Review Article

Bisphenol A in dental sealants and its estrogen like effect

Manu Rathee, Poonam Malik[1], Jyotirmay Singh[2]

Department of Prosthodontics, Post Graduate Institute of Dental Sciences (PGIDS), Pt. B.D. Sharma University of Health Sciences, Rohtak, [1]Department of Prosthodontics, SGT Dental College, Hospital and Research Institute, Gurgaon, Haryana, [2]Department of Orthodontics and Dentofacial Orthopedics, Dr. B.R. Ambedkar Institute of Dental Sciences and Research, Patna, Bihar, India

ABSTRACT

Bisphenol A or BPA-based epoxy resins are widely used in the manufacture of commercial products, including dental resins, polycarbonate plastics, and the inner coating of food cans. BPA is a precursor to the resin monomer Bis-GMA. During the manufacturing process of Bis-GMA dental sealants, Bisphenol A (BPA) might be present as an impurity or as a degradation product of Bis-DMA through esterases present in saliva. Leaching of these monomers from resins can occur during the initial setting period and in conjunction with fluid sorption and desorption over time and this chemical leach from dental sealants may be bioactive. Researchers found an estrogenic effect with BPA, Bis-DMA, and Bis-GMA because BPA lacks structural specificity as a natural ligand to the estrogen receptor. It generated considerable concern regarding the safety of dental resin materials. This review focuses on the BPA in dental sealants and its estrogen-like effect.

Key words: Bisphenol A, dental sealants, estrogen

Bisphenol A-Based Dental Resins

Bisphenol A or BPA-based epoxy resins are widely used in the manufacture of commercial products, including dental resins, polycarbonate plastics, and the inner coating of food cans. The dental resin bisphenol A glycidyl dimethacrylate, or Bis-GMA (2,2-bis[4'-(2'-hydroxy-3'-methacryloxy) phenyl] propane), is the reaction product of diglycidyl ether of BPA and methacrylate.[1] Although BPA-based epoxy resins are relatively stable, in the laboratory the carbonate linkages can be hydrolyzed at high temperatures, resulting in the release of BPA.[2,3] BPA is a precursor to the resin monomer Bis-GMA and to bisphenol A dimethacrylate, or Bis-DMA. During the manufacturing process of Bis-GMA dental sealants, BPA might be present as an impurity if the synthetic reactions do not stoichiometrically reach completion. BPA also might be present as a degradation product of Bis-DMA through esterases present in saliva, which can hydrolyze the susceptible ester bond contained in Bis-DMA monomers.[4]

Researchers found an estrogenic effect with BPA, Bis-DMA, and Bis-GMA but not with triethylene glycol dimethacrylate, or TEGDMA, in an estrogen-sensitive cell line—MCF7.[5] Because BPA lacks structural specificity as a natural ligand to the estrogen receptor, the estrogenic potential of BPA has been reported to be much lower than that of the natural estrogen estradiol.[6-8]

A dental resin sealant serves as a protective coating or barrier that effectively isolates pits and fissures to help prevent caries in children and adults.[9-11] When sealants are applied to tooth structures, they are polymerized *in situ*.[12] As there may be incomplete conversion to polymer, chemicals such as Bis-DMA and Bis-GMA might leach into the salivary fluid of the oral cavity.[6,13] Leaching of these monomers from resins can occur during the initial setting period and in conjunction with fluid sorption and

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Corresponding Author: Dr. Manu Rathee, Senior Professor & Head of Department, Prosthodontics, Post Graduate Institute of Dental Sciences (PGIDS), Pt. B. D. Sharma University of Health Sciences, Rohtak, Haryana-124001, India. E-mail: ratheemanu@gmail.com

desorption over time.[14-16] Thus, this chemical leach from dental sealants may be bioactive.[17-20]

Little information exists regarding the potential health implications of BPA exposure from the environment or from dental sealants. Olea and colleagues[6] reported that 90 to 931 μg of BPA was detected in the saliva of patients in whom 50 mg of a sealant had been placed 1 hour earlier. They also reported that BPA and Bis-DMA-stimulated breast cancer cell MCF7 proliferation increased the number of progesterone receptors and showed competitive binding to estrogen receptors. These results generated considerable concern regarding the safety of dental resin materials.

Two *in vitro* studies examined components released from seven commercially available light-activated pit and fissure sealants and detected mainly TEGDMA and Bis-GMA.[21,22] As TEGDMA is a chemical that closely elutes with BPA in a gas or liquid chromatogram, its presence may be identified mistakenly as BPA. An animal study showed that low doses of BPA administered to pregnant mice resulted in a significant increase in adult prostrate weight in male offspring compared with controls, although a dose-dependent relationship was not observed.[23] Other animal studies showed that BPA was effective in stimulating prolactin secretion from the pituitary glands[24] and increased proliferative activity in epithelial cells of the mammary glands.[8]

It remains uncertain if biological effects of BPA similar to those reported in cell culture studies and in animals via systemic administration of BPA will occur in humans. Humans are exposed to BPA environmentally through food cans and dental restorative materials. A study suggested that the maximum potential dietary exposure to BPA from food and beverage cans that are coated with BPA-based epoxies to be about 2.2 ppb.[25] Limited information is available, however, regarding the pharmacokinetic profile of BPA leaching from dental sealants *in vivo* and regarding the potential health implications of bisphenol-A exposure from the environment or from dental sealants.

Several researchers have studied whether BPA leaches from cured dental composites or sealants. In 1996, Olea and coworkers applied a commercially available sealant to 12 molars each of 18 men and women, using about 50 mg of sealant per person. Saliva samples were collected 1 hour before and 1 hour after application. After treatment, all saliva samples were reported to contain BPA in amounts ranging from 90 to 931 μg (3.3–30 ppm).[26]

In a similar study, Arenholt-Bindslev and coworkers applied two commercially available sealants to four molars of four men per sealant. Saliva samples were collected before and immediately after application, as well as 1 and 24 hours after application. The only saliva samples reported to contain BPA were those collected immediately after application of one of the sealants, which was the same sealant studied by Olea. The level of BPA reported ranged from 0.3 to 2.8 ppm, which is approximately 10 times lower than the amount of BPA reported by Olea. No BPA was found in the saliva samples collected at 1 and 24 hours after application of this sealant or in any of the saliva samples collected after application of the other sealant, with a 0.1 ppm limit of detection.[27]

In another study, Fung and coworkers applied the same sealant studied by Olea and Arenholt-Bindslev to the teeth of 18 men and 22 women. Half of the subjects received 8 mg of sealant applied to one tooth while the other half received 32 mg of sealant applied to four teeth. Both saliva and blood samples were collected before application of the sealant and at intervals of 1, 3, and 24 hours, and 3 and 5 days after application. Some, but not all, of the saliva samples collected at 1 and 3 hours after application were found to contain BPA in the range of 5.8–105.6 ppb. No BPA was found in saliva samples collected after 24 hours or in any of the blood samples, in both cases with a detection limit of 5 ppb. The maximum level of BPA detected was more than 250 times lower than the maximum amount reported by Olea.[28]

Based on the data reported in the three studies involving application of sealant to teeth, it appears that low levels of BPA may be released from certain sealants, although only during a short time period immediately after application of the sealant. Further, no detectable levels of BPA have been found in blood after application of a sealant that releases low levels of BPA into saliva.

Although a wide range of BPA levels have been reported in saliva, the validity of the high levels reported by Olea has been questioned. The analytical method used by Olea may not have been capable of distinguishing between BPA and TEGDMA, which is known to be a predominant component released from dental sealants but not reported by Olea. The maximum amount of BPA that could reasonably be released from the dental sealant has been estimated to be less than the lowest level reported by Olea. Consequently, TEGDMA may have been misidentified as BPA in the Olea study. Additional complicating factors may have been the excessively large amount of sealant applied per subject in the Olea study, potentially resulting in incomplete polymerization and higher leachability.[27-30]

The validity of the lower levels of BPA reported by Fung

and Arenholt-Bindslev is supported by *in vitro* leachability studies on cured dental sealants. Nathanson and coworkers at the Boston University tested the leachability of seven dental sealants that were cured in glass dishes. None of the seven sealants showed detectable amounts of BPA after extracting with ethanol with a detection limit of 0.0001 μg BPA/mg sealant. Similarly, Hamid and Hume tested the leachability in water of seven dental sealants that were applied to extracted teeth or stainless steel molds and cured. None of the seven sealants showed detectable amounts of BPA.[21] In a later study from Olea's laboratory, samples of composites and sealants polymerized in glass dishes were extracted with water of varying pH for 24 hours. Low levels of BPA (<1 μg BPA/mg sealant) were reported for these materials.[6] Although these studies may not be fully predictive of sealant leachability *in vivo*, since they do not consider potentially important factors such as mastication or the effect of salivary enzymes, they do suggest that high levels of BPA are not expected.[4,6,21,22,30-34]

Source of Bisphenol A

Dental sealants typically contain monomers that are derived from BPA, such as Bis-GMA and Bis-DMA, but there is no known use of BPA itself in dental sealants. Since it is known that these monomers may leach from dental sealants, the stability of the monomers has been studied under a variety of conditions, including in saliva, to determine if they may hydrolyze to form BPA. Bis-GMA, the base monomer for many composite resins, has been found to be stable to various hydrolytic conditions.[33] However, two researchers have reported that Bis-DMA is hydrolyzed to BPA, which likely accounts for the BPA detected in extracts from certain sealants.[27,33]

Potential Exposure and Margin of Safety

The highest amount of BPA reported in saliva by Olea, 931 μg, forms the basis for the calculation of potential exposure and margin of safety. This quantity was reported in saliva after the application of one brand of dental sealant in one individual in a single study. Further studies by other researchers have reported much lower levels of BPA and have suggested that BPA may have been misidentified in the Olea study due to interferences in the analytical method. In addition, no detectable amounts of BPA were found in the blood, indicating that while some BPA may leach into saliva, systemic exposure does not occur.

The highest value found in the literature is 931 μg (0.931 mg) of BPA in saliva. This is the highest value even if one assumes that 100% of Bis-DMA converts to BPA. Exposure subsides in the hours immediately following application and no BPA detected in samples after 3 hours.

Since exposure to BPA from dental sealants occurs only in a short time period immediately after the sealant is applied, and dental sealants are applied only very infrequently, safety is most appropriately evaluated as an acute exposure event. In laboratory animals, BPA has been found to have very low acute oral toxicity, with LD50 values greater than 2000 mg/kg of body weight.

In comparison, the potential exposure to BPA from use of dental sealants on a child of average weight is 0.037 mg/kg of body weight. This exposure level is more than 50,000 times lower than the LD50 values that have been reported for BPA. As noted, actual exposure to BPA from dental sealants is most likely well below the highest reported value, which further increases the margin of safety. This indicate that exposure to BPA is less than the maximum acceptable dose of 0.05 mg/kg of body weight/day.[29] The EPA reference dose is set for a lifelong daily intake of a substance and includes a considerable safety margin for sensitive stages of life such as childhood. Although exposure to BPA from dental sealants would not occur daily for a lifetime, this comparison further indicates that even the worst-case exposure to BPA from dental sealants represents no harm.

The US EPA calculated the reference dose by dividing the Lowest-Observed-Adverse-Effect-Level (LOAEL, 50 mg/kg body weight/day) from an earlier chronic toxicity study by an uncertainty factor of 1000.[29] Applying that same uncertainty factor to the No-Observed-Adverse-Effect-Level (NOAEL, 50 mg/kg body weight/day) from the Tyl study confirms the safety of the reference dose, 0.05 milligrams BPA per kilogram body weight/day.[34] Since the maximum estimate of BPA exposure from dental sealants is less than the reference dose, human exposure to BPA from dental sealants is minimal and poses no known health risk.[4,6,21,22,27-34] The reference dose for BPA has been confirmed and has been found to have no adverse effects on reproduction from BPA at doses of 50 mg/kg body weight/day and lower.[34]

Conclusions

Small amounts of BPA may leach from dental sealants immediately after application of the sealants to the teeth. The source of BPA that leaches from dental sealants is likely to be from hydrolysis of Bis-DMA, a common monomer used in dental resin formulations. No BPA has been detected in blood samples, indicating that there is no detectable systemic exposure to BPA from dental sealants.

A three-generation study in rats has confirmed the safety of the maximum acceptable or "reference" dose for BPA of 0.05 mg/kg body weight/day. Although BPA exposure from dental sealants does not occur daily throughout a lifetime, the highest level of BPA reported is also below the maximum acceptable dose for BPA of 0.05 mg/kg body weight/day. When evaluated as an acute exposure event, the highest level of BPA reported in saliva from dental sealants is more than 50,000 times lower than the LD50 values that have been reported for BPA. Human exposure to BPA from dental resins is minimal and poses no known health risk.

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