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β-Blocker/thiazide combination for treatment of hypertensive children: a randomized double-blind, placebo-controlled trial

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Abstract Antihypertensive medications are used extensively in children despite a paucity of randomized, placebo-controlled trials. This study was among the first randomized, controlled pediatric antihypertensive medication trials, in which the combination drug bisoprolol fumarate/hydrochlorothiazide (B/HT) was compared with placebo. The study comprised a 2-week single-blind placebo screening period, a 6-week double-blind dose titration period, a 4-week double-blind dose maintenance period, and a 2-week double-blind dose-tapering period. One hundred and forty subjects were enrolled to achieve 94 randomized subjects treated either with B/HT (n=62) or placebo (n=32). B/HT induced significant reductions compared with placebo for average sitting systolic blood pressure (SiSBP) (9.3 vs. 4.9 mmHg, P<0.05) and sitting diastolic blood pressure (SiDBP) (7.2 vs. 2.7 mmHg, P<0.05). The placebo-subtracted BP reductions were greater in younger children and those with more-severe baseline hypertension. The percentage of subjects with BP less than the 90th percentile at study completion was 45% for B/HT and 34% for placebo (P=NS). Although the study demonstrated that B/HT reduced BP safely compared with placebo, the large placebo effect and failure of most subjects to achieve target BP control make it uncertain whether B/HT is appropriate first-line therapy for pediatric hypertension, particularly in adolescents with mild-to-moderate BP elevation.

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Introduction

Pediatric hypertension and its potential sequelae have been recognized for almost 4 decades[1]. While once thought to be rare, primary pediatric hypertension has become increasingly common in association with the same risk factors as in adults [2, 3]. These factors include obesity, inactivity, ethnic predisposition to essential hypertension, and family history of hypertension. As for adults, the initial therapeutic recommendations are lifestyle modifications, such as weight loss, decreased dietary salt intake, and increased exercise [4]. However, these measures are often inadequate to lower blood pressure (BP) to the normal range, thereby necessitating the use of pharmacological therapy.

Although antihypertensive medications have been studied extensively in adults and used extensively in children, no antihypertensive medications are currently approved for use in children less than 12 years of age in the United States due to the lack of randomized controlled clinical trials. To address this issue, the United States Food and Drug Administration Modernization Act enacted in 1997 offered extension of market exclusivity in return for approved clinical trials of medications with pediatric indication [5]. This legislation has resulted in a significant increase in pediatric trials of antihypertensive medications. One of the first of these pediatric trials was for the combination drug bisoprolol fumarate/hydrochlorothiazide (B/HT). B/HT is a drug that incorporates two antihypertensive agents: bisoprolol fumarate, a selective β_1-adrenoceptor blocking agent, and hydrochlorothiazide (HCTZ), a thiazide diuretic that decreases renal tubular sodium absorption. A previous pediatric study of a β-blocker/diuretic combination, propranolol and chlorthalidone, showed significant reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared with placebo over a

30-month period [6]. In adults, the specific B/HT combination product has been shown to have a significant antihypertensive effect, with a side effect profile comparable to that seen with placebo [7, 8]. Since no data were available for B/HT in hypertensive children, the Ziac Pediatric Hypertension Study was conducted to determine the safety and efficacy of B/HT in hypertensive children compared with placebo.

Patients and methods

Subjects were recruited from 22 centers in the United States and Brazil that care for children with hypertension. This double-blind, parallel group, dose escalation study evaluated the safety and effectiveness of B/HT compared with placebo in children with confirmed hypertension. The study comprised four periods: a 2-week single-blind placebo screening period, a 6-week double-blind dose escalation period, a 4-week double-blind dose maintenance period, and a 2-week double-blind dose tapering period at the end of the trial (Fig. 1).

Inclusion criteria were children aged 6–17 years at the time of enrollment with average sitting systolic blood pressure (SiSBP) and/or sitting diastolic blood pressure (SiDBP) above the 95th percentile, as defined by the Task Force on High Blood Pressure Control in Children [9]. Exclusion criteria included severe hypertension (>99th percentile), correctable secondary hypertension, hypertensive encephalopathy or neurovascular event within the past 6 months, cardiovascular events within the last 6 months, resting bradycardia or any cardiac arrhythmia, renal impairment (creatinine >1.5 mg/dl), and concomitant medication that might induce BP elevation. Subjects already receiving antihypertensive medications were eligible to participate provided that the current medication(s) was discontinued for at least 1 week prior to study entry and the subject qualified for the study by all other criteria. Informed consent was obtained from the parents or legal guardians in all cases, and all patients gave assent.

Throughout the study, BP measurements were taken in the same arm with a standard mercury manometer by a trained and certified observer, using the recommended cuff size as specified by the American Society of Hypertension Public Policy Committee recommendations [10]. BP was measured while seated after 5 min of rest. SiDBP was determined by the 5th Korotkoff sound. Three measurements were taken at 2-min intervals in each arm at the study initiation visit. The arm with the highest BP was used for the duration of the study, with the average of three measurements in that arm used as the subject's BP for that visit. Subjects were seen weekly during the single-blind placebo screening period and then every other week for the remainder of the study. At each visit, subjects were evaluated for adverse experiences and for compliance with study medications. Subjects who demonstrated less than 80% compliance by pill count during the placebo screening phase were discontinued from the study.

To qualify for randomization, subjects were required to have an average SiSBP and/or SiDBP greater than the 95th percentile at the last visit of the 2-week single-blind screening placebo period. At that confirmation visit, subjects were randomly assigned to receive B/HT or placebo in a 2:1 ratio. Randomization was performed within each center and within each of the two developmental strata (less than Tanner stage 3, greater than or equal to Tanner stage 3). At the initiation of the study, only two treatment groups, B/HT and placebo, were included with randomization in a 2 B/HT: 1 placebo ratio. Subsequently, a HCTZ treatment group was added. However, due to the late addition of this study group, few subjects received HCTZ alone, and the data from those subjects are not included in this analysis.

Randomized subjects were entered into the dose escalation period of the study. Study medication was administered once daily in the morning, except on the day prior to a scheduled study visit when medication was administered 24 h prior to the anticipated

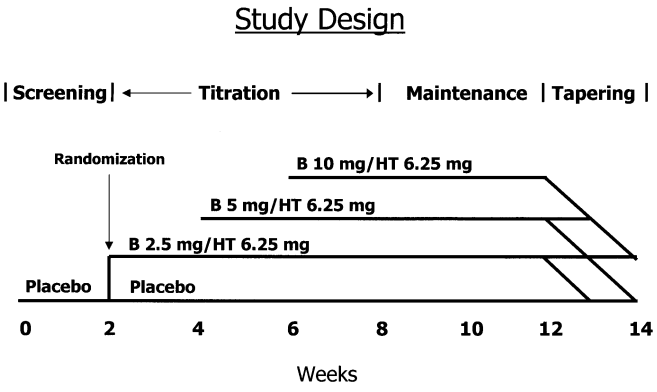

Fig. 1 Schema for study design (*B* bisoprolol, *HT* hydrochlorothiazide)

time of the study visit to allow trough BP to be measured at each study visit. During the dose escalation period, study drug dose was increased only if BP (SBP or DBP) did not reach the target value (<90th percentile). If BP was greater than the 90th percentile at visit 4 (week 5), the dose of study drug (or placebo) was increased from 2.5 mg to 5 mg of bisoprolol. If BP was greater than the 90th percentile at visit 5 (week 7), the dose of study drug (or placebo) was increased to 10 mg of bisoprolol (if the dose had been increased at visit 4) or to 5 mg (if the dose had not been increased at visit 4). After visit 5 (week 7), dosing remained stable until the end of the 4-week dose maintenance period. Following the dose maintenance period, subjects entered a 2-week, double-blind, dose-tapering period during which study medications were withdrawn. Subjects were discontinued from the study during placebo screening, dose escalation, dose maintenance, or dose-tapering for reasons that included documented severe hypertension (>99th percentile), intercurrent illness, requirement for therapy that might interfere with the study medication, use of concomitant antihypertensive medication, compliance less than 80% during the placebo screening period, or subject request.

Baseline data included demographic characteristics (sex, race, age, height, and weight), SiSBP and SiDBP, and heart rate (HR). Baseline demographic data were obtained at visit 1, and the baseline BP and HR data were taken from the last observation of the placebo screening period (visit 3) at the point of randomization. Baseline comparisons were made between the two treatment groups (B/HT and placebo). The categorical variables (sex, race) were analyzed using Fisher's exact test. Continuous variables were analyzed using a one-factor (treatment) analysis of variance model. The study endpoints were: (1) absolute reduction in SiSBP and SiDBP at the end of the dose maintenance period (visit 3 BP minus visit 8 BP), (2) the percentage reduction in SiSBP and SiDBP [(visit 3 BP minus visit 8 BP)/visit 3 BP]×100%, and (3) the percentage of patients whose BP was controlled (i.e., SiSBP and SiDBP <90th percentile) at visit 8.

The primary analysis was conducted using the intent-to-treat population that included all subjects who had at least one visit during the double-blind phase of the study. Subjects who did not remain in the study through the final visit of the dose maintenance phase (visit 8) were analyzed using a last-observation-carried-forward approach. Comparisons between treatment groups of absolute and percentage reduction from baseline were conducted using analysis of covariance with Tanner group (less than Tanner stage 3 or greater than or equal to Tanner stage 3) and the corresponding baseline value as covariates. Cochran-Mantel-Haenzel's test stratifying by Tanner group was used to compare the treatment groups with respect to the percentage of subjects who reached target BP (SiSBP and SiDBP <90th percentile). The relationship between per kilogram dosing and the reduction in BP from visit 3 to visit 4 was analyzed by Spearman correlation coefficient. All statistical tests were conducted at the two-sided 5% level of significance.

Table 1 Baseline demographic and clinical data (*SBP* systolic blood pressure, *DBP* diastolic blood pressure, *B* bisoprolol, *HT* hydrochlorothiazide)

Demographic variables	Placebo(n=32)		B/HT (n=62)		P value
Age (years)					
Mean (SD)	14.0	(2.7)	13.8	(3.1)	0.84
Age group: *n* (%)					
6–12 years	8	(25%)	20	(32%)	0.64
13–17 years	24	(75%)	42	(68%)	
Tanner stage: *n* (%)					
<3	9	(28%)	13	(21%)	0.45
≥3	23	(72%)	49	(79%)	
Sex: *n* (%)					
Male	19	(59%)	35	(56%)	0.83
Female	13	(41%)	27	(44%)	
Race: *n* (%)					
Caucasian	12	(38%)	28	(45%)	0.80
Black	14	(44%)	25	(40%)	
Asian	0	(0%)	1	(2%)	
Hispanic	6	(19%)	7	(11%)	
Multiracial	0	(0%)	1	(2%)	
Randomization criteria: *n* (%)[a]					
SBP only	16	(50%)	28	(45%)	0.49
DBP only	3	(9%)	12	(19%)	
SBP and DBP	12	(38%)	22	(35%)	
Body weight (kg)					
Mean (SD)	79.8	(28.3)	75.4	(23.2)	0.43
Height (cm)					
Mean (SD)	164.0	(16.8)	163.4	(14.9)	0.87
Body mass index (kg/m^2)					
Mean (SD)	28.9	(7.3)	28.0	(7.2)	0.58

[a] One patient was randomized without qualifying BP

Results

One hundred and forty subjects were enrolled in the study. The overall rate of study non-completion was 27% (38/140). The reasons for non-completion were normalization of BP during the placebo screening period (17%), patient request (4%), medical indication (3%), and severe hypertension (3%) [11]. Sixty-two subjects randomized to receive B/HT and 32 subjects randomized to receive placebo were included in the analysis. Demographic and anthropometric data by study group are shown for randomized subjects in Table 1. There were no significant differences between the treatment groups in age, maturation level (Tanner stage), racial distribution, randomization criteria (SBP hypertension, DBP hypertension, or both), body mass index (BMI), or baseline hemodynamic variables.

Treatment with B/HT resulted in significant reduction in SiSBP compared with placebo, expressed as either absolute reduction or percentage reduction from baseline (Table 2). The absolute reduction in SiSBP was greater for subjects treated with B/HT compared with those treated with placebo (9.3 vs. 4.9 mmHg, P=0.045) (Table 2), resulting in a placebo-subtracted reduction in SiSBP of 4.4 mmHg. Treatment with B/HT also resulted in significant reductions in SiDBP compared with placebo (Table 2). The absolute reduction in SiDBP was greater for subjects treated with B/HT than for those treated with placebo (7.2 vs. 2.7 mmHg, P=0.012), resulting in a placebo-subtracted reduction in SiDBP of 4.5 mmHg. The absolute reductions in SiSBP and SiDBP did not differ based on gender, Tanner stage, or race.

Analyses of specific subgroups of subjects revealed trends in the extent of BP reduction by treatment, based on stratification by age and by severity of baseline BP elevation. Stratification by age revealed that for 6- to 12-year-old subjects (n=28), the differences between B/HT and placebo treatment were significant for both SiSBP absolute reduction (10.0 vs. 1.2 mmHg, P=0.03) and SiDBP absolute reduction (8.5 vs. 2.7 mmHg, P=0.038). In contrast, in 13- to 17-year-old subjects (n=66), the differences between B/HT and placebo treatment were not significant for either SiSBP absolute reduction (9.6 vs. 6.7 mmHg, P=0.27) or SiDBP absolute reduction (5.9 vs. 2.7 mmHg, P=0.15). Stratification by severity of baseline hypertension revealed that for subjects with either SiSBP or SiDBP ≥5 mmHg above the 95th percentile at the time of randomization (n=57), the differences between B/HT and placebo treatment were highly significant for both SiSBP absolute reduction (11.1 vs. 1.9, P=0.003) and SiDBP absolute reduction

Table 2 BP response data from baseline visit to final treatment visit [mean (standard error)]

	Placebo		B/HT		*P* value
SBP (mmHg)					
Baseline (visit 3)[a]	133.8	(1.3)	133.8	(1.3)	0.98
Treatment (visit 8)[a]	128.5	(1.9)	124.0	(1.7)	0.105
Absolute reduction[b]	4.9	(1.8)	9.3	(1.5)	0.045
Percentage reduction[b]	3.6%	(1.4%)	6.8%	(1.1%)	0.044
DBP (mmHg)					
Baseline (visit 3)[a]	81.8	(1.6)	83.0	(1.2)	0.55
Treatment (visit 8)[a]	79.5	(2.0)	76.0	(1.4)	0.143
Absolute reduction[b]	2.7	(1.5)	7.2	(1.2)	0.012
Percentage reduction[b]	3.0%	(1.8%)	8.5%	(1.4%)	0.011

[a] Arithmetic means with *P* value from one-way ANOVA
[b] Least squares means from analysis of covariance with baseline and Tanner stage as covariates

(7.9 vs. 1.4, *P*=0.012). In contrast, in subjects with SiSBP and SiDBP <5 mmHg above the 95th percentile at randomization (*n*=37), the differences between B/HT and placebo treatment were not significant for SiSBP absolute reduction (7.5 vs. 8.4, *P*=0.78) or SiDBP absolute reduction (4.7 vs. 3.6, *P*=0.67). There was no interaction in the treatment effects for the extent of BP reduction to B/HT or placebo by randomization criteria (i.e., SBP hypertension, DBP hypertension, or both).

Although there was a trend toward a higher percentage control of BP in the B/HT treatment group, the difference between treatment groups for the percentage that achieved BP control (SiSBP and SiDBP <90th percentile) at the end of the double-blind treatment period did not reach statistical significance. The percentage of subjects with BP less than the 90th percentile was 45% for B/HT compared with 34% for placebo. Among subjects treated with B/HT who achieved BP control (*n*=28), 46% achieved control on low dose, 32% on medium dose, and 21% on high dose. There was no difference between subjects who did or did not achieve BP control, based on age, age range, Tanner stage, gender, race, or BMI.

The study was not designed to assess BP response based on a per kilogram dosing or to specifically test dose response. However, post hoc analysis of all treated subjects at the initial lowest dose showed a positive correlation between the dose per kilogram of the bisoprolol component of B/HT (0.037±0.013 mg/kg, range 0.019–0.081 mg/kg) and the reduction in SiDBP between visit 3 and 4 (*r*=0.38, *P*=0.002), but not for reduction in SiSBP (*r*=–0.003, *P*=0.98). Twenty-five patients in the B/HT treatment group were escalated to the highest dose level, and therefore received all three doses of B/HT during the course of the study. For these patients, there was a significant linear increase in absolute reduction in SiSBP (*P*<0.001) (Fig. 2) and SiDBP (*P*<0.001) (Fig. 3) with increasing dose. For the placebo patients, this trend was not observed for either SiSBP (*P*=0.52) or SiDBP (*P*=0.89). These results indicate that the effect of B/HT in patients escalated to the highest dose could not be attributed to a placebo effect or an effect of time (potentially confounded with dose in this analysis).

Adverse event profiles are shown in Table 3. Of the B/HT group, 53% reported at least one adverse event, compared with 75% in the placebo group. The most commonly reported adverse event in each study group was headache, reported in 26% of subjects receiving B/HT and 31% receiving placebo. The most-common serious adverse event requiring discontinuation from the study was severe hypertension, reported in 2 subjects receiving placebo and 1 subject receiving B/HT. No signif-

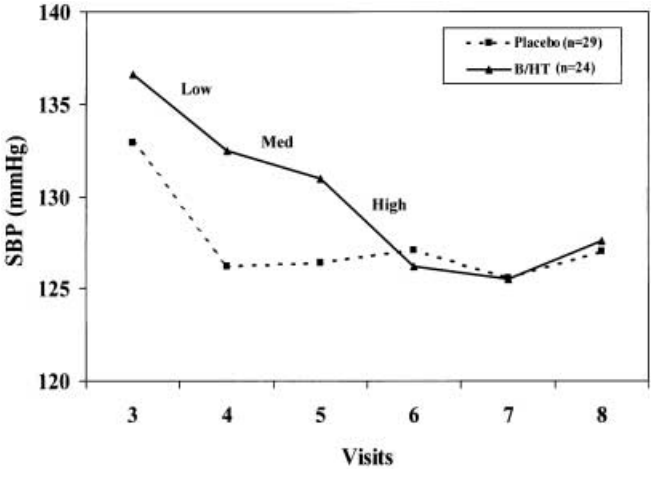

Fig. 2 Sitting systolic blood pressure (*SiSBP*) at study visits 3 through 8 in subjects treated with all dose levels of B/HT and in subjects treated with placebo

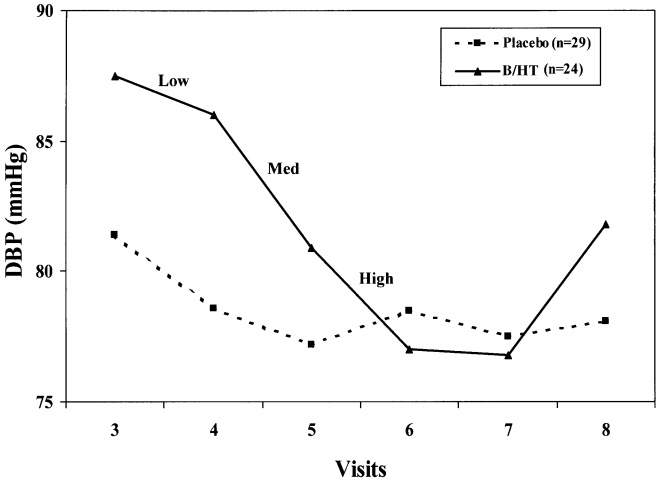

Fig. 3 Sitting diastolic blood pressure (*SiDBP*) at study visits 3 through 8 in subjects treated with all dose levels of B/HT and in subjects treated with placebo

Table 3 Subjects reporting adverse events (AE)

	B/HT (*n*=62)	Placebo (*n*=32)
Any AE[a]	33 (53%)	24 (75%)
Most-frequent AEs[a]		
Headache	16 (26%)	10 (31%)
Infection	2 (3%)	5 (16%)
Rhinitis	3 (5%)	3 (9%)
Pharyngitis	5 (8%)	2 (6%)
Serious AE[a]	1 (2%)	5 (16%)

[a] Number (percentage)

icant difference in baseline and post-treatment serum potassium concentration was found for either of the study groups. The B/HT group had fewer overall adverse events (P=0.047) and fewer serious adverse events (P=0.016) than subjects treated with placebo.

Discussion

The passage of the Food and Drug Modernization Act in 1997 has had the intended outcome of stimulating interest in the performance of pharmaceutical clinical trials in children [5]. Although antihypertensive medications have been used in children with hypertension for decades, no antihypertensive medication of any class to date has pediatric labeling in children less than 12 years of age. As the prevalence of hypertension in children has increased, the need for pediatric trials of antihypertensive medications has become more pressing. For these reasons, the FDA specifically targeted antihypertensive medications and, in response, approximately ten new clinical trials of these medications have been performed over the last 2–3 years. The current study reports the results from one of the first of these trials, the Ziac Pediatric Hypertension Study.

The current study demonstrated that treatment with B/HT resulted in a statistically and clinically significant reduction in both SiSBP and SiDBP compared with placebo. However, several differences between the results from the current study and from previous studies of hypertensive adults highlight potentially critical issues in the design and interpretation of antihypertensive medication trials in children. In the current study, the absolute reductions in SiSBP and SiDBP of 9.3 mmHg and 7.2 mmHg, respectively, were lower than the reductions of 14.5 mmHg and 12.7 mmHg reported in a comparable trial of adults [12]. However, representation of pediatric efficacy data as the absolute reduction in BP may be misleading. Since the threshold values of SBP for study inclusion in children in the current study may be as low as 110 mmHg (95th percentile for an average sized 6-year-old female), an absolute reduction in BP equal to that of an adult, whose baseline SBP may be 160 mmHg, is unlikely. When expressed instead as percentage reduction in SiSBP from baseline, the pediatric and adult data are more comparable (6.8% vs. 9.7%).

The current study design is unique among other pediatric antihypertensive medication trials by the presence of a completely independent placebo arm. By virtue of this design, a substantial reduction of BP in placebo-treated subjects was clearly demonstrated. In the current study, the placebo-subtracted BP reduction was less than 5 mmHg for both SiSBP and SiDBP, compared with a 13 mmHg SBP and 11 mmHg DBP placebo-subtracted reduction in adults [12]. When expressed as percentage reduction from baseline, the placebo-subtracted SiSBP reduction was only 3.2% for children, compared with 8.7% in adults. This relatively large placebo effect in children was evident despite the 2-week, single-blind, placebo screening period at study entry. As shown in Figs. 2 and 3, the greatest decrease in BP in the placebo-treated subjects occurred between visit 3 and visit 4, after which there was little change in BP through the end of the maintenance phase of the study at visit 8.

Although previous analysis of the data from the screening phase suggested a stabilization of the placebo effect by the end of the 1st week of screening [11], further analysis from the independent placebo arm of the study suggests a more-prolonged period of screening may be needed to reduce the confounding effect of a BP decrease in the absence of study medication. This contention is supported by the results from a previous pediatric antihypertensive study, which showed reductions in BP over a 6-month treatment period in a parallel, untreated control group, despite five confirmatory BP measurements over a 4-month observation period prior to study entry [6]. These observations have clear implications for clinical practice. The data from the current study and from previous studies seem to indicate that children without severe hypertension often have normalization of BP without pharmacological therapy, and therefore, observation for several months without antihypertensive medications may be indicated.

Further stratification of the subjects in the current study provides additional insight into the potential indications for treatment in hypertensive children and adolescents. The placebo-subtracted BP responses were substantially higher in the younger compared with the older subjects for SiSBP (8.8 vs. 2.9 mmHg) and SiDBP (5.8 vs. 3.2 mmHg). Similarly, the placebo-subtracted BP responses were higher in subjects with more-severe compared with less-severe BP elevation at baseline for SiSBP (9.2 vs. –0.9 mmHg) and SiDBP (6.5 vs. 1.1 mmHg). This latter observation is consistent with a previous study showing a 76% prevalence of white coat hypertension by ambulatory BP monitoring in children with mild-to-moderate elevation of clinic BP [13]. Thus, repeated documentation of hypertension prior to enrollment in pediatric clinical trials of antihypertensive medications may be required to minimize the placebo effect, especially in adolescents with mild BP elevation. In this regard, ambulatory BP monitoring may be useful as a screening procedure in future trials of antihypertensive medication in children.

Several other issues raise concern over whether B/HT should be recommended for the majority of hypertensive pediatric patients. The proportion of subjects who achieved target BP control (i.e., less than the 90th percentile) was less than 50% and did not differ significantly from placebo. These data suggest that the majority of hypertensive children would need other antihypertensive medications in addition to B/HT to achieve the BP target of less than the 90th percentile. In addition, the lack of an independent bisoprolol arm in the study makes it impossible to determine whether combination therapy is superior to the β-blocker component alone. Finally, the absence of data from the current study concerning primary versus secondary hypertension in the subjects does not allow differentiation of likelihood of response based on the etiology of hypertension. Although this is an issue of particular concern for pediatricians who care for hypertensive children, the large numbers of children from multiple centers required to perform analyses and draw conclusions on this important topic remains a major difficulty for investigators.

In summary, B/HT was found to reduce BP in children and adolescents compared with placebo. Adverse events were relatively infrequent. However, the relatively large placebo effect and failure of most subjects to achieve BP control leaves unanswered the most-critical questions of who needs to be treated, when treatment should be initiated, and whether B/HT should be use as first-line therapy. While it is commendable that several classes of antihypertensive drugs are currently undergoing long overdue pediatric trials, further studies are needed in children to establish evidence-based target BP values to guide decisions regarding initiation of pharmacological treatment and titration of medication doses.

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