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Recent advances in fluoride delivery for clinical dentistry

Współczesne osiągnięcia w dostarczaniu fluorku w stomatologii klinicznej

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Abstract

The current state of knowledge of fluoride activity against dental caries is reviewed, and recent research on substances for providing fluoride, and materials capable of releasing fluoride in situ is described. Contemporary clinicians have a wide range of means for delivering fluoride to caries-susceptible patients, including fluoridated toothpastes and varnishes, and substances such as silver diamine fluoride and stannous fluoride. Materials capable of releasing fluoride include both glass-ionomers and resin-based systems, and applications of these materials include full restorations and pit-and-fissure sealants. These are all considered in this article, which provides a snapshot of the current situation with regards to fluoride delivery in clinical dentistry.

Keywords: fluoride, remineralisation, glass-ionomers, resin systems, clinical effectiveness.

Streszczenie

W pracy przedstawiono przegląd piśmiennictwa na temat obecnego stanu wiedzy dotyczącej przeciwpróchnicowego działania fluorku oraz zaprezentowano aktualne badania nad substancjami mogącymi dostarczać fluorek, a także materiałami posiadającymi właściwości uwalniania fluorku *in situ*. Klinicyści dysponują obecnie dużym wyborem środków dostarczających fluorek pacjentom narażonym na próchnicę, należą do nich pasty i lakiery fluorowe oraz takie substancje jak fluorek dwuamina srebra czy fluorek cynawy. Materiały posiadające zdolność uwalniania fluorku to cementy szkłojonomerowe oraz materiały na bazie żywic. Są one stosowane zarówno jako wypełnienia, jak i do uszczelniania bruzd i szczelin. Wszystko to zostało omówione w niniejszej pracy, która w sposób zwięzły przedstawia obecną sytuację w odniesieniu do sposobu dostarczania fluorku w praktyce klinicznej w stomatologii.

Słowa kluczowe: fluorek, remineralizacja, cementy szkłojonomerowe, systemy na bazie żywic, skuteczność kliniczna.

Introduction

The fact that fluoride has a role in the prevention of dental caries has been known since the 1930s [1] following the observation that individuals with fluorosis had very low levels of tooth decay. It was originally thought that this was a systemic effect but many years of study since the earliest observations have shown the effect to be topical rather than systemic [2]. In other words, fluoride is effective when applied to the surface of the fully erupted tooth. It does not need to be part of the diet while the tooth is being formed.

Further studies have established the value of long-term exposure to fluoride. Such long-term exposure is the best way to exploit the topical action of fluoride and reduce or eliminate the susceptibility of the tooth to caries [3, 4].

The disease of dental caries is very widespread and is probably the most common disease in humans throughout the world [5]. It is caused by the interaction of three factors, namely:

a) The occurrence of fermentable carbohydrates (specifically sugars) in the diet;
b) The presence of specific bacteria within the dental plaque, mainly *Streptococcus mutans*, which are able to metabolise these carbohydrates to produce weak organic acids, mainly lactic acid [6];
c) The mineral phase of the tooth.

The acids produced cause the pH to fall to about 4.5 [6], at which point the mineral phase of the tooth, hydroxyapatite, begins to be attacked and solubilised [7]. This leads to the removal of the hard structure of the tooth and leaves behind only collagen fibres. This collagen causes discolouration of the tooth and the development of a leathery texture [5].

A tooth attacked in this way becomes permeable to the developing front of caries. The front penetrates the dentine more rapidly than it does the enamel, so that once it reaches the dentine, it spreads out [8]. Left undetected, it will move into the dental pulp, causing inflammation and severe pain. Subsequent infection of the pulp is potentially serious and life-threatening for the patient, and this is the reason that the condition of dental caries requires rapid and effective treatment.

Mode of action of fluoride

At the surface of a healthy tooth, there is a balance between the two processes of demineralisation and remineralisation [2]. This balance has incorrectly been called an equilibrium, but it is not, as equilibria can only occur in closed systems. The region at the tooth surface is an open system, i.e. one that can exchange matter with the surroundings. In this case, it can take up calcium and phosphate ions which have been taken into the body and into the saliva from the diet, i.e. remineralisation. Similarly, the tooth surface can lose calcium and phosphate ions to the saliva (demineralisation), from where it can be swallowed and eventually excreted from the body.

In a tooth affected by caries, this remineralisation-demineralisation balance is altered, and favours the latter process [2]. This causes the net loss of hydroxyapatite from the mineral fraction of the tooth, leading to observable decay.

The presence of fluoride has an effect on this balance. Specifically, it enhances the rate of the remineralisation process [2, 9], which leads to additional hydroxyapatite mineral being deposited. The remineralisation part of the process is caused by the growth of hydroxyapatite crystals by means of the controlled deposition of calcium and phosphate ions from the saliva onto the mineral surface [10]. Fluoride ions enhance the rate of this activity by two mechanisms. First they can interact with calcium and phosphate and effectively replace hydroxide ions in hydroxyapatite, forming fluorapatite. This is less soluble than hydroxyapatite, so precipitates more readily. Second, fluoride ions can interact with calcium ions to form calcium fluoride, a substance of low solubility, which promptly precipitates and thereby forms sites that can act as nucleation centres for hydroxyapatite to crystallise onto. This also promotes a more rapid deposition of the mineral phase at the tooth surface [4].

The initial substance deposited is mainly amorphous, but is capable of crystallising quickly, and this contributes to the remineralisation step [11]. The newly deposited mineral phase contains a small amount of fluoride in a thin layer at the surface. Molecular dynamics calculations designed to model the remineralisation process have shown that these fluoridated layers are no more than three atom layers thick [12]. The fluoride-containing surface layer is less soluble than true hydroxyapatite, but this reduced solubility is considered to make only a minor contribution to the mechanism of caries inhibition by fluoride [13].

Because of this well-established usefulness of fluoride in combating caries, fluoride is provided to patients in a variety of forms. These include in the water supply, in toothpastes, in professionally applied drops and varnishes, and in restorative materials [14]. Considerable amounts of research on these approaches continue to be carried out and reported. The remainder of the present paper looks at recent developments on these topics, and highlights some of the more important of them.

Recent developments: Fluoride delivery

Toothpastes

The daily use of fluoridated toothpaste (dentifrice) is widely considered to be one of the most effective methods of exploiting the anti-caries properties of fluoride. Toothpastes typically contain 1000 ppm of fluoride or less [15], with levels in children's toothpaste being at around 500 ppm [16, 17]. This latter level is sufficient to reduce or eliminate caries in the target population. Overall, this approach has been associated with substantial reductions in the incidence of caries in those regions where fluoridated toothpastes have become established and used extensively [18].

Recent studies have examined the potential of toothpastes containing much higher levels of fluoride to improve the oral health status of individuals who are at particular risk from caries. A recent review has considered this topic and concluded that the findings of randomised clinical trials support the use of high fluoride toothpastes for caries prevention in high risk children and adolescents [19] These products typically contain more than 1500 ppm of fluoride, and consequently need to be used on prescription only, and considered to be oral pharmaceuticals. Clinicians need to undertake careful risk assessments before allowing their use, in order to minimise the possibility of unsightly fluorosis occurring.

Research is continuing on the use of these products in high risk populations, with a limit in fluoride concentration of around 2800 ppm, since the evidence to support the use of higher concentrations is lacking [19].

Topical varnishes

Topical varnishes containing fluoride are a useful alternative to toothpastes for the supply of fluoride in high caries risk groups. These varnishes are typically formulated with sodium fluoride or difluorosilane [20]. The latter generally have fluoride concentrations of 1000 ppm, whereas the former contain up to 2.26% fluoride, equivalent to 22600 ppm [21, 22]. The fluoride compounds are either dissolved or dispersed in an organic solvent such as ethanol, and the formulation includes a natural resin such as shellac. When the varnish is applied to the tooth surface, the solvent evaporates and leaves behind the insoluble fluoride compound in the resin, and in this way, it can promote the remineralisation reaction.

Recent improvements to these varnishes have included the addition of substances such as tricalcium phosphate and amorphous calcium phosphate, which enhance the availability of remineralising ions at the tooth surface. Formulations have also been designed to release higher amounts of fluoride in the time immediately after application [20]. However, to date, the evidence for the clinical effectiveness of such approaches is inconclusive.

Silver diamine fluoride

There has recently been growing interest in the use of silver diamine fluoride (SDS) in the treatment of caries [23, 24]. This substance has been available for many years [23], but is only now being investigated in detail for its effectiveness in the treatment and management of caries. It is a colourless liquid containing between 24.4% and 28.8% silver on a weight/volume basis, and 5.0–5.9% fluoride [25]. When applied to carious lesions, it not only arrests the progress of caries in the target tooth, but it also arrests the progress of caries at the adjacent tooth surfaces [26]. It has been used both for children [26, 27] and in elderly patients [28, 29]. In the latter, it has been found to be useful against root caries.

Although reported to give satisfactory results, SDF does have some distinct disadvantages. It requires repeated application to be effective [30] and has an unpleasant metallic taste which patients may find objectionable. It has also been reported to be potentially irritating to the gingiva and mucosa, and to cause a black stain to develop in treated teeth [24]. Whether these disadvantages outweigh its advantages and limit the use of SDF remains to be seen. Further clinical studies are necessary before this question can be answered definitively.

Stannous fluoride

Stannous fluoride has long been known to be a particularly effective way to deliver fluoride in toothpastes [31], and that it shows greater anticaries behaviour than the alternatives of sodium fluoride and sodium monofluorophosphate. A recent study has confirmed its superiority over the modern remineralising agents, casein phosphopeptide-amorphous calcium phosphate with fluoride and calcium sucrose phosphate [32]. These agents were compared in an *in vitro* study in which recently demineralised enamel samples were subjected to each remineralising agent for 7 days, after which the Vicker's microhardness was measured. All samples increased in hardness, with those treated with SnF_2 showing the greatest increase [32].

These studies have provided useful empirical evidence to support the use of SnF_2 as a remineralising agent, but the literature on the subject is confused about the mechanism. This is largely because researchers studying the biological processes have not appreciated the nature of the compound SnF_2. Thus they have attributed its effectiveness to the role of the Sn^{2+} ions [33], including toxicity towards oral bacteria [34–36]. This is in spite of the overwhelming evidence from chemical studies that solutions of SnF_2 are hardly dissociated at all, and any dissociation that does occur does not yield stannous ions, but SnF^+ and F^- [37–39]. Indeed, these latter ions are in equilibrium with the un-dissociated stannous fluoride, which itself exists as a hydrated molecule in aqueous solution [37]. The equilibrium is:

$$SnF_2 \rightleftharpoons SnF^+ + F^-$$

The equilibrium constant for this dissociation process in water has been found to be 8.8 x 10^{-5} (± 1.2 x 10^{-5}) mol dm^{-3} [39], which shows that the overwhelming proportion of stannous fluoride exists as un-dissociated SnF_2. This supports results using a combination of ^{19}F and ^{119}Sn NMR spectroscopy and ^{119m}Sn Mössbauer spectroscopy [37]. Instead, the most abundant species present in a solution of stannous fluoride is un-dissociated SnF_2 co-ordinated to a single water molecule [37]. These findings are summarised in **table 1**.

These findings to not rule out the possibility that SnF_2 provides a toxic species for oral bacteria, but they do show that such a species is unlikely to be Sn^{2+}. On the evidence of these chemical studies, it seems more likely that it is SnF_2 itself that is toxic towards these bacteria.

Table 1. Species indentified in aqueous solutions of stannous fluoride

Tabela 1. *Zidentyfikowane typy w roztworach wodnych fluorku cynowego*

Species	Comment
Hydrated SnF_2	The predominant species (more than 99% of any sample)
SnF^+	The main cation but less than 1% of the total
F	Also less than 1% of the total
SnF_3^-	Identified in mixed solutions of SnF_2 and NaF

Further studies on the interaction of SnF_2 solutions with hydroxyapatite have shown that tin is taken up as well as fluoride [40–42]. Experiments using ^{119m}Sn Mössbauer spectroscopy to study the interaction of SnF_2 with synthetic hydroxyapatite suggested that the species taken up is SnF^+ [40], and this is consistent with results obtained from a combination of fluoride analysis in solution using an ion-selective electrode and EDAX using a scanning electron microscope to analyse hydroxyapatite samples that had been exposed to SnF_2 in solution [39]. More recent results have confirmed the uptake of tin from SnF_2 solutions by both enamel [41] and dentine [42], and these have also demonstrated that such uptake is associated with significant reductions in erosion when the samples of enamel and dentine were exposed to citric acid solutions [41, 42]. These results show that the uptake of SnF^+ confers distinct anti-caries properties on the tooth tissues, and that the effectiveness of SnF_2 in protecting teeth from caries is not solely due to any toxic effect on oral bacteria,

Recent developments: Fluoride-releasing materials

Glass-ionomers

Glass-ionomer cements are widely used restorative materials in dentistry, with particular application for children [43, 44]. One of the features is that they release fluoride, and are able to do so for considerable periods of time. This feature is of continuing interest, as new approaches to enhancing the setting of glass-ionomers are developed and as modifications aimed at improving their physical properties are introduced.

The setting of glass-ionomers can be enhanced by either the application of ultrasound [45] or by subjecting them to radiant heat from a dental cure lamp [46]. Both of these result in cements that reach high strengths in much shorter times than cements left to cure without assistance [46, 47]. Recently the effect of these approaches on fluoride release has been reported [48]. In both cases, treatment increased surface hardness, a finding that is consistent with earlier findings of enhancement in physical properties. However, they both reduced fluoride release, as measured at 7, 14 and 28 days [48].

Fluoride release is typically measured at neutral pH. Where it has been measured at acidic pH values, it is enhanced [49, 50]. This finding has recently been confirmed in a detailed study for both a conventional and a resin-modified brand of glass-ionomer [45], though pH had a smaller effect on the latter type of cement. Selected results from this latter study are shown in **table 2**.

The physical properties of conventional glass-ionomers can be improved by the addition of reinforcing fillers. One recent study used whiskers of hydroxyapatite at a loading of 8% [51], and results suggested that the resulting cements released the same amount of fluoride as equivalent cements with no hydroxyapatite. Such cements were also able to take up fluoride from toothpastes containing 500 ppm, and this resulted in significant increases in fluoride release. Overall, it was found that the fluoride recharge of a hydroxyapatite-reinforced glass-ionomer was similar to that of one without reinforcement [51].

Two studies have recently appeared on the reinforcement of glass-ionomer cements with zirconia powder [52, 53]. This is a commercial product, produced by the Shofu company (Kyoto, Japan). Zirconia itself is known to be a strong material and including it in a glass-ionomer cement as a filler is claimed to improve the strength of the resulting cement.

Fluoride release has been found to be good (**table 3**) [53] and to exceed that of the conventional

Table 2. Fluoride release from glass-ionomers at different pH values [45]

Tabela 2. *Uwalnianie fluoru z glassjonomerów przy różnych wartościach pH*

Material	pH	Release/ppm (Standard deviation)
Conventional glass-ionomer	7	48×10^{-4} (12×10^{-4})
	5	86×10^{-4} (21×10^{-4})
	3	130×10^{-4} (31×10^{-4})
Resin-modified glass-ionomer	7	32×10^{-4} (4×10^{-4})
	5	44×10^{-4} (9×10^{-4})
	3	47×10^{-4} (6×10^{-4})

Table 3. Fluoride release from zirconia-reinforced glass-ionomer compared with a conventional glass-ionomer and compomer (standard deviations in parentheses)

Tabela 3. *Uwalnianie fluorku z glassjonomerów wzmocnionych cyrkonem w porównaniu z konwencjonalnym glassjonomerem i kompomerem (w nawiasie odchylenie standardowe)*

Material	Day 1	Day 7	Day 14	Day 21
Zirconomer	33.31 (0.32)	40.88 (0.05)	26.69 (0.14)	15.43 (0.08)
Fuji IX	16.70 (0.25)	19.56 (0.09)	10.46 (0.12)	5.51 (0.10)
Compoglass	2.11 (0.01)	3.13 (0.01)	2.00 (0.02)	1.07 (0.04)

glass-ionomer Fuji IX (GC, Tokyo, Japan), as well as that of the commercial company Compoglass (Ivoclar Vivadent, Lichtenstein). These high values suggest that Zirconomer is formulated with extra fluoride, either within the glass, or as an additional component of the powder. It is not a function of the addition of zirconia as reinforcing filler.

A related study showed that Zirconomer had enhanced anti-microbial activity against both *Streptococcus mutans* and *Lactobacillus casei* at 48 h [52]. This may be the result of additional fluoride release compared with the conventional glass-ionomer, and is potentially important in clinical application (**Table 4**).

Table 4. Zones of inhibition (mm) for zirconia reinforced glass-ionomer and conventional glass-ionomer cements (Standard deviations in parentheses)

Tabela 4. *Strefy inhibicji (mm) dla glassjonomera wzmocnionego cyrkonem i konwencjonalnych cementów glassjonomerowych (w nawiasie odchylenie standardowe)*

Material	S. mutans	L. casei
Zirconomer	11.14 (0.77)	14.06 (0.71)
Fuji IX	8.51 (0.43)	11.70 (0.39)

Pit-an-fissure sealants

Materials placed in the occlusal pits and fissures of recently erupted teeth in patients who are susceptible to caries are known as sealants. Their function is to protect those parts of the tooth surface which, because of their morphology, are difficult to clean and hence may allow bacterial colonisation and subsequent caries development [54]. Current clinical practice is to seal the first and second molars shortly after eruption, because these are the most susceptible teeth to occlusal caries. Research has shown this to be a highly effective preventive method and confirms that such sealants interfere with the progression of early carious lesions [55].

The choice of material has been the subject of considerable research over the past 30 years, with the choice being either resin-based materials or glass-ionomer cement. Broadly speaking, resin-based pit-and-fissure sealants have been found to perform better in terms of retention [56], though glass-ionomers have been shown to perform well in terms of preventing caries, presumably as a result of their fluoride release [57]. This effect of fluoride is considered significant, and has led to the development of fluoridated resin materials, where fluoride is added to the resin system as an extra component, such as amine fluoride or YbF_3. However, these materials are known to deliver lower levels of fluoride than glass-ionomers, and there is currently no evidence about how effective they are.

Current brands of glass-ionomer cement, formulated to be of higher viscosity and to set so as to give stronger materials, appear to provide better retention rates [57]. As a result, they now compare well with composite sealants, so that their use in fissure sealing seems assured.

Recently, the ability of resin-based sealants to be recharged on exposure to fluoride solutions [58] or fluoride varnish [59] has been studied. In both studies, the uptake of fluoride was not measured directly, but indirectly by monitoring any enhancement in the amount delivered following exposure to the fluoride solution or varnish. In both cases, the experiments demonstrated that fluoride release was enhanced by this treatment, though the effect was much greater with glass-ionomers. This suggests that these resin-based sealants have a lower capacity for fluoride exchange than glass-ionomers [58, 59], implying that glass-ionomers have a further advantage over resin-based materials in this application.

Adhesives for orthodontic brackets

It has been known for some time that the use of brackets for orthodontic fixed appliances is associated with enamel demineralisation [60]. This demineralisation is associated with the formation of white spots in the enamel in the region surrounding the brackets. A recent review and meta-analysis has reported on the effectiveness of fluoride-containing materials for use as adhesives for orthodontic brackets that are able to inhibit the formation and progression of white spot lesions [60]. This detailed analysis demonstrated that patients had a 58% less risk of developing a white spot lesion when fluoride-releasing materials were used.

The review concludes that the use of fluoride-releasing adhesives is able to reduce the risk of white spot lesions forming around orthodontic brackets. However, in those cases where the white spot had already formed, no evidence could be found to show that the extent of the lesions was reduced by the use of fluoride-releasing materials [60].

Conclusions

The importance of fluoride in enhancing enamel remineralisation and hence preventing caries in clinical dentistry is well established. This has led to a variety of approaches for the provision of this element to patients who are susceptible to caries. Considerable amounts of work have gone into establishing the role of fluoride, and how it may be delivered, and this paper reviews these approaches. Recent studies have shown that the substances silver diamine fluoride and stannous fluoride have particular value as vehicles for providing fluoride directly to the tooth surface. Fluoride release by glass-ionomers has a particular advantage, and can be sustained, even in materials with added zirconia designed to possess enhanced mechanical strength. The fluoride-releasing ability of glass-ionomers also makes them good materials for use as pit-and-fissure sealants, especially as contemporary versions of these materials now have such good retention characteristics. This review confirms the variety of effective fluoride delivery systems available to the modern dentist, and indicates those areas where further resarch is necessary and additional evidence is needed concerning clinical effectiveness.

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