A Comparison of Blood Lipid and Blood Pressure Responses During the Treatment of Systemic Hypertension with Indapamide and with Thiazides

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Thiazide diuretics in high dosage adversely affect the lipid profile. The non-thiazide indoline, indapamide, appears to be free of this effect, but it is unclear whether this apparent metabolic advantage of indapamide is superior to thiazides used in low dose. Since there are no large direct comparative studies to test this distinction, I surveyed the literature and pooled the findings of all published reports giving data on both lipid and blood pressure effects of thiazides in various doses and of indapamide, 2.5 mg daily, used as monotherapy of hypertension. I found 31 reports of thiazides; 12 of them examined low-dose regimens, i.e., ≤25 mg/day of hydrochlorothiazide or its equivalent in other thiazides. Larger doses of thiazides were tested in 19 studies (median daily dose of 50 mg, maximum dose of 112.5 mg): There were 430 subjects in the low-dose studies and 559 subjects in the high-dose regimens. There were 13 studies of indapamide, comprising 558 subjects. Regarding lipids, total cholesterol increased from baseline by 1.4% on indapamide, 3.8% on low-dose thiazides, and 6.3% on high-dose thiazides. The change from baseline was significantly greater for high-dose thiazides than for indapamide ($p < 0.01$). Changes in high-density lipoprotein cholesterol did not differ among groups. The change in triglycerides differed among regimens, −0.5%, 10.8%, and 19.5% for indapamide, low-dose thiazides, and high-dose thiazides, respectively ($p < 0.01$). Systolic blood pressure (SBP) decreased by 13 and 18 mm Hg on low-dose and high-dose thiazides, respectively ($p < 0.05$ between doses). Indapamide lowered SBP by 16 mm Hg, not different from either thiazide dose. Diastolic blood pressure did not differ among groups. From these noncomparative studies, I conclude that (1) indapamide has no adverse lipid effect and lowers blood pressure equally to thiazides; (2) thiazide effects on lipids and SBP are dose-dependent; and (3) thiazides adversely affect the lipid profile even in low dose.

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Thiazide diuretics, when used in the treatment of hypertension, are known to raise blood lipid concentrations.[1] This effect has been observed primarily with high-dose therapy. Both low-dose thiazides and indapamide have been shown in some studies to avert this adverse lipid effect.[2,3] However, the evidence regarding thiazides is not uniform,[4] and it is unclear whether low-dose thiazides and indapamide differ with respect to lipid effects. Further, a question remains whether antihypertensive effectiveness is maintained with low-dose therapy. To answer these questions, a large-scale trial comparing various doses of thiazides with indapamide would be needed. No such study has ever been done. A small-scale study of this type showed equivalence of metabolic effects, but indapamide seemed to affect high-density lipoprotein (HDL) cholesterol more favorably.[3] To fill the information gap, I undertook a meta-analysis of all studies giving information on both lipid and antihypertensive effects of thiazides in various doses and of indapamide 2.5 mg/day.

METHODS

A review of the literature was undertaken for reports giving data on both lipid and antihypertensive effects of indapamide and thiazide diuretics. Articles were identified by Medline search and by inspection of references from retrieved articles. To be acceptable for this analysis, measurements of blood pressure and at least one lipid component had to be reported during a nondrug control period and during monotherapy with indapamide or with a thiazide agent. In most studies, the control period preceded the drug-treatment phase. However, in a few studies of thiazides, the control measurements were made after discontinuing the drug. In some studies the only lipid constituent reported was total cholesterol. Apolipoproteins were assayed too infrequently to be included in this report. The selection criteria for both lipid and blood pressure data in this analysis allowed the ascertainment of both efficacy and lipid effects in the same patient groups.

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In the statistical analysis, the overall mean value of each index was obtained by weighting the means of individual studies by the number of subjects examined. The standard deviations and standard errors were based on the variance of the weighted means. Comparison of group means was conducted by unpaired *t* tests or 1-way analysis of variance. The degrees of freedom used for the intergroup comparisons were derived from the number of studies and not from the number of subjects; *t* tests were 2-tailed, and significance was designated at the 0.05 level.

RESULTS

A total of 13 studies provided data on both lipid and blood pressure effects of indapamide.[3,5–17] Lipid data from these reports are displayed in Figure 1. The figure shows the mean percent change from baseline for total cholesterol, HDL cholesterol, and triglycerides for each report. The studies are arranged according to increasing duration of treatment with indapamide. Five studies provided data on >1 time-point during treatment.[5,7,9,15,17] Each datum point during treatment was included in the figure. Thus, there are 21 bars of data on the percent change in total cholesterol during treatment with indapamide. This arrangement allows for a quick visual assessment of whether there is a trend over time in lipid effects. Actually, total cholesterol trends from a slight upward change in short-term therapy to a downward change during treatment of ≥1 year. However, all the data on treatment of ≥1 year were provided by 1 small study.[15] When this study was omitted, the trend became statistically nonsignificant. Hence, confirmation is needed for a downward trend over time in the change of total cholesterol during treatment with indapamide.

The overall mean and standard deviation of each lipid index is shown at the far right of each row of bars. The number of subjects examined in obtaining this mean is noted at the right. As stated previously, some studies did not test for HDL cholesterol. Hence, the number of subjects comprising this mean is smaller.

The mean percent change from baseline in total cholesterol was 1.4% during treatment with indapamide. The mean change in HDL cholesterol was 5.5%, and in triglycerides was −0.5%. None of these changes was statistically significant.

Thiazides were examined in a similar manner, as shown in Figure 2. Hydrochlorothiazide was the most commonly studied thiazide. Hence, all other thiazides are expressed as approximate milligram equivalents of hydrochlorothiazide. For example, chlorthalidone was considered equivalent to hydro-

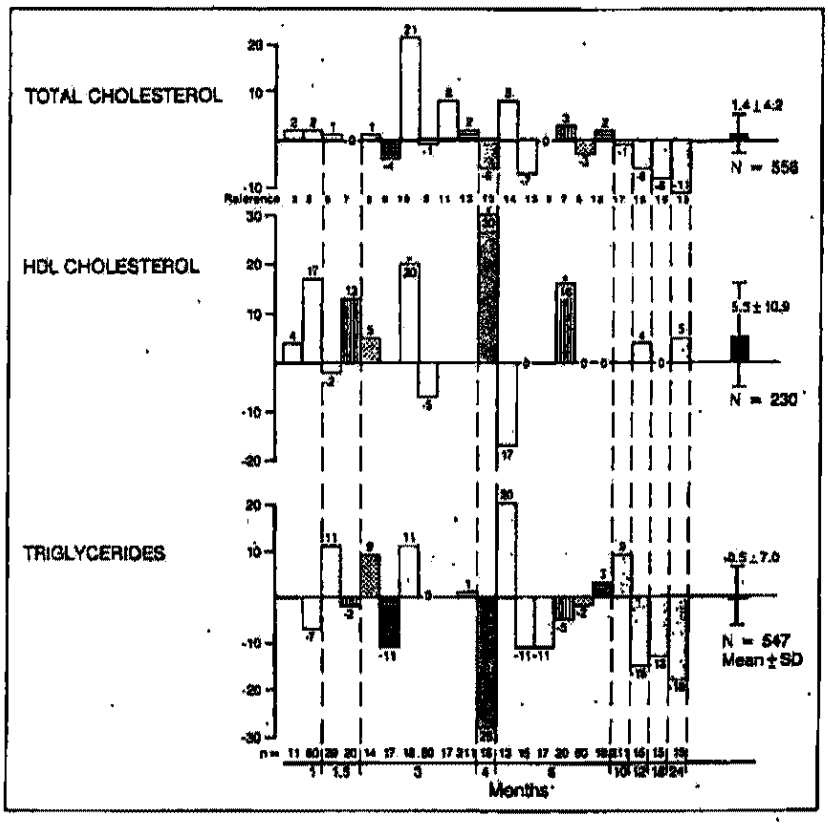

FIGURE 1. Percent change from baseline in total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides arranged according to the duration of monotherapy with indapamide 2.5 mg/day. *p <0.05 versus baseline. The shading of some bars is intended to be a visual aid in identifying vertically the lipid values of individual studies. (Reprinted with permission from W. B. Saunders.[38])

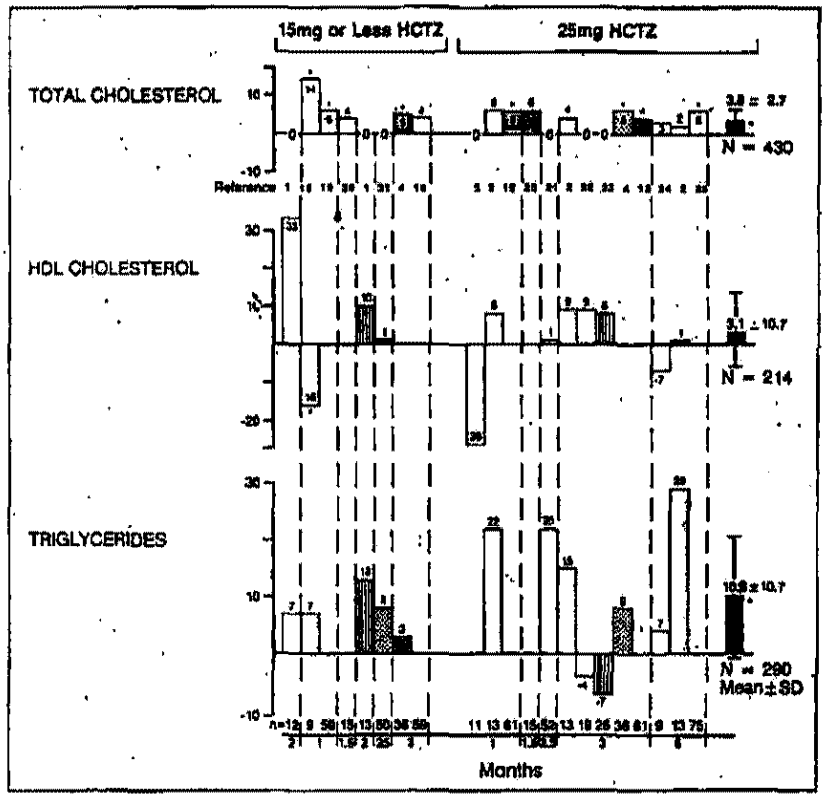

FIGURE 2. Percent change from baseline in total cholesterol, HDL cholesterol, and triglycerides arranged according to the duration of monotherapy with various doses of thiazide diuretics. HCTZ = hydrochlorothiazide. *p ≤0.05 versus baseline. (Reprinted with permission from W. B. Saunders.[38])

chlorothiazide on a milligram basis. Cyclopenthiazide and bendroflumethiazide were judged 10 times more potent than hydrochlorothiazide on a milligram basis.

In Figure 2, thiazide trials are separated into 2 groups, termed very-low-dose and low-dose hydrochlorothiazide groups. Very-low-dose represents studies of ≤15 mg of hydrochlorothiazide or its equivalent in other thiazides. There were 6 studies providing 8 data points concerning effects of very-low-dose thiazides on total cholesterol.[2,4,17–20] There were 10 studies providing 13 data points on the effects of low-dose hydrochlorothiazide on total cholesterol.[2,4,19–25] Low-dose hydrochlorothiazide was 25 mg/day or its equivalent. In contrast to indapamide, none of the data points for thiazides showed a decrease in total cholesterol. As shown in Figure 2, 3 of 8 data points for very-low-dose hydrochlorothiazide showed statistically significant increases. The overall mean change in lipids on very-low-dose hydrochlorothiazide did not differ from low-dose hydrochlorothiazide. Hence, these 2 subgroups were combined to obtain the overall mean shown at the right of the respective rows. The combined subgroups were subsumed under the term "low-dose thiazides." The mean percent increase in total cholesterol was 3.8%, in HDL cholesterol was 3.1%, and in triglycerides was 10.8%. The increases from baseline in total cholesterol and triglycerides were statistically significant, $p < 0.01$.

A similar analysis was undertaken for doses of hydrochlorothiazide >25 mg/day or its equivalent in other thiazides. In this dosage range, there were 19 studies.[2,4,11,18,20,23,24,26–37] The median and modal daily dose of these studies was 50 mg of hydrochlorothiazide. The maximum dose was 112.5 mg/day of hydrochlorothiazide.[18] The raw data for these studies are not shown. The weighted overall mean change in total cholesterol was 6.3%, in HDL cholesterol was −0.5%, and in triglycerides was 19.5%. The percent increases from baseline in total cholesterol and triglycerides were statistically significant.

Figure 3 is a comparison of overall mean percent changes from baseline in each lipid index among the 3 treatment groups, namely, indapamide, low-dose thiazides, and high-dose thiazides. The bars for indapamide and low-dose thiazides represent the bars at the far right of each row from Figures 1 and 2. Analysis of variance reveals a significant difference among groups in total cholesterol. Specifically, high-dose thiazides caused a greater increase than indapamide. There was no significant difference in HDL cholesterol among the 3 groups. Changes from baseline in triglycerides differed significantly among groups, $p < 0.01$. That is, low-dose thiazides caused a significantly

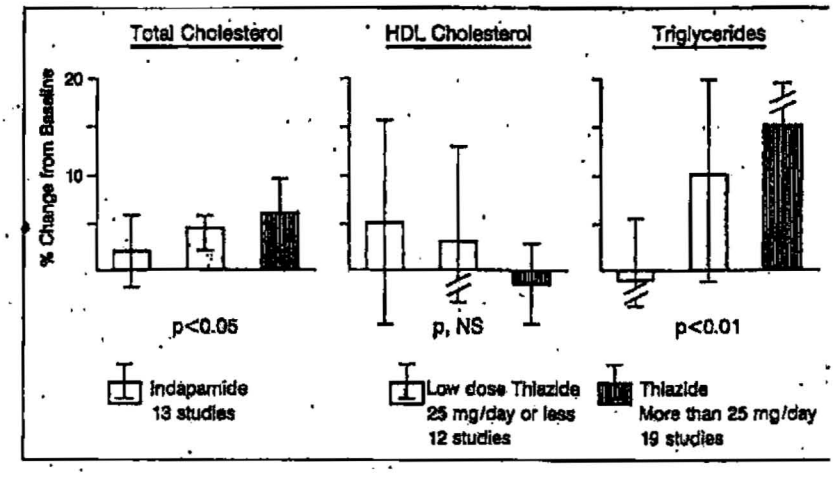

FIGURE 3. Comparison of overall mean change from baseline in serum lipid components during treatment with indapamide 2.5 mg/day, low-dose thiazides, and high-dose thiazides. The left bar in each panel of 3 bars represents indapamide; the middle bar, low-dose thiazides, the right bar, high-dose thiazides. (Reprinted with permission from W. B. Saunders.[38])

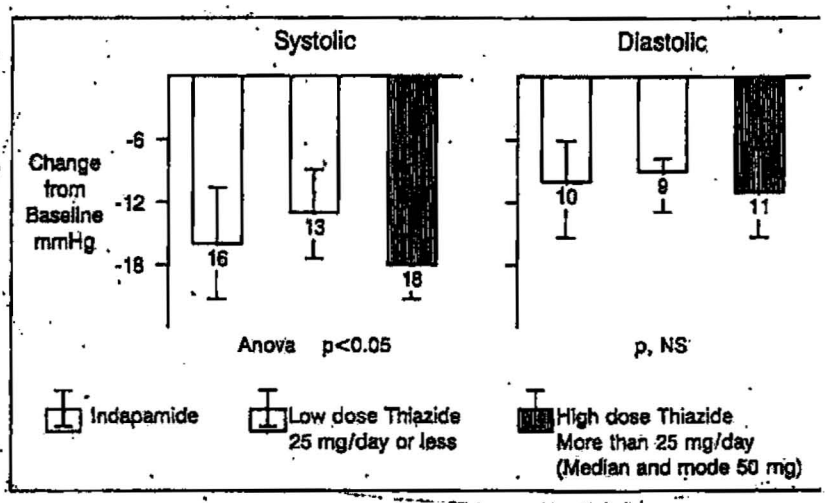

FIGURE 4. Comparison of overall mean change from baseline in systolic and diastolic blood pressure during treatment with indapamide, low-dose thiazides, and high-dose thiazides. The 3 bars in each panel are arranged as in Figure 3. ANOVA = 1-way analysis of variance. NS = not significant. (Reprinted with permission from W. B. Saunders.[38])

greater increase than did indapamide. High-dose thiazides caused a greater increase in triglycerides than did low-dose thiazides and indapamide.

Changes in blood pressure in these hypertensive subjects were averaged in the same groups. Overall mean changes from baseline are depicted in Figure 4. The data for the individual studies are not shown. Concerning the overall group means, systolic blood pressure decreased more with high-dose thiazide therapy than with low-dose thiazide treatment, $p < 0.05$. The effect of indapamide on systolic arterial pressure was intermediate between, and not statistically different from, either thiazide dose. Decreases in diastolic blood pressure did not differ among groups.

COMMENT

Meta-analysis provides the advantage of pooling data from similar studies for greater statistical power. Consequently, where event rates are low or differences among groups are small, statistical differences may be demonstrable by meta-analysis. However, meta-analysis is scientifically less rigorous than a randomized trial. The major advantage of the trial is that randomization assures that similar subjects are being compared. Selection bias is avoided by this technique. The double-blind feature helps to assure that the groups are treated similarly. In addition, meta-analysis is dependent on the quality of the individual studies. These statements are introduced to indicate that meta-analysis does not represent the ultimate scientific method.

With these caveats in mind, this meta-analysis suggests that indapamide is lipid neutral and thereby superior in this respect to both low- and high-dose thiazides. High doses of thiazides increase both the total cholesterol and triglycerides significantly more than does indapamide. Low-dose thiazides increase triglycerides more than does indapamide. Low-dose thiazides also raise total cholesterol significantly from baseline. In contrast, indapamide does not increase total cholesterol or triglycerides significantly above baseline. However, changes in total cholesterol from baseline did not differ significantly between indapamide and low-dose thiazides. It is important to bear in mind that "low-dose thiazides" includes

doses of 6.25–15 mg/day of hydrochlorothiazide. These very low doses caused a similar increase in total cholesterol, as did 25 mg daily doses of hydrochlorothiazide. Thus, it is doubtful that there is a dose of thiazide that is low enough to be free of lipid effects and yet retain some antihypertensive potency.

This study also brought out the finding that thiazide effects on systolic blood pressure are dose dependent. In moving to low-dose thiazide therapy, loss of antihypertensive effectiveness will be noted. A corollary of this observation is that low-dose therapy may be sufficient in stage I or mild hypertension, but additional therapy will be needed for all other degrees and stages of hypertension.

In conclusion, indapamide 2.5 mg/day is equipotent to 50 mg of hydrochlorothiazide but has better lipid tolerability. When a diuretic is indicated as initial therapy for hypertension, indapamide is an appropriate choice.

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