REVIEW DERLEME

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The Effects of Drugs Used by Children with Chronic Systemic Diseases on the Oral Cavity: Traditional Review

Kronik Sistemik Hastalığı Olan Çocukların Kullandığı İlaçların Oral Kavite Üzerindeki Etkileri: Geleneksel Derleme

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ABSTRACT Children with chronic diseases are prescribed various drugs by pediatricians. In children with chronic systemic disease, daily use of pediatric liquid form medications may be routine. Drugs such as analgesics, antibiotics, antihistamines, antiepileptics, multivitamins and antitussives are chronically prescribed to children. Sweeteners and sugars are added to make the flavors of the drugs prescribed by pediatricians in suspension forms acceptable to pediatric patients. The high sugars such as sucrose and glucose in the content of these drugs cause the dissolution of tooth enamel by lowering the pH of the dental biofilm as a result of bacterial fermentation. These drugs can cause tooth erosion due to their acidic properties and reducing saliva flow as a side effect. In addition to their corrosive and cariogenic properties, pediatric drugs also have side effects such as periodontal disease, changing orthodontic tooth movement, decreasing or increasing saliva flow, and causing tooth discoloration. Various recommendations can be made to parents, dentists and pharmaceutical companies in terms of preventive measures related to chronic drug use. In children with chronic drug use, rinsing the mouth with water after taking these drugs may not be enough to prevent tooth damage. Regular topical fluoride applications and the addition of calcium, fluoride or phosphate to drug formulations can be recommended for these patients as reduce the risk of dental caries and erosion. The aim of this review is to evaluate the effects of frequently used drugs on oral and dental health in pediatric patients based on current literature research.

Keywords: Child; drug; chronic disease; oral health

ÖZET Kronik hastalıkları olan çocuklara pediatristler tarafından çeşitli ilaçlar reçete edilmektedir. Kronik sistemik hastalığı olan çocuklarda günlük olarak pediatrik sıvı formdaki ilaçların kullanımı bir rutin olabilir. Analjezikler, antibiyotikler, antihistaminikler, antiepileptikler, multivitaminler ve antitusifler gibi ilaçlar kronik olarak çocuklara reçete edilmektedir. Pediatristlerin süspansiyon formlarda reçete ettikleri ilaçların tatlarının kabul edilmesi ve çocuk hastalar tarafından daha rahat kullanılması için içerisine etken maddelerin dışında tatlandırıcılar ve şekerler eklenmektedir. Bu ilaçların içeriğindeki yüksek sükroz ve glikoz gibi şekerler, bakteriyel fermantasyonun bir sonucu olarak diş biyofilminin pH'sini düşürerek diş minesinin çözünmesine neden olmaktadır. Bu ilaçlar asidik özellikleri ve yan etki olarak tükürük akışını azaltması nedeniyle diş erozyonuna yol açabilir. Pediatrik ilaçların aşındırıcı ve karyojenik özelliklerinin yanı sıra periodontal hastalık, ortodontik diş hareketini değiştirme, tükürük akışını azaltma veya artırma, dişlerde renklenmelere neden olma gibi yan etkileri de vardır. Kronik ilaç kullanımı ile ilgili önleyici tedbirler açısından ebeveynlere, diş hekimlerine ve ilaç firmalarına çeşitli önerilerde bulunulabilir. Kronik ilaç kullanımı olan çocuklarda bu ilaçlar alındıktan sonra ağzın suyla çalkalanması diş hasarını önlemede yeterli olmayabilir. Diş çürüğü ve erozyon riskini azaltmak için bu hastalara düzenli topikal florür uygulamaları ve ilaç formülasyonlarına kalsiyum, florür veya fosfat eklenmesi önerilebilir. Bu derlemenin amacı, güncel literatür araştırmalarına dayanarak çocuk hastalarda sık kullanılan ilaçların ağız ve diş sağlığına etkilerini değerlendirmektir.

Anahtar Kelimeler: Çocuk; ilaç; kronik hastalık; ağız sağlığı

Various drugs are prescribed by pediatricians in chronic diseases such as respiratory allergies, asthma, cardiopathy and epilepsy in children or in recurrent acute conditions such as tonsillitis, otitis, sinusitis and allergic rhinitis.[1] Commonly prescribed drugs in pediatric patients are analgesics, antibiotics, antihis-

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tamines, antiepileptics, multivitamins and antitussives.[2]

Since drugs in tablet and capsule form cause swallowing problems in pediatric patients, liquid forms of drugs such as syrup, solution and suspension are often preferred.[3] Drugs prescribed to children contain various sweeteners, sugars, acids and preservatives, as well as active ingredients. Since the drugs have a bad taste due to their chemical structure, the added sugars in the drugs ensure the acceptability of the taste of the drug and its more comfortable use by pediatric patients.[4] It is known that many pediatric drugs will directly affect the cariogenic potential because of their high sucrose and glucose content.[5] Sugars such as sucrose, fructose, and glucose in the formulation of pediatric drugs may lower the pH of the dental biofilm as a result of bacterial fermentation, causing the dissolution of hydroxyapatite crystals and dental caries. In addition, pediatric drugs in suspension form often have a corrosive potential due to a pH below the critical value for enamel dissolution.[6,7] In addition to sweeteners, acids can be added to pediatric drugs as buffering agents and to maintain chemical stability.[8] In vitro studies have reported that low pH pediatric drugs erode enamel due to their acid content.[9] Long-term and frequent use of acidic drugs in children with chronic diseases may cause tooth erosion. In addition, some medications can contribute to tooth erosion by reducing saliva flow as a side effect.[10] Deciduous teeth have less enamel and dentin thickness than permanent teeth, have more organic content, and have a more irregular distribution of enamel prisms, making these teeth less resistant to caries and erosion.[11] Adding calcium, fluoride and phosphate to pediatric liquid medications, using topical fluoride agents, rinsing the mouth with water after medication use and chewing sugar-free gum can reduce the risk of erosion and caries caused by these medications.[12]

Apart from their erosive and cariogenic properties, pediatric drugs also have side effects such as periodontal disease, changing orthodontic tooth movement, decreasing or increasing saliva flow, and causing tooth discoloration.[13]

ANTIANEMICS/IRON DRUGS

Iron deficiency is one of the most common nutritional disorders affecting more than 2 billion people in the world. Although iron deficiency can result from defects in the body's metabolism of iron, the most common cause is insufficient dietary iron intake, a disease that can be treated with supplements. These supplements are usually drops or syrups containing iron salts, folic acid and vitamin B_{12}. Vitamin B_{12} and iron medications are usually prescribed to children under 5 years of age.[2,14] Iron deficiency anemia is the most common nutritional deficiency in the world. Hematological and non-hematological iron deficiency can cause growth retardation and cognitive impairment.[15]

Iron drugs, which are often prescribed in children, can cause enamel to dissolve due to low pH levels and accelerate the destruction process.[16] In a study investigating the effects of iron syrups on teeth, it was reported that the acidity of solutions with a pH in the range of 1.5-8.56 was associated with dental caries, and it was recommended to take the drug with a pipette in children using iron syrup.[17] Hekmatfar et al. reported that iron and multivitamin drops or syrups have a low pH and can reduce the microhardness of primary tooth enamel.[18] Pasdar et al. reported that ferrous sulfate drop can cause pH decrease with acid content.[16] Martinhon et al. showed that in the cariogenic environment, ferrous sulfate reduces enamel demineralization and surface microhardness.[19]

The incidence of dental erosion was found to be 41-42% in iron syrup users.[20] In a study, it was reported that an iron-containing mouthwash caused erosion of the enamel surface and a decrease in the microhardness value of the enamel. It was thought that this situation may be caused by the precipitation of phosphate ion, which reduces tooth tissue loss by acting as a barrier on the enamel surface, as ferric phosphate.[21] In a study, the effects of pH and acidity of multivitamin and iron preparations in syrup form on the surface roughness, microhardness and topography of teeth were investigated. As a result of drug application, the surface roughness of the enamel increased, while the surface microhardness decreased.

It was concluded that low pH and high acidity had a significant effect on the erosive effect.[22]

There are many studies that show iron discoloration in the teeth of children using iron syrup, drops and other iron preparations.[14] It is suggested that the discoloration of the teeth caused by iron drugs may be due to the insoluble form of the iron sulfide compound, which is formed as a result of the interaction of iron ions in the gingival groove fluid or saliva with hydrogen sulfide ions produced by bacteria.[23]

Iron discoloration in primary teeth creates anxiety for parents and it has been reported that it can negatively affect the social interactions of preschool children. Although low dose iron containing syrups in the form of ferrous fumarate have been shown to produce less coloration, these syrups are not thought to provide enough iron to prevent anemia.[2] It was observed that iron drug caused more discoloration in anterior teeth of individuals with high saliva lactoferrin concentration. In addition, it has been reported that the degree of discoloration is directly related to the contact time of the drug with the tooth, and brushing before using the drug is effective in reducing the rate of discoloration.[24] In order to protect the teeth from discoloration, effective and regular oral hygiene practices are recommended instead of using low iron content formulas. However, if discoloration occurs on the teeth, a dentist should be consulted and dietary iron sources should be evaluated.[14]

ANTIEPILEPTICS/ANTICONVULSANTS

Epilepsy is a chronic neurological disease that occurs in 40-70 out of every 100,000 people. Options for the treatment of epilepsy are surgery, antiepileptic drugs and vagus nerve stimulation. If the treatment is successful in patients who require surgical intervention, patients generally continue to use drugs.[25] Since the drugs used in the treatment of epilepsy have side effects on oral health, it is very important for these patients to prevent oral diseases and carefully plan their dental treatments.[26]

Epilepsy is one of the most common neurological diseases of childhood and the main component of its treatment is antiepileptic drugs.[26] Its prevalence in the pediatric population is 0.5-1%. Seizure control is achieved in approximately 70% of children with epilepsy using antiepileptic drugs in monotherapy.[27] Antiepileptic drugs are known to be teratogenic. Children exposed to these drugs before birth have a higher risk of developing congenital abnormalities, depending on the type, frequency and dose of the drug. It has been reported that children exposed to antiepileptic drugs prenatally have an increased incidence of developmental enamel defects such as enamel opacities and hypoplasia.[28] In addition, congenital deformities involving the midface and permanent tooth deficiencies may occur in these children.[29]

Drug-induced gingival enlargement is a term used to describe drug-induced gingival hypertrophy or hyperplasia, and although it is associated with many factors, its etiology has not yet been clarified.[30,31] It is a condition often induced by drugs such as anticonvulsants, antihypertensives, calcium channel blockers, and immunosuppressants. Among the antiepileptics, diphenylhydantoin causes the most drug-induced gingival enlargement. Other anticonvulsants with the same effect are vigabatrin, primidone, phenobarbital and sodium valproate.[30] Nayyar et al. reported a positive correlation between decreased serum folate level and increased gingival enlargement severity due to antiepileptic drug use.[32] In addition, it was concluded that decreased serum folate level may lead to early onset of oral side effects of antiepileptic drugs. Depending on the use of antiepileptic drugs, there may be deterioration of bone metabolism and decrease in bone mineral density in children and adolescents. This condition has been associated with an increased risk of rickets, osteomalacia, osteoporosis, and abnormal dentition.[33] In a study on rats and cats, diazepam was shown to increase cyclic adenosine monophosphate (cAMP) levels in rat brain, cat heart muscle and central nervous system cells by inhibiting cAMP phosphodiesterase. This drug may similarly affect periodontal tissue cells. Increase in cyclic nucleotide level may increase orthodontic tooth movement by changing the rate of bone resorption.[34]

Valproic acid and carbamazepine are antiepileptic drugs commonly used in pediatric patients with epileptic seizures. These drugs are known to have an effect on bone metabolism.[35] Valproic acid increases

the loss of calcium and phosphorus by causing tubular dysfunction in the kidneys. Carbamazepine, on the other hand, causes a decrease in bone density by changing the hepatic cycle of vitamin D. In a study on rats, the effects of carbamazepine and valproic acid on bone metabolism were investigated by evaluating orthodontic tooth movement.[36] As a result of the study, it was observed that the decrease in bone density caused by these drugs increased orthodontic tooth movement. In the group using antiepileptic drugs, an increase was observed in the periodontal ligament space of the teeth, which was associated with orthodontic tooth movement.

It is known that the use of phenytoin, one of the most commonly used antiepileptics, causes gingival hyperplasia. Gingival hyperplasia, which develops approximately 1-3 months after the start of phenytoin therapy, is characterized by overgrowth of gingival subepithelial connective tissue and epithelium. This tissue growth starts from the interdental papilla and progresses to the crowns of all teeth. The hyperplastic gingiva is not painful, but may be traumatized during chewing and increase the deposition of dental plaque, causing bleeding in the interdental papillary tissue. As a result of all these factors, it becomes difficult for patients to maintain oral hygiene.[37]

ANTIPSYCHOTIC DRUGS

Antipsychotic drugs can cause xerostomia, oral pigmentation and dysphagia.[38] Low-potency classical antipsychotic drugs, especially chlorpromazine and thioridazine, can cause hyposalivation by blocking parasympathetic stimulation of the salivary glands (anticholinergic effect). This situation causes periodontal disease and dental caries as a result of dry mouth.[39] Dry mouth also causes a decrease in the resistance of mucosal tissues to mechanical trauma. Lack of a normal amount of saliva causes difficulty in speaking, chewing and swallowing, especially in patients using removable prostheses and appliances.[40]

BRONCHODILATORS

Bronchodilator drugs are drugs commonly used in the treatment of chronic obstructive pulmonary disease and asthma. For bronchodilation, both sympathetic system activation (beta-2 receptors) and inhibition of the parasympathetic system (antimuscarinic effect) must be required.[41]

Asthma is an inflammatory pulmonary disease that causes reversible airway obstruction.[42] It is usually seen in children aged 6-11 years and is a very common disease affecting approximately 300 million children.[43] In severe asthma cases, depending chronic mouth breathing, decreased salivary flow, changes in saliva composition and pH, gingivitis, increased incidence of caries, mucosal changes, posterior open bite can be seen.[44,45]

Asthma treatment is based on controlling symptoms with bronchodilator medications. Salbutamol sulfate is a bronchodilator commonly used in chronic asthma patients.[46] Salbutamol sulfate has a pH of 3.6 (below the critical pH needed to dissolve enamel) and contains citric acid, a powerful calcium chelator. The citric acid in the bronchodilator drugs is a strong abrasive agent that can damage the tooth surface. It shows this effect by reducing the saturation of saliva and dissolving the surface of enamel crystals. It has the potential to form complexes with calcium ions dissolved from the surface. It also causes decreased salivary flow due to its effect on β-adrenergic receptors.[10]

Most pediatric bronchodilators have an acidic pH and the sucrose ratio is quite high like other pediatric drugs. Therefore, these drugs have a high risk of causing caries.[47] There are many studies showing that children with asthma have a higher risk of caries than healthy children.[43] Chellaih et al. reported that the risk of dental caries in children using daily inhaled corticosteroids was 6 times higher than in the healthy control group.[45] In addition, the number of bacteria in the saliva of children with asthma was found to be significantly higher than the control group. It is known that asthma can cause a decrease in salivary flow rate, which is a very important risk indicator for dental caries.[48] Guergolette et al. reported a high prevalence of developmental enamel defects in pediatric asthma patients in relation to asthma severity, symptom onset, and pharmacological treatment.[49] Scatena et al. reported that salbutamol sulfate has an abrasive effect on primary tooth enamel and dentin tissue.[10]

INHALED CORTICOSTEROIDS

Corticosteroids are frequently used in the long-term control of chronic respiratory diseases due to their anti-inflammatory effects. Inhaled corticosteroids affect the oropharyngeal area during inhalation. In addition, these drugs pass from the alveoli to the systemic circulation and indirectly affect the saliva content, concentration and flow rate, leading to negative consequences on oral health. This situation causes health problems due to local side effects, and oral health is affected by long-term use of inhaled corticosteroids, causing dental caries, tooth loss and periodontal diseases. For this reason, gargling after inhalation is recommended for patients using inhaled medications.[50-52]

It has been reported that inhaler drugs cause periodontal disease, tooth decay and erosion in children with asthma due to their effects on salivary secretion and pH.[53,54]

Oral and dental problems are seen as an important cause of comorbidity in patients receiving inhaled corticosteroid therapy.[50,55,56] Possible effects due to the use of inhaled drug groups should be taken into consideration when evaluating oral findings in individuals with chronic respiratory disease. It should be known that especially inhaled steroids may cause difficulties in the use of patients due to their oral-oropharyngeal side effects.

ANXIOLYTICS

In the treatment of child and adolescent psychiatric disorders, pharmacological treatment is important as well as supportive psychotherapy.[57] Significant oral health problems have been reported in individuals with chronic psychiatric disease.[58] It is known that the side effects of psychotropic drugs contribute to poor oral health in patients with psychiatric disorders. Xerostomia has been frequently reported as a result of long-term use of these drugs. Psychiatric drugs change the quality and quantity of saliva, cause endocrine dysfunction by changing the oral microbial flora, reduce resistance to infections, and increase the frequency and degree of periodontal disease.[59]

ANTIHISTAMINES

Antihistamine drugs are drugs that provide relief of histamine-mediated symptoms prescribed in food allergy, allergic rhinitis, childhood asthma, atopic dermatitis, chronic spontaneous urticaria, anaphylaxis, respiratory tract infection, otitis media, allergic conjunctivitis and acute allergic reactions.[60,61] Antihistamine drugs can increase the risk of tooth erosion due to their acidic components and adverse effects on saliva (decreased salivary flow rate, increased viscosity).[12,62] Costa et al. reported that the use of antihistamine drug can reduce the hardness of primary tooth enamel.[12] It is thought that the erosive feature of this drug is due to the presence of citric acid, which causes low pH, the absence of fluoride - phosphate, and the minimum calcium content. As a result of the study, it was reported that antihistamine syrup reduces the hardness of tooth enamel, but this erosive effect can be reduced with fluoride application.[5] Neves et al. reported that many pediatric drugs, including the antihistamine drug group, are risk factors for tooth erosion in their studies that determined the acidity and viscosity of the pediatric drug.[63]

ANALGESICS

Pediatric analgesic syrups are frequently prescribed pediatric drugs because of their high parental and child acceptability.[64] However, the assessment and management of pain in children is changing as a result of the development of pharmacological knowledge. Acetaminophen, ibuprofen, and opioids are commonly used drugs for the treatment of acute pain in children.[65] The groups of analgesic drugs used by children modulate different mechanisms and differ according to pain management in adults. Therefore, it is very important for clinicians to know the pharmacodynamic and pharmacokinetic differences of drugs used in adults and children.[66]

Analgesics, especially when used regularly and for a long time, cause the risk of dental caries and erosion in the patient. The amount of sucrose in these drugs is high, because sucrose has antioxidant, solvent, taste acceptability enhancing properties. Acids used in these drugs have buffering properties to ensure chemical stability and physiological compatibility.[64] Although many developed countries have a

public health policy that includes limiting the amount of sugar and acid used in medicines, some developing countries do not have a policy on pediatric drug use because there is not enough information on this subject.[67]

Many studies have reported that pediatric analgesics are mostly acidic. Passos et al. in 44% of these drugs, Cavalcanti et al. in 56% of them reported that the pH was below 5.5. Xavier et al. evaluated the pH values and sugar ratios of pediatric drugs and reported that the average pH value was 4.8 and the average sugar ratio was 33.7%.[5,64,68] These results show that the erosive and cariogenic potential of analgesics is high. Saeed et al., on the other hand, evaluated the pH, sucrose ratio and viscosity of different brands of pediatric syrups belonging to the paracetamol and ibuprofen group, and reported the average pH value as 4.63±0.57 and sucrose ratio as 7.31-85.9%.[69]

VITAMINS

Major nutrients-proteins, carbohydrates, fats, minerals and vitamins-are extremely important for oral health. Fat-soluble vitamins are A, E, D and K. Vitamin A plays a role in the early development of enamel. It controls the proliferation of epithelial cells and its deficiency affects all ectodermal formations. Vitamin D contributes to the mineral density of teeth, the development of tooth enamel, and the absorption of calcium in tooth and bone tissue. Vitamin C or ascorbic acid is a water-soluble vitamin. Vitamin C is required to hydrolyze proline and lysine in collagen synthesis. Vitamin C deficiency causes scurvy, a connective tissue defect.[70]

Vitamins play a role as organic catalysts in metabolic reactions in the human body. Although vitamins are necessary to support health, they are not a direct source of energy, but rather function to facilitate energy metabolism.[71]

Syrups containing multivitamins are drugs used by children for long-term supplementation. Studies on these syrups have been reported to have an acidic effect due to their low pH values.[72] In a study examining the erosive effect of pediatric syrups on the tooth surface, it was observed that atypical rough areas were revealed in the enamel regardless of the application time of multivitamins.[73] In another study, it was reported that the pH value of the pediatric multivitamin syrup included in the study was 4.3 and the roughness of the surface increased as the time the syrup remained in contact with the enamel surface.[48,72]

CONCLUSION

Various suggestions can be made to parents, dentists and pharmaceutical companies regarding chronic drug use in terms of preventive measures:

- It is thought that the erosive and cariogenic effects of drugs can be reduced by companies changing the type of acid added to drugs, reducing the use of sugar such as sucrose, and using artificial sweeteners such as xylitol or sorbitol.
- Pediatricians should be aware of their high erosive potential due to the fact that many of the drugs they prescribe are acidic, and should adapt parents for oral hygiene and routine dental examination.
- It is important for the oral health of the child that dentists have knowledge about the risk of erosion of the drug used in pediatric patients using chronic drugs, increase the frequency of routine examinations in these patients, and apply preventive dental treatments in routine controls.
- Brushing teeth before taking medication is effective in reducing discoloration caused by the medication used.
- Raising awareness of parents that pediatric drugs should be taken with food or that the child should rinse their mouth with water after drug use contributes to preventing erosion.
- Teeth should not be brushed immediately after taking the medication to reduce the abrasive effect of toothpaste on enamel.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or mem-

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Authorship Contributions

This study is entirely author's own work and no other author contribution.

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