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Feasibility of using acetazolamide in the treatment of tooth resorption

Viabilidade de uso da acetazolamida no tratamento de reabsorções radiculares

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Abstract

Objective: Since acetazolamide is a carbonic anhydrase inhibitor, it presents relevant aspects with regard to the treatment of late reimplanted teeth, and therefore, this is the aim of the present literature review. **Data Sources**: The databases used were Pubmed and Bireme. **Selection of works**: was performed using the keywords Tooth reimplantation, Dental ankylosis, Acetazolamide and Carbonic anhydrase inhibitors. **Conclusions**: In spite of contemporary guidelines for the treatment of late reimplantation, there is still a very high loss of avulsed teeth due to resorption, particularly by replacement resorption, so that the search for new substances or means of treatment is of the utmost importance.

Keywords: Tooth reimplantation. Dental ankylosis. Acetazolamide. Carbonic anhydrase inhibitors.

Resumo

Objetivo*: Uma vez que a acetazolamida é uma inibidora da anidrase carbônica, ela apresenta aspectos relevantes quanto ao tratamento de dentes reimplantados tardiamente, justificando assim o objetivo da presente revisão de literatura.* ***Fontes de dados****: as bases de dados utilizados foram Pubmed e Bireme.* ***Seleção dos***

trabalhos*: foi realizada por meio das palavras-chave Reimplante dentário, Anquilose dentária, Acetazolamida e Inibidores da anidrase carbônica.* ***Conclusões****: Apesar das diretrizes atuais para o tratamento do reimplante tardio, ainda a perda de dentes avulsionados por reabsorção é muito alta, principalmente diante da reabsorção por substituição, sendo premente a busca por novas substâncias ou meios de tratamento.*

Palavras-chave*: Reimplante dentário. Anquilose dentária. Acetazolamida. Inibidores da anidrase carbônica.*

Introduction

Tooth avulsion is the traumatic expulsion of the tooth from its alveolus, with the involvement of the circumjacent tissues, more specifically the periodontal ligament, cement, pulp tissue, alveolar bone and gingiva (1-5).

The prognosis of avulsed teeth depends on adequate measures while still at the site of the accident, in order to minimize the time in which the tooth remains out of the alveolus. If immediate reimplantation is not possible, an adequate storage medium must be used, with transport occurring in the medium term, and the root surface and periodontal ligaments must be protected against aggression (1-3, 5-21). However, the ideal treatment for an avulsed tooth is its immediate reimplantation. The critical time for an incorrectly stored tooth is 15 minutes (1, 22).

In practice, the ideal conditions for immediate reimplantation rarely occur. Nevertheless, even under unfavorable conditions, such as extra-alveolar time in excess of 30 minutes and inadequate means of conservation of the tooth, reimplantation is the treatment of choice (23, 24), this procedure being denominated *late reimplantation*.

Late reimplantation of teeth is not considered a definitive treatment, because of the expected complications, such as inflammatory and replacement resorptions after dentoalveolar ankylosis (1, 6, 8, 12-14, 25, 26). However, in spite of the survival of the late reimplanted tooth being compromised, it is preferable, in order to maintain the tooth in function and re-establish esthetics for a certain period of time. Moreover, it is pointed out that tooth avulsion mostly affects young patients who, due to their age, are frequently unable to be submitted to the insertion of dentures and/or implants (24, 27, 28).

The first reaction after reimplantation of a tooth with a damaged root surface is inflammation. This inflammatory response includes root resorption mediated by osteoclasts, proportional to the initial damage. If the inflammation is localized in a small area of the root and no additional inflammatory incentive is present, the root surface will be repaired with cement. On the other hand, if the damage covers a large area, there will be fusion between bone and root and afterwards the root will be replaced by bone (12).

The mineralized tissues of permanent teeth are protected by pre-dentin and a layer of odontoblasts within the root canal, and by pre-cement, cementoblasts and the periodontal ligament at the root surface. Due to these protective layers, under normal conditions, the mineralized tissues of permanent teeth do not undergo resorption. However, if the layers become mineralized, or if the pre-cement is removed or damaged, multinucleated cells will colonize the mineralized or exposed surfaces, leading to the onset of the resorption process (29).

Dentoalveolar ankylosis is the fusion of the root cement and dentin of a tooth to the alveolar bone. It occurs after extensive necrosis of the periodontal ligament, with bone formation in an unprotected area of the root surface. It is one of the complications of luxation lesions, especially in avulsed teeth that remain out of the mouth for a long period of time, in which the cells on the root surface dry and disintegrate (22, 30).

In healthy individuals, abundant periodontal ligament fibroblasts block osteogenesis within the periodontium by releasing regulators such as cytosines and growth factors that act locally, maintaining the separation of the tooth root from the alveolar bone. Necrosis of the periodontal ligament cells by desiccation, crushing or mechanical damage interrupts this normal homeostatic mechanism. Ankylosis is established not only via inflammatory pathway, but also because insufficient functional cellular elements survive to suppress osteogenic activity. This disruption allows growth of bone across the periodontal ligament, leading to fusion of the tooth root with the bone (31). The osteoclasts in contact with dentin resorb the tooth root, while the osteoblasts will deposit bone in the region (16).

If less than 20% of the root surface is involved, reversal of the ankylosis may occur (20). Otherwise, the ankylosed teeth are incorporated into the alveolar bone and become part of the normal process of bone remodeling. As a result, the roots will gradually be resorbed and replaced by bone (22, 32).

Although resorption by replacement leads to complete destruction of the tooth, it cannot be considered a process of disease, but an "error", due to the fact that the cells involved in bone remodeling are incapable of distinguishing between the root, cement, dentin and bone. Osteoclasts will resorb dental tissues as easily as they resorb bone (29).

When osteoclasts are in activity, they are in contact with the bone surface, emitting villosities that secrete proteolytic enzymes, which are responsible for organic degradation, and citric and lactic acids, responsible for the dissolution of mineral salts. Mineral dissolution occurs at low pH, mediated by these acids. After demineralization, the organic part of the bone becomes accessible to the action of enzymes that degrade it (33).

The chemical reaction for the formation of hydrogen ions is catalyzed by the carbonic anhydrase enzyme, which is in the cytoplasm, plasmatic membrane and in the organelle membranes of the clasts (34).

Within the osteoclasts, the carbonic anhydrase enzyme catalyzes the intracellular formation of carbonic acid from carbon dioxide and water. Carbonic acid is unstable and dissociates inside the cells into hydrogen ions and bicarbonate ions. Bicarbonate ions, accompanied by sodium ions cross the plasmatic membrane and enter into the neighboring capillaries. The proton pump located in the osteoclast membranes actively transports hydrogen ions to the extracellular environment, reducing the pH. The inorganic component of the matrix is dissolved as the environment becomes acid, and the minerals released are absorbed by the neighboring capillaries (35-39).

At present there is no treatment for this process. The speed with which the tooth is replaced by bone varies, and is dependent on the metabolic rate of each body, among other factors. In the majority of cases, it may take years, sometimes decades before the tooth root is completely resorbed (16, 29).

The recommended intracanal medication is calcium hydroxide, as it has the capacity to control the progression of inflammatory resorption because of its high alkalinity, capable of reflecting on the root surface and periodontium of the tooth, particularly if there are areas with irregularities present in the root cement (1, 40-44).

In late reimplantation, the avulsed tooth must be submitted to root surface treatment before it is reimplanted. At present this is performed with sodium hypochlorite to eliminate necrotic remains adhered to the tooth root without affecting the cement layer, and a solution of 2% acidulated sodium fluoride to strengthen the root structure by the formation of fluorapatite, or even to inhibit the formation of clastic cells (1, 40, 45).

In spite of these guidelines, complications after reimplantation of avulsed teeth are common, with a reported prevalence of 57% to 80% (2, 3, 8, 9, 17, 19).

Acetazolamide

Acetazolamide (5 acetamide-1,3,4-thiadiazole-2-sulfonamide) (46, 47), with the molecular formula $C_4H_6N_4O_3S_2$ and molecular mass of 222.245 g/mol, is derived from sulfonamide (48-50), with low diuretic action, is weakly acid (50) and an inhibitor of carbonic anhydrase (47-49, 50-57).

Acetazolamide is liposoluble, which allows it to diffuse into the cytosol through the lipid bilayer of the cell membrane, inhibiting carbonic anhydrase (48, 49, 51, 58, 59), causing an imbalance between the carbon dioxide and bicarbonate, regulating the extra and intercellular pH (35-37). Many of the body's metabolic functions are sensitive to pH and normal function occurs only in a narrow range. The pH range from 6.8 to 7.8 (160 to 16 mEq/l of H+) in the extracellular fluid is generally compatible with life. Normally, the extracellular fluid pH is maintained between 7.35 and 7.45 (60).

In the same way, it is suggested that due to the inhibition of carbonic anhydrase, this imbalance also occurs in the leukocytes (36), as they are the dominant cells in the acute phase of the inflammatory response and represent an important component of the reaction as host to the invading microorganisms. This response includes the generation of toxic radical oxygen species and production of immunomodulatory molecules, such as interleukin 8 (61). Exactly how the imbalance due to the inhibition of carbonic anhydrase in leukocytes contributes to their cellular function in the inflammatory response is not completely understood (36).

Couloigner et al. (51) evaluated the effects on the pH of luminal fluid in the endolymphatic sac of guinea pigs, and observed that acetazolamide applied locally caused a rapid and sustained reduction in pH. They also reported that this luminal acidification may have been the result of various effects of acetazolamide, including insufficiency of the acid-base transport systems. Nevertheless, the simplest explanation is that acetazolamide induced an imbalance in the pH of luminal acid due to the inhibition of carbonic anhydrase in functional contact with the luminal fluid.

Acetazolamide causes a change in the intracellular pH and concentration of calcium ions (38). The role of calcium in the function of leukocytes has been examined, and it appears that its concentration plays an important role, reported as being that of primary mediator of the locomotion cell (62, 63).

Kawaai et al. (36) analyzed the alterations in leukocyte migration during carbonic anhydrase activity inhibition, and concluded that acetazolamide could stimulate their migration, due to its participation in the regulation of intracellular pH, and also as a result of an anti-inflammatory effect that sustains leukocyte migration during inflammatory reactions, without lowering the extracellular calcium concentration.

If carbonic anhydrase is inhibited, it may be possible that the acid produced by the spontaneous ionization of carbonic gas may be dissolved sufficiently fast enough by diffusion or the flow of blood to diminish the painful stimulus (39).

The cause of the systemic side effects of acetazolamide that limit its clinical use may be because it easily diffuses into the cytosol, acting both on the cell membrane and the cytoplasm (59). But the adverse effects are minimal when it is used in a moderate posology for short periods (48).

Bone resorption results from three successive stages that can be regulated individually by physiopathologic factors or pharmacologic agents. The first involves the formation of osteoclast progenitor cells in the hematopoietic tissue, followed by their vascular dissemination and the generation of pre-osteoclasts and osteoclasts in bone. The second consists of the activation of osteoclasts in the mineralized bone. Osteoblasts appear to control this stage, exposing the mineral to the osteoclasts and pre-osteoclasts and/or releasing a soluble factor that activates these cells. In a third stage, the osteoclasts resorb the mineral and organic part of bone mineralized by the action of agents that segregate in the subjacent zones. The mineral appears to be solubilized by hydrogen ions secreted by the adenosine triphosphate proton pump located on this margin and fed by protons generated from the carbonic gas of carbonic anhydrase. Removal of the organic matrix, which can be prepared by osteoblast collagenase at the level of the mineralized bone surfaces, appears to be dependent on acid proteinases, particularly cysteine proteinases secreted together with other lysosomal enzymes in the acid microenvironment of the resorption zone (64).

The isoenzyme carbonic anhydrase II is essential during bone resorption (52, 65), being characteristic of the initial stage of osteoclast differentiation (65), by means of the generation of protons used by the mature osteoclasts (65, 66).

Bone resorption depends on the secretion of protons and lysosomal proteinases from osteoclasts in the extracellular microenvironment (Howship lacunae) around them. In osteoclasts, the protons are generated by carbonic anhydrase II and actively transported by the triphosphate adenosine - hydrogen ion (vacuolar type) driven proton pump at the frontier line with the lacuna, which participate in bone resorption. At one time it was thought that the lysosomal proteinases, possibly cysteine proteinases, played an important role in the lysis of bone collagen and the protons could help in the secretion of protease. The secretion of protons and lysosomal proteinases may play an essential role in the mechanism of bone resorption. During bone resorption it may be that the removal of calcium precedes the degradation of bone collagen matrix (67).

Lehenkari et al. (65) studied the manner in which carbonic anhydrase II influences the process of osteoclast differentiation in bone marrow cultures. In this model, acetazolamide diminished the formation of vitamin D_3 ($1,25(OH)_2D_3^-$), which increases the replication of both lymphocytes and monocytes, Monocyte-Tropic HIV-1 Strains, mononuclear cells from peripheral blood, and tartrate-resistant acid phosphatase cells induced from peripheral-blood monocytes. They performed measurements of pH and intracellular calcium ions in cultivated osteoclasts and observed that the addition of acetazolamide caused a rapid and temporary increase in both parameters. In cell cultures of rat calvaria, the inhibition of bone resorption was acetazolamide dose-dependent at extracellular pH 7.4, while inhibition was lower at extracellular pH of 7.0. In both processes, however, the crucial role of carbonic an-

hydrase II is, at least partially, due to the effect on the regulation of intracellular pH of the osteoclasts.

In 2002, Mori (68) treated the root surfaces of avulsed rat teeth that were late reimplanted, using different solutions (1% sodium hypochlorite solution; 1% sodium hypochlorite solution followed by the application of 2% sodium fluoride; and 1% sodium hypochlorite and 5% acetazolamide). He found that none of the tested treatments prevented the occurrence of ankylosis and root resorption, and all were inefficient in promoting repair.

In 2005, Mori (34) evaluated anti-resorptive substance-based solutions inside the root canals of late reimplanted rat teeth. The results showed that both, alendronate and gallium nitrate solutions, as well as the calcium hydroxide paste (control group) limited root resorption, but did not prevent its appearance. Whereas, with the use of the 10^{-5} M acetazolamide solution, root resorption was absent at 60 days and that conjunctive tissue similar to the periodontal ligament was formed more significantly than with the other medications.

The action of intracanal medication changes with the quantity of medication used and is limited by the small volume of the root canal. In addition, the concentration of the active substances in medications in a liquid state may rapidly be diminished by diffusion through the foramen and through the dentinal tissue. The sum of these two factors critically limits the molecular quantity of therapeutic agents, diminishing their action (8).

Mori et al. (69) investigated the biocompatibility of acetazolamide-based pastes in rat subcutaneous tissues. Two pastes containing acetazolamide as main component were used, with the vehicles used being physiological solution and propylenoglycol. The paste with physiological solution promoted an inflammatory process at seven days, but its intensity diminished with time and it was practically absent at 45 days. However, the paste with propylenoglycol promoted an inflammatory reaction in all the experimental periods. Thus, the experimental acetazolamide paste with physiological solution was considered biocompatible.

Conclusions

In spite of contemporary guidelines for the treatment of late reimplantation, there is still a very high loss of avulsed teeth due to resorption, particularly by replacement resorption, so that the search for new substances or means of treatment is of the utmost importance.

From the reports in this literature review, acetazolamide presents relevant aspects with regard to the treatment of late reimplanted teeth, which should be investigated, such as its physical, chemical, microbiologic and inflammatory properties.

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