Risk of Developing Life-Threatening Ventricular Arrhythmia Associated with *Terfenadine* in Comparison with Over-the-Counter Antihistamines, *Ibuprofen* and *Clemastine*

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An observational, historical cohort evaluation was performed to examine the hypothesis that terfenadine (Seldane®) exposure increases the risk of developing life-threatening ventricular arrhythmias. The study population consisted of Medicaid recipients from 4 states that were included in the Computerized On-Line Medical Pharmaceutical Analysis and Surveillance System (COMPASS). The drug exposure period was defined prospectively as 30 days in all treatment cohorts. The primary end point was the development of life-threatening ventricular arrhythmias (ventricular tachycardia, fibrillation and flutter, and cardiac arrest and sudden death). The comparison cohorts included terfenadine (n = 181,672), over-the-counter antihistamines (n = 150,689), ibuprofen (n = 181,672) and clemastine (Tavist®; n = 83,156).

Over the exposure period, a total of 317 life-threatening ventricular arrhythmic events occurred, 244 of which were cardiac arrests. The incidence of total life-threatening ventricular arrhythmic events and cardiac arrests were more frequent in patients receiving over-the-counter antihistamines (relative risk 0.36) than in those receiving terfenadine, a finding that was consistent across all subgroups. There was no increased risk of life-threatening ventricular arrhythmias in the terfenadine cohort as compared with the ibuprofen cohort (relative risk 0.62), and in some analyses, the ibuprofen cohort had a significantly higher arrhythmic event rate. In all comparisons with the clemastine cohort, the terfenadine cohort had a statistically indistinguishable relative risk (1.08). Age, race, sex and cardiovascular risk were all considered in the adjusted relative-risk analyses. No baseline historical characteristic or imbalance of baseline medications explained the differences between groups. The previously described interaction between terfenadine and ketoconazole was identified (relative risk of terfenadine 23.56; p <0.001), and a trend was observed with erythromycin (relative risk 1.36; p = NS).

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Terfenadine is marketed in the United States under the trademark Seldane® as a prescription drug indicated for the treatment of seasonal allergic rhinitis. It has been marketed worldwide for more than a decade with a safety experience in >100 million patients. However, in the past few years, individual case reports have alerted the pharmaceutical company and the Food and Drug Administration (FDA) to a relationship between the administration of terfenadine and life-threatening ventricular arrhythmias, including torsades de pointes ventricular tachycardia.[1–4] Some compounds, especially ketoconazole, interfere with the normal hepatic metabolic degradation resulting in an accumulation of native terfenadine, which has a significant effect on repolarization manifested by an increase in QT interval on the scalar electrocardiogram.[4,5] This potentially serious drug interaction, as well as an interaction with macrolide antibiotics,[6] led the FDA to relabel terfenadine, contraindicating these drug combinations.

However, the larger, unresolved public health question is: Does the administration of terfenadine to the population as a whole represent any increased risk for developing fatal arrhythmias? Although reliance on random, infrequent, adverse event reports is a good tool for initial surveillance,[7] it cannot provide insight into the magnitude of this important public health question. However, because of the clinical importance of detecting even an extremely low incidence of terfenadine-related, life-threatening ventricular arrhythmias, the only feasible approach is to use a data base that enables the identification of large numbers of subjects who receive terfenadine and comparison drugs.[8–11]

METHODS

The data base chosen was the Computerized On-Line Medical Pharmaceutical Analysis and Surveillance System (COMPASS), which is maintained by Health Information Designs Inc. The data of 4 state Medicaid pro-

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TABLE I Demographic Characteristics of Patients in the Medicaid Data Base

	Terfenadine	OTC Antihistamine	Ibuprofen	Clemastine
Number of patients	181,672	150,689	181,672	83,156
Number of prescriptions	366,814	292,525	371,659	135,713
Age (%)				
0–19 years	16.2	15.4	13.3	37.4
20–44 years	48.1	32.8	42.8	40.4
45–64 years	17.9	15.1	19.4	11.2
65–74 years	8.4	9.4	10.4	4.8
> 75 years	9.4	27.2	14.1	6.2
Sex (%)				
Male	22.1	31.1	20.6	30.1
Female	77.9	68.9	79.4	69.9
Race				
White	68.2	70.0	67.7	61.0
Nonwhite	31.8	30.0	32.3	39.0
Cardiovascular status				
High risk	31.8	28.1	25.5	22.3
Not high risk	68.2	71.9	74.5	77.7

OTC = over-the-counter.

grams were selected. The COMPASS data base is a longitudinal claims data base from which consistent outcome classification was obtained, and careful attention to quality assurance and control methodology were used.[8] Diagnoses are classified according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) coding scheme. The hypothesis to be tested was that terfenadine exposure is associated with an increased risk of developing life-threatening ventricular arrhythmias. The design and performance of the research were delineated prospectively, emphasizing the maintenance of scientific integrity. To examine the role of concomitant drug therapy and the evaluation of intermittent drug exposures, we chose a prescription-based analysis, considering the outcome from each drug exposure as an independent event.

Terfenadine and 3 comparison drugs were studied. Practical considerations led to the selection of these 3 comparison cohorts that were all available (in the period 1986 to 1990) in the COMPASS Medicaid data base. The comparison groups were as follows: (1) over-the-counter (OTC) antihistamines, selected because they are widely available and frequently used for indications similar to those of terfenadine. This group consisted primarily of diphenhydramine (94%), with the remaining 6% representing chlorpheniramine, brompheniramine and triprolidine; (2) ibuprofen, a nonantihistamine control, selected because of no known cardiac arrhythmic toxicity; and (3) clemastine, selected because it was a more recently approved OTC antihistamine, whose labeled indication is essentially identical to that of terfenadine (seasonal allergic rhinitis). Thus, this is a comparison drug without confounding by indication.

To ensure identical exposure periods, we defined the exposure period as 30 days in all 4 cohorts; however, a 7-day period was analyzed also. Patients who received terfenadine together with a comparison drug at any time were considered in the terfenadine cohort. Patients who were included in the OTC antihistamine, ibuprofen, and clemastine cohorts had no known terfenadine exposure. We selected the codes most closely related to life-threatening ventricular arrhythmias to be the primary study end point; these included paroxysmal ventricular tachycardia, ventricular fibrillation and flutter, cardiac arrest and sudden death. Torsades de pointes ventricular tachycardia was not coded separately. Lethal episodes of torsades de pointes would be detected under 1 code selected as the primary end point (e.g., cardiac arrest).

To validate outcomes identified in the data base and identify cases of torsades de pointes ventricular tachycardia, we requested medical records of all inpatient claims for arrhythmia and sudden death. To identify patients who died due to life-threatening ventricular arrhythmia before hospitalization, we requested records of all outpatient claims for ventricular arrhythmia or sudden death occurring in those who were lost to follow-up within 1 day of the outpatient claim. Investigators retrieving medical records were unaware of the study cohort. Independent, blinded review was performed by a cardiologist outside the study. We prospectively defined a subgroup with documented cardiovascular disease (high risk) who were more likely to develop a life-threatening ventricular proarrhythmia.[12–20] This subgroup included subjects with myocardial infarction, coronary artery disease, congestive heart failure, hypokalemia, hypomagnesemia, history of cardiac arrhythmias or antiarrhythmic therapy, cardiac glycosides, and rheumatic and congenital heart disease. We independently analyzed the high-risk subgroup from the remaining population that comprised a non–high-risk subgroup. The other prospective subgroup analyses specified were ketoconazole, erythromycin and liver disease.

Statistical methodology: Standard epidemiologic and statistical procedures were used. Demographic characteristics of subjects were summarized using percentages. Crude relative risks and 95% confidence intervals were calculated, comparing the risk of terfenadine-associated, life-threatening ventricular arrhythmias with that of each comparison cohort. Logistic regression procedures were used to assess the risk for development of

TABLE II Individual Data for Development of Life-Threatening Ventricular Arrhythmias in the Total Study Cohort

	Terfenadine	OTC Antihistamine	Ibuprofen	Clemastine
Number of subjects	181,672	150,689	181,672	83,156
Number of prescriptions	366,814	292,525	371,659	135,713
Days of F/U per prescription	30	30	30	30
Cardiac arrest	47	106‡	81‡	10
Other life-threatening ventricular arrhythmias*	21	22	23	7
Total	68	128‡	104§	17
Events/10,000 prescriptions†	1.8	4.4	2.8	1.2

*Includes ventricular fibrillation, flutter, fibrillation/flutter and tachycardia, and sudden death.
†Represents crude rates unadjusted for differences in risk.
‡$p < 0.001$; §$p < 0.01$, compared with terfenadine.
F/U = follow-up; OTC = over-the-counter.

TABLE III Relative Risk for Life-Threatening Ventricular Arrhythmias: Terfenadine in Relation to Each Comparison Drug

		Crude Analysis			Adjusted Analysis*		
Cohort	No. of Events	Relative Risk	Confidence Interval	p Value	Relative Risk	Confidence Interval	p Value
Full cohort							
Terfenadine	68						
OTC	128	0.42	0.32–0.57	<0.001	0.36	0.27–0.50	<0.001
Ibuprofen	104	0.66	0.49–0.90	<0.01	0.62	0.45–0.85	<0.01
Clemastine	17	1.48	0.87–2.52	0.15	1.08	0.63–1.85	0.79
High risk							
Terfenadine	53						
OTC	93	0.40	0.29–0.56	<0.001	0.37	0.26–0.52	<0.001
Ibuprofen	73	0.59	0.41–0.84	<0.01	0.61	0.43–0.88	<0.01
Clemastine	12	1.15	0.61–2.15	0.67	1.05	0.56–1.99	0.88
Not high risk							
Terfenadine	15						
OTC	35	0.36	0.20–0.66	<0.01	0.35	0.19–0.67	<0.01
Ibuprofen	31	0.54	0.29–0.99	0.04	0.65	0.35–1.22	0.18
Clemastine	5	1.26	0.46–3.48	0.65	1.18	0.42–3.35	0.75
Male							
Terfenadine	19						
OTC	41	0.52	0.30–0.89	0.02	0.46	0.26–0.81	<0.01
Ibuprofen	22	0.82	0.44–1.51	0.51	0.83	0.45–1.55	0.57
Clemastine	7	1.37	0.58–3.25	0.48	0.88	0.36–2.14	0.77
Female							
Terfenadine	49						
OTC	87	0.40	0.28–0.56	<0.001	0.33	0.22–0.47	<0.001
Ibuprofen	82	0.62	0.43–0.88	<0.01	0.56	0.39–0.81	<0.01
Clemastine	10	1.63	0.83–3.21	0.16	1.21	0.61–2.41	0.58

*See Methods.
OTC = over-the-counter.

life-threatening ventricular arrhythmias on terfenadine with that of each comparison cohort. A p value <0.05 was used to assess the statistical significance of the findings. Because it is important to adjust for covariates known to have prognostic significance for the development of life-threatening ventricular arrhythmias, several logistic regression models were analyzed. Models included age, sex, race, high-risk cardiovascular status, presence of hepatic disease, and concomitant use of ketoconazole or erythromycin; this provided a relative risk for terfenadine-associated, life-threatening ventricular arrhythmias after adjustment. Sample size and power were computed under conventional assumptions for a dichotomous end point, with a 2-sided α error of 0.05.[21]

RESULTS

Patient population: The COMPASS data base cohort comprised >596,000 patients. Life-threatening ventricular arrhythmias were evaluated using the experiential data base of 1,165,000 prescriptions in the 4 drug cohorts over the 30-day exposure window. The size of the data base provided large cohorts in all age groups, in both sexes and across races, enabling the study of subgroups (Table I). Patients in the OTC antihistamine and ibuprofen groups were older than in the terfenadine cohort, whereas those in the clemastine cohort were

TABLE IV Relative Risk for Life-Threatening Ventricular Arrhythmias: Terfenadine Versus Comparison Drug Use by Age

Cohort	No. of Events	Crude Analysis			Adjusted Analysis*		
		Relative Risk	Confidence Interval	p Value	Relative Risk	Confidence Interval	p Value
Full cohort							
Terfenadine	68						
OTC	128	0.42	0.32–0.57	<0.001	0.36	0.27–0.50	<0.001
Ibuprofen	104	0.66	0.49–0.90	0.01	0.62	0.45–0.85	<0.01
Clemastine	17	1.48	0.87–2.52	0.15	1.08	0.63–1.85	0.79
Age 0–19 years							
Terfenadine	4						
OTC	1	3.04	0.34–27.21	0.30	2.26	0.22–22.73	0.49
Ibuprofen	1	3.32	0.37–29.72	0.22	2.28	0.25–20.97	0.47
Clemastine	0	—	—	—	—	—	—
Age 20–44 years							
Terfenadine	18						
OTC	24	0.41	0.22–0.75	<0.01	0.31	0.16–0.59	<0.001
Ibuprofen	13	1.25	0.61–2.55	0.54	0.90	0.44–1.88	0.79
Clemastine	3	1.86	0.55–6.32	0.31	2.06	0.60–7.07	0.25
Age 45–64 years							
Terfenadine	32						
OTC	44	0.49	0.31–0.77	<0.01	0.37	0.23–0.60	<0.001
Ibuprofen	45	0.78	0.50–1.22	0.28	0.67	0.42–1.06	0.09
Clemastine	9	0.82	0.39–1.72	0.60	0.74	0.35–1.57	0.43
Age 65–74 years							
Terfenadine	4						
OTC	22	0.16	0.06–0.47	<0.001	0.12	0.04–0.34	<0.001
Ibuprofen	19	0.27	0.09–0.78	0.01	0.20	0.07–0.59	<0.01
Clemastine	1	0.85	0.10–7.62	0.88	1.02	0.11–9.15	0.98
Age > 75 years							
Terfenadine	10						
OTC	37	0.63	0.31–1.26	0.18	0.53	0.26–1.06	0.07
Ibuprofen	26	0.59	0.28–1.22	0.15	0.54	0.26–1.13	0.10
Clemastine	4	0.61	0.19–1.95	0.40	0.65	0.20–2.10	0.47

*See Methods.
OTC = over-the-counter.

younger. A larger percentage of patients in the terfenadine cohort were in the high-risk subgroup, and terfenadine-treated patients more frequently had congenital heart disease (both p <0.001 vs comparators). This prescription analysis enabled the evaluation of patients with only one 30-day exposure, as well as those with many exposures to 1 of the 4 cohort drugs. The percentages of patients in each cohort who had only 1 drug exposure were as follows: terfenadine, 63%; OTC antihistamines, 70%; ibuprofen, 63%; and clemastine, 51%.

Comparison of rates and relative risks of life-threatening ventricular arrhythmias: In all, 317 life-threatening ventricular arrhythmias occurred, 244 of which were cardiac arrests (Table II). Although this was a prescription-based analysis, no patient had >1 life-threatening ventricular arrhythmia. In comparison with patients on terfenadine, those on OTC antihistamines and ibuprofen had a higher rate of life-threatening ventricular arrhythmias. The rates for terfenadine and clemastine were statistically indistinguishable. In subset analysis, the relative risk for developing a life-threatening ventricular arrhythmia on terfenadine was not significantly greater than that of any comparison drug cohort (Table III). There was a consistent, excessive risk of OTC antihistamines throughout all analyses in the terfenadine-OTC antihistamine comparison.

Table IV presents an age comparison of the risk for life-threatening ventricular arrhythmias associated with terfenadine in relation to comparison drug use. In many groups, there was a statistically significant increase in the relative risk associated with a comparison drug (OTC and ibuprofen) compared with terfenadine. There was no statistically significant, increased risk associated with terfenadine in any age group in relation to any comparison drug. In addition to the 30-day window exposure, an analysis of the incidence of life-threatening ventricular arrhythmias occurring within 7 days of the cohort prescription was also performed. With use of the 7-day treatment window, only the relative risk of terfenadine-OTC antihistamine achieved statistical significance (relative risk 0.5; 95% confidence interval 0.29–0.84; p <0.01); the terfenadine-ibuprofen and terfenadine-clemastine comparisons were not statistically different. The rates of age-related, life-threatening ventricular arrhythmia events for all study cohorts are shown in Figure 1. A patient-based analysis (in contrast to the prescription-based analyses) yielded nearly identical results.

To evaluate the COMPASS data base's sensitivity to detect drug-related toxicity, concomitant administration of terfenadine/ketoconazole (a known risk) was examined. Other potential hazardous effects of terfenadine in the presence of erythromycin, as well as hepatic dis-

TABLE V Examination of Terfenadine Interactions in the Medicaid Data Base

	Unadjusted Relative Risk			Adjusted Relative Risk*		
	Relative Risk	Confidence Interval	p Value	Relative Risk	Confidence Interval	p Value
Ketoconazole (n = 648)	26.08	8.22–82.77	<0.001	23.55	7.31–75.92	<0.001
Erythromycin (n = 41,308)	1.36	0.70–2.66	0.37	1.36	0.69–2.67	0.37
Hepatic disease (n = 24,327)	1.88	0.90–3.92	0.09	1.09	0.51–2.34	0.82

*See Methods.

ease, were evaluated. A highly significant relative risk of the ketoconazole-terfenadine combination was identified when patients receiving both terfenadine and ketoconazole were compared with those receiving terfenadine only (Table V). The terfenadine-erythromycin and terfenadine–hepatic disease relative risks were both >1.0, but not statistically significant. Power computations reveal that this data base had 85% power to detect a relative risk of 1.4. Because a retrospective analysis of selected treatment cohorts would be anticipated to have baseline imbalances, the impact of baseline imbalances were further assessed.

To assess the comparability of cohorts, the following concomitant disease categories were considered: all cardiovascular diseases, asthma, chronic obstructive lung disease, liver disease, diabetes, hyperlipidemia, hypercholesterolemia, hypertension, alcohol/drug abuse, and electrolyte abnormalities. An equal or greater percentage of patients receiving terfenadine was present in each category in relation to each comparison cohort. The terfenadine cohort had an equal or greater frequency of all cardiovascular drugs, phenothiazines, bronchodilators and decongestants in comparison with either the ibuprofen or clemastine cohort. The terfenadine–OTC antihistamine comparison revealed greater digitalis, phenothiazine and antidepressant usage in the OTC antihistamine cohort, and greater antiarrhythmic and bronchodilator usage in the terfenadine group. Therefore, additional analyses of the impact of medication imbalances were performed by calculating the relative risks of subjects in the terfenadine-OTC cohorts both on and off each concomitant medication. The OTC cohort, both on and off each concomitant medication, consistently had a statistically significant, increased relative risk of developing life-threatening ventricular arrhythmias as compared with that of the terfenadine cohort. Thus, the observed increased risk in the OTC cohort is not explained by any imbalance in baseline medications.

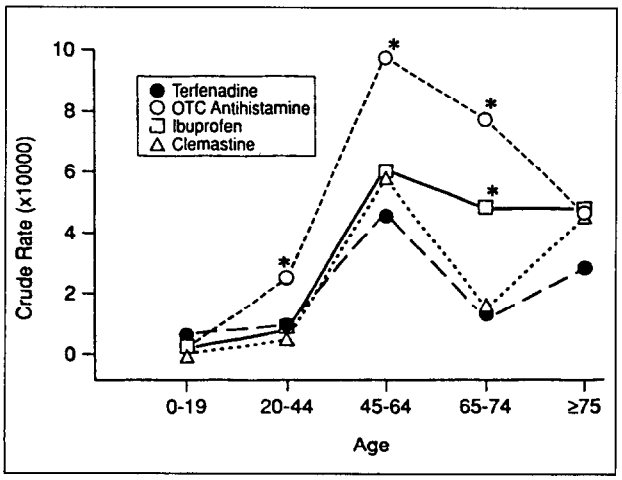

FIGURE 1. Crude rate/10,000 prescription exposures of developing life-threatening ventricular arrhythmia is represented for 4 drug cohorts over age categories assessed in study. OTC = over-the-counter.

DISCUSSION

Terfenadine safety is of great concern to regulatory agencies and the practicing physician. Implementation of a randomized clinical trial could not be used to examine this issue, because of its logistic impossibility when examining an extremely low frequency event. The sample size for a prospective clinical trial assuming a 2-sided, type I error of 0.05, power of 90% and an observed control group life-threatening ventricular arrhythmia rate of 2/10,000 is huge, needing >5,000,000 patients to detect a relative risk of 1.2. The impracticality of the clinical trial pathway focused this investigation on a historical cohort approach. This approach has the advantage of studying large populations that are representative of medication users. The results of this analysis do not support the hypothesis of a terfenadine-associated excessive risk of life-threatening ventricular arrhythmias in the absence of potent cytochrome P-450 inhibitors including ketaconazole and erythromycin. The specific arrhythmia previously associated with terfenadine, torsades de pointes ventricular tachycardia, is not specifically identified in the ICD-9-CM coding scheme. Therefore, the primary analysis included all life-threatening ventricular arrhythmia categories, because the clinical consequence of concern is that torsades de pointes ventricular tachycardia will lead to cardiac arrest/sudden death. With the use of this approach, the increased risk of developing a life-threatening ventricular arrhythmia with the combination of ketoconazole and terfenadine, anticipated from previous work, was identified (relative risk 23.55).[2,4,5] A surprising finding was an increase in life-threatening ventricular arrhythmias in the OTC antihistamine cohort (which was dominated by diphenhydramine prescriptions), which achieved statistical significance in almost all subsets. The medical record review performed by an independent cardiologist found 2 cases of torsades de pointes ventricular tachycardia in patients on diphenhydramine; the same number was found on terfenadine. A very conservative view of the terfenadine-ibuprofen comparison is that there was no excessive risk attributed to terfenadine. The comparison between terfenadine and clemastine (whose labeled indication most closely

emulates terfenadine) is near unity and not statistically significant. The equal risk in the terfenadine-clemastine comparison is noteworthy considering that the risk of the terfenadine cohort was higher; the terfenadine cohort was older, and had significantly more high-risk cardiovascular patients and congenital heart disease patients.

Analysis of the comparability of study cohorts: The main focus of the study was the evaluation of terfenadine safety in the general population. Several methods were used to evaluate the comparability of the selected cohorts. The comparison groups were selected for practical reasons. OTC antihistamines and clemastine are also used for seasonal allergic rhinitis. Ibuprofen was selected as a non-antihistamine control with no known cardiac toxicity. In many cases, imbalances in baseline characteristics increased the probability of life-threatening ventricular arrhythmic events occurring in the terfenadine cohort. OTC antihistamines may be administered to promote sleep, and ibuprofen is indicated for its anti-inflammatory properties. Despite confounding by indication, the critical question is whether each comparison cohort had a comparable baseline risk for developing life-threatening ventricular arrhythmias. Thus, we scrutinized known factors that influence the risk for developing life-threatening ventricular arrhythmias (the primary end point of this investigation). First, a "high-risk" cardiovascular group was identified prospectively, which was subsequently found to have a sevenfold increased risk of life-threatening ventricular arrhythmias. A significantly greater number of patients receiving terfenadine were in this category than in any comparison cohort, strengthening the conclusion of the absence of excessive risk with terfenadine. Likewise, an equal or greater number of patients receiving terfenadine had relevant co-morbidity (hypertension, cardiovascular disease, hyperlipidemia, hypercholesterolemia and diabetes) and an equal or greater frequency of obstructive lung disease, asthma and liver disease than did those in each of the 3 comparison cohorts. No baseline medication imbalance explains the significantly increased relative risk in the OTC antihistamine group, although all relevant imbalances were scrutinized. Because of concern that the specified 30-day exposure window may include excessive and disproportionate periods off the cohort drug, a 7-day exposure analysis was performed and revealed essentially the same results. Likewise, although we selected a prescription-based analysis, a patient-based analysis led to the same conclusion. Methodologic precautions were used to minimize ascertainment bias. The study's primary end point determinations were made in the absence of knowledge concerning the drug cohort. In addition, the exposure time of each drug cohort was identical (30 days). To examine potential misclassification bias, we sought medical records of all subjects with inpatient claims for arrhythmias, and all those who were lost to follow-up subsequent to an outpatient claim for a specific ventricular arrhythmia. Forty-five percent of 943 medical records that we requested were given to us by hospitals and providers. The true-positive and the true-negative rates from subjects with arrhythmia codes were both 92%. This low rate of misclassifications was consistent across drug cohort groups. Drug compliance is an important issue in a retrospective analysis. The established interaction of terfenadine and ketoconazole was detected powerfully (relative risk 23.55), which is consistent with an acceptable degree of compliance and adds validity to the primary end point selected.

The primary end point of this investigation: An important issue is the primary end point selected for analysis. There is no ICD-9-CM code for the specific arrhythmia of concern in relation to the established terfenadine-ketoconazole drug interaction, torsades de pointes ventricular tachycardia. The primary end point selected included all codes representing life-threatening ventricular arrhythmias, dominated by a preponderance of cardiac arrests (244 of 317). This end point is valid because the clinical concern is that torsades events may result in a sustained ventricular tachycardia or fibrillation resulting in cardiac arrest. With the use of this end point, the well-established terfenadine-ketoconazole toxicity was shown convincingly. To ensure the validity of the cardiac arrest code as a marker for mortality in outpatients who were lost to follow-up, the medical records of all retrievable, cardiac arrest–coded patients (n = 63) were analyzed. Of these patients, 62 were confirmed to be dead; 1 was presumed dead, but not confirmed. Thus, the cardiac arrest code accurately reflected mortality. All retrievable records were examined for additional cases of torsades de pointes. Four cases of torsades were found (terfenadine cohort [n = 2], and OTC cohort [n = 2]). Of the 2 terfenadine-associated cases, 1 had a cardiac arrest and was detected by the primary end point selected; this subject died. The second subject was found in a nonspecific arrhythmia code and was discharged alive. Both OTC cohort–associated cases were identified from the nonspecific arrhythmia codes, and both died. Neither OTC-related case had been included in the primary end point data. Although it will not be possible to be certain that each torsades case was identified, it is very unlikely that more than 2 to 3 additional cases with significant clinical consequences would remain undetected in any cohort or would affect a primary end point analysis that included 317 life-threatening ventricular arrhythmia events.

Because of the size of the study cohort, even a modest increase in the risk of terfenadine could have been detected. Power computations reveal that for a control group event rate of 4/10,000, the COMPASS data base provides 85% power to detect a relative risk of 1.4, or an excessive risk in life-threatening ventricular arrhythmia event rates as small as 1.6 events/10,000 prescriptions. The conservative conclusion of this analysis is that: (1) In the absence of potent metabolic inhibitors, there is no evidence supporting an excessive risk for developing life-threatening ventricular arrhythmias in patients taking terfenadine. (2) The strong, consistent increased risk in the OTC antihistamine cohort (relative risk 0.36; 95% confidence interval 0.22–0.50; $p < 0.001$) merits further investigation in a separate confirmatory trial, because there are significant public health implications.

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