acids (FFAs), glycerol, glucose, triglycerides, HDL-cholesterol and LDL-cholesterol. The atherogenic index (AI) was calculated. Results: Over the time of the study (0-240 min), the experimental group showed an increase in HDL-cholesterol (from 42.0 to 55.6 mg/dl; p=0.01), FFAs (from 0461 to 1009 mMol/l; p=0.01), and glycerol (from 0.123 to 0.170 mMol/lt; p=0.01). There was a significant decrease in AI (from 5.87 to 5.26; p=0.01). The placebo group showed a significant increase only in FFAs (from 0436 to 0824 mMol/lt; p=0.01) and a significant decrease in AI (from 4.51 to 4.05; p=0.01). Conclusion: These results suggest that clobenzorex hydrochloride has peripheral lipolytic activity, which can be considered as an additional effect, synergistic with its central pharmacological mechanism.

Keywords: clobenzorex hydrochloride, drug treatment, obesity.

Introduction

Clobenzorex hydrochloride is among the anti-obesity agents used in Mexico. This drug is a phenethylamine anorectic with sympathomimetic effects that act on the lateral hypothalamus, increasing the release of catecholamines that favor satiety and diminish the consumption of food, thus considerably reducing caloric intake. This drug is absorbed rapidly and completely 4-6 hours after being taken [1, 2]. It is recommended for patients with a BMI above 30 kg/m^2 that do not respond to diet and exercise [3]. In addition to its central

action mechanism, it has been reported that clobenzorex hydrochloride has peripheral effects [4], including a lipolytic effect that may be another mechanism of this drug [5].

It is known that lipolysis is a catabolic process that leads to the decomposition of triglycerides stored in adipocytes and therefore to the release of fatty acids and glycerol [6, 7]. Recent studies have revealed that the metabolic pathway of lipolysis is not just stimulated by catecholamines and inhibited by insulin [8]. It also involves the participation of the endocrine system and regulation by the paracrine system, as well as the intervention of molecular mechanisms in the hydrolysis of triglycerides [3, 9].

Catecholamines modulate lipolysis through beta-adrenergic and alpha-2-adrenergic receptors. This action is due to the *in vivo* participation of these receptors in the physiological control of lipolysis in subcutaneous adipose tissue [10, 11]. However, the only report that evidences the lipolytic action of anorectics is that published in 1972 by Charbonnier. Hence, the aim of the present study was to evaluate lipolytic action of clobenzorex hydrochloride by determining the serum levels of free fatty acids (FFAs) and glycerol after the administration of a 90-mg dose. We hypothesized that the serum levels of free fatty acids (FFAs) and glycerol will be increase after administration of a 90mg of clobenzorex hydrochloride.

Material and Methods

Study design

A longitudinal, prospective study was carried out with control groups related to time. The participants in the study were randomly assigned to the treatment with clobenzorex hydrochloride or the placebo. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013 as well as the International Conference on Harmonized Tripartite Guideline for Good Clinical Practice and the Mexican norm. Informed consent was obtained from all patients.

Research subjects

There were 33 participants in the present study, 16 of whom received clobenzorex hydrochloride and 17 the placebo. The patients were 18-60 years old and had a BMI ≥30 kg/m^2, with class I or II obesity according to the classification of the World Health Organization. All were evaluated by elaborating the clinical history recommended by the Mexican Academy for the Study of Obesity, with the aim of discarding any possibly comorbidity related to obesity.

Treatment

The experimental group (n=16) received a single oral dose of 90 mg of clobenzorex hydrochloride after a fast of 12 hours, while the control group (n=17) received an oral dose of the placebo under the same conditions.

Anthropometric measurements

These parameters were evaluated according to the guidelines established by the manual of the International Society for the Advance of Kineanthropometry (ISAK, 2006). Weight was measured with a physician's scale (SECA 700, Spain) after a 12-hour fast and evacuation of the bladder, placing the individual in an upright position with arms hanging loosely to the side and without movement. The BMI was calculated with the Quetelet formula. The waistline and hip were measured with an anthropometric flexible plastic tape measure (Hergom-Mexico). The individual was placed in the previously described upright position, but with arms crossed over the thorax. To calculate the waist-hip ratio (WHR), the waistline value was divided by the hip circumference.

Biochemical measurements

A 5-ml blood sample was taken from each participant by puncture of the median cubital vein of the left arm. As aforementioned, the drug or placebo was administered after a 12-hour fast. Blood was taken at 0, 60, 120, 180

and 240 min post-administration , placing samples in a vacutainer tube (K2E/KE EDTA, New York). Immediately afterwards, the blood was centrifuged with a clinical apparatus (SMART R17-Korea) at 4200 rpm for 10 min to obtain serum, which was frozen to -70 °C (freezer, MDF-U5486SC-USA/Canada) to await further processing.

Values were obtained for the concentration of glucose (Glu), total cholesterol (Chol), high density lipoprotein (cHDL), low density lipoprotein (cLDL), triglycerides (TGs), FFAs and glycerol. The atherogenic index (AI) was calculated by dividing total cholesterol by cholesterol bound to cHDL. Colorimetric enzyme analysis (GOD/PAP Randox, United Kingdom) was used to obtain values for glucose and TGs, taking a reading with a standard spectrophotometer (Microlab 200, Mexico). The wavelength was 546 nm for glucose and 505 nm for TGs, in each case using 5 µL of serum and 500 µL of the reactive, and comparing the results to a standard. Values for non-esterified fatty acids (NEFA) and glycerol were obtained by using spectrometry (VV2150-New York) and quantitative in vitro colorimetric enzyme analysis.

Statistical analysis

One-way analysis of variance (ANOVA) was performed, with a paired analysis for independent variables as well as multiple comparisons (MSD, minimum significant difference) and correlations, comparing the variables before and after the interventions. The SPSS version 19 program was used for all statistical analysis.

Results

Basal characteristics

All 33 participants had a BMI greater than 30 and less than 40 g/m2, with a comparable average age between the experimental and control groups (41.3 ± 12.5 vs. 38.7 ± 13.2, respectively; p = 0.57). Regarding gender, the group administered clobenzorex hydrochloride had 12 women and 4 men, while the placebo group had 12 women and 5 men. (Table I)

Table I. Anthropometric indicators of the clobenzorex versus placebo group by gender.

Indicators	Women		p*	Men		p*
	Clobenzorex n=12	Placebo n=12		Clobenzorex n=4	Placebo n=5	
BMI	31.6 ± 2.6	33.5 ± 3.9	t=-1.42, p=0.17	32.6 ± 3.4	33.7 ± 1.4	t=-0.66, p=0.55
Weight	77.7 ± 8.1	83.7 ± 8.1	t=-1.83, p=0.08	97.3 ± 18.8	102.2 ± 7.3	t=-0.5, p=0.65
Size	1.57 ± 0.05	1.58 ± 0.04	t=-0.92, p=0.37	1.72 ± 0.07	1.74 ± 0.05	t=-0.46, p=0.66
Waist	96 ± 5.3	96.7 ± 9.1	t=-0.25, p=0.81	106.5 ± 7.5	108.8 ± 3.3	t=-0.57, p=0.60
Hip	111.4 ± 6.3	116.6 ± 9.0	t=-1.61, p=0.12	109.3 ± 8.5	112 ± 3.1	t=-0.62, p=0.57
WHR	0.89 ± 0.07	0.83 ± 0.07	t=2.09, p=0.05	0.97 ± 0.04	0.98 ± 0.02	t=-0.44, p=0.68

Abbreviations: BMI – body mass index, WHR – waist-hip ratio; Women with the clobenzorex (n=12) and placebo (n=12) treatment. Men with the clobenzorex (n=4) and placebo (n=5) treatment. Values are expressed as the mean ± SE. *P<0.05 treatment vs placebo.

Biochemical variables

The initial values of the blood parameters showed no significant differences between groups (p>0.05), except that cLDL had a significantly higher value for the clobenzorex hydrochloride group (Table II; p=0.04).

Table II. Values for the biochemical indicators for patients receiving a single 90 mg dose of clobenzorex (n=16) or the placebo (n=17).

Indicators	**Time (min)**					**p (ANOVA)**
	Basal	**60**	**120**	**180**	**240**	
Chol (mg/dl)						
Clobenzorex	209.6 ± 36.1	215 ± 43.5	215.8 ± 45.6	223.3 ± 45.2	217.2 ± 36.1	F=0.22, p=0.92
Placebo	201.1 ± 41.4	201.1 ± 47.5	211.2 ± 45.6	205.6 ± 37	205.1 ± 43.3	F=0.16, p=0.96
p (Student *t*)	t=0.63, p=0.53	t=0.88, p=0.39	t=0.29, p=0.77	t=1.23, p=0.23	t=0.87, p=0.39	
cHDL (mg/dl)						
Clobenzorex	42 ± 16.8	39.4 ± 12.5	40.5 ± 15.2	45.7 ± 14	55.6 ± 15.9	F=3.09, p=0.02
Placebo	47.8 ± 12.5	41 ± 15.3	43.7 ± 18.7	54 ± 33	53.7 ± 12.2	F=1.48, p=0.22
p (Student *t*)	t=-1.12, p=0.27	t=-0.33, p=0.75	t=-0.54, p=0.6	t=-0.95, p=0.35	t=0.37, p=0.71	
AI						
Clobenzorex	5.87 ± 2.86	5.97 ± 2.34	5.92 ± 2.2	5.26 ± 1.8	4.15 ± 1.14	F=36.0, p=0.01
Placebo	4.51 ± 1.65	5.64 ± 2.77	5.73 ± 3	4.52 ± 1.74	4.05 ± 1.52	F=48.4, p=0.01
p (Student *t*)	t=1.66, p=0.11	t=0.37, p=0.71	t=0.21, p=0.84	t=1.2, p=0.24	t=0.22, p=0.83	
cLDL (mg/dl)						
Clobenzorex	107.1 ± 30.6	101.6 ± 22.2	106.9 ± 33.4	101.7 ± 24.5	103.1 ± 26.3	F=0.16, p=0.96
Placebo	85.7 ± 25.3	84.9 ± 30.1	90.5 ± 28.1	92 ± 24.8	96.2 ± 33.8	F=0.45, p=0.77
p (Student *t*)	t=2.19, p=0.04	t=1.82, p=0.08	t=1.52, p=0.14	t=1.13, p=0.27	t=0.66, p=0.51	
Glu (mg/dl)						
Clobenzorex	63.7 ± 13.7	63.1 ± 8.4	59.1 ± 9.9	58.2 ± 9.9	57.3 ± 14	F=1.06, p=0.38
Placebo	61.6 ± 14.5	59.6 ± 12.3	60.7 ± 13.2	58.9 ± 9.8	59 ± 9.2	F=0.16, p=0.96
p (Student *t*)	t=0.44, p=0.67	t=0.95, p=0.35	t=-0.39, p=0.7	t=-0.19, p=0.85	t=-0.41, p=0.69	
TGs (mg/dl)						
Clobenzorex	147.8 ± 70	151.1 ± 74.8	146.3 ± 70.4	153.5 ± 72.6	162.2 ± 73.3	F=0.12, p=0.97
Placebo	129.8 ± 49.5	124.9 ± 50.6	123.7 ± 53.7	124.7 ± 48.4	125.7 ± 45.6	F=0.04, p=0.99
p (Student *t*)	t=0.85, p=0.4	t=1.17, p=0.25	t=1.03, p=0.31	t=1.33, p=0.19	t=1.71, p=0.10	
FFAs						

(mMol/lt)						
Clobenzorex	0.461 ± 0.206	0.552 ± 0.187	0.73 ± 0.315	0.875 ± 0.365	1.009 ± 0.381	F=8.93, p=0.01
Placebo	0.436 ± 0.169	0.516 ± 0.185	0.564 ± 0.215	0.708 ± 0.265	0.824 ± 0.263	F=8.25, p=0.01
p (Student *t*)	t=0.37, p=0.72	t=0.55, p=0.59	t=1.76, p=0.09	t=1.5, p=0.15	t=1.61, p=0.12	
Glycerol (mMol/lt)						
Clobenzorex	0.123 ± 0.027	0.15 ± 0.064	0.16 ± 0.052	0.178 ± 0.055	0.17 ± 0.038	F=3.12, p=0.02
Placebo	0.12 ± 0.03	0.136 ± 0.039	0.129 ± 0.043	0.141 ± 0.036	0.138 ± 0.031	F=0.89, p=0.47
P	t=0.26, p=0.8	t=0.81, p=0.43	t=1.89, p=0.07	t=2.3, p=0.03	t=2.62, p=0.01	

Abbreviations: Chol – total cholesterol; cHDL – high-density lipoprotein; AI – atherogenic index, cLDL – low-density lipoprotein; Glu – glucose; TGs – triglycerides; FFAs – free fatty acids. Clobenzorex (n=16); PB – Placebo (n=17). Values are expressed as the mean ± SE. *P<0.05 treatment vs placebo.

For the FFAs, there was a significant increase from the basal to final measurement in both groups (Table II; p=0.01). Upon making the comparison between the differences in the basal and final state, there was a significant increase in favor of the clobenzorex hydrochloride group (Table III; p=0.05). The correlations between both groups were significant (Table III; p=0.01).

Table II. Correlations and differences between basal and final values of biochemical indicators: a single dose of 90 mg clobenzorex (n=16) versus placebo (n=17).

Indicators	**Difference: Basal-final**	**P-value for the difference: Basal-final**	**r-Pearson**
Chol (mg/dl)			
Clobenzorex	7.6 ± 26.3	t=-1.16, p=0.26	r=0.74, p=0.01
Placebo	4.0 ± 23.1	t=-0.72, p=0.48	r=0.85, p=0.01
p (Student *t*)	t=0.41, p=0.68		
cHDL (mg/dl)			
Clobenzorex	13.6 ± 12.2	t=-4.45, p=0.01	r=0.72, p=0.01
Placebo	5.9 ± 7.7	t=-3.15, p=0.01	r=0.8, p=0.01
p (Student *t*)	t=2.13, p=0.04		
AI			
Clobenzorex	-1.72 ± 2.21	t=3.11, p=0.01	r=0.71, p=0.01
Placebo	-0.46 ±	t=2.47, p=0.03	r=0.89,

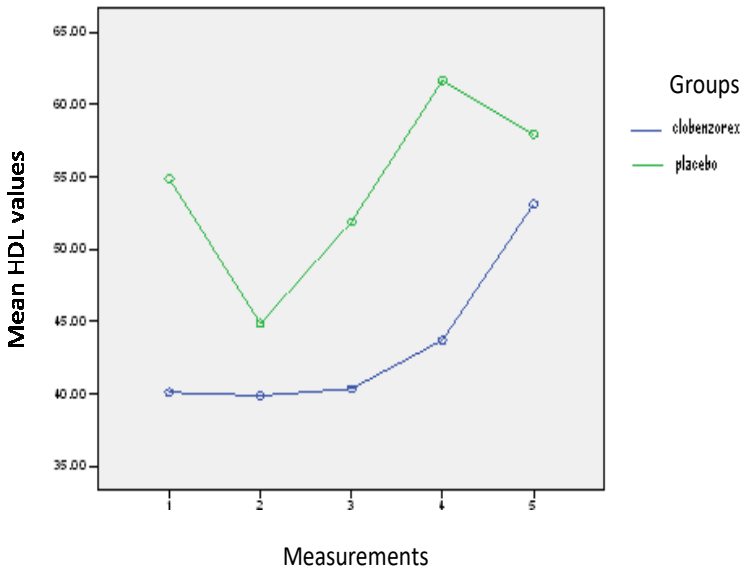
	0.77		p=0.01
p (Student *t*)	t=-2.16, p=0.04		
cLDL (mg/dl)			
Clobenzorex	-4 ± 18.9	t=0.84, p=0.41	r=0.79, p=0.01
Placebo	10.5 ± 21.1	t=-2.05, p=0.06	r=0.78, p=0.01
p (Student *t*)	t=-2.08, p=0.05		
Glu (mg/dl)			
Clobenzorex	-6.41 ± 17.5	t=1.47, p=0.	r=0.21, p=0.45
Placebo	-2.58 ± 14.5	t=0.73, p=0.47	r=0.32, p=0.21
p (Student *t*)	t=-0.68, p=0.5		
TGs (mg/dl)			
Clobenzorex	14.41 ± 34	t=-1.7, p=0.11	r=0.89, p=0.01
Placebo	-4.08 ± 24.1	t=0.7, p=0.5	r=0.87, p=0.01
p (Student *t*)	t=1.79, p=0.08		
FFAs (mMol/lt)			
Clobenzorex	0.548 ± 0.28	t=-7.84, p=0.01	r=0.7, p=0.01
Placebo	0.388 ± 0.142	t=-11.28, p=0.01	r=0.87, p=0.01
p (Student *t*)	t=2.06, p=0.05		
Glycerol (mMol/lt)			
Clobenzorex	0.047 ± 0.034	t=-5.65, p=0.01	r=0.51, p=0.04
Placebo	0.018 ± 0.023	t=-3.16, p=0.01	r=0.71, p=0.01
P	t=2.9, p=0.01		

Abbreviations: Chol – total cholesterol; cHDL – high-density lipoprotein; AI – atherogenic index, cLDL – low-density lipoprotein; Glu – glucose; TGs – triglycerides; FFAs – free fatty acids. Clobenzorex (n=16); PB – Placebo (n=17). Values are expressed as the mean ± SE. *P<0.05 treatment vs placebo.

Glycerol showed a statistically significant increase in the clobenzorex hydrochloride group from the basal to final value (Table II; p=0.02), while this increase was small and insignificant for the placebo group (Table II). The comparison of the differences between the basal and final value was significant for both groups (p=0.01), as were the correlations

(Table III; p=0.01). The value for cHDL increased significantly during the study for the clobenzorex hydrochloride group (Table II; p=0.02), while the increase was small and insignificant for the placebo group. The difference between the basal and final value of this parameter was significant (p=0.04) when comparing the two groups, as was the correlation between the initial and final states (Table III; p=0.01).

The placebo group began with a higher average cHDL value than the clobenzorex hydrochloride group. In both groups, this value decreased at 60 min post-administration of the respective treatment, and then increased at 180 min. In the placebo group the level of cHDL stabilized between 180 and 240 min, while there was a significant increase during this lapse of time for the clobenzorex hydrochloride group (Graph 1).



Graph 1. *c-HDL values*
Concentration-time curve for cHDL in plasma (post-administration time in hours): Clobenzorex (n=16) vs placebo (n=17). *P<0.05.

The difference between the basal and final value was significant for AI in both groups (p=0.01), but was greater for the clobenzorex hydrochloride group (p=0.01 vs p=0.03), as was the correlation between the initial and final states (Table III; p= 0.01).

The value for cLDL decreased gradually and significantly during the study for the clobenzorex hydrochloride group, while increasing in the placebo group (Table II). This difference was significant for the former group (Table III; p<0.05). The correlations between both groups in the basal and final state were significant (Table III; p=0.01).

The correlations between the measured variables (without considering the particular time of measurement) is shown in Table IV for the clobenzorex hydrochloride group and Table V for the placebo group.

Since the anthropometric measurements were only taken at the basal state, correlations were established with the initial measurements of the biochemical indicators. In the clobenzorex hydrochloride group, the BMI and the WHR were inversely associated with cholesterol. For the placebo group, the important positive correlations were the

BMI with TGs, the WHR with TGs, and FFAs with glycerol, while an inverse correlation was found for WHR with cHDL (Tables IV and V). or patients in the clobenzorex hydrochloride group, age directly influenced the values for CT, Glu and FFAs, while for patients in the placebo group age was positively associated with CT, Glu and TGs (Tables IV and V). Additionally, Chol was positively associated with FFAs in the clobenzorex hydrochloride group and with AI in the placebo group. The value of cHDL was not associated with Chol in either of the two groups in the study. In the clobenzorex hydrochloride group, an increase in cHDL was associated with a decrease in AI and TGs.

Table IV. Correlations (r-Pearson) between anthropometric and biochemical indicators in patients receiving clobenzorex.

Indicators		Chol	HDL	AI	LDL	Glu	TGs	FFAs	Glycerol
Weight	r	.306	-.230	-.282	.224	.465	.206	.262	-.172
	p	.249	.391	.289	.404	.069	.444	.327	.525
Size	r	.068	-.368	**-.513***	.361	.420	.131	.464	-.356
	p	.802	.161	**.042**	.170	.105	.629	.070	.176
BMI	r	**.548***	.021	.190	-.001	.396	.225	-.098	.273
	p	**.028**	.938	.480	.997	.129	.402	.719	.307
Waist	r	.211	-.187	-.141	.242	.445	.421	.080	-.103
	p	.433	.487	.604	.367	.085	.104	.767	.703
Hip	r	.229	-.016	.476	-.242	.155	.206	-.015	-.232
	p	.394	.953	.062	.366	.566	.444	.956	.387
WHR	r	**-.520***	-.345	-.272	.302	.048	.203	-.173	-.180
	p	**.039**	.190	.308	.256	.859	.452	.523	.504
Age	r	**.383***	-.01	.01	.16	**.215**	.03	**.279***	-.06
	p	**.01**	.95	.99	.17	**.05**	.79	**.01**	.64
Chol (mg/dl)	r		.06	.18	**.552***	-.09	.04	**.277***	.05
	p		.57	.14	**.01**	.41	.75	**.01**	.67
cHDL (mg/dl)	r			**-.241***	.02	-.05	**-.468***	.10	.19
	p			**.03**	.87	.65	**.01**	.39	.09
AI	r				.07	-.03	-.04	-.09	-.09
	p				.54	.81	.73	.44	.43
cLDL (mg/dl)	r					-.12	.12	.07	.02
	p					.30	.28	.56	.87
Glu (mg/dl)	r						**.235***	.04	-.09
	p						**.04**	.75	.43
TGs (mg/dl)	r							**.401***	.15
	p							**.01**	.18
FFAs (mMol/l)	r								**.564***
	p								**.01**
Glycerol (mMol/l)	r								
	p								

[1] In nmol/ml [2] In nmol/mg prot. $p<0.05$, significant

Abbreviations: Chol – total cholesterol; AI – atherogenic index, cHDL – high-density lipoprotein; cLDL – low-density lipoprotein; Glu – glucose; TGs – triglycerides; FFAs – free fatty acids. Clobenzorex.

Table V. Correlations (r-Pearson) between anthropometric and biochemical indicators in patients given the placebo.

Indicators		Chol	cHDL	AI	cLDL	Glu	TGs	FFAs	Glycerol
Weight	r	-.181	**-.517***	.129	.222	.252	**.664****	**.754****	.306
	p	.488	**.034**	.622	.391	.330	**.004**	**.001**	.232
Size	r	.048	**-.622***	.184	.432	.497*	.417	**.761****	.065
	p	.856	**.008**	.479	.084	.042	.096	**.001**	.803
BMI	r	-.284	.001	-.065	-.174	-.237	**.478**	.163	.385
	p	.270	.999	.805	.505	.360	**.053**	.532	.127
Waist	r	-.082	-.303	.352	.184	.202	**.677****	.465	**.518***
	p	.755	.236	.166	.479	.437	**.003**	.060	**.033**
Hip	r	-.097	.352	.299	-.288	-.211	.092	-.333	-.030
	p	.710	.166	.243	.262	.417	.725	.192	.909
WHR	r	-.064	**-.561***	.159	.356	.313	**.564***	**.728****	**.521***
	p	.808	**.019**	.542	.160	.221	**.018**	**.001**	**.032**
Age	r	**.235***	0.02	.02	0.08	**.317***	**.245***	-0.03	0.10
	p	**0.03**	0.85	.83	0.49	**0.01**	**0.02**	0.77	0.35
Chol (mg/dl)	r		0.08	**.220***	**.501***	0.20	0.04	-0.08	0.19
	p		0.49	**.04**	**0.01**	0.07	0.71	0.45	0.09
cHDL (mg/dl)	r			-.206	0.19	-0.08	0.00	0.13	0.18
	p			.06	0.09	0.48	0.99	0.25	0.09
AI	r				-.04	.01	-.09	**-.256***	-.11
	p				.72	.92	.44	**.02**	.34
cLDL (mg/dl)	r					-0.07	0.09	0.09	**.276***
	p					0.54	0.42	0.44	**0.01**
Glu (mg/dl)	r						0.19	-0.02	**.314***
	p						0.08	0.87	**0.01**
TGs (mg/dl)	r							**.276***	**.274***
	p							**0.01**	**0.01**
FFAs (mMol/l)	r								**.539***
	p								**0.01**
Glycerol (mMol/l)	r								
	p								
	p								

[1] In nmol/ml [2] In nmol/mg prot. p<0.05, significant

Abbreviations: Chol – total cholesterol; cHDL – high-density lipoprotein; AI – atherogenic index, cLDL – low-density lipoprotein; Glu – glucose; TGs – triglycerides; FFAs – free fatty acids. Placebo.

Discussion

Obesity is associated with a 3-fold or greater increase in the risk of acute myocardial infarction [(12)]. The American Heart Association (AHA) has reclassified obesity as a modifiable risk factor for coronary heart disease (CHD). One of the main contributors to the morbidity of cardiovascular disease (CD) is an alteration in plasmatic lipids and the levels of lipoproteins [(13)]. Recent epidemiological data show that a low plasmatic level of cHDL also represents a risk factor for cardiovascular disease (CD) [(14)]. On the contrary, an increase of 1 mg/dl in the plasmatic level of cHDL is associated with a decrease in the risk of CHD by 2-3% [(15)].

A significant difference in cHDL was observed when comparing the difference

between the basal and final states between groups, since the change in cHDL was significantly greater in the group treated with clobenzorex hydrochloride (p = 0.04). In this respect, some studies suggest that certain amines improve the profile of lipids, increasing the levels of cHDL [16, 17]. There are also studies suggesting that clobenzorex hydrochloride tends to increase the level of cHDL in the short run [3, 5, 18]. It has been reported that this increase in cHDL may be due to the fact that clobenzorex hydrochloride is a sympathomimetic amine that acts on the ventrolateral nucleus of the hypothalamus, prompting the release of noradrenaline and dopamine in the synaptic spaces, and consequently specific metabolic modifications (20).

On the other hand, there are studies that consider cLDL as one of the main indicators of risk for CD (19-22). Yet in the present study, there was no significant modification of this parameter in either group during the time of the experiment. However, there was a significant difference between the value found in the clobenzorex hydrochloride group and that observed in the placebo group ($p<0.05$), due to the gradual decrease in the former. The levels of cLDL cholesterol are significantly lower after the administration of sympathomimetic amines that act on the ventrolateral nucleus of the hypothalamus (23), which explains the gradual decrease in cLDL due to the treatment with clobenzorex hydrochloride. This same effect was also described by Charbonnier (5).

Multiple studies have shown that lipidic indexes, such as that represented by CT/c-HDL, are better predictors of the risk of CHD than the separate measurement of CT, cHDL, cLDL or TGs (24). It has been observed that the atherogenic index in particular is a good predictor of the intimal medial thickness of the common carotid artery, having a predictive power of this parameter as well as the development of atherosclerosis that is superior to any of the isolated variables (25). With respect to the atherogenic index in the present study, a greater reduction was shown for patients in the clobenzorex hydrochloride than placebo group (Table III; p=0.04).

Although a significant increase in FFAs was observed for both groups, this change was significantly greater for patients receiving clobenzorex hydrochloride than those given the placebo (Table IV). There was a clear tendency in the former group to a lineal increase in FFAs as time passed (from 0-240 min post-administration).

It is known that fasting stimulates lipolysis in an acute manner, as well as positively regulating the serum level of fatty acids and glycerol, which act as oxidative substrates to maintain the energy requirements for other metabolic tissues (26). Catecholamines are the primary activators of the lipolysis triggered by fasting (27-29), but this mechanism is altered in obese people (30). In the present study, there was a significantly greater rise in the concentration of FFAs in the clobenzorex hydrochloride versus placebo group, which can be explained by the effect that this anorectic has on beta-adrenergic receptors due to being a phenethylamine. By binding to this receptor, clobenzorex hydrochloride prompts the formation of cAMP, thus promoting the activation of the hormone-sensitive lipase (HSL) and consequently indirectly causing an increase in the mobilization of lipids through the release of endogenous catecholamines (10, 31, 32). The study done by Charbonnier in 1972 measured the variation in FFAs during 4 hours of fasting, observing only a slight increase that did not reach statistical significance (5). In the present study, the rise in FFAs was significant when comparing the value of this parameter between the clobenzorex hydrochloride and placebo group (Table IV), demonstrating that this medication accelerates the increase in FFAs by stimulating lipolysis in the periphery, possibly by the previously described mechanism.

Regarding the level of glycerol, the tendency in the clobenzorex hydrochloride group was for a constant rise from the basal to final measurement (Table III), resulting in a

significant overall increase (p=0.02). This was not the case for the placebo group. It has been clearly established that a simultaneous increase in FFAs and glycerol is associated with lipolytic activity and an increase in the metabolism of fatty acids (33, 34). Pharmacological evidence suggests that dopaminergic mechanisms, which are found with clobenzorex hydrochloride, can also be involved in the control of thermogenesis (18, 20, 35), activating lipolysis in peripheral adipose tissue (21, 36) and promoting the release of fatty acids (37, 38).

The mobilization of lipids from fat reserves is an important part of providing for energy demand. In vitro studies have demonstrated the capacity of catecholamines to stimulate the mobilization of lipids from subcutaneous adipose tissue, a process which is found to be altered in obese individuals (39, 40). This is an important mechanism that contributes to the development of obesity, since catecholamines are the only hormones with a pronounced stimulatory effect on lipolysis in human fat cells (27, 41).

The correlations identified in the current contribution show that age does not directly influence the anthropometric variables in either of the two groups. However, age did indeed directly influence the values of FFAs, Chol and Glu in the patients receiving clobenzorex hydrochloride. The process of ageing is one of the factors that alters lipid metabolism (42). At a younger age in men and women, there is a greatly reduced risk of an adverse cardiovascular event. The reasons for the protection provided against CD in younger women and men are complex, but a significant contribution can be attributed to the greater levels of cHDL observed in younger people. Moreover, previous studies have demonstrated that there is a relation between age and an increase in Glu and FFAs (43).

Particularly important in the present study is the association between the increase in cHDL and the decrease in AI found only in the group treated with clobenzorex hydrochloride. An increase in cHDL levels has been associated with a decrease in the incidence and prevalence of adverse cardiovascular events (44). Many of the therapies aimed at promoting a rise in cHDL levels have not demonstrated a consistent clinical benefit (15). In the present study, this parameter was beneficial, having a direct effect on the atherogenic index in the patients receiving clobenzorex hydrochloride.

Conclusions

The present results suggest that clobenzorex hydrochloride has peripheral lipolytic activity, which could be considered as a pharmacological action for possible use in treating obesity and preventing the complications of this disease. According to the present results, it would be convenient to perform measurements of catecholamines in urine in order to identify whether there is a correlation between the changes that are shown in FFAs and glycerol, and in this way, be able to evaluate if there is a correlation between these hematological variables and the results of these tests.

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All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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