Is fluoride varnish safe?

Validating the safety of fluoride varnish

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ABSTRACT

Background. Fluoride varnish is widely used in dentistry as a caries preventive measure with recommendations for its use even in infants. In addition, nondental providers are also applying varnish on children's teeth in various settings. However, there are questions from these nondental providers as to the safety of fluoride varnish.

Methods. To evaluate and describe the adverse events (AEs) related to fluoride varnish, the US Food and Drug Administration's Manufacturer and User Facility Device Experience database was used. AEs reported for the dental product code for "varnish, cavity," "varnish," and "fluoride" were evaluated. The identified AEs were then reviewed and categorized using appropriate key words for the various signs and symptoms, outcomes, and treatment.

Results. Over the 10-year period, only 65 AEs were reported for fluoride varnish products. Swelling (33.8%); burning, itching, or soreness (23.1%); and rash (16.9%) were the most common signs and symptoms reported. The most common site reported was the lips (27.7%). The most common outcome was that the patient was taken to the hospital (18.5%) or emergency department (15.4%). No deaths were reported. The patients were treated primarily using diphenhydramine (Benadryl, Johnson & Johnson Consumer) (26.1%), followed by an epinephrine autoinjector (EpiPen, Mylan) and other forms of epinephrine (15.4%), and prednisolone (9.2%). In 16.9% of the cases with AEs there was a history of allergies. The rate of AEs is estimated to be between 0.099 and 0.105 per million for fluoride varnish. A concern is the likelihood of underreporting AEs in the Manufacturer and User Facility Device Experience database.

Conclusions. Given the widespread use of fluoride varnish in the United States, the number of AEs reported to the US Food and Drug Administration were few. Thus fluoride varnish can be considered a safe dental product.

Practical Implications. Provides data on the safety of fluoride varnish that can be used by the dental profession to allay concerns by nondental providers and patients on this important caries preventive measure.

Key Words. Fluoride varnish; safety; adverse events; US Food and Drug Administration; Manufacturer and User Facility Device Experience.

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Fluoride in its many forms is used in dentistry as an effective caries preventive measure. Fluoride in lower concentrations is self-applied by the person and in higher concentrations professionally applied. Several fluoride vehicles have been in use, with fluoride varnish being the favored professionally applied fluoride over the past 20 years owing to its effectiveness, acceptability, and ease of use.[1] It is also one of the most commonly reimbursed procedures by dental insurance companies. Owing to fluoride varnish's effectiveness, it is widely recommended for use in children,[2,3] even infants.[4] Furthermore, because of access to dental care issues and ease of use, several nondental providers such as pediatricians, family physicians, and nurses, who are advocates for good oral health as integral to good overall health, are now also applying varnish to children's teeth as recommended by the US Preventive Services Task Force.[5] Fluoride varnish is now used in dental offices, medical offices, school-based settings, and other community settings.

However, there are questions from some of these nondental providers as to the safety of fluoride varnish, particularly as some of these providers practice in nontraditional community settings where the ability to treat an adverse event (AE) if it were to occur may be restricted. The dental literature is replete with studies on the general health and dental effects including fluorosis and safety of fluoride.[6-10] Nevertheless, when it comes to the specific safety of fluoride varnish, particularly for an AE after a fluoride varnish application, there is a paucity of studies or available data.[2] One study of 3 clinical trials with a total sample size of 2,424 children aged 0 through 5 years reported no AEs related to fluoride varnish treatments in children, so it was unable to describe AEs related to fluoride varnish use.[11] One reason was possibly the stricter definition used—"health events that resulted in a medically attended visit within a prescribed time frame ... after the fluoride varnish application"—thus missing any events that did not result in a medical visit.

Thus the primary objective of this study is to evaluate the immediate safety of fluoride varnish and describe the AEs related to fluoride varnish using other available databases.

METHODS

A search for a suitable database to conduct this study and analyses was conducted. The US Food and Drug Administration's (FDA) Manufacturer and User Facility Device Experience (MAUDE) database was identified as a suitable database.[12] In the United States, the FDA is the federal agency whose mission is to protect and advance public health through making drugs, food, cosmetics, biologics, products that emit radiation, and medical devices including dental devices more effective and safer. The FDA has broad regulatory authority, which includes premarket approval and postmarket device surveillance. Postmarket surveillance is done through MAUDE, a database of medical device–associated AE reports such as deaths, serious injuries, and malfunctions submitted to the FDA by mandatory and voluntary reporters. Device manufacturers, importers, and user facilities are considered mandatory reporters, and health care professionals, patients, and consumers are considered voluntary reporters. At any given time, 10 years of data are available through MAUDE. A dental device manufacturer or importer knows that they are required to report suspected device-associated deaths, serious injuries, and malfunctions to the FDA using the medical device reports mechanism.

The MAUDE database was used and queried over a 10-year period from January 2010 through August 2020 for the dental product terms "varnish, cavity," "varnish," and "fluoride." Each of these queries resulted in a dataset that was downloaded in Excel. These 3 dental product terms were used to capture a complete dataset of all available reports on fluoride varnish. The fields of interest and relevance included in the MAUDE database are date of event, event type, manufacturer, product, device problem, and event description.

Each resulting dataset was then sorted and reviewed to ensure that only reports related to the various fluoride varnish products were included. The 3 datasets were then merged and again sorted and reviewed to remove duplicate entries.

Using the detailed event description field, each report was then reviewed and categorized using appropriate key words for signs and symptoms, affected site, outcomes, and treatment provided. The description was also reviewed to categorize if the report was an AE or a serious adverse event (SAE). FDA definitions[13] used were

- AE: "Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."
- SAE: " ... if in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect."

Data analyses performed were descriptive analyses summarizing the signs and symptoms, affected site, outcomes, and treatment provided using percentages. For signs and symptoms, search key words were burning, itching, soreness, rash, redness, swelling, and difficulty breathing; site consisted of lips, gums, tongue, and throat; outcomes considered were emergency department visit, hospitalization, and death; and treatment, which was use of diphenhydramine (Benadryl, Johnson & Johnson Consumer), epinephrine autoinjector (EpiPen) or other forms of epinephrine, and prednisolone.

Using US Census data for 2010 through 2019, the rate of AEs for fluoride varnish was estimated using 2 strategies.[14-16] In the first strategy, as data for the overall prevalence of fluoride varnish use

ABBREVIATION KEY

AE: Adverse events.
FDA: US Food and Drug Administration.
MAUDE: Manufacturer and User Facility Device Experience.
SAE: Serious adverse event.

Table. Signs, symptoms, site, outcome, and treatment for fluoride varnish adverse events.

CHARACTERISTIC	NO. (%)
Signs and Symptoms	
Swelling	22 (33.8)
Burning, itching, soreness	15 (23.1)
Rash	11 (16.9)
Vomiting	10 (15.4)
Difficulty breathing	3 (4.6)
Tightening of throat	3 (4.6)
Loss of consciousness	1 (1.5)
Site	
Lips	18 (27.7)
Face	8 (12.3)
Throat	8 (12.3)
Tongue	7 (10.8)
Outcome	
Taken to hospital	12 (18.5)
Taken to emergency department	10 (15.4)
Hospitalization	5 (7.7)
Treatment	
Diphenhydramine (Benadryl, Johnson & Johnson Consumer)	17 (26.1)
Epinephrine autoinjector (EpiPen, Mylan)	3 (4.6)
Epinephrine	7 (10.8)
Prednisolone	6 (9.2)

in the United States were not available, the prevalence of dental visits from Healthy People 2020 was used as a proxy. In the publicly available MAUDE data, the age of the person in whom the AE occurred is redacted; thus an assumption was also made that all AEs reported were in children aged 2 through 17 years of age, as this is predominantly the age group in which fluoride varnish is applied in the United States. Furthermore, from the event description a large number seemed to be children as the narrative included terms like "parent," "child," "son," and "daughter."

In the second strategy, the 2019 prevalence of fluoride varnish use in a privately insured Midwestern US population was used. This Midwestern state is representative of the United States, and the market share of the insurance company is about 34%, similar to that nationally. Here, the assumption was made that the AEs reported in MAUDE were across the life span.

RESULTS

Over this 10-year period of 2010 through 2019, using the search strategy, 66 cases that involved a fluoride varnish product were reported to the FDA. With 1 exception, 65 cases reported AEs, resulting in an average of 6.5 AEs per year, with a range of 1 through 10 cases reported yearly. When each of these was reviewed, 5 of the AEs (7.7%) were SAEs requiring hospitalization. In 11 of the AEs (16.9%), there was a history of allergies and 55 (84.6%) were categorized as "injury." Most (53; 81.5%) were reported by the dental office to the manufacturer, and only 12 (18.5) were reported by the parent or patient to the manufacturer or FDA.

Signs and symptoms presented were categorized: 22 (33.8%) reported swelling; 15 (23.1%) reported burning, itching, or soreness; 11 (16.9%) had a rash; 10 (15.4%) reported vomiting; 3 each (4.6%) reported difficulty breathing and tightening of throat; and 1 (1.5%) reported loss of consciousness (Table).

The most common site reported for the sign and symptoms was the lips in 18 (27.7%) cases, followed by face and throat with 8 each (12.3%), and tongue in 7 cases (10.8%). After the episode

or reaction, 12 (18.5%) were taken to the hospital and 10 (15.4%) went to an emergency department. Five (7.7%) were hospitalized. No deaths were reported.

Several patients were treated with medications. Benadryl was the most common, with 17 (26.1%) administered diphenhydramine, followed by EpiPen or epinephrine in 10 (15.4%) and prednisolone in 6 (9.2%).

To estimate the rate of AEs for fluoride varnish, 2 separate strategies were used. In the first, US Census data showed that over the 10-year period, there were 657,429,839 children aged 2 through and 17 years.[14-15] Healthy People 2020 data for the oral health objective 7 (to increase the proportion of children, adolescents, and adults who used the oral health care system in the past year) report estimates of dental visits by children aged 2 through 17 years from 2010 through 2016.[16] Using these estimates, it was calculated that on average 49.7% of children in this age group had a dental visit. Thus over this 10-year time period, 326,874,116 children had a dental visit. Assuming all these children would have received at least 2 fluoride varnish applications each year, which is the minimal American Academy of Pediatric Dentistry recommendation,[17] the AEs are estimated to be 0.099 per million fluoride varnish applications.

In the second strategy, to validate this previous estimate, data from a large dental insurance company in the Midwest were sought. The data showed that in 2019, 32% of the insured population had at least 1 fluoride varnish application. Using US Census data, over the 10-year period 2010 through 2019 there were a total of 2.5 billion adults in the United States and 657.4 million children. If we estimate, using Centers for Disease Control and Prevention data and reports,[18] that 50.2% adults with dental coverage and 100% of children were covered, there would be 1.93 billion Americans with dental coverage in the United States. Using private insurance data, of the 32% of children receiving 1 fluoride varnish application each year, 617.6 million varnish applications were applied over 10 years. With only 65 AEs over the 10-year period, the AEs are estimated to be 0.105 per million.

DISCUSSION

Analyses of reports to the FDA using MAUDE data provide a retrospective review of reported AEs for fluoride varnish applications in the United States and show that AEs and SAEs arising from a fluoride varnish application over a 10-year period are low. Furthermore, it is reassuring that no deaths were reported and only 5 people had a serious event that needed to be hospitalized. Given the number of fluoride varnish applications performed in the United States each year, I attempted to calculate or estimate the rate of AEs using 2 scenarios and estimates. The rate of AEs is estimated to be between 0.099 per million and 0.105 per million for fluoride varnish. The close approximates of these estimates to each other provide confidence in their accuracy. Such a low rate should allay concerns of dental and nondental providers who are providing these procedures in nontraditional settings that may not have the capacity to deal with an AE.

The finding that those with a history of allergies could have an AE or reaction to fluoride varnish is interesting but should not be unexpected. This finding should be used to urge clinicians to obtain an appropriate history that includes previous allergies, document in the patient chart, and monitor patients with previous allergies after the procedure. Some of the reported allergies were to dairy, soy, seafood, nuts, pineapple, animal fur, palm oil, colophony (rosin).

Most AEs were treated with an antihistaminic such as Benadryl. The EpiPen was used in 3 reports and was available from the parent as the child had a history of allergies. Thus, it is recommended that in nontraditional settings where fluoride varnish might be applied, such as in schools and Head Start centers, to keep diphenhydramine available. In the United States, emergency kits generally have an EpiPen, but this is a more expensive alternative.

Several limitations, most related to the use of the MAUDE database, need to be considered. As the FDA suggests, this is passive surveillance, so there exists "the potential submission of incomplete, inaccurate, untimely, unverified, or biased data" and caution must be taken in calculating incidence.[12] Furthermore, although device manufacturers, importers, and user facilities are required to submit adverse reports for fluoride varnish to the FDA, the adverse reports can only be submitted to the FDA if they were reported by the health professional or patient to the manufacturers or importers of the fluoride varnish products, as seen in 82% of the cases in this study. Most likely there is substantial underreporting of events. In addition, owing to the nature of the reported data, a cause-effect cannot be assumed. Furthermore, as the FDA does not verify the report and the quality

and completeness of the information reported varies, conclusions should be made with care. Thus, for the AE rate estimates calculated here, caution was taken to be conservative. An article in the dental literature using MAUDE suggests that it "is an important, if imperfect, contributor to our profession's knowledge about threats to patient safety"[19] and encouraged the dental profession to report device-related AEs to the FDA and MAUDE. In this study, I agree and echo this sentiment. In medicine, other databases such as the FDA AE Reporting System database, the National Electronic Injury Surveillance System database, and those of large hospital systems have been used. In dentistry, similar databases are not available or are not appropriate.

Notwithstanding all the limitations of the data, over a 10-year period only 65 AEs related to fluoride varnish were reported to the FDA. Even if this was a gross underestimate because minor events or some serious events that likely occurred were not reported and, therefore, not included in the MAUDE database of an order of magnitude of 10 times given the large number of fluoride varnish applications performed in the United States over this period, the estimated AEs would still be low, ranging from 0.099 per million through 0.99 per million or 0.105 per million through 1.05 per million based on which estimate is used. Together with knowledge of varnish safety from pharmacokinetic studies,[10] the evidence that fluoride varnish is safe is compelling.

CONCLUSIONS

Given the widespread use of fluoride varnish in the United States, the number of AEs reported to the FDA were few even after taking into consideration potential underreporting. Thus, fluoride varnish can be considered a safe dental product. ■

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