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.

Keywords Hypertension · Clinical trial · Placebo · Blood pressure · Antihypertensive agents

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 $\beta_1$-adrenoceptor blocking agent, and hydrochlorothiazide (HCTZ), a thiazide diuretic that decreases renal tubular sodium absorption. A previous pediatric study of a $\beta$-blocker/diuretic combination, propranolol and chlorothalidone, 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 (SisSBP) and/or sitting diastolic blood pressure (SisDBP) 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. SisDBP was determined by the fifth 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 SisSBP and/or SisDBP greater than the 95th percentile at the last visit of the 2-week single-blind screening placebo period. At the randomization visit, subjects were randomized 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 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, age, height, and weight), SisSBP and SisDBP, 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 SisSBP and SisDBP at the end of the dose maintenance period (visit 3 BP minus visit 8 BP), (2) the percentage reduction in SisSBP and SisDBP [(visit 3 BP minus visit 8 BP)/visit 3 BP]×100%, and (3) the percentage of patients whose BP was controlled (i.e., SisSBP and SisDBP <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 (SisSBP and SisDBP <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.