5. The effects of Antihypertensive Drugs on Serum Lipids and Lipoproteins in patients with Mild to Moderate Hypertension

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The purpose of antihypertensive therapy is to prevent the development and exacerbation of complications in target organs, such as the brain, heart and kidney. Thus, the efficacy of an antihypertensive drug should be based on the reduction in these complications as well as the frequency and severity of side effects. From this point of view, several clinical trials to assess the benefits of long-term treatment with antihypertensive drugs have been performed in Western countries (1-8). They have shown a significant reduction in the incidence of stroke, congestive heart failure, renal failure and aneurysmal rupture, but little effect on coronary heart disease (CHD), although hypertension is one of the three major risk factors for CHD. It has been proposed that antihypertensive drugs may have an adverse effect on plasma lipids and lipoproteins metabolism, offsetting their beneficial effects in CHD. To evaluate this hypothesis, the relationship between changes in lipids and lipoproteins and the incidence of CHD in long-term antihypertensive

drug therapy must be investigated. Unfortunately few reports have examined this correlation, and consequently little information is available for determining the extent to which changes in lipids or lipoproteins contribute to CHD. Therefore, we have summarized the effect of antihypertensive drugs on lipids by reviewing published reports, including our own, and analyzed these changes in terms of the probability of developing CHD using the published risk table (9). It is important to appreciate the significance of small changes in serum cholesterol and establish criteria for the selection of antihypertensive drugs.

We reviewed 44 reports on diuretics, 46 on β -blockers without intrinsic sympathomimetic activity (ISA), 17 on β -blockers with ISA, 10 on α - β -blockers, 21 on α_1 -blockers, 5 on α_2 -agonists, 5 on other antiadrenergic drugs, 8 on Ca^{++} -antagonists and 6 on angiotensin converting enzyme inhibitors (ACE inhibitors). Table 1 summarizes the effects of these drug therapies on serum

Table 1. Effects of Antihypertensive drugs on Serum lipids and Lipoproteins

Agents		T. chol.	TG	HDL-C	LDL-C
Thiazide type diuretics	(Bendroflumethiazide, Chlorthalidone, Polythiazide)	↑↑ ~	↑↑	~ ↓	↑↑
Loop diuretics	(Furosemide, Mefurside)	↓	↑↓	↓↓	↑
β -blocker					
ISA (-)	(Propranolol, Nadorol, Timolol, Sotalol, Atenolol, Metoprolol)	↑↑ ~	↑↑	↓↓	↑↑ ~
ISA (+)	(Oxprenolol, Pindolol, Acebutolol)	↓ ~	↑↓	↑↑	~
α - β -blocker	(Labetalol, Bunibetolol)	↓ ~	↑↓	~ ↓↓	↓
α_1 -blocker	(Prazosin, Bunazosin, Terazosin, Doxazosin)	↓↓ ~	↓↓ ~	↑↑ ~	↓↓
α_2 -agonist	(Guanabenz, Guanfacine)	↓↓	~	~	↓
Other antiadrenergic	(Methyldopa, Clonidine)	↑ ~	~	↓↓	↓↓
Ca^{++} -antagonist	(Verapamil, Nifedipine, Diltiazem, Nifedipine)	~	~	~	~
ACE inhibitor	(Captopril, Enalapril)	↑↑ ~	~ ↓	↑ ~	~

↑↑ ↑↓ : statistically significant change, ↑ ↓ : small change, ~ : no change

Table 2. Antihypertensive drug therapy and the probability of coronary heart disease

Drug	Study	No patients	Age (y/o)	SBP mmHg Before (Δ)	TC mg/dl Before (Δ)	TG mg/dl Before (Δ)	HDL-C mg/dl Before (Δ)	Probability of CHD (%/8 years) [†]		
								no Treatment	Treatment	If no changes of TC
HCTZ	Ames et al ¹⁰⁾	47	55	150 (-15)	225 (+12)	139 (+39)	47 (-1)	15.4	13.2	12.4
PROP	Day et al ¹¹⁾	16	46	169 (-37)	252 (+15)	124 (+61)	—	10.4	7.9	7.0
PIND	Leven et al ¹²⁾	10	55	166 (-16)	260 (-12)	147 (-13)	50 (+2)	19.3	15.1	15.9
ATENO	Author et al	23	52	162 (-14)	229 (-10)	181 (-26)	58 (-1)	11.6	8.8	9.5
LABET	Author et al	11	52	185 (-24)	216 (+6)	158 (-22)	50 (+4)	14.4	10.8	10.7
PRAZO	Author et al	40	57	165 (-14)	218 (-7)	171 (-34)	52 (+1)	15.3	12.7	13.2
GUANA	Author et al	38	55	173 (-21)	207 (-7)	174 (+3)	51 (-5)	15.9	12.2	12.8
GUANF	Author et al	21	57	168 (-18)	219 (-7)	141 (-37)	61 (-1)	16.1	12.8	13.3
NIFED	Author et al	55	56	169 (-28)	192 (-1)	133 (-1)	50 (-1)	14.0	9.6	9.7
CAPTO	Author et al	21	52	161 (-19)	187 (0)	119 (+5)	51 (-2)	9.0	6.9	6.9

[†]: calculate the probability according to the Risk Table, on the assumption that patients are all men who have no other risk factor

Δ : changes during therapy

lipids and lipoproteins. In generally, adverse effects were reported with thiazide diuretics and β -blockers without ISA, desirable effects with α_1 -blockers, α_2 -agonists and ACE inhibitors, and no significant effect with loop diuretics, β -blockers with ISA, and Ca^{++} antagonists.

Table 2 shows the probability of hypertensive patients developing CHD over 8 years, with and without drug therapy, assuming that no other risk factors are present. It is necessary to assume that the risk table is applicable to therapeutically manipulated blood pressures and serum cholesterol levels and that these values remain constant during therapy. Obviously even a small change in the serum cholesterol level has a significant effect on the probability of developing CHD and should not be ignored. There is evidence that the incidence of CHD also may be affected by a number of other factors, for example the levels of serum triglyceride (TG) and HDL-C, smoking habits, and glucose tolerance. Therefore, it is possible that the actual changes in serum lipids or lipoproteins with therapy may be sufficient to reduce or offset the beneficial effect of blood pressure control on the development of CHD.

In conclusion, antihypertensive drugs which have no adverse effect on lipids metabolism should be chosen for the treatment of mild to moderate hypertension.

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