CLINICAL TRIALS WITH GUGULIPID

A New Hypolipidaemic Agent

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Summary

We repor the results of the multicentric clinical trial of the efficacy of gugulipid a new hypolipidaemic drug which was conducted at Bombay, Bangalore, Delhi, Jaipur, Lucknov, Nagpur and Varanasi. Two hundred and five patients completed the 12 wk open trial with gugulipid in a dose of 500 mg tds after 8 wk diet and placebo therapy. One patient showed gastrointestinal symptoms which did not nece sitate withdrawal of the drug. A significant lowering of serum cholesterol (average 23.6%) and serum triglycerides (average 22.6%) was observed in 70-80% patients. Double-blind, crossover study was completed in 125 patients with gugulipid, and in 108 patients with clofibrate. Two patients had flu-like syndrome with clofibrate and opted out from the study. With gugulipid the average fall in serum cholesterol and triglycerides was 11% and 16.8% respectively and with clofibrate 10% and 21.6% respectively. The lipid lowering effect of both drugs became evident 3-4 wk after starting the drug and had no relationship with age, sex, and concomitant drug intake. Hypercholesterolemic patients responded better to gugulipid therapy; hypertri-glyceridemic patients responded better to clofibrate therapy. In mixed hyper-lipidaemic patients, response to both drugs was comparable. HDL-cholesterol was increased in 60% cases who responded to gugulipid therapy; clofibrate had no effect on HDL-cholesterol; a significant decrease in LDL-cholesterol was observed in the responder group to both drugs.

Introduction

In a search for hypolipidaemic agents, a number of medicinal plants used in the Indian traditional systems of medicine for reducing obesity, blood lipids and hypertension have been tested by us in experimental models. Some of the plants including fractions of gum guggul, the resin from *Commiphora mukul*, were found to significantly lower blood lipids and change ljpoprotein profile[1,2]. Crude guggul resin had been shown earlier by Satyavati and Dwarkanath[3] to cause lowering of lipid in rabbits, which was followed by some clinical reports[4,5,6].

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In a detailed chemo-pharmacologicaI study, some of the sterones present in the resin were found to be responsible for the activity; however, one of the fractions containing these sterones named "Gugulipid" was almost as active as the pure sterones and was, therefore, taken up for development as a hypolipidaemic agent. Chemical assay and bioassay methods have been developed for quality control and standardisation of this product[7]. Gugulipid caused significant lowering of serum and tissue lipids in rats, rabbits and monkeys comparable to that produced by clofibrate. It showed inhibition of platelet aggregation and weak anti-inflammatory activity. It inhibited cholesterol biosynthesis, had antilipolytic action and was devoid of any hormonal, CNS, cardiovascular or diuretic effects. In hyperlipidaemic rats, rabbits and rhesus monkeys, it caused a significant change in lipoprotein profile, which included lowering of serum cholesterol and triglycerides and change in LDL/HDL ratio and regression of atheromatous lesions[8,9,10]. In six-month toxicity and teratogenic studies in rats, monkeys and beagles, gugulipid showed no adverse effeets[11,12]

In single (200-2400 mg) and multiple dose (400 mg tds x 4 wk) phase I study was carried out in 35 normal volunteers and 20 hyperlipidaemic patients respectively. Gugulipid was found not to affect liver function, blood sugar and blood urea levels, haematological parameters and electrocardiogram[13]. In the present communication, the results of multicentric trials of the clinical efficacy of gugulipid in comparison to that of clofibrate are reported.

Materials and methods

Selection of Cases

The criteria for inclusion of patients in the study were males over 20 years of age and females over 40 years of age with persistently elevated overnight fasting serum cholesterol levels of more than 220 mg/dl and/or a triglyceride level above 150 mg/dl, with no secondary causes of hyper1ipidaemia such as liver or renal disease, hypothyroidism and diabetes mellitus. Patients of angina pectoris having normal ECG at rest or of hypertension or patients with myocardial infarction were included in the trial only when their condition had stabilised. Patients with concomitant haemopoetic disease and women of child-bearing age were excluded from the study. Informed consent was obtained from all patients. All the patients were on dietary restrictions but none had taken any lipid-lowering agents for at least 8 wk prior to enrolment in the study.

Design of multicentric drug trial

Open Trial : The trial comprised of five stages. In the pre-diet period, patients were asked to attend the clinic, after an overnight fast, at weekly intervals for 3 wk. If the

lipid levels were persistently elevated, the subjects were placed on controlled diet for six weeks. If at the end of six weeks the fasting lipid levels were still raised and the weight of the patients was stable, they were given placebo tablets (comprising the excipient used for gugulipid in a dose of one tablet (500 mg) tds for 2 wk. After 2 wk of placebo, the patients were administered gugulipid in a dose of 500 mg tds for 12 wk and serum cholesterol and triglycerides were estimated at 2 wk intervals. After 12 wk, gugulipid was stopped and placebo in the same dosage was given for the next 8 wk. (Fig. 1).

Double-Blind Crossover :

Patients were put on Drug 1 (either gugulipid or clofibrate) in a dose of 500 mg tds daily for 12 weeks, followed by a placebo washout period till their lipid value returned to predrug levels. The patients were subsequently crossed over to Drug II (clofibrate to subjects who had earlier received gugulipid and vice versa) followed by another pdacebo washout period.

These trials were conducted at the following centres :
St. John's Medical College : Bangalore
Seth G.S. Medical College : Bombay
All India Institute of Medical Seiences : New Delhi
S.M.S. Medical College : Jaipur
K.G. Medical College : Lucknow
Govt. Medical College : Nagpur
Institute of Medical Sciences : Varanasi

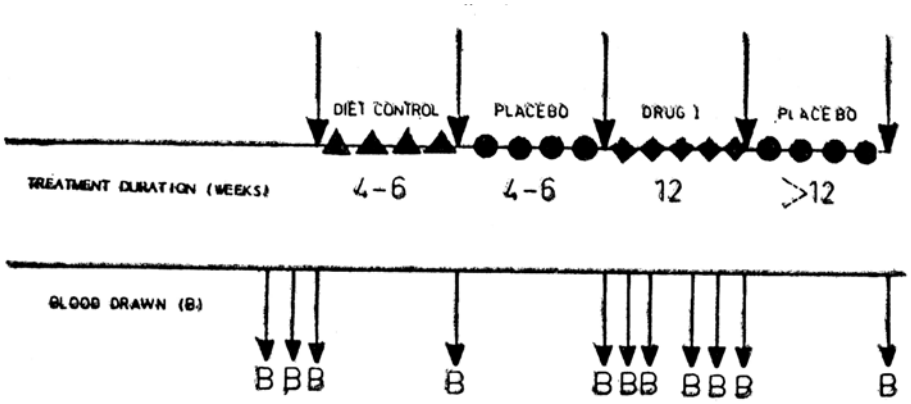

Fig.1 Design of open trial with gugulipid, arrows indicate time of blood sampling.

Serum cholesterol[14], serum triglycerides[15], HDL-cholesterol[16] were estimated by enzymatic methods at Lucknow which acted as Quality control centre.

Analysis at other places was with the method of Zlatkis *et al*[17], (cholesterol) triglycerides according to Van-Handel and Zilversmit[18] methods LDL-cholesterol was calculated according to Friedwald (1972)[19] Formula.

During the period of drug trial, patients continued to receive antianginal, antihypertensive and diuretic drugs, according to individual needs. Alcohol and smoking were discontinued. The dietary restrictions advised initially were continued throughout the study period.

Criteria of Response

Patients showing a fall in serum cholesterol and triglyceride levels of more than 6 and 11% respectively were taken as responders[12].

Statistical analysis

The results were expressed as the mean ± standard deviation. Statistical analysis of the results was performed by paired student t-test.

Results

In the present study, the data of responders and non-responders has been clubbed together and the pooled data has been analysed by paired t test for statistical significance[29], while in previous reports, lowering in serum cholesterol and triglycerides has been considered in responders. At Varanasi, serum triglycerides were estimated in only 3 patients at 12 wk study and therefore, t test could not be applied.

Phase I Study : The results of Phase I multiple dose clinical study given in Table I shows an average fall of 14.13% in serum cholesterol. In this study one patient complained of epigastric fullness three days after starting gugulipid, which could be controlled by oral antacid treatment[13].

Table I

Effect of gugulipid on serum cholesterol (values in mg% are expressed as mean ± SD)

No. of Patients	Duration (wk)	Dose (mg/day)	Serum Cholesterol (mg/dl) % Initial	Final	Fall
20	4-6	1200-1500	267.6±97.5	229.7±111.4*	14.13

*P<0.01; Responders-16 (80%)

Table II

Effect of gugulipid on serum cholesterol and triglycerides (Values mg% expressed as mean ± SD) Open Trial

Centre (No. of Patients)	Serum Cholesterol (mg/dl)			Serum Triglycerides (mg/dl)		
	Initial	Final	% Fall	Initial	Final	% Fall
Bombay (20)	250 ± 65.2	234 ± 51.7+	6.4	205 ±54.6	148 ± 76.2**	27.89
Delhi (26)	437 ±177.7	344 ±156.6**	20.7	296.25± 211	225.7±140.3**	23.81
Jaipur (a) (7)	272.22±29.49	228.69±31.98**	18.44	254.79±98.9	188.56±56.62**	24.86
Jaipur (b) (39)	285.22±45.26	222.98±40.57**	24.41	237.34±85.83	173.74±49.09**	27.96
Nagpur (15)	243.5 ±46.7	212.8 ±72.4*	13.6	137.9 ±89.4	120.9 ±98.6*	12.3
Lucknow (a) (22)	296.68±78.82	255.27±89.11**	16.48	208.86±96.13	154.59±92.11**	25.98
Lucknow (b) (19)	249.32±51.6	213.89±45.49**	14.21	309.68±200.65	216.53±110.5**	30.7
Varanasi (a) (45)	302.36± 7.05	261.53± 4.94**	14.29	98.22±6.49	79.71±4.56*	21.25
Varanasi (b) (12)	316.6 ±19.75	231.3 ± 33.66 + +	26.8	275.8±44.54	248.76±50.64	10.25

P Value + < 0.05; + + < 0.02; * < 0.01; ** < 0.001;

Multicentric Trials

A total of three hundred and thirty patients completed these trials. Though both the drugs were tolerated well, the compliance with gugulipid in general appeared to be better as many patients on clofibrate wanted to shift to gugulipid; two patients on clofibrate, one each in Bombay and Lucknow complained of flu like syndrome and had to be withdrawn from the trial; one patient with gugulipid complained of mild gastrointestinal symptom but did not require withdrawal of the drug.

Open Trial

Two hundred and five patients (164 males and 41 females) with mean age 52.2 years Completed the 12 wk trial with gugulipid therapy. A significant fall in serum cholesterol and triglycerides was observed at all centres. The average fall in serum cholesterol was 23.6% in 180 patients and in serum triglycerides 22.6% in 159 cases (Table II). By pooling the data of all the centres, it was observed that 87.8% patients responded to serum cholesterol and 77.5% to serum trigycerides. There were at least 20-30% patients who did not respond to gugulipid therapy.

Double-Blind Crossover

One hundred and twenty five patients (111 males, 14 females) with gugulipid and one hundred and eight patients (98 males, 10 females) with clofibrate completed the double blind cross over trial. Seventeen patients did not complete the study with clofibrate. 5 were lost to follow up and 12 refused to continue because of the previous experience of headache and nausea with clofibrate (Table III). A significant fall in serum cholesterol with both gugulipid and

Table III.

Number, age & sex of patients treated with gugulipid and clofibrate.

Centre	Gugulipid			Clofibrate			Mean Age
	No. of patients	Sex		No. of patients	Sex		(Yrs)
		Male	Female		Male	Female	
Bangalore	43	43	-	43	43	--	43.2
Bombay	18	14	4	18	14	4	50.0
Jaipur (a)	14	9	5	13	9	4	52 0
Jaipur (b)	9	7	2	5	5	-	48.6
Lucknow (a)	28	26	2	16	15	1	47.2
Lucknow (b)	13	12	1	13	12	1	51.6
Total	125	111	14	108	98	10	48.75

Table IV
Effect of gugulipid and clofibrate on serum cholesterol (Values mg% expressed as mean S.D.)
(Double blind trial)

Centre	No. of patients	Gugulipid Initial	Gugulipid Final	%Fall	No. of patients	Clofibrate Initial	Clofibrate Final	% Fall
Bangalore	43	282.7±11.17	227.67±15.5*	15.95	43	284.4±12.5	221.06±35.22*	22.28
Bombay	18	246.1±27.25	229.4 ±25.14*	6.9	18	194.2±103.36	183.5 ±70.5	5.5
Jaipur (a)	14	246.46±16.09	212.06±17.5*	17.0	13	248.2± 18 2	226.0 ±19.79*	8.9
Jaipur (b)	9	245.0 ±10.9	224.5 ±9.76*	8.5	5	240 8± 14.9	227.2 ±12.7*	5.66
Lucknow (a)	28	250.1 ±131.07	236.2 ±105.6+	5.6	16	224.0± 84.42	198.9 ±51.49+	11.2
Lucknow (b)	13	230.15±67 6	203.92±59.3·*	11.73	13	215.38±60.5	203.0 ±43.3	5.7
Total	125				108			

P Value *<0.001; +<0.05

Table V
Effect of gugulipid and clofibrate on serum triglycerides (Values mg% expressed as mean ± S.D.)
(Double blind trial)

Centre	No. of patients	Gugulipid Initial	Gugulipid Final	%Fall	No. of patients	Clofibrate Initial	Clofibrate Final	%Fall
Bangalore	43	174.3 ±9.3	148.4 ±17.75	14.8	43	175.7 ±19.2	155.3 ±15.5*	11.65
Bombay	18	161.58±48.07	135.27±57.63*	16.28	18	143.75±51.39	124.68±34.17	13.28
Jaipur (a)	14	167.33±16.94	143.0 ±15.58*	14.56	13	170.53±16.0	130.20±16.39*	23.72
Jaipur (b)	9	168.7 ±13.9	142.0 ± 9.9*	15.89	5	158.8 ±13.6	145.8 ±11.5+	8.22
Lucknow (a)	28	273.0 ±103.3	238.3 ± 84.33+	12.71	16	304.4 ± 60.7	180.8 ±54*	40.61
Lucknow (b)	13	335.07±168	244.23 ±114.4*	27.11	13	394.27±185.9	272.5 ± 164*	30.88
Total	125				108			

P Value *<0.001; +<0.01

Table VI

Response to gugulipid and clofibrate therapy in patients of primary hyperlipidaemia

(Values mg% are expressed as mean ± S.D.)

Drug	Responders		Mixed Hyperlipidaemia		Hypertriglyceridemia		Hypercholesterolemia	
	No.	Percentage	R/T	Percentage	R/T	Percentage	R/T	Percentage
Gugulipid (n=125)	110	88	86/91	94.5	16/24	66.6	8/10	80
Clofibrate (n=108)	90	83.3	67/75	89.3	19/22	86.6	4/11	36.3

$$R/T = \frac{\text{Responders}}{\text{Total cases}}$$

Table VII

Effect of gugulipid and clofibrate on HDL-cholesterol (Values mg% are expressed as mean ± S.D.)

(Double blind trial)

Centre	Gugulipid				Clofibrate			
	No. of patients	Initial	Final	%Increase	No. of patients	Initial	Final	%Increase
Bombay	7	48.57±4.75	55±5.77*	13.3	4	46.25±2.5	53.75±2.5*	16.3
Jaipur (a)	14	33.86±7.09	44.06±7.94*	30.1	13	35.6 ±5.84	37.86±6.38	5.57
Jaipur (b)	7	34 1 ±5.0	36.3 ±5.45	6.4	5	39.8 ±10.8	43.8 ±10.8	10.0
Lucknow	9	28.32±3.36	33.98±7.4*	20.2	10	33.2 ± 4.8	34.54± 4.7	3.9
Total	37				32			

*P Value < 0.01

Table VIII

Effect of gugulipid and clofibrate on LDL-cholesterol (Values mg% are expressed as mean ± S.D.)
(Double blind trial)

Centre	Gugulipid				Clofibrate			
	No. of patients	Initial	Final	%Fall	No. of patients	Initial	Final	%Fall
Bombay	7	170.8±33.6	146.7±31.2*	14.11	4	205.8 ±35.16	161.8±30.6+	21.46
Jaipur (a)	14	179.8±16.3	139.6±18.55*	22.34	13	175.07±15.64	157.69±14.37++	10.2
Jaipur (b)	7	165 ±39.8	151.6±29.8	8.84	5	165.8 ±18.5	153.8 ±13.42	8.9
Lucknow	8	141.2±91.9	118.8±79.7+	16.31	4	147.4 ±96.4	115.35±86.5+	22.69
Total	36				26			

P Values * < 0.001; + < 0.01; ++ < 0.05

Table IX

Ratio of LDL-C/HDL-C and Total cholesterol (TC)/HDL-C in Gugulipid and Clofibrate

Centre	No. of patients	Gugulipid				Clofibrate			
		LDL-C/HDL-C		TC/HDL-C		LDL-C/HDL-C		TC/HDL-C	
		Initial	Final	Initial	Final	Initial	Final	Initial	Final
Lucknow	13	4.41±3.31	3.8 ±2.88*	7.9 ±2.63	6.5 ±1.96**	3.68±2.52	3.6 ±1.55	7.25±2.52	6.37±1.29
Jaipur	14	5.60±1.05	3.38±0.82**	7.3 ±1.49	4.98±1.49**	5.27±0.72	4.34±0.63*	7.30±0.91	6.09±0.76+
Bombay	18	3.31±0.96	3.27±0.87	5.13±1.21	4.8 ±1.6	3.46±1.01	3.87±0.98	4.99±0.79	5.41±0.89

P Value * < 0.05; ** ≤ 0.001
+ < 0.01

clofibrate was observed in all centres, except in Bombay where the fall was observed only with gugulipid therapy. The average fall in serum cholesterol was 11% and 10% with gugulipid and clofibrate therapy respectively (Table IV). An average lowering of serum triglycerides 16.83% and 21.6% with gugulipid and clofibrate respectively was observed in all centres, except at Bombay (Table V). (Percentage responders to gugulipid and clofibrate in different types of primary hyperlipidaemia are shown in Table VI). In hypercholesterolemic patients, response with gugulipid was better and in patients of hypertriglycerinemia, clofibrate gave a better response. In mixed hyperlipidaemic patients response to both drugs was comparable. HDL-cholesterol estimation was carried out at Bombay, Jaipur, and Lucknow and it was significantly increased in 60% cases, who responded to gugulipid therapy. However, only 4 out of 40 cases showed an increase in HDL-cholesterol with clofibrate (Table VII). LDL-cholesterol decreased significantly with both drugs except in Jaipur (Table VIII). Non responder patients (30%) to one drug did not respond to the second drug also. No significant difference between the responder and the non-responder groups was noted in relation to age, sex, body weight, initial lipid levels, smoking and concomitant drug therapy. A significant decrease in LDL-C/HDL-C and total cholesterol HDL.-C ratio was observed with gugulipid (Table IX).

Conclusion

The present communication reports the findings of multicentric clinical trials carried out with gugulipid, a new antihyperhyperlipidemic agent, in primary hyperlipidaemic cases at seven centres in India coordinated by and in collaboration with the Central Drug Research Institute (CDRI), Lucknow.

Phase I clinical study, carried out at CDRI in 35 normal human volunteers established the safety of gugulipid after a single oral dose (200-2400 mg). On multiple dose administration at 400 mg tds for 4-6 wk in 20 patients of primary hyperlipidaemia, gugulipid was found to be safe and deyoid of adverse effect on haematological and biochemical parameters and electrocardiogram. The fall of serum cholesterol 14.13% was observed in 80% patients[13].

A pilot study to evaluate the efficacy of gugulipid in primary hyperlipidaemic patients was carried out at K.G. Medical College, Lucknow with a dose of 500 mg tds for 6 wk in 22 patients; gugulipid produced an average fall in serum cholesterol and triglycerides of 16.48% and 25.98% respectively[21]. The second study at the same centre on 19 primary hyperlipidaemic patients for a period of 12 wk showed a fall in serum cholesterol and triglycerides by 14.21% and 30.7% respectively which was highly significant. In both studies the lipid levels started to fall within 2-4 Wk of starting gugulipid and statistically significant lowering persisted after 6-8 wk of drug withdrawal. No side-effects were observed except in one patient who developed mild gastro-intestinal symptoms which did not necessitate withdrawal of the drug[22].

In double-blind crossover trial, the percentage lowering both of serum cholesterol and triglycerides was less variable with drugs. Gugulipid showed an edge over clofibrate in cholesterol-lowering effect and clofibrate over gugulipid in case of triglycerides, although percentage fall in both groups was not significantly different.

The effect of gugulipid on serum cholesterol and triglycerides is comparable to that of other hypolipidaemic agents. Clofibrate[20,23], nicotinic acid[20,24] and cholestyramine[25] lowered serum cholesterol by 6-12, 10-17 and 20-27 percent respectively. Beta-sitosterol[26] produced reduction in cholesterol by 10-15 percent. Clofibrate and nicotinic acid lowered triglyceride levels by 20-25 and 26 percent respectively[20]. HDL-cholesterol level has been shown to be strongly but inversely correlated with coronary artery disease risk[27]. In the present study a significant increase in HDL cholesterol was found in responders to gugulipid therapy. Clofibrate has been reported to cause a rise in HDL-cholesterol[28] but in this study this was not confirmed. Lowering of LDL-cholesterol was found with both drugs which could be indirectly due to decrease in serum cholesterol by diet and drugs. In this study a reduction in the ratio of LDL-C/HDL-C and TC/HDL-C was observed, more with gugulipid than with clofibrate in 45 patients. Larger sample studies have shown that reduction in total cholesterol and/or in low-density lipoprotein cholesterol/or an elevation in high-density lipoprotein cholesterol results in amelioration in cardiovascular end points[27].

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