Biochemical Effects of Adenosine in the Treatment of Oral Acute Ulcers

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Adenosine is an immune modulator natural molecule with anti-inflammatory properties. Adenosine is the main agent of A-Bio-Fast™, classified as tissue regenerating product, which contains DNA nucleotides, silanol mannuronat, nisin, nucleotides and lactic acid. The main objective of this study was to prove the efficiency and the effectiveness of adenosine in the topical treatment of acute ulcers in oral mucosa, by comparing the healing period in the treated patients with A-Bio-Fast™ and the untreated control cases. After 5 days of using A-Bio-Fast™ with adenosine compound, the viral/autoimmune acute ulcers of the oral mucosa were healed much faster compared to those treated without adenosine compound (64.1% vs 35.9%).

Key words: Adenosine, oral mucosa, acute ulcers

Adenosine (ADO) is a natural purine nucleotide (a heterocyclic aromatic organic compound) composed of a molecule of adenine attached to a ribose sugar molecule (ribofuranose) by a β-N_9-glycosidic connection (fig. 1) [1].

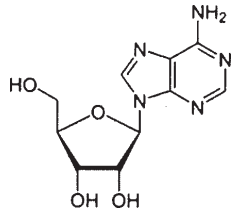

Fig. 1. Chemical formula of adenosine

Adenosine is a key endogenous molecule that regulates tissue function by activating four G-protein-coupled adenosine receptors: A_1, A_{2A}, A_{2B} and A_3. Cells of the immune system express these receptors and are responsive to the modulatory effects of adenosine in an inflammatory environment [2.].

Adenosine plays an important role in bio-chemical processes, such as energy transfer - as adenosine triphosphate (ATP) and adenosine diphosphate (ADP) - as well as in signal trans-duction as cyclic adenosine monophosphate (cAMP). It is also a neuromodulator, believed to play a role in promoting sleep and suppressing arousal [1].

Under physiological conditions adenosine concentrations inside of the cell are relatively low (<1 μM) and the major regulatory enzyme is adenosine kinase (AK) which mediates the initial phosphorylation step, via AMP, back to ATP [3-6]. By this way the nucleoside pool is kept in the cells. The levels of adenosine are raised in case of increased phosphatase activity, in metabolic stress, tissue injury, increased cells activity or cell's death. Another natural metabolic pathway for adenosine is its irreversible rapid dissemination into inosine which is further divided into hypoxanthine, xanthine and uric acid. This is done mainly inside the cells but also in the plasma. This makes adenosine a powerful vasodilator agent used as an antiarrhythmic drug for the rapid treatment of supraventricular tachycardia and in cardio imaging during stress tests to detect coronary fractional flow reserve in order to measure the severity of coronary stenosis [7]. It is an immune modulator with effective anti-inflammatory and anti-edematous properties induced by the up-regulation of cytokine release in macrophages and mast cells, the production of superoxide in neutrophils and the promotion of endothelial barrier function [8].

Adenosine is an active principle which can bind to four G-protein-coupled receptors (A_1, A_{2A}, A_{2B} and A_3) that modulate intracellular cAMP levels. Cells of the immune system express these receptors and are responsive to the modulator effects of adenosine in an inflammatory environment [9]. Animal models of asthma, ischemia, arthritis, sepsis, inflammatory bowel disease and wound healing have helped to elucidate the regulatory roles of the various adenosine receptors in dictating the development and progression of disease. This recent expressed awareness of the role of adenosine in the control of immune and inflammatory systems has generated excitement regarding the potential use of adenosine-receptor-based therapies in the treatment of infection, autoimmunity, ischemia and degenerative diseases [2].

A relaxation response to adenosine diphosphate (ADP), an endothelium-dependent vasodilator, of 15% or more from the stable tension induced by KCl triggered depolarization was considered as functioning endothelium [10]. The mitotic and angiogenesis stimulation allows the renormalization of microcirculation overload inhibition of Ca+ in ischemic cells preventing thus the reticular development of mitochondrial rupture and restoring the balance of cellular energy homeostasis [11-13].

After Moisin C. and all, a better understanding of the processes involved in the modifications of membrane ATPase activity allows to consider their different behaviour to isoproterenol and adenosine triphosphate as the expression of intrinsic mechanisms, in order to preserve the mitochondria role of ATP supplier [14].

Another important role is played by the adenosine receptors which are expressed in osteoblasts. A1 promotes human monocyte fusion into giant cells in vitro and induces formation and function of osteoclasts [15].

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All authors have equal contributions in the realization of this paper.

In present there is currently strong evidence for the adenosine's role in bone homeostasis, and these signaling pathways with significant relevance in bone diseases such as osteoporosis and arthritis [11].

Experimental part

Method and material

A-Bio™ Fast is a fluid spray product with high regenerating, proliferative, antiedema, anti-inflammatory properties, which acts as painkiller. DNA-Na is an active molecule, which has shown to be effective on traumatic injures of the mucous membranes and on diabetic sores and bed-sores. Its action also allows severely burnt and damaged skin to restore.

In order to demonstrate the effectiveness of this product, we compared two groups of patients diagnosed with acute oral ulcers (recurrent acute ulcers, herpetic infection and shingles).

The first batch of patients (group A) consisted of 30 patients treated with A-Bio™ Fast with adenosine content, and the other batch of patients (group B), represented the control group, with the same number of patients, treated without adenosine.

The patients were consulted and diagnosed in the Oral Medicine services of the Dental Medicine Faculties of Bucharest (Titu Maiorescu and Carol Davila University) and of Tîrgu Mures.

The diagnosis was established according to international protocols for oral diseases, as follows:

- for recurrent acute ulcers: on the basis of the anamnesis (subjective symptoms, evolution of the disease) and clinical aspect;
- for herpetic infection: the history, the symptoms, clinical lesions;
- for herpes zoster secondary infection (shingles): on the basis of clinical manifestations and the presence of the viral antigens (in most cases).

All the patients that were part from the study, returned for control in 5 days after using the topical treatment with adenosine content product A-Bio™ Fast (group A) or without adenosine content product (group B).

The lesions were photographed in the initial moment and after 5 days of treatment.

The written informed consent was obtained from all patients who participated to this study.

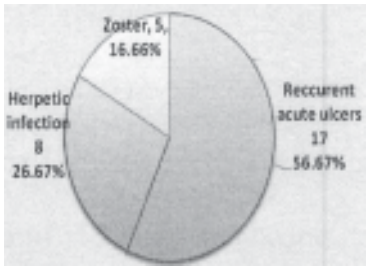

Fig. 2. The diagnosis in the selected groups (A and B) of patients

Group A of patients (30) included 17 patients diagnosed with recurrent acute ulcers (56.67%), 8 with secondary herpetic infection patients (26.67%), with shingles 5 patients (16.66%).

Group B of patients (30) included the same number of diagnosis as in group A.

Results and discussions

The total rate of healing in group A of patients, treated with adenosine contain product, after 5 days was 83.33%.

The 15 patients with recurrent acute ulcers presented 88.23% rate of healing, the 6 patients with secondary herpes 75%, the 4 patients with shingles were healed (80%).

In group B, from 17 patients with recurrent acute ulcers, 8 patients (47.06 %) healed in 7 days; 4 patients with secondary herpes (out of all 8) cured in 7 days, and from the total of 5 herpes zoster patients 2 healed in 10 days; the total recovery rate was 46.67 % for 7 to 10 days.

The healing results, between the selected two groups of patients (A and B) with recurrent aphtous ulcers are presented in figure 3.

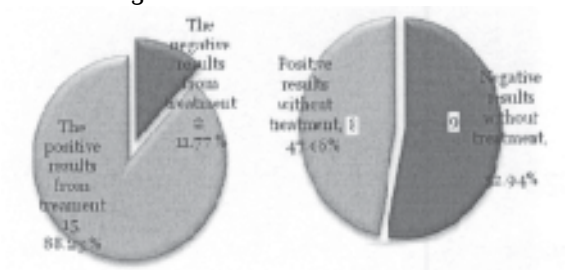

Fig. 3. Compared diagram with the healing results, between the two groups of patients (A and B) with recurrent aphtous ulcers

The healing results, between the selected two groups of patients (A and B) with Herpes are presented in figure 4.

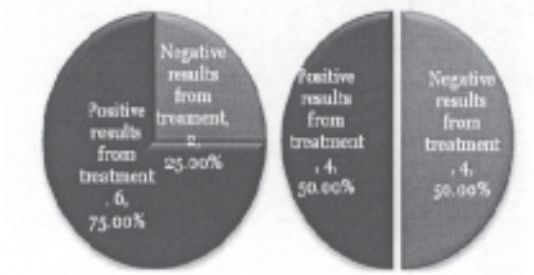

Fig. 4. Compared diagram with the healing results, between the two groups of patients (A and B) with Herpes

The healing results, between the selected two groups of patients (A and B) with zona zoster are presented in figure 5.

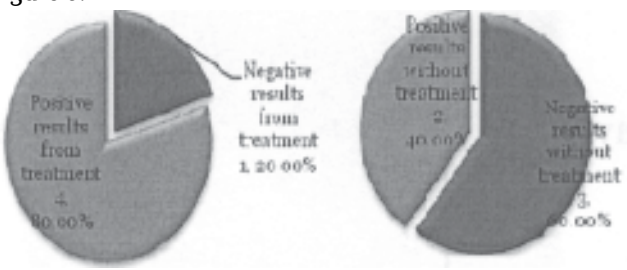

Fig. 5. Compared diagram with the healing results, between the two groups of patients (A and B) with Zona Zoster

Comparing the results by statistical means (Chi-square test) we detected that the results are statistically significant ($p=0.002<0.05$) (table 1).

The results of this study, of the patients suffering from the same disease, reveals the efficiency and efficacy of adenosine in patients of group A, compared with those who have not benefited from therapy with adenosine (group B).

Recent developments in tissue engineering approaches involve the use of three-dimensional scaffolds to function as the template for cellular activities to repair, rebuild and regenerate damaged tissues [16].

Due to the characteristics of adenosine, its topical use favours an accurate reconstruction of damaged oral lining tissues, by stimulating the mitosis and the angiogenesis processes and by shortens the duration of healing [17-19].

A-Bio™ Fast, with adenosine content, allows fast and effective, optimal tissue restructuring, clinically detectable.

	Positive results		Negative results	
	Group A	Group B	Group A	Group B
Recurrent acute ulcers	15 patients (88.23%)	2 patients (11.77%)	8 patients (47.06%)	9 patients (52.94%)
Herpetic ulcerative lesions	6 patients (75.00%)	2 patients (25.00%)	4 patients (50.00%)	4 patients (50.00%)
Zona zoster ulcers	4 patients (80.00%)	1 patients (20.00%)	2 patients (40.00%)	3 patients (60.00%)

Table 1
TREATMENT RESULTS

The effect is explained through an effective tissue cleansing and a powerful restorative action and by physiological healing, allowing prevention and therefore formation of keloids and/or anomalous tissues. It is specifically useful and appreciable in Dental field because it leads to a fast and proper reconstitution of bone tissues and mucous membranes of oral cavity, shortening the physiologic healing time drastically. By mitosic and angiogenic stimulation, renormalisation of microcirculation is allowed and is prevented the development of contractures and/or mitochondrial and reticular contractures and/or ruptures, restoring normal homeostatic energy cellular balance, showing a strong anti-ischemic tissue and anti-degenerative activity. It allows optimal tissue restructuring, which can be fast and efficient and can be clinically proven (the effect is explained by an effective cleaning and initial tissue reparative action with strong physiological scarring or keloid formation which allows abnormal tissue [20,21].

The tissue restorative A-Bio Fast is a medical product in compliance with the essential requirements of The Coach of the European Directive 93/42 EEC and subsequent amendments, as per certificate issued by MED 28002 Notified Body CERMET Scarl No. 0476, and is marketed in accordance with Legislative Decree 46/97 and subsequent amendments.

Conclusions

The results of study demonstrate the reparative and healing action of adenosine.

Through the biochemical features, the topical application of adenosine compound product A-BioTM Fast favoured the reducing of duration in healing oral mucosa ulcers.

All authors have equal contributions in the realization of this paper.

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