Pre- and Posteruptive Fluoride: Do Both Actions Control Caries?

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Abstract

Discussion, which can get spirited, has been going on about fluoride's primary mode of action for some years. In the early days of fluoride research, it was assumed that the anticaries benefits of fluoride came from preeruptive effects; however, posteruptive action was soon evident. Today the primacy of the posteruptive hypothesis is hardly questioned; remaining questions concern the role of preeruptive fluoride. We are in the age of evidence-based dentistry, where we expect scientific evidence to shape our conclusions. In this cursory look at the data from fluoride studies, the data to support the posteruptive hypothesis are consistent from laboratory to epidemiology; findings in human populations support the mechanisms of action that have been demonstrated in the laboratory. With the preeruptive hypothesis, there is some evidence in support; however, the data are not consistent across the different areas of study. As a result, the posteruptive hypothesis can be readily adopted as the primary mechanism for fluoride's anticariogenic action. Preeruptive fluoride may have some anticaries action; but when the evidence-based philosophy is applied, the inconsistencies around the preeruptive hypothesis make it hard to adopt.

Key Words: caries, fluoride, fluoridation, preeruptive hypothesis, posteruptive hypothesis, evidence-based dentistry, epidemiology, laboratory.

The issue we are discussing today, i.e., the relative actions of pre- and posteruptive fluoride, was a subject very dear to Hersh's heart. Hersh Horowitz knew how to challenge our collective thinking and how to promote spirited discussion, something we need more of in our scientific meetings. If Hersh can leave us with the legacy of constant inquiry and frank discussion, then I know he will be happy. I don't doubt that he is with us in spirit today.

The argument about whether fluoride exerts its main effects preeruptively or posteruptively has been going on for years, and a lot of research effort has been devoted to the question. The debate can be intellectually stimulating and can bring up new questions to challenge us, and that is good. The dark side is that the issue can also become personalized, with individual egos getting in the way of objective scientific debate, and that is bad. The part that bothers me most about the preeruptive/posteruptive

debate is that some still tend to see water fluoridation only as a preeruptive mechanism for caries prevention. I have had people listen to an explanation of the posteruptive mechanism and then say, "Oh, so you don't support water fluoridation?" That view is out of place in public health, for it betrays a serious misunderstanding of how fluoride works. Espousing the posteruptive hypothesis as the primary mechanism for preventing caries in no way takes away from support for water fluoridation. There are just too many reasons, such as reducing the socioeconomic disparities in caries experience (1), to support fluoridation as a keystone of public health policy. The theme of this brief reaction paper is to assess the nature of the evidence that supports the preeruptive and posteruptive models of fluoride's action.

Pre- and Posteruptive Models of Fluoride's Anticariogenic Action

Both models have received detailed discussion in the earlier papers by

Featherstone and Newbrun in this symposium. To briefly repeat what these terms mean, the preeruptive hypothesis focuses on the developing hydroxyapatite crystal in the unerupted tooth enamel. When fluoride enters the environment of the developing tooth, the theory states, it becomes incorporated into the developing enamel to form a more acid-resistant crystal, which will then be less soluble in the presence of decay-causing acids in dental plaque. The posteruptive hypothesis, by contrast, holds that fluoride's principal action comes after the tooth has erupted. When plaque pH drops and the first dissolution of the enamel crystal begins, fluoride, calcium, and phosphate held in plaque immediately begin to remineralize the lesion. The new enamel thus laid down is richer in fluoride than was the now-dissolved original. Posteruptive fluoride from dental plaque can also be an antibacterial, and it can disrupt glycolysis (the process by which cariogenic bacteria metabolize fermentable carbohydrates).

There is substantial acceptance in the research community that fluoride acts posteruptively, and most accept that this is the primary mechanism for its anticariogenic action. There is still some divergence about preeruptive effects.

Assessing the Evidence

To be able to say whether a particular exposure causes a particular outcome, the best study design is always the randomized controlled trial. This is a design in which the most likely confounders can be controlled by means of random allocation and blind recording procedures. The snag of course is that for many of the questions facing us in science and in the clinic it is not possible to run such trials. In these instances, cause-effect has to be inferred from laboratory data and hu-

man observational studies that are necessarily less well controlled than a clinical trial. These issues are familiar to anyone who follows the development of evidence-based dentistry. Some observational studies are better than others, so issues of both quantity and quality arise. To help us interpret the data from epidemiologic studies, we turn to the guidelines attributed to the British statistician Bradford Hill (2), shown in Table 1. The only one of these criteria that is absolutely essential is the time sequence: we must be able to say that the exposure preceded the outcome to infer cause and effect. If we can do that, then we use our judgment in deciding how the other criteria affect the strength of the conclusions.

One part of the Bradford Hill model that does not always get the attention it should from public health people is the biological plausibility of the associations found. Dr. Newbrun, with his background in biological and clinical research, stressed that the ultimate proof of a proposition was epidemiologic evidence. My background is epidemiology and public health, so I'm going to stress the importance of biological plausibility. (There's some irony here—Hersh would have loved it!) Actually, my point is that we need the findings from *both* human populations and from the laboratory—and, ideally, from clinical studies, as well. If the results from these different lines of inquiry on any question are consistent, then it is likely we are looking at truth. If they are not consistent, then the hypothesis remains uncertain, no matter how well conducted any or all of the individual studies might have been. Let's see how the evidence stacks up for the preeruptive and posteruptive hypotheses.

Posteruptive Hypothesis

The substantial volume of laboratory research on posteruptive fluoride action was elegantly summarized in the earlier paper by Dr. Featherstone, and will not be repeated here. The upshot from this body of research is that we now have a clear vision of what fluoride is doing at the plaque-enamel interface when the caries process starts. The most recent research confirms that in the remineralization process fluoride binds calcium in the outer enamel layers (3), which is in harmony with the posteruptive hypothesis.

TABLE 1
Criteria for Causality from Observational Studies ("Bradford Hill Criteria")

Time Sequence of Events: To be causal, an exposure must precede the occurrence of the disease. Demonstration of this temporal sequence requires longitudinal study. This is the only condition in this list that is absolute, a *sine qua non*.

Consistency of Association: If there are a good number of studies on whether an exposure is a cause of a disease, and if all of them produce fairly similar positive results, it is more likely that the factor is causal.

Strength of Association: In valid studies, the stronger the association between exposure and outcome, the more likely it is that the association is causal.

Specificity of Association: If a given exposure is related to other diseases as well as the disease in question, it is less likely to be seen as causal. However, lack of specificity by itself does not justify rejecting causality (e.g., tobacco is nonspecific in its effects, but is clearly a causal factor in many of them.

Degree of Exposure (Dose-Response): If an exposure is causal, then the risk of disease should be related to the degree of exposure. An exception could be a toxin with a threshold effect.

Biological Plausibility: The association must make biological sense from our knowledge of the disease. It follows that the better understood a disease is, the more stringent this criterion can become.

Source: Adapted from Bradford Hill 1965 (2).

For epidemiologic evidence, some posteruptive effects were noted in early studies of naturally fluoridated areas in the 1940s (4-6). The early fluoridation trials in Grand Rapids and Newburgh also recorded posteruptive effects (7,8). A four-year British longitudinal study began with 12-year-old children in a community that was beginning fluoridation. Four years later, i.e., when the children were 16, the children in the fluoridated community had developed 27 percent fewer carious lesions than comparable children in a nonfluoridated control community (9). Most of this differential was on teeth already erupted when fluoridation began.

What I see as the most compelling epidemiologic evidence for posteruptive fluoride action, epidemiologic in nature, comes from the Tiel-Culemborg study in the Netherlands. This landmark longitudinal study compared caries experience in fluoridated Tiel with that in nonfluoridated Culemborg over more than 20 years. It was found that when the comparisons were of *all* carious lesions, noncavitated as well as cavitated, there was virtually no difference between the cities. But when the comparison was restricted to dentinal lesions, the ex-

pected 50 percent or so difference was seen in favor of fluoridated Tiel (10). This finding tells us that fluoride does not prevent the initial carious lesion from forming, but it does prevent many of them from developing into dentinal lesions. This can only happen through remineralization of the initial noncavitated lesion. Data of this sort are telling us that fluoride is more correctly seen as a treatment for early carious lesions, rather than strictly as a primary preventive.

Preeruptive Hypothesis

Epidemiologic evidence suggests there are some preeruptive effects from fluoridated water, both from secondary analyses of existing data (11,12) and from a field trial for fluoride supplements (13). Meticulous and useful though these studies are, secondary analyses do not have the same ability to control all likely confounders that clinical trials have. In addition, field trials always have the problem of determining whether the benefit is truly preeruptive or the result of teeth erupting into an intraoral environment where they are exposed to fluoride throughout eruption.

Some epidemiologic studies do not fit with the preeruptive hypothesis. It

had become evident to researchers as early as the 1970s that a higher concentration of enamel fluoride could not by itself explain the extensive caries reductions produced by exposure to fluoridated water (14). Enamel biopsy studies around the same time also found that enamel fluoride levels correlated poorly with waterborne fluoride concentrations (15). Furthermore, if the preeruptive hypothesis is true, enamel fluoride levels should be inversely related to caries experience—i.e., the higher the enamel fluoride level, the lower the caries experience. Such is not the case; enamel fluoride levels are not related to DMF scores (16).

Laboratory data also do not all support the preeruptive hypothesis. Some of the enamel biopsy data were quoted above, and studies show shark enamel, which is almost all fluorapatite and contains fluoride at 30,000 ppm, was only a little more resistant to carious attack than was human enamel at around 2,000 ppm (17). If the preeruptive hypothesis was correct, one would expect shark enamel to be almost totally resistant to caries, but that is not so.

We are in the age of evidence-based dentistry, where scientific evidence should be shaping our conclusions. In this cursory look at the data from fluoride studies, the data to support the posteruptive hypothesis are consistent from laboratory to epidemiology; findings in human populations support the mechanisms that have been demonstrated in the laboratory. With the preeruptive hypothesis, there is some evidence in support, but the data are not consistent across the different forms of study. As a result, the posteruptive hypothesis can be readily adopted as the primary method for fluoride's anticariogenic action. Preeruptive fluoride may have some anticaries action, but when the evidence-based philosophy is applied, the inconsistencies in the data make the preeruptive hypothesis hard to adopt with any enthusiasm.

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