

In vitro comparative fluoride release, and weight and volume change in light-curing and self-curing glass ionomer materials

Angela Wandera, BDS, MS Paulette Spencer, DDS, PhD Brenda Bohaty, DDS, MS

Abstract

The purpose of this study was to evaluate and compare in vitro fluoride release from and weight and volume changes of Photac-Fil™, a light-curing polymaleinate restorative glass ionomer, with Ketac-Fil™, a self-curing glass ionomer, and Ketac-Silver™, a metal reinforced glass ionomer. Five discs of each material, measuring 2 mm height and 5 mm diameter, were suspended in separate vials of distilled water and laboratory artificial saliva. Fluoride release into the solutions was measured using a calibrated fluoride-sensitive ion meter initially at 24 hr and then weekly from 1 to 9 weeks. These results were evaluated statistically using repeated measures analysis of variance. Volumes and weights were recorded at the start and end of the experiment and analyzed using the paired *t*-test. Photac-Fil released similar amounts of fluoride to Ketac-Silver, but significantly less than Ketac-Fil in distilled water ($P \leq 0.05$). In artificial saliva, Photac-Fil released similar amounts to Ketac-Fil, but significantly more than Ketac-Silver ($P \leq 0.05$). Photac-Fil volume increased in distilled water and artificial saliva ($P \leq 0.05$) as did Ketac-Fil and Ketac-Silver in artificial saliva ($P \leq 0.05$). The only material that demonstrated significant net weight increase was Ketac-Silver in artificial saliva ($P \leq 0.05$). In summary, differences in fluoride release between these three glass ionomer materials varied as a function of the media in which they were stored. Whereas Ketac-Fil exhibited significantly greater fluoride release than the other materials in distilled water, in artificial saliva Ketac-Fil and Photac-Fil exhibited comparable fluoride release. Dimensional change, as evaluated by volume and weight differences, was also affected by storage media. (*Pediatr Dent* 18:210–14, 1996)

Since their introduction, glass ionomer materials have attracted the attention of the dental community. The suggested application for these materials runs the gamut from luting agents to filling materials. Early glass ionomer restorative materials were

plagued by problems associated with moisture contamination and premature desiccation.¹ In an effort to address these problems, dental manufacturers have recently introduced light-cured glass ionomers.^{2,3}

The light-polymerized glass ionomer materials differ chemically from their self-curing counterparts. For example, photopolymerizing pendant monomers in these materials allow for their polymerization using blue light (470 nm).⁴ The addition of organic polymers in these materials contributes to decreased solubility and thus, potentially reduced fluoride release.^{4,5}

Comparative studies report significant differences in fluoride release between self-curing and metal-reinforced glass ionomer materials.^{6,7} Differences in the amounts of fluoride release also exist within product types. This has been demonstrated between metal reinforced glass ionomers Miracle Mix™ (GC Dental Industrial Corp, Tokyo, Japan) and Ketac-Silver™ (Espe Premier, GmbH, Seefeld, Germany), and between self-curing materials Fuji II (GC Dental Industrial Corp, Tokyo, Japan) and Ketac-Fil™ (Espe Premier, GmbH, Seefeld, Germany).^{6,7} It has been postulated that these differences are a function of varying formulations.⁸

Although abundant literature exists on self-curing and metal reinforced glass ionomer materials, there are few studies evaluating fluoride release from the newer light-curing products. Mitra,⁹ in 1991, compared light-cured and self-curing glass ionomer liner/bases and reported comparable cumulative amounts of fluoride release. In 1993, Forss¹⁰ reported considerable variability in the pattern and amounts of fluoride released in four light-cured glass ionomer liner/bases.

Photac-Fil™ (Espe Premier, GmbH, Seefeld, Germany) is a new light-curing polymaleinate glass ionomer recommended by the manufacturer for use in minimal Class I, III, and V cavities; primary teeth; fissure sealing; temporary restorations; and core build-ups. Previous literature has indicated that it is difficult, if not impossible, to predict fluoride release from this new filling material based on results from work using

other light-curing products.^{6,7} In view of the variable fluoride release reported in the literature, light-curing, self-curing, and metal-reinforced materials from the same commercial manufacturer were chosen for comparison. Ketac-Fil is a self-curing glass ionomer material that is indicated for restorations of minimal Class I cavities and anterior teeth. It is sensitive to moisture, and has low fracture and wear resistance. Ketac-Silver is metal reinforced and has enhanced mechanical properties, allowing its use in stress bearing areas. It has been shown to release lower levels of fluoride than Ketac-Fil in distilled water.⁷

The purpose of this study is to compare in vitro fluoride release and changes in weight and volume in three glass ionomer restorative materials in artificial saliva and distilled water.

Materials and methods

A light-curing polymaleinate glass ionomer dental restorative, Photac-Fil Aplicap (PF) [lot number x144], a self-curing glass ionomer, Ketac-Fil Aplicap (KF) [lot number 013A14 W139], and a metal-reinforced glass ionomer Ketac-Silver Aplicap (KS) [lot number 395/34 W282], were used in the study. All the materials are capsule mix systems and were triturated following the manufacturers' instructions. The mixed materials were placed in 10 2-mm-high x 5-mm-diameter lubricated acrylic molds. A 3-in. piece of non-fluoridated unwaxed dental floss was incorporated into each disc. The light-cured material was polymerized by a 60-sec exposure of each flat surface to a Visilux Curing Lamp™ (3M Dental Products, St Paul, MN). All of the materials were kept in the molds under glass slides for 2 hr.

The discs were removed from the molds and stored at 37°C for 24 hr in a dry heat oven. Dry heat was chosen to ensure accurate determination of weight and volume. Sample weights and volumes were then recorded in duplicate and averaged. No statistically significant differences were present within each material. Ten unwashed discs from each material group were randomly assigned to distilled water (DW) and laboratory artificial saliva¹¹ (AS), resulting in allocation of five discs of each material to each medium. Components of the artificial saliva were sodium bicarbonate (1.68020 g), sodium dihydrogen orthophosphate (0.46803 g), and calcium chloride (0.14702 g) dissolved in 1 L of distilled water. The pH of the solution was 7.2.¹¹ Each disc was placed in 20 ml of the respective solution in a plastic scintillation vial. The vial tops were sealed with parafilm paper and screw tops to prevent evaporation of the solution. The vials were placed on an orbital shaker at 70 revolutions/min at room temperature.

The fluoride ion concentration of each solution was measured at 24 hr and then weekly for 9 weeks. Prior to measurement, each disc was rinsed in 5 ml distilled water and transferred to new media. The rinse water and 2.5 ml of Total Ionic Strength Adjust-

ment Buffer™ (Fisher Scientific, St Louis, MO) was added to the corresponding solution. Following equilibration of the solution, the fluoride ion concentration was measured in duplicate using an ion-sensitive electrode (Fisher 925 pH/Ion Meter, Fisher Scientific, St Louis, MO). The ion meter was calibrated with a series of standard sodium fluoride solutions. The fluoride concentration of each sample solution was calculated from the calibration curve and recorded in ppm/mm³.

After the last measurement at 9 weeks, the discs were placed in a dry heat oven at 37°C for 48 hr. The weights of the dried specimens were re-recorded. It was noted at this time that the artificial saliva discs were coated with a fine, powdery, white precipitate. The samples were placed in a desiccator for 4 weeks and then reweighed at the end of this time period. Volume measurements were recorded after desiccation.

Statistical differences in fluoride release were analyzed using repeated measures ANOVA at the $P < 0.05$ level. Differences in the weights and volumes of the materials were analyzed using paired student *t*-tests ($P < 0.05$).

Results

Mean and mean cumulative fluoride release results are presented in Tables 1 and 2. Statistically significant differences were seen in mean cumulative fluoride release between all materials in distilled water ($P \leq 0.005$). In artificial saliva, statistically significant differences in mean cumulative fluoride release were noted between PF/KS and KF/KS ($P \leq 0.005$).

In distilled water, there were statistically significant differences in mean fluoride release between PF/KF ($P \leq 0.005$) and KF/KS ($P \leq 0.001$). There were statistically significant differences in mean fluoride release in artificial saliva between PF/KS ($P \leq 0.005$) and KF/KS ($P \leq 0.05$). There was no statistically significant difference in mean fluoride release in distilled water between PF/KS ($P \leq 0.05$). Similarly there was no statistically sig-

TABLE 1. MEAN CUMULATIVE FLUORIDE RELEASE (PPM/MM³)

| Time | PFDW* | KFDW* | KSDW* | PFAS | KFAS | KSAS* |
|-------|--------|---------|--------|-------|-------|-------|
| 24 hr | 63.45 | 102.59 | 19.84 | 18.22 | 13.28 | 2.52 |
| 1 w | 147.75 | 359.18 | 72.50 | 32.19 | 26.04 | 4.19 |
| 2 w | 195.05 | 537.56 | 100.97 | 37.63 | 30.21 | 4.86 |
| 3 w | 225.31 | 662.45 | 121.51 | 39.48 | 31.38 | 5.38 |
| 4 w | 250.30 | 765.34 | 139.27 | 44.48 | 34.10 | 6.05 |
| 5 w | 268.39 | 846.44 | 152.67 | 54.39 | 43.67 | 8.87 |
| 6 w | 285.55 | 919.61 | 165.36 | 64.87 | 49.36 | 11.06 |
| 7 w | 300.74 | 981.89 | 176.39 | 70.37 | 50.90 | 12.02 |
| 8 w | 313.51 | 1030.87 | 185.51 | 71.63 | 51.66 | 12.54 |
| 9 w | 326.52 | 1081.89 | 194.58 | 74.19 | 52.49 | 13.06 |

* Statistically significant ($P \leq 0.05$).

PFDW = Photac-Fil in distilled water; KFDW = Ketac-Fil in distilled water; KSDW = Ketac-Silver in distilled water; PFAS = Photac-Fil in artificial saliva; KFAS = Ketac-Fil in artificial saliva; KSAS = Ketac-Silver in artificial saliva.

TABLE 2. MEAN FLUORIDE RELEASE FROM GLASS IONOMER MATERIALS (SD)(PPM/MM³)

| Time | PFDW | KFDW* | KSDW | PFAS | KFAS | KSAS* |
|---------|---------------|----------------|--------------|--------------|--------------|-------------|
| 24 hr | 63.45 (11.61) | 102.59 (36.49) | 19.84 (6.72) | 18.22 (5.85) | 13.28 (3.25) | 2.52 (0.80) |
| 1 week | 84.29 (7.76) | 256.59 (80.70) | 52.66 (6.03) | 13.97 (2.19) | 12.76 (8.95) | 1.67 (0.71) |
| 2 weeks | 47.30 (4.17) | 178.38 (47.48) | 28.47 (2.82) | 5.44 (1.98) | 4.17 (1.88) | 0.67 (0.05) |
| 3 weeks | 30.26 (2.79) | 124.89 (26.49) | 20.54 (1.65) | 1.85 (0.43) | 1.17 (0.75) | 0.52 (0.02) |
| 4 weeks | 24.99 (2.72) | 102.89 (14.24) | 17.76 (2.30) | 5.00 (2.52) | 2.72 (1.00) | 0.67 (0.17) |
| 5 weeks | 18.09 (2.15) | 81.10 (9.29) | 13.40 (1.42) | 9.92 (2.74) | 3.64 (1.06) | 1.87 (1.05) |
| 6 weeks | 17.16 (1.90) | 73.17 (3.12) | 12.69 (1.01) | 10.48 (1.23) | 5.69 (2.93) | 2.19 (0.61) |
| 7 weeks | 15.18 (1.28) | 62.28 (2.94) | 11.03 (1.41) | 5.49 (0.88) | 1.53 (0.75) | 0.96 (0.77) |
| 8 weeks | 12.78 (1.21) | 48.98 (5.13) | 9.11 (1.51) | 1.26 (0.85) | 0.76 (0.24) | 0.52 (0.02) |
| 9 weeks | 13.01 (1.11) | 51.02 (2.40) | 9.07 (1.12) | 2.56 (1.12) | 0.83 (0.13) | 0.52 (0.02) |

* Statistically significant ($P \leq 0.05$).

PFDW = Photac-Fil in distilled water; KFDW = Ketac-Fil in distilled water; KSDW = Ketac-Silver in distilled water; PFAS = Photac-Fil in artificial saliva; KFAS = Ketac-Fil in artificial saliva; KSAS = Ketac-Silver in artificial saliva.

TABLE 3. EFFECT OF FLUORIDE RELEASE, DISTILLED WATER, AND ARTIFICIAL SALIVA ON GLASS IONOMER VOLUME (SD) AND WEIGHT (SD)

| Material | Volume (mm ³) | | Weight (mg) | | |
|----------|---------------------------|---------------|-----------------|------------------|------------------|
| | Baseline | 13 Weeks | Baseline | 9 Weeks | 13 Weeks |
| PFDW | 60.06 (2.92) | 65.21 (4.45)* | 0.12332 (0.006) | 0.13056 (0.007)* | 0.13012 (0.008) |
| KFDW | 58.11 (1.39) | 58.02 (1.16) | 0.11966 (0.003) | 0.12464 (0.003)* | 0.11800 (0.003) |
| KSDW | 56.29 (3.71) | 58.70 (3.29) | 0.17914 (0.008) | 0.18968 (0.010)* | 0.18204 (0.012) |
| PFAS | 58.89 (3.16) | 67.46 (4.88)* | 0.12196 (0.005) | 0.13368 (0.008)* | 0.13034 (0.013) |
| KFAS | 57.60 (3.03) | 63.42 (1.92)* | 0.12212 (0.005) | 0.13028 (0.005)* | 0.12618 (0.005) |
| KSAS | 57.77 (2.78) | 63.39 (3.60)* | 0.17928 (0.007) | 0.19540 (0.008)* | 0.18774 (0.010)* |

* Statistically significant ($P \leq 0.05$).

PFDW = Photac-Fil in distilled water; KFDW = Ketac-Fil in distilled water; KSDW = Ketac-Silver in distilled water; PFAS = Photac-Fil in artificial saliva; KFAS = Ketac-Fil in artificial saliva; KSAS = Ketac-Silver in artificial saliva.

nificant difference in mean fluoride release in artificial saliva between PF/KF ($P \leq 0.05$).

Mean weight and volume changes are shown in Table 3. Statistically significant differences in weight were found in all materials in both distilled water and artificial saliva between baseline and 9 weeks but only in Ketac-Silver between baseline and 13 weeks after desiccation. Statistically significant increases in volume were noted for Photac-Fil in distilled water and for all materials in artificial saliva ($P \leq 0.05$).

Discussion

The release of fluoride from glass ionomer materials has been related to surface erosion, dissolution from cracks and fissures, and dissolution by solid-state diffusion from the bulk.¹² The pattern of fluoride release from the glass ionomer materials in distilled water suggests contributions from each of these factors. After a maximum release at 1 week, the rate of fluoride release gradually decreases over time. This pattern corresponds with the observations re-

ported in previous studies with Ketac-Silver¹³ and Ketac-Fil.¹⁴

The fluoride release in artificial saliva, however, does not follow this pattern.

These differences may be related to the absence of a well-defined concentration gradient in the artificial saliva. Chemical species, such as sodium, hydrogen, phosphate, calcium, and carbonate contained in the laboratory artificial saliva, have the potential to react with fluoride or to be adsorbed by the material.^{12, 15} It is hypothesized that the white precipitate noted on the dried artificial saliva specimens represented such adsorbed chemical species. These ions may act as a barrier to reduce fluoride availability.¹⁵

At the 3- to 4-week interval, all the materials in artificial saliva exhibited an increase in rate of release. The increase was more pronounced in PF at 4-5 weeks and in KF at 5-6 weeks. A similar increase appeared to occur at 8 weeks, but since the experiment did not continue beyond 9 weeks, it was not possible to follow this cycle of release. A possible explanation for this is deple-

tion of fluoride from the outer layers and creation of a solid state concentration gradient in the disc, as discussed by Kuhn and Wilson.¹² Ions moved to the sub-surface region under the adsorbed surface coating and availability for leaching then increased. It is postulated, however, that the presence of the coating impeded the time-dependent release mechanics. The lubricant used in the disc preparation procedure may have had a similar effect on fluoride release.

In comparing the materials, PF released more fluoride in artificial saliva than did KF. This release was remarkably different from that seen in distilled water. Mitra⁹ found similar release patterns comparing light-curing and self-curing glass ionomers in a buffered solution of pH 6.8. The pH of the artificial saliva used in this study was 7.2. El Mallakh et al.¹⁶ recorded a reversal in release in distilled water and artificial saliva between KF and Fuji II. This supports the contention that fluoride release in distilled water may give little information on in vivo fluoride release.^{8,17}

A large difference in cumulative release (700 ppm/mm³) was seen between KF in distilled water and the other materials. This differs from other work and may be due to the different units of measurement we used.^{8,16} The units used in this study refer to the weight of fluoride released into a volume of solution from a volume of material. Units commonly used in other studies refer to the weight of fluoride released into a volume of solution, weight of fluoride released from a weight of material, or weight of fluoride released from surface area of material.^{6,7,9} The dry heat may have increased the initial rate of fluoride release into solution.

For all materials, the mean weight increases from baseline to 9 weeks were statistically significant. This appears to be due to water sorption in distilled water and water sorption and precipitate in artificial saliva. PF in artificial saliva showed the highest relative increase. The resin component of PF may contribute to high water sorption seen as weight increases in distilled water and artificial saliva. However, minimal reduction was achieved by exposing any of the PF discs to desiccant. This suggests tightly bound water in the material structure.

KS in artificial saliva was the only material that increased significantly in weight from baseline to 13 weeks. The silver in the material may have interacted with the ionic components of the artificial saliva more extensively than the other materials and formed larger quantities of precipitate.

Between baseline and 13 weeks, weight changes potentially attributable to loss of material into fluid were detected in KF in distilled water. This was not totally unexpected because of the high amounts of fluoride released. No other material group had negative weight differences.

After desiccation, KF in distilled water demonstrated significant weight loss (week 9 to 13). This is

consistent with self-cured glass ionomer sensitivity to moisture. KF in artificial saliva did not show significant weight decrease, which may be due to the precipitation of salts from the solution. The mean cumulative amount of fluoride lost by KF in artificial saliva was much less than in distilled water. This may be reflected in weight change variance.

Volume increases of PF in distilled water ($P \leq 0.05$) and of all materials in artificial saliva ($P \leq 0.05$) were statistically significant. It seems plausible that hygroscopic expansion occurred in all materials except for KF in distilled water, which may have decreased in volume due to a high leaching rate and exposure to dry heat and desiccation. Polymerization contraction and water sorption are resin and glass ionomer factors that would influence volume variance in PF, KF and KS.¹⁸ A balance between the factors would result in unchanged volumes, and a shift in either direction would result in a net increase or decrease. Both polymerization shrinkage and loose water incorporation may explain volume decrease in KF. Curing contraction probably was counteracted by tight water sorption in PF distilled water and KS distilled water. The additive effect of the surface coating in artificial saliva is the most likely cause of generalized higher volumes.

In summary, fluoride release from glass ionomer materials stored in artificial saliva does not follow the gradual decrease noted in distilled water. In vivo results have shown increases of fluoride concentration in children's unstimulated saliva ranging from 0.55 to 0.84 ppm after 3 weeks of placement of glass ionomer restorations.¹⁷ A well-controlled comparative in vitro/in vivo study would demonstrate similarities and differences of fluoride release patterns in laboratory media and the oral milieu.

Conclusions

1. Photac-Fil releases significantly less mean fluoride and cumulative fluoride than Ketac-Fil in distilled water, but comparable amounts in laboratory artificial saliva over 9 weeks.
2. Photac-Fil releases similar mean fluoride to Ketac-Silver in distilled water. Cumulative fluoride release from Photac-Fil is significantly greater than Ketac-Silver in distilled water and laboratory artificial saliva over 9 weeks.
3. Ketac-Silver significantly increased in weight after exposure to laboratory artificial saliva for 9 weeks.
4. Photac-Fil showed significant increases in volume after exposure to distilled water as did Photac-Fil, Ketac-Fil, and Ketac-Silver after exposure to laboratory artificial saliva for 9 weeks.

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During this study, Dr. Wandera was a research fellow, University of Missouri—Kansas City School of Dentistry and is currently a clinical assistant professor, department of orthodontics and pediatric dentistry, University of Michigan, Ann Arbor. Dr. Spencer is director of graduate studies and research, department of oral biology; and Dr. Bohaty is an associate professor, department of pediatric dentistry, both at the University of Missouri—Kansas City School of Dentistry, Kansas City.

1. Wilson AD: Developments in glass ionomer cements. *Int J Prosthodont* 2:438–46, 1989.
2. Croll TP, Killian CM, Helpin ML: A restorative dentistry renaissance for children: light-hardened glass ionomer/resin cement. *ASDC J Dent Child* 60:89–94, 1993.
3. Fricker JP: A 12-month clinical evaluation of a light-activated glass polyalkenoate (ionomer) cement for the direct bonding of orthodontic brackets. *Am J Orthod Dentofacial Orthop* 105:502–5, 1994.
4. Tam LE, McComb D, Pulver F: Physical properties of proprietary light-cured lining materials. *Oper Dent* 16:210–17, 1991.
5. Mathis RS, Ferracane JL: Properties of a glass-ionomer/resin-composite hybrid material. *Dent Mater* 5:355–58, 1989.
6. DeSchepper EJ, Berry EA III, Cailleteau JG, Tate WH: A comparative study of fluoride release from glass-ionomer cements. *Quintessence Int* 22:215–19, 1991.
7. Forsten L: Short- and long-term fluoride release from glass ionomers and other fluoride-containing filling materials in vitro. *Scand J Dent Res* 98:179–85, 1990.
8. Hörsted-Bindslev P: Fluoride release from alternative restorative materials. *J Dent* 22:S17–20, 1994. (Suppl 1)
9. Mitra SB: In vitro fluoride release from a light cured glass-ionomer liner/base. *J Dent Res* 70:75–78, 1991.
10. Forss H: Release of fluoride and other elements from light-cured glass ionomers in neutral and acidic conditions. *J Dent Res* 72:1257–62, 1993.
11. Joyston-Bechal S, Kidd EAM: The effects of three commercially available saliva substitutes on enamel in vitro. *Br Dent J* 163:187–90, 1987.
12. Kuhn AT, Wilson AD: The dissolution mechanisms of silicate and glass-ionomer dental cements. *Biomaterials* 6:378–82, 1985.
13. Takahashi K, Emilson CG, Birkhed D: Fluoride release in vitro from various glass ionomer cements and resin composites after exposure to NaF solutions. *Dent Mater* 9:350–54, 1993.
14. Thornton JB, Retief DH, Bradley EL: Fluoride release from and tensile bond strength of Ketac-Fil and Ketac-Silver to enamel and dentin. *Dent Mater* 2:241–45, 1986.
15. Rezk-Lega F, Øgaard B, Rølla G: Availability of fluoride from glass-ionomer luting cements in human saliva. *Scand J Dent Res* 99:60–63, 1991.
16. El Mallakh BF, Sarkar NK: Fluoride release from glass-ionomer cements in deionized water and artificial saliva. *Dent Mater* 6:118–22, 1990.
17. Hatibovic-Kofman S, Koch G: Fluoride release from glass ionomer cement in vivo and in vitro. *Swed Dent J* 15:253–58, 1991.
18. Bowen RL, Marjenhoff WA: Dental composites/glass ionomers: the materials. *Adv Dent Res* 6:44–49, 1992.

Potentially deadly combination of drugs still prescribed

WARNINGS HAVE SIGNIFICANT IMPACT, BUT HAVE NOT ELIMINATED PROBLEM

Despite widespread warnings that taking the prescription antihistamine terfenadine (Seldane™) along with a certain type of antibiotic or antifungal medication could cause life-threatening side effects, some patients are still taking the drugs in tandem, according to an article in a recent issue of *The Journal of the American Medical Association*.

David Thompson, PhD, and Gerry Oster, PhD, Policy Analysis, Inc., Brookline, Mass., reviewed pharmacy claims from a large health insurer in New England between January 1990 (six months before the first warning was issued) and June 1994. After finding patients with paid claims for terfenadine, they checked for antibiotics or antifungals that were either dispensed on the same day or had therapy days that overlapped with terfenadine. The drugs that have been found to interact negatively with terfenadine are macrolide antibiotics including erythromycin, clarithromycin, and troleandomycin; and imidazole antifungals including ketoconazole and itraconazole.

The researchers found that the rate of same-day dispensing of terfenadine with contraindicated drugs declined by 84% from 1990 to 1994. The rate of overlapping use of terfenadine and contraindicated

drugs declined by 57% between 1990 and 1994.

But despite these declines, the researchers found that during the first six months of 1994, as many as 2–3% of all persons prescribed terfenadine had overlapping claims for either a macrolide antibiotic or imidazole antifungal.

In June 1990, the U.S. Food and Drug Administration (FDA) issued a report naming macrolide antibiotics and the imidazole antifungal, ketoconazole, as risk factors for serious ventricular arrhythmias among patients taking terfenadine, according to the study. Later the list was expanded. In August 1990, the FDA ordered the manufacturer of terfenadine (Hoechst Marion Roussel) to send a letter to all practicing physicians in the U.S. alerting them to this problem. In July 1992, warning labels were added to all products containing terfenadine.

In addition, providers have been alerted to the possibility of drug-drug interactions involving terfenadine through published reports.

The researchers conclude: "Despite substantial declines following reports of serious drug-drug interactions and changes in product labeling, concurrent use of terfenadine and contraindicated macrolide antibiotics and imidazole antifungals continues to occur."