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Cough in Pediatric Patients Receiving Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Therapy in Randomized Controlled Trials

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Abstract

The incidence of cough in children receiving angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) is unknown. We analyzed patient-level data from 6 ACEi and 2 ARB randomized trials for the treatment of pediatric hypertension. The incidence of cough in children receiving ACEi (3.2%) and ARB (1.8%) was similar ($P=0.34$). Reports of cough were lower among children than adults.

Keywords

hypertension; adverse drug events

Cough is one of the most common adverse events reported in adults receiving angiotensin-converting enzyme inhibitors (ACEi).¹ ACEi are frequently used to manage congestive heart failure and hypertension in children.² Previous reports of cough in children receiving ACEi are limited by cohort design or small sample size.^{3, 4} The goal of this study is to determine the incidence and prevalence of cough in children receiving ACEi and ARB during the course of randomized placebo-controlled trials.

METHODS

Individual patient data were obtained from clinical trials of antihypertensive agents submitted to the Food and Drug Administration (FDA) as part of the pediatric exclusivity provision. Between January 1, 1998, and December 31, 2005, data from 6 ACEi and 2 ARB trials were submitted electronically to the FDA Division of Cardiovascular and Renal Products. Patients were excluded from the trials if they had severe hypertension, renal dysfunction, or therapy-related contraindications.

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DISCLOSURES

The views expressed are those of the authors. No official endorsement by the U.S. Food and Drug Administration is provided or should be inferred. The Duke Clinical Research Institute was the coordinating center for the fosinopril trial. Duke Clinical Research Faculty potential conflict of interest disclosures related to relationships with industry are available at <http://www.dcri.duke.edu/research/coi.jsp>. The authors had full access to all data in the study and had final responsibility for the manuscript content and the decision to submit for publication.

Trials were designed to include a lead-in phase during which all previously administered antihypertensive agents were discontinued (Figure 1). Five of the trials were type C (enalapril, fosinopril, lisinopril, irbesartan, losartan), 2 were type D (benazepril and ramipril), and one was type A (quinapril). For type C studies, we only considered coughs reported as adverse events during the placebo-controlled period of the study. No patients in the 5 type C trials were discontinued from study drug during the double-blind period for cough-related adverse events.

We obtained study data sets from the FDA electronic document room. Data from the 8 antihypertension trials were merged using STATA 10.0 (College Station, TX). From each trial, the following common variables were assembled: study drug, study identification number, age, sex, race, therapy received during placebo-controlled phase of the study (placebo or active drug), start and stop dates for the placebo-controlled phase, start date of reported adverse event, and adverse event description. We used a categorical variable of “white/black/other” for race because several trials used this format to report race, and more specific information was unavailable.

Descriptors of adverse events that were defined as cough for this analysis included: cough, congestive cough, cough (intermittent), cough with emesis, cough/headache common cold, coughing, cough aggravated, cough increased, dry cough, hacking cough, headache and cough, intermittent cough usually at night, moist cough, night cough, persistent cough, productive cough, sporadic cough with mild expectoration, ear pain/sinus congestion/cough, and cough/red throat. Observations for subjects with missing dates for the start (n=10) or stop (n=16) date of the placebo-controlled portion of the trial were not considered in the analyses as the relationship of the adverse event to the study phase could not be determined. Only 1 of the excluded subjects reported cough as an adverse event (fosinopril study subject that received placebo).

Estimates of the proportion of children who reported cough were performed using the total number of subjects with cough divided by the total number subjects. Comparisons of proportions were performed using Fisher's exact test. Kaplan Meier curves were constructed with failure defined as time at first episode of cough. We used the Wilcoxon-Breslow-Gehan test of equality to compare the survivor functions between the subjects who received ACEi, ARB, and placebo therapy. Statistical significance was defined as $P < 0.05$. Analysis was performed using STATA 10 (College Station, TX).

RESULTS

Of the 1,299 subjects identified, 551 (42%) received placebo and 748 (58%) received active drug during the placebo-controlled phase. The demographic features of the patient population were similar across the 8 trials (Table 1). The median age of trial participants was 13 years (interquartile range: 10, 15 years), and the majority of studied trial participants were white (54%) and male (61%). The median number days that subjects were in the placebo controlled phase of the trial was 14 days (interquartile range; 13, 18).

There was no difference in the proportion of subjects who reported cough in the cohort receiving active drug vs. those receiving placebo (21/748 [2.8%] and 14/551 [2.5%], respectively; $P=0.86$). There was no statistical difference in the proportion of subjects who reported cough in the cohort receiving ACEi vs. those receiving ARB (17/524 [3.2%] and 4/224 [1.8%], respectively; $P=0.34$). Similarly, there was no difference observed between the time to first cough between active drug vs. placebo ($P=0.28$) or ACEi therapy vs. ARB therapy ($P=0.99$). Cough was most common in those subjects who received benazepril (10/66 [15.2%]) (Table 1). However, the placebo rate of cough was also higher in the benazepril trial than in the other 7 trials (2/19 [10.5%] and 12/532 [2.3%], respectively).

The incidence rate of first-reported cough among subjects receiving ACEi, ARB, or placebo were 1.9/1,000 days, 1.4/1,000 days, and 1.9/1,000 days, respectively ($P=0.81$). We observed no difference in the proportion of subjects receiving ACEi reporting cough by race: white, 8/224 (3.6%), black, 5/142 (3.5%), and other, 4/1,158 (2.5%) ($P=0.86$). Additionally, we observed no sex differences in the proportion of subjects receiving ACEi reporting cough: male, 7/316 (2.2%), and female, 10/208 (4.8%) ($P=0.13$).

DISCUSSION

We found no difference in the rate of cough reported as an adverse event in pediatric subjects receiving ACEi, ARB, and placebo in randomized controlled trials. In contrast to adult randomized trials where the average adverse event rate of cough related to ACEi therapy was 10%, only 3.2% of the pediatric subjects reported cough while receiving ACEi during the placebo phase of this study.¹ In the largest randomized adult hypertension trial comparing ACEi and ARB for the treatment of hypertension, 44/609 (7.2%) of ACEi subjects and 6/604 (1.0%) of ARB subjects reported cough.⁵ This trial lasted 16 weeks, compared with only 2–4 weeks for the pediatric trials examined in this report. Several factors have been identified as potential risks for ACEi-induced cough in adults including increasing age, female sex, congestive heart failure, East Asian ethnicity, and history of smoking.^{6–8} We observed no difference between white (3.5%) and black (3.6%) pediatric patients receiving ACEi. Although the proportion of girls reporting cough (4.8%) was higher than boys (2.2%), this difference was not statistically significant ($P=0.13$).

The cough associated with administration of ACEi has been described as an insidious and persistent, dry cough.⁹ Proposed mechanisms of ACEi-related cough include the inhibited breakdown of bradykinin by ACEi resulting in increased circulating levels of bradykinin and activation of proinflammatory agents and local release of histamine.⁹ Unlike rash and angioedema, which is increased among users of the sulfhydryl group containing ACEi such as captopril, cough is not thought to vary by type of ACEi.¹⁰ The highest incidence of cough was among subjects receiving benazepril. This may be explained, in part, by the longer duration of the placebo-controlled portion of the benazepril trial compared with the other 7 studies (median 28 days vs. 14 days, respectively) and the higher incidence in the placebo arm of the benazepril trial. In addition, the benazepril trials (type D) initially titrated drug to higher doses and a carryover effect may have contributed to higher levels of reported cough in both the active drug and placebo arms during the subsequent placebo controlled phase.

In adult patients, current recommendations for management of individuals with ACEi-related cough involve discontinuation of ACEi therapy and initiation of another class of antihypertensive agent (i.e., ARB or calcium channel blockers). However, changing antihypertensive class may prevent patients from receiving the renal and cardiac benefits of ACEi therapy. Among the pediatric subjects participating in these trials, we observed no statistical difference in the proportion of cough reported as an adverse event between subjects receiving ACEi (3.2%) and ARB (1.8%) ($P=0.34$). Failure to account for the true prevalence of cough associated with ACEi may result in premature discontinuation of ACEi therapy and elimination of the potential benefits associated with this class of antihypertensive agents.

Strengths of this study include the large number of pediatric patients identified from 8 prospective randomized antihypertension trials. Assuming the adult cough incidence of 15% among ACEi subjects, we had 80% power to detect a 50% relative difference in the incidence of cough between ACEi recipients and ARB recipients. Limitations of our study include: slight variations in study design including variations in the duration of the placebo-controlled phase. Variations in duration of therapy were taken into account by analyzing the time to first reported cough using survival functions and reporting rates of cough/1,000 study days. Differences in

drug exposure between adults and pediatric subjects may account for the lower rates of cough observed in the pediatric subjects enrolled in these trials. Finally, our analysis was limited to the time period of the placebo-controlled portion of the trials. While onset of cough following administration of ACEi can occur within hours to days of administration, the onset of cough in some patients may occur only after weeks of ACEi therapy.⁸

In this study, we investigated the first-reported cough in pediatric subjects administered ACEi and ARB for the treatment of mild to moderate hypertension during blinded placebo-controlled trials. Overall, reports of cough were lower among the children in these studies than those reported from studies in adult subjects. We found no difference in the rate of reported cough among pediatric subjects receiving ACEi vs. ARB or active drug vs. placebo.

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Figure 1a–d.
Trial designs.

Table 1

Demographic data

	Total	Benazepril	Enalapril	Fosinopril	Lisinopril	Quinapril	Ramipril	Irbesartan	Losartan
N	1299	85	101	222	104	112	217	293	165
Age (yrs), median (IQR)	13 (10, 15)	13.0 (12, 15)	12 (9, 14)	12 (10, 14)	13 (10, 14)	13 (10, 15)	12 (10, 14)	13 (11, 15)	13 (10, 14)
Sex									
Male, n (%)	798 (61)	51 (60)	57 (56)	145 (65)	69 (66)	66 (59)	124 (57)	196 (67)	90 (54)
Race									
White, n (%)	708 (54)	48 (56)	38 (38)	129 (58)	44 (42)	41 (37)	63 (29)	254 (87)	91 (55)
Black, n (%)	277 (21)	19 (22)	22 (22)	47 (21)	12 (12)	39 (35)	89 (41)	30 (10)	19 (12)
Other, n (%)	314 (24)	18 (21)	41 (41)	46 (21)	48 (46)	32 (29)	65 (30)	9 (3)	55 (33)
Dosing									
Active drug, n (%)	748 (58)	66 (78)	51 (51)	106 (48)	53 (51)	85 (76)	163 (75)	147 (50)	77 (47)
Placebo, n (%)	551 (42)	19 (22)	50 (49)	116 (52)	51 (49)	27 (24)	54 (25)	146 (50)	88 (53)