

Topical timolol and serum lipoproteins

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Abstract

Oral timolol taken for the treatment of systemic hypertension has been shown to affect adversely serum lipoprotein levels. In a 15-week study on 19 patients topical timolol therapy for raised intraocular pressure was found to have no significant adverse effect on serum lipoprotein levels. This is reassuring in view of the large number of patients on this form of long term therapy, and selection of the type of β blocker to use should not be influenced by lipid changes associated with the oral form of the drug.

β Blockers taken orally for antihypertensive therapy have been shown in numerous studies to have a significant effect on serum lipoproteins.¹⁻⁵ Of the various types of β blockers in use those that are non-selective and without intrinsic sympathomimetic activity (ISA), such as propranolol or timolol, cause the most pronounced changes, with an average increase in serum triglycerides (TG) of 32%, while high density lipoproteins (HDL) were lowered by 16%.¹ HDL concentration bears an inverse relation to coronary heart disease, as was pointed out by Miller and Miller and since confirmed in several prospective studies.⁶⁻⁹ The relation of TG concentration to coronary heart disease, however, remains unclear.^{9,10}

Topical β blockers are widely used and often the first line of therapy in many patients requiring treatment for glaucoma or ocular hypertension. A large proportion of these patients are or will be on long term therapy over many years. With other systemic adverse effects from topical β blocker therapy already described,¹¹ we decided to carry out a prospective study using a non-selective β blocker to ascertain that a side effect on serum lipoprotein levels was not going undetected in so many patients on treatment for glaucoma.

Materials and methods

This was a prospective study to see if there was any change in serum lipoprotein levels at 5 and 15 weeks from the beginning of topical timolol therapy. Patients to be started on topical timolol for raised intraocular pressure presenting or

already attending the ophthalmic outpatients department were enrolled in the study.

Procedure. A fasting lipid sample was obtained without venous stasis on the morning before starting therapy, with abstinence from alcohol the previous day. All patients were prescribed timolol 0.5% twice daily to both eyes, and repeat fasting lipid samples were taken at 5 and 15 weeks. Laboratory lipid analysis was carried out on a COBAS BIO centrifugal analyser using Technicom methodology with frequent control serum analysis. TG, HDL, and total cholesterol (TC) only were measured.

Exclusion criteria. Patients excluded were those already on oral β blockers or thiazide diuretics; those who were grossly overweight or with known hyperlipidaemias or with a family history of such; and those with obstructive airways disease, heart block or failure, or with moderate to heavy alcohol intake.

Results

A total of 19 patients were enrolled in the study. Their mean age was 67.5 years, median 63 years, and range from 46 to 80 years. The male to female ratio was 11 to 8. All patients completed five weeks of therapy; however, two were withdrawn before 15 weeks, one because of poor compliance and the other because of drainage surgery.

Table 1 shows the mean values obtained for the various lipid fractions at baseline and at 5 and 15 weeks with standard deviations (SD), mean change, and *t* values. No significant change in any of the lipid fractions was observed at any time.

Retrospective analysis of the data was carried out to establish adequate study power to detect a difference from baseline of 0.3 mmol/l (minimum) in the TG fraction for a type II error of 0.1 (power 90%). The 95% confidence intervals for the true mean difference are -0.22 to 0.14 mmol/l at 5 weeks and -0.11 to 0.3 mmol/l at 15 weeks by the usual formula based on the *t* distribution.

Discussion

The risk of coronary heart disease is known to be influenced by blood lipid levels. There is a

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Table 1 Mean values for lipid fractions with standard deviation, mean change, and *t* values

	5 weeks figures (19 patients)				15 weeks figures (17 patients)			
	Baseline Mean (SD)	5 Weeks Mean (SD)	Difference	<i>t</i>	Baseline Mean (SD)	15 Weeks Mean (SD)	Difference	<i>t</i>
TC	6.03 (0.96)	6.12 (1.08)	+0.09	0.258	5.91 (0.94)	6.11 (1.09)	-0.2	0.572
TG	1.54 (0.62)	1.505 (0.59)	-0.035	0.177	1.482 (0.49)	1.59 (0.76)	+0.108	0.494
HDL	1.45 (0.3)	1.4 (0.24)	-0.05	0.54	1.435 (0.27)	1.376 (0.26)	-0.059	0.649

TC: total cholesterol. TG: triglycerides. HDL: high density lipoproteins.

significant correlation between total cholesterol and risk of disease but weak correlation between triglyceride concentration and risk.⁹ Of the cholesterol subfractions, the low density lipoprotein (LDL) concentration (the main transporting lipoprotein) appears to have the most significant effect,¹²⁻¹³ while HDL concentration correlates inversely with risk and would appear to be cardioprotective.⁶⁻⁹ Systemic β blockers are known to affect serum lipoproteins levels adversely, the amount of change depending on the type of β blocker. Oral therapy with non-selective β blockers without ISA cause the most pronounced changes, with an average increase in serum TG concentration of 32% and lowering of HDL concentration by 16%. Selective β blockers without ISA have less pronounced effect (TG: +20%, HDL: -7%), while non-selective blockers with ISA have least effect (TG: +18%, HDL: -1%).¹

Drug therapy for hypertension has failed to show a definite protection against coronary heart disease, and some workers consider that the benefit from blood pressure reduction may be outweighed by the adverse influence of therapy on serum lipoproteins levels.¹⁴ Topical β blockers are now an established first line treatment in glaucoma. There is a significant incidence of systemic side effects (some serious), and, because of these, topical β blockers must be prescribed with caution in certain patients. That such small doses of drug applied to the eye can produce such systemic side effects has been attributed in part to the fact that, unlike oral β blockers, which are extensively metabolised in the liver before entering the general circulation,¹⁵ topical β blockers are absorbed directly through the conjunctiva and nasal mucosa (first order pass). However, studies show that topically applied β blockers rarely reach serum levels normally considered therapeutic for antihypertensive treatment,^{16 17} and despite this side effects are still experienced. Moreover, studies on healthy volunteers show that topical β blockers reduce exercise induced tachycardia and slightly decrease the resting pulse rate.^{16 18}

Our lipid analysis at 5 and 15 weeks should detect any change in lipid fractions if present, as the change produced by oral therapy occurred by

8 weeks and was little changed thereafter. The results show no significant adverse effect on serum lipoproteins as a consequence of topical β blocker therapy. This is reassuring in view of the large number of patients on long term therapy for raised intraocular pressure, and there appears to be no justification for using selective β blockers, or those drugs with ISA, on the basis of the adverse effects on serum lipoproteins shown for the oral form of therapy.

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