A STUDY OF HYPOLIPIDEMIC EFFECTS OF METRONIDAZOLE

K. Shamkhani, M. Azarpira and M. H. Akbar

Doctor Heshmat Cardiovascular Research Center, Gilan University of Medical Sciences, Rasht, Iran

Abstract - Metronidazole, a synthetic derivative of the nitroimidazole class is a known antibacterial and antiprotozoal agent. The hypolipidemic effect of metronidazole was not known. The authors noticed it incidentally for the first time. After quazi experimental studies on several cases, it was revealed that 750 mg of metronidazole for 10 days significantly decreased serum cholesterol. This trial was performed in three stages of 14 days each as challenge, de-challenge and re-challenge on 30 subjects including 6 male and 24 female in the age limits of 40 to 73 years (mean 58.7 years). Results of present trial revealed that metronidazole 750 mg daily in divided doses for 14 days decreased the average of total blood cholesterol in 30 cases by 14.6% (P = 0.025) and LDL cholesterol by 19.1%. (P = 0.005). Decrease in serum cholesterol and triglyceride and increase in HDL cholesterol also accompanied fall of LDL cholesterol level. While comparing the mean of final results in 19 cases, with that of 30 subjects pre trial serum lipid profile it was revealed that treatment with 84 tablets of metronidazole in divided doses within six weeks of whole trial period was able to decrease the mean total cholesterol, LDL cholesterol and serum triglyceride by 16.23%. 21.2% and 23.9% respectively along with a rise of mean HDL cholesterol level by 9.85%. Further controlled study is recommended in large scale to evaluate the long-term benefit of metronidazole in controlling lipid disorders. Acta Medica Iranica 39 (3): 141-146; 2001

Key Words: Metronidazole, coronary artery disease, lipid correcting agent

INTRODUCTION

Metronidazole [1-(beta - hydroxyethyl) - 2 methyl - 5 - nitroimidazole], a synthetic derivative of the nitroimidazole class, is a known antibacterial and antiprotozoal agent. It is effective in therapy against protozoa such as trichomonas vaginalis, amebiasis, and giardiasis (1). In addition, it is one of the most effective drugs available against anaerobic infection. it is also useful in treating Crohn's disease, antibiotic - associated diarrhea, and rosacea. The two principal metabolites of metronidazole result from oxidation of side chains. Both have antitrichomonal activity. Formation of glucuronides is also observed.

Small quantities of reduced metabolites are formed by the gut flora (2).

Metronidazole is usually promptly and completely absorbed after oral administration reaching the plasma concentration of about 10 μg/ml approximately an hour after a single 500 mg dose; and the plasma concentration pertain for doses between 200 mg and 2000 mg. The half-life of this drug is about 8 hours, and its volume of distribution is approximately that of total body water. Liver is the main site of metabolism, which accounts for over 50% of the systemic clearance of metronidazole.

Studies in vitro and in vivo indicate that metronidazole has direct anti-inflammatory effects and effects on neutrophil motility, lymphocyte transformation and some aspects of a cell mediated immunity. Effects of metronidazole in vitro on neutrophil is dose-dependent inhibitory effects on generation of hydrogen peroxide and hydroxyl radicals, oxidants that may cause tissue injury at the site of inflammation.

The hypolipidemic effect of metromdazole was not known till to date. The authors have noticed it incidentally for the first time. In fall 1999, one of the known hyperlipidemic patients, a 45 year middle aged Guilani female who was taking metronidazole 1500 mg in three divided doses for fasciola hepatitis, showed significant decrease in total and LDL cholesterol along with 80% increase of her HDL cholesterol in routine serum lipid tests. On follow up blood tests after two months completion of her antiprotozoal course, albeit without metronidazole, her blood lipids were raised to the previous levels.

After quaziexperimental studies on several cases, it was revealed that 750 mg of metronidazole for 10 days significantly decreased serum cholesterol.

Our enthusiastic review of medical literature and search of archives of various medical and pharmaceutical journals did not show any hypolipidemic action of metronidazol. With the hypothesis that metronidazole may have a hypolipidemic side effect, this research project was designed as a drug trial.

MATERIALS AND METHODS

This drug trial was carried on 30 subjects who volunteerly agreed to participate in this drug trial. The subjects included 6 male and 24 female in the age limits of 40 years to 73 years (mean age 58.7 years). Selection of the subjects was according to formal consent and the following exclusion criteria.

Exclusion criteria

A - Those with these condition(s)

Active bone marrow suppression	Severe hepatic diseases
CNS diseases	Pregnancy
CHF (Congestive Heart Failure) Functional class III-IV	Breast feeding

B - Those who take these drugs

Disulfiram	Phenobarbital
Alcohol	Carbamazepine
Warfarin	Methadone
Cimetidine	Opium
Lithium	

During the trial period, subjects did not use any drug, interacting with metronidazole, or any drug that effects the lipid metabolism including diuretics and beta blockers. The subjects were on low tin diets including abstinence from hydrogenated cooking oils, animal fat and the dairy products. They continued the dietery routine, and did not alter their dietery habit.

This trial was performed in three stages of 14 days each as challenge, de-challenge and re-challenge. Blood sample of each patient was investigated for total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides and some other tests before and after each stage as followings.

Requested Laboratory-Data

Hematological	WBC & Diff, RBC, Hb. Hct.Platelets, PT, PTT, ESR
Metabolic	FBS, BUN, Creatinine, Uric acid
Enzymatic	AST, ALT, CPK

The above tests and blood lipids were performed four times for each subject in either Rasht social security medical laboratory or a private medical laboratory under the same professional superviser using fully enzymatic colorimetric test (CHOD-PAP) standard commercial kits, supplied by the Pars Azmun Comany, Tehran, Iran. The fully enzymatic colorimetric test kit for LDL cholesterol was supplied by the RANDOX Laboratories, Crumlin, UK.

The pre-trial laboratory reports were tabulated as intact levels. Metronidazole 250 mg tablets manufactured by Amin pharmaceuticals Tehran were bought from a pharmacy. They were removed from the commercial and titled package, put into the ordinary envelopes and 42-tablet were delivered to each of the subjects for 14 days regular intake.

In first stage (challenge stage), after having the baseline blood lipid profile (Intact), the subjects started taking metronidazole 250mg tablets three times daily for 14 days.

After two weeks of ingestion of the drug, second blood samples were tested for serum lipids to get the result of drug challenge.

Other hematology and liver function tests were also carried out to rule out any side effects. During the drug trial probable intolerance or side effects of the drug were asked from each subject and noted down according to the following proforma.

Side effects of Meronidazole

Gastrointestinal		Dermatological
Metallic taste	Nausea	
Vomiting	Anorexia	
Abdominal pain		Urticaria
		Pruritus
		Exanthema
Nervous system		Miscellaneous
Light headiness	Dizziness	Flushing
	Photophobia	
		Phlebitis
Head ache	Parasthesia	
Ataxia	Seizure	
Encephalopathy	Mood changes	

The second stage (de-challenge stage) was fourteen drug-free days to assess the fading effects of metronidazole on serum lipids. At the end of 14 days of de-challenge, 21-patients who had been participating in challenge and de-challenge stages were called for blood test. After blood sampling they were advised to start taking metronidazole 250 mg three times a day for another 14 days (re-challenge). The final blood sample was examined from each case for serum lipids and other tests. Reports of 20 cases were available for analysis.. Report of LDL cholesterol was missing in one case.

Data were analyzed according to standard health system research methodology and with the help of statistical package for social sciences (SPSS) using students t test.

RESULTS

Among 30 cases, the mean total cholesterol in this drug trial was decreased by 14.6% (Fig. 1). (P= 0.025). The mean LDL cholesterol decreased by 19.1% (P = 0.005) with the drug challenge (Fig. 2).

After de challenging, the total cholesterol and LDL cholesterol were risen near to the pre challenge level. At the end of re-challenge; mean total cholesterol fell down by 17% and LDL cholesterol decreased by 22% (Table 1).

Table 1. Summary of Results

Blood lipids	Effects of metronidazole, 250 mg			
	Re-challenge 84 tablets		challenge 42	
	Alteration rate	P value	Alteration rate	P value
Total cholesterol	-14.60%	0.025	-16.23%	0.005
LDL-C	-19.12%	0.005	-21.19%	0.005
HDL-C	(+) 2.84	NS	(+) 9.85%	
Triglyceride	-2.22%	NS	-23.95%	

NS = Non significant.

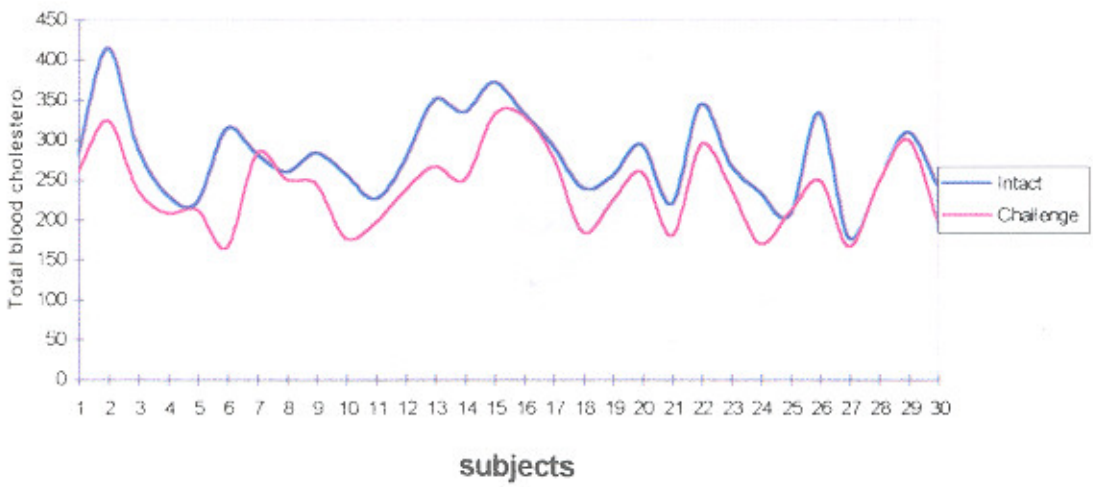


Fig. 1. Effects of Metronidazole on total blood cholesterol (Intact vs Challenge)
BC = Blood Cholesterol (mg/dl)

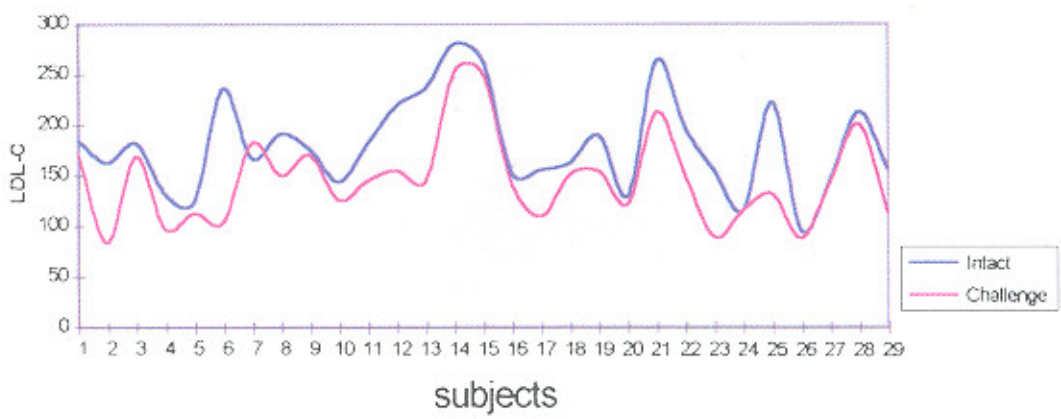


Fig. 2. Effect of Metronidazole on LDL-C (Intact vs Challenge)
LDL-C = Low density lipoprotein cholesterol (mg/dl)

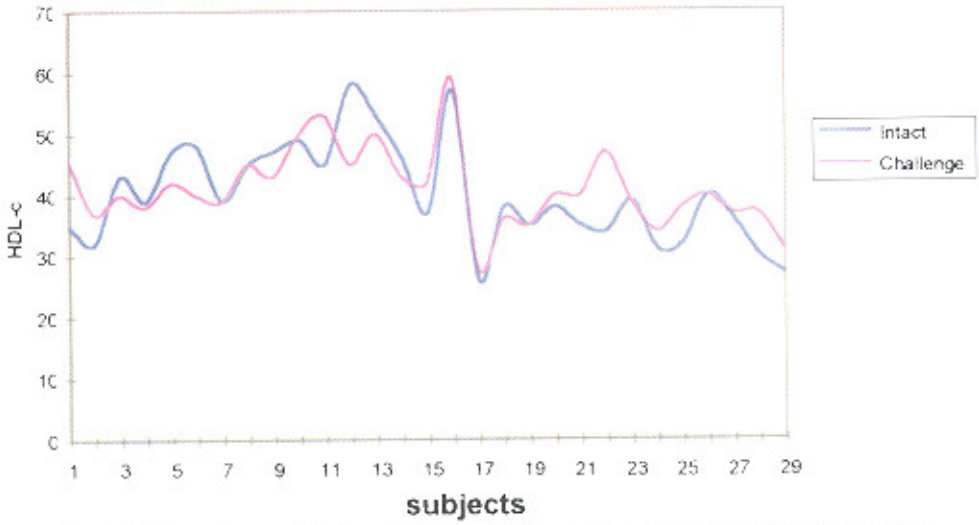


Fig. 3. Effects of metronidazole on High density lipoprotein - cholesterol (intact vs challenge)
HDL-C = High density lipoprotein - cholesterol (mg/dl)

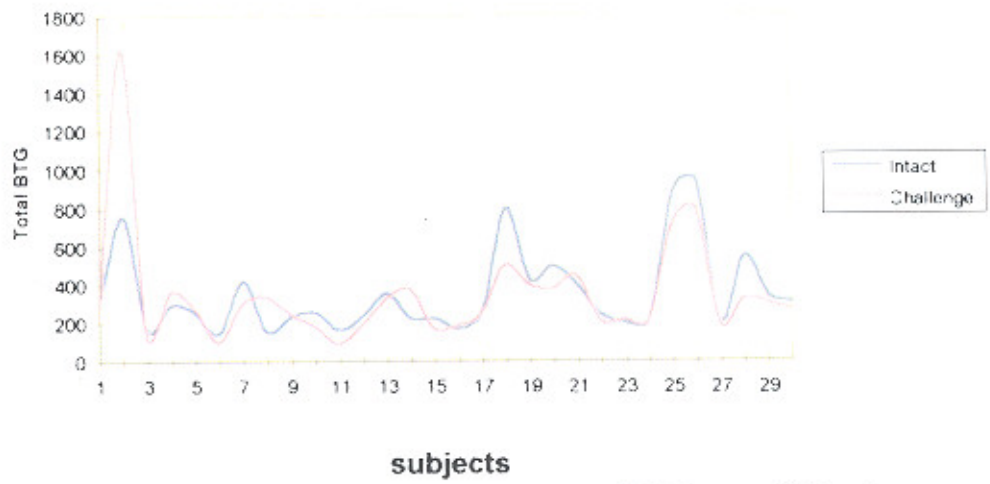
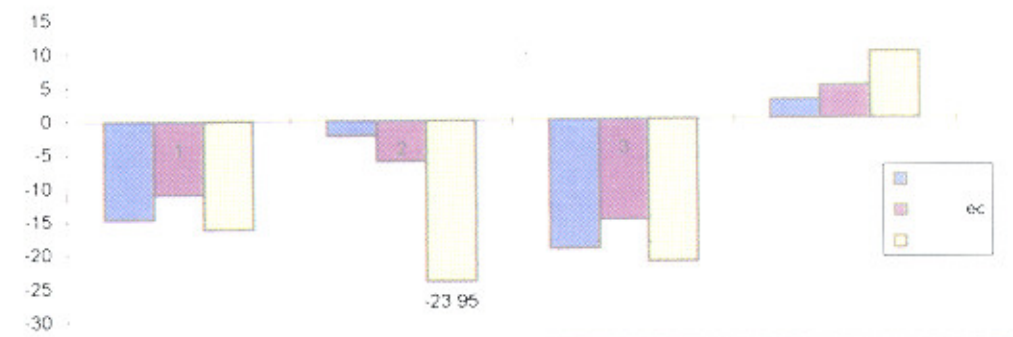


Fig. 4. Effects of Metronidazole on total BTG (Intact vs Challenge)
BTG = Blood triglyceride (mg/dl)



BC = blood cholesterol, TG = triglyceride, LDL-c = low density lipoprotein cholesterol
HDL-c = high density lipoprotein cholesterol, I-Ch = intact vs. challenge
Dec-Rec = dechallenge vs. rechallenge, I-Rec = Intact vs. rechallenge

Fig. 5. Effects of Metronidazole on Blood Lipids (in percent)

Changes in the mean of HDL level in all the three stages were positive but not significant. Rise of HDL cholesterol at challenge stage has been illustrated in Figure3. Insignificant increase of blood triglyceride average has been shown in Figure 4. No pathologic change was noticed in other parameters of blood tests including blood cell counts and liver function tests. While comparing the mean of final results in 19 cases with that of 30 subjects pre-trial serum lipid profile it was revealed that treatment with 84 tablets (250 mg each) of metronidazole in divided doses within six weeks of whole trial period was able to decrease the mean total cholesterol, LDL cholesterol and serum triglycerides by 16.2%. 21.2% and 23.9% respectively along with a rise of mean HDL cholesterol level by 9.85% (Table 2). The final results illustrating the effects of metronidazole on lipid profile of 30 subjects have been summarized in figure 5.

DISCUSSION

Lipid disorders are common and are an important cause of premature coronary artery disease (3). Intervention with diet and drugs to reduce cholesterol has been proven to decrease the risk of subsequent cardiovascular events, including total mortality (4).

Based on the wealth of clinical trial data, it is widely agreed that virtually all patients with coronary artery disease (CAD) should be on lipid lowering drug therapy to reduce their risk of subsequent event (5).

The mechanism of action of the metronidazole is reflected in a selective toxicity to anaerobic or microaerophillic microorganism and for anoxic or hypoxic cells. The nitro group of metronidazole accepts electron from electron transport proteins such a flavoproteins in mammalian cells and ferodoxins or their equivalent in bacteria and diverts them from normal energy yielding pathways. The source of electrons for the reduction may be a number of endogenous reduced substitutes such as reduced nicotinamide adenine dinucleotide phosphate (NADPH) or sulfide. Reduced metronidazole then disrupts DNA's helical structure, thereby impairing bacterial nucleic acid synthesis (6). This eventually results in bacterial cell death.

On the other hand, imidazole, being the basic structure of nitroimidazole, is a potent anti fungal agent. The major effect of imidazole on fungi is inhibition of sterol 14-alpha - demthylase, a microsomal cytochrome pseudo - dependent enzyme system (7). Inhibition of this enzyme impairs the biosynthesis of ergosterol for cytoplasm membrane and finally leads to impairment of certain membrane bond enzyme systems function and inhibiting growth. Lipid - lowering effect of metronidazole has not yet been described in any scientific literature or medical texts. The author of this paper incidentally noticed this for the first time. Results of present trial suggest that metronidazole 750 mg daily in divided doses lowers total cholesterol by 14.5% and LDL cholesterol by 19.1%. Decrease in serum cholesterol and LDL cholesterol was accompanied by decrease in serum triglyceride along with increase in HDL cholesterol.

In quazi experimental basis, in a patient 1500 mg daily intake of metronidazole for 15 days led to 50% decrease in LDL cholesterol with an 80% increase in HDL level. While comparing the mean of final results in 19 cases with that of 30 subjects pre-trial serum lipid profile it was revealed that 84 tablets (250 mg each) of metronidazole in divided doses within six weeks of whole trial period were able to decrease the mean total cholesterol, LDL cholesterol and serum triglycerides by 16.2%. 21.2% and 23.9% respectively along with a rise of mean HDL cholesterol level by 9.85%.

Regarding the changes in serum lipid profiles revealed by this drug trial, it seems that besides the cholesterol lowering effect, metronidazole also corrects the dyslipidemia. The inhibition of cholesterol synthesis by metronidazole might be involved in the lipid lowering mechanism. Antimicrobial effect of metronidazole cannot clearly explain the antilipidemic effect. There is most probably another intracellular biochemical action, which is involved in lipid correcting effect.

Lowering LDL cholesterol and increasing HDL cholesterol means correcting the lipid profile. Further controlled study is recommended in large scale to evaluate the long-term benefit of metronidazole in controlling lipid disorders.

Acknowledgements

We thank Dr. AR. Dehpour, and Dr. Ali Nikpour and his medical team in Rasht Social Security medical insurance polyclinic.

REFERENCES

1 .Goldsniith RA: Antiprotozoal drugs, In: Katzung, BG (Ed.) Basic and Clinical Pharmacology (6th. Ed.); Prentice Hall Int. London. 780-802; 1995.

2. Sande, MA, Man deli, GL et al; Chemotherapy Of microbial diseases. In: Goodman & Gilman (eds.) The Pharmacological Basis of Therapeutics. 8th edition Maxwell Macmillan, New York. 1018-1200; 1991.

3. Ellsworth DL, Sholinsky P. Jaquish C, et al: Coronary heart disease. at the interface of molecular genetics and preventive medicine. Am J Prev Med. 16:122-133; 1999.

4. Heinekens CH: Increasing burden of cardiovascular disease: Current knowledge and future directions for research on risk factors. Circulation. 97:1095-1102; 1998.

5. 4S Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (45). Lancet. 344: 1383-1389; 1994.

6. Webster, LT; Drugs used in chemotherapy of protozoal infection. In: Goodman & Gillman (eds.) The Pharmacological Basis of Therapeutics. 8th edition Maxwell Macmillan, New York. 999-1007; 1991.

7. Bennett JE; Antimicrobial agents; In: Goodman & Gillman (eds.) The Pharmacological Basis of Therapeutics. 8th edition Maxwell Macmillan, New York. 1165-1181; 1991.