CLINICAL RESEARCH STUDY

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Angiotensin-converting Enzyme-related Cough among Chinese-Americans

Daniel S. Tseng, MD, MS,[a] Jan Kwong, MD,[a] Firozeh Rezvani, MD,[a] Ashley O. Coates, MPH[b]

[a]Department of Medicine, Kaiser Permanente of Northern California, Santa Clara; [b]Division of Research, Kaiser Permanente of Northern California, Oakland.

ABSTRACT

BACKGROUND: Few studies have examined the relationship between ethnicity and tolerance of hypertension medications. We investigated the perception that Chinese-Americans may have a higher incidence of chronic cough from angiotensin-converting enzyme inhibitors.

METHODS: We searched electronic databases to identify patients who had received a new lisinopril prescription. This cohort was separated into 295 patients of Chinese descent and 4263 patients in the general population group with an instrument that used surnames to identify Chinese ethnicity. For those who discontinued lisinopril within 1 year, we reviewed medical records to determine reasons for discontinuation. We compared rates of discontinuation overall and due to cough by ethnic group (Chinese vs general population).

RESULTS: The Chinese population was more likely to discontinue their medication (47%) than the general population (31%). When the cause for discontinuation was examined, cough was significantly higher among Chinese, with a relative risk of 2.53; 95% confidence interval (CI), 2.11-3.03. The risk for angioedema was <1%, and no difference in the risk of angioedema was found between the 2 groups. When controlled for age, sex, and smoking, the risk of cough among Chinese-Americans remained significant (relative risk 2.63; 95% CI, 2.20-3.15).

CONCLUSIONS: We observed that our Chinese group was more than twice as likely as the general population to discontinue lisinopril due to cough, controlling for the influence of sex, age, and smoking.
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KEYWORDS: Angiotensin-converting enzyme inhibitors; Antihypertensive agents; Cough; Lisinopril; Race

The majority of studies examining the influence of ethnicity on hypertension involve whites and blacks. Very little is known about how hypertension treatment affects Asians.[1] European and US guidelines for the treatment of hypertension are often applied universally for patients from different ethnic and social backgrounds. There are some indications that the approach to the treatment of hypertension should be different in Asians. The prevalence of hypertension in Chinese in the US and in Asia is similar to that of whites.[2-4] But Chinese are more likely to have hypertension when controlling for demographic factors and comorbidity.[2] The prevalence of ischemic heart disease in Asia (China, Korea, and Japan) is similar to that in the US, but stroke rates are several times higher.[3,5] Also, there is evidence that Asians have a different sensitivity and therapeutic drug response to treatment.[6]

Angiotensin-converting enzyme (ACE) inhibitors are commonly prescribed for hypertension. They also are indicated in the treatment of congestive heart failure, after myocardial infarction, and are important in the renal protection of diabetic patients. A common adverse effect of ACE inhibitors such as lisinopril is a chronic, dry cough. Various studies have placed the risk of chronic cough as being between 5% and 20%.[7] The cause for the cough is unknown but is probably related to an inflammatory state in the upper airways. Other possible adverse effects of ACE

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Requests for reprints should be addressed to Daniel Tseng, MD, Kaiser Permanente, 710 Lawrence Expressway, Dept 360, Santa Clara, CA 95051.

E-mail address: daniel.tseng@kp.org

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inhibitors include hyperkalemia, renal failure, and gastrointestinal disturbances.

Asians may be more susceptible to suffering from the chronic cough related to ACE inhibitors.[8,9] ACE inhibitor and angiotensin receptor blocker use among Chinese is significantly less than in other ethnic groups.[2] We have noted a high incidence of significant ACE inhibitor-related cough among the Asian population in our own clinical practice. To investigate the theory that Chinese might have a higher risk of cough associated with ACE inhibitors, we performed a medical record review of patients given lisinopril or lisinopril with hydrochlorothiazide at our medical center.

CLINICAL SIGNIFICANCE

- Chinese-Americans were significantly more likely to experience chronic cough associated with the use of lisinopril when compared with the general population.
- Clinicians should consider ethnicity when deciding on therapy for hypertension, congestive heart failure, or kidney disease.

METHODS

Study Design

We performed a retrospective cohort study using existing medical records and computerized data of patients who received a new prescription for lisinopril or lisinopril/hydrochlorothiazide between January 1, 2005 and December 31, 2005, and did not obtain a prescription for either in 2004. We did not distinguish between those given lisinopril for hypertension or other indications. Discontinuation of lisinopril was defined as the last refill picked up from a Kaiser pharmacy occurring <1 year after the first prescription. (Pharmacy data were searched for at least 9 months after the last refill picked up.) We compared the rate of discontinuation due to cough or intolerance from other causes between Chinese and the non-Asian general population.

Study Subjects

Our study involved patients from Kaiser Permanente Santa Clara Medical Center in Santa Clara, California and its 3 affiliated satellite offices, which together serve about 289,000 members. The San Francisco Bay area in California has one of the most diverse populations in the US. The proportion of Asians is markedly higher than in the US overall: 11% compared with 1.2%.[10] Data from Kaiser Permanente show that members are very similar to the general population in ethnicity, sex, and age.[11] The electronic databases and medical records at Kaiser Permanente contain information about demographics, outpatient clinic and hospital visits, laboratory and radiology tests, and pharmacy records.

Measurements

The medical center does not record information on ethnic background for outpatients, so we separated Chinese patients from the general population with language preference and an instrument that utilized a list of Chinese surnames.[12] The tool has a sensitivity of 77.7% and positive predictive value of 80.5%.[12] Specificity and negative predictive value were over 99%.

We developed a subset of Chinese patients and a comparison cohort of general population (non-Asian/Pacific Islander) patients with the following algorithm. Using the language of preference in our patient contact information database, those subjects who listed Mandarin or Cantonese as their language of preference were considered Chinese; those with other Asian/Pacific Islander languages of preference were considered Asian (non-Chinese). For patients with English or other preferred languages, we used the list of Chinese surnames to classify patients as Chinese (vs general population.). Using an Asian surname instrument,[13] we classified patients with Asian surnames (who were not classified Chinese) as Asian. We excluded Asians other than Chinese from all analyses to prevent confounding.

We required study subjects to have continuous membership in Kaiser Foundation Health Plan for at least 1 year before the first prescription in 2005, and 21 months afterwards. A review of online data and paper charts of those patients who discontinued lisinopril was performed. The possible causes for medication discontinuation included: ineffective, intolerant from cough, intolerant from other cause, noncompliance, angioedema, other cause, and unknown.

Of 1710 subjects determined to be discontinuers using pharmacy data, 236 (13.8%) were noted in the chart to be obtaining their medication at non-Kaiser pharmacies. These subjects were reclassified as starters, not discontinuers. Of the remaining discontinuers, 9 were determined to be ineligible due to never starting the medication, having taken the medication outside Kaiser before study start, or having their drug insurance benefit stop.

Data Analysis

Data were analyzed using SAS Software, version 9.1 (SAS Institute, Cary NC 2002-2003). The incidence of discontinuation of lisinopril was calculated separately for the Chinese and general population cohorts using the total number of eligible subjects who started lisinopril as the denominator, and incidences were combined to create the relative risk of discontinuation for Chinese vs general population. Incidence of discontinuation due to specific reasons was calculated, excluding the 13 Chinese and 290 general population members for whom a reason could not be determined. We moved subjects to the denominator if they discontinued for a reason other than the reason of interest.

Categorical variables were compared with the chi-squared test and continuous variables with the *t* test. The