Influence of nifedipine on gingiva of Wistar rats

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Noninflammatory hyperplastic growth of gingiva induced by calcium channel blockers, mostly nifedipine, is often seen in everyday dental practice. In order to establish an association of nifedipine and gingival hyperplasia, experimental model was used. Wistar rats were given water solution of nifedipine in different daily doses, using specially designed cannula. At the beginning of the experiment, before the application of nifedipine and in the determined time periods, gingival volume was measured. The volume of lower incisors interdental central papillas, represented multiplied values of vertical hight, mesio-distal width, and bucco-lingual depth, expressed in millimeters. The results indicated that gingival hyperplasia was more excessive in the experimental animals, which were given higher doses of the drug for longer time period. Nifedipine is a drug which induces gingival fibroblasts to produce higher quantity of collagen that causes gingival overgrowth.

Key words: nifedipine; gingival hyperplasia.

Introduction

Calcium antagonists, pharmacologically defined as calcium channel blockers, have been in use for many years in the treatment of cardiovascular diseases (1).

According to their therapeutic effects, these drugs can be divided into the ones for the treatment of angina pectoris, systemic hypertension, and the ones for the treatment and prophylaxis of supraventricular arrhythmia. According to their chemical structure, the drugs of this group can be divided into the derivatives of phenylalkylamine, benzodiazepine, and dihydropiridine. The most used dihydropiridines are amlodipine, nicardipine, and nifedipine.

Besides the well-known positive effects of nifedipine in the treatment of cardiovascular diseases, there still exists the lack of knowledge about the adverse effects, which may occur in periodontium, genitals, and skin (2).

Pharmacokinetically, calcium channel blockers are orally active agents. They are characterized by high first pass effect, high plasma-protein binding, and extensive metabolism (3). Their administration during longer period of time might have negative effects on periodontal tissues, and they might generate gingival hyperplasia, which in the later phase causes the destruction of deeper periodontal tissues. As a consequence of periodontal destruction, there occurs tooth migration and tooth loss. Calcium cannel blockers can also change immune response of periodontal tissues to dental plaque bacteria, and in that way initiate and stimulate the onset and progression of inflammatory process.

In 1939, Kimball published data that indicated close relation between gingival overgrowth and the use of some drugs (4). The first case of gingival overgrowth caused by nifedipine was reported in 1987 by Lederman.

Gingival hyperplasia as a result of nifedipine use is usually generalized, and front teeth interdental papillas are most affected. In the regions without teeth, hyperplasia was not registered. Sometimes gingival overgrowth might be so massive that the whole tooth is covered with the tissue which may cause masticatory problems.

Hyperplastic gingiva is usually of pale pink color, with compact consistency and tiny granular surface. The combination of nifedipine and some other drugs like aspirin or hydantoins, permanent mouth breathing, as well as the presence of some systemic disorder (systemic hypertension), might contribute to hyperplastic growth of gingiva.

There are literature data (6) that nifedipine stimulates gingival fibroblasts to produce collagen, thus causing gingival hyperplasia.

Gingival enlargement increases gingival sulcus depth, and as a result gingival pocket is formed. It makes the ade-
quate maintenance of oral hygiene almost impossible, and gingival inflammation occurs. The reason for gingival enlargement is hyperplastic process induced by drug use, and inflammation is a secondary complicating factor.

The aim of this study was to explore the influence of nifedipine on experimental animals’ gingiva, depending on dosage and time period.

Methods

The research was performed on 50 male Wistar rats, aged 6 weeks, weight between 150 and 250g, divided into 3 groups of 15 animals. Other 5 animals were sacrificed at the beginning of the experiment in order to record the basic state of gingiva, i.e. the state of gingiva before the administration of nifedipine.

Experimental animals received water solution of nifedipine by special cannula in daily doses of 10 and 15 mg (nifedipine dissolved in 0.5 ml of saline), and the control group received only saline solution without nifedipine. During the experiment, animals were fed regularly.

Gingiva was measured at the beginning of the experiment, before nifedipine administration, and in time intervals of 3, 6, and 9 weeks. The volume of central papilla was obtained as the result of multiplication of vertical height, mesio-distal width, and bucco-lingual depth in millimeters.

Measurement was performed by special millimetric graduated probe at the beginning of the experiment, and after 3, 6, and 9 weeks, which was the overall time of nifedipine administration to experimental animals. After 3 weeks, 5 animals from each group were sacrificed (15), after 6 weeks another 5 from each group, and after 9 weeks the remaining 15.

The obtained values were expressed as mean values, and were processed by adequate statistical methods with standard deviation and standard error.

Results

The size of central interdental papilla was monitored at the beginning of the experiment, and in the determined time intervals during the experiment. At the beginning of the experiment, the volume of lower incisor central papilla was 12 mm³.

The dose of nifedipine of 10 mg/d, after 3, 6, and 9 weeks, did not cause statistically significant change in the volume of lower incisor central papilla of the experimental animals (Table 1).

The dose of nifedipine of 15 mg/d, after 3, 6, and 9 weeks, caused statistically significant change in the volume of lower incisor central papilla of the experimental animals.

Larger dose of the drug caused change in the volume of lower incisor papilla of the experimental animals during the time interval of 6 and 9 weeks, compared to the state after 3 weeks of drug administration. This confirmed that lower incisor central papilla was enlarged after 6 weeks of drug administration, and then stagnated during another 3 weeks period (Table 2).

<table>
<thead>
<tr>
<th>Time period</th>
<th>n</th>
<th>x ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 weeks</td>
<td>5</td>
<td>26.00 ± 4.47</td>
</tr>
<tr>
<td>6 weeks</td>
<td>5</td>
<td>43.20 ± 3.92*</td>
</tr>
<tr>
<td>9 weeks</td>
<td>5</td>
<td>43.20 ± 3.92*</td>
</tr>
</tbody>
</table>

* p <0.001

There was no change in the volume of lower incisor central papilla, comparing 6 and 9 weeks of higher dose administration, so the value of t-test was zero.

The second aim of this study was to compare the volume of lower incisor central papilla in the experimental animals at the beginning of the experiment, when Wistar rats received 0.5 ml of saline solution (control group), lower dose (10 mg/d), and higher dose (15 mg/d) of the drug in the defined time intervals.

During the first 3 weeks, comparing the lower and the higher dose of the administered drug, there was no statistically significant change in the volume of lower incisor central papilla, in contrast to the control group, where statistically significant change occurred, comparing the values measured by standard deviation and by t-test (Table 3).

<table>
<thead>
<tr>
<th>Drug dose</th>
<th>n</th>
<th>x ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5</td>
<td>11.40 ± 2.24</td>
</tr>
<tr>
<td>Lower</td>
<td>5</td>
<td>22.40 ± 1.96*</td>
</tr>
<tr>
<td>Higher</td>
<td>4</td>
<td>26.40 ± 4.47*</td>
</tr>
</tbody>
</table>

* p<0.01

During 6 weeks time period, statistically significant change in the volume of the lower incisor central papilla was noticed, particularly comparing to the higher dose group, and the control group (Table 4).
Comparison of the size of lower incisor central papilla of the experimental animals after the administration of the control, lower, and higher drug dose during time period of 6 weeks

<table>
<thead>
<tr>
<th>Drug dose</th>
<th>n</th>
<th>( x \pm SD )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control dose</td>
<td>5</td>
<td>11.40 ± 2.24</td>
</tr>
<tr>
<td>Lower dose</td>
<td>5</td>
<td>28.40 ± 7.58*</td>
</tr>
<tr>
<td>Higher dose</td>
<td>5</td>
<td>43.20 ± 3.92*</td>
</tr>
</tbody>
</table>

* p<0.01

After 9 weeks, statistically significant change was obvious between the lower and the higher dose of the drug (p<0.05), the lower dose and the control, with somewhat higher standard deviation (p<0.01), and the most significant change occurred between the higher dose and the control (p<0.001) for 9 weeks time period (Table 5).

Table 5

Comparison of the size of lower incisor central papilla of the experimental animals after the administration of the control, lower, and higher drug dose during time period of 9 weeks

<table>
<thead>
<tr>
<th>Drug dose</th>
<th>n</th>
<th>( x \pm SD )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control dose</td>
<td>5</td>
<td>11.40 ± 2.24</td>
</tr>
<tr>
<td>Lower dose</td>
<td>5</td>
<td>29.60 ± 8.16*</td>
</tr>
<tr>
<td>Higher dose</td>
<td>4</td>
<td>43.20 ± 3.92*</td>
</tr>
</tbody>
</table>

* p<0.001

Discussion

The results of this study demonstrated that there was more significant gingival hyperplasia at the experimental animals, which were given the higher dose of the drug during the longer time period. During the 6 weeks time period, lower and higher doses of the drug caused changes in the volume of lower incisor central papilla, compared to the control group. Similar results were obtained during the 9 weeks time period, when more significant changes occurred in the volume of lower incisor central papilla for the lower and higher doses of drug, compared to the control.

Gingival overgrowth caused in the experimental animal model indicated that nifedipine had a significant role in interdental papilla enlargement of Wistar rats. These findings were in accordance with the results derived from the experiments on Sprague-Dawley animals, in which the dependence between gingival growth and the dose of the drug was also demonstrated after nifedipine administration (7). Gingival growth may also be a consequence of the increased number of fibroblasts in the tissue, induced by nifedipine (8).

Collagen decomposition is important for physiological remodeling of connective tissue. Nifedipine participation in collagen production may increase the imbalance of collagen degradation (9).

Investigations performed by Myrales GJ, in 1999 (10), regarding fibroblasts of healthy and hyperplastic gingiva approved the existence of different fibroblast subtypes, which variously reacted on stimulus, including drugs. These investigations confirmed the findings of this study.

Latest investigations of Morton RS et al. in 1999 (11), showed that nifedipine in combination with dental plaque bacteria reduced interleukin 6 secretion, and increased it in the presence of interleukin 1 beta.

Interleukin 6 is a cytokine with more than one effect. It has positive effect on the activation and differentiation of B cells into plasma cells, which secrete immunoglobulins. Interleukin 6 is a differentiating factor for cytotoxic T cells, and a growth factor for B cells, T cells, and for mesenchymal cells. It has also been proved that interleukin 6 has stimulation effect on growth and metabolism of connective tissue cells like fibroblasts, thus it is assumed that it has pathogenetic role in the diseases where transformations occur on fibroblasts (12).

Gingival fibroblasts secret considerable amount of interleukin 6 with or without stimulation, so they might be one of primary interleukin 6 sources in animals that received nifedipine (13). It is also possible that nifedipine stimulatory effect is not directly manifested only on the fibroblasts of gingiva, but that it also causes a complex interaction with dental plaque and inflammatory cytokines (14).

It is approved that there are quantitative and qualitative differences in the reaction of gingival fibroblasts, concerning the increase or the decrease of interleukin 6 secretion.

Inside fibroblast population there are phenotypic variations, thus it is assumed that nifedipine effect on a population of fibroblasts depends on relative presence of those subtypes that react to nifedipine (15). If such fibroblasts exist, the presence of nifedipine will cause the increased secretion of interleukin 6, resulting in the proliferation of fibroblasts and the increase of their activity, as well as the increase of extracellular matrix.

Although according to the obtained data, bacteria do not directly increase interleukin 6 secretion, they act synergistic with nifedipine in secretion increase.

Conclusion

Based on the data from this study, it is possible to conclude:

Higher dose of nifedipine induces overgrowth of lower incisor central papilla in experimental animals;

Length of administration also has the influence on lower incisor central papilla overgrowth;

Lower incisor central papilla overgrowth was registered during the first 6 weeks of drug administration, and then gingival growth stagnated.
REFERENCES


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A p s t r a k t


UTICAJ NIFEDIPINA NA GINGIVU PACOVA SOJA WISTAR

Neinflamatorno hiperplazijsko uvećanje gingive izazvano blokatorima kalcijumskih kanala i to najčešće nifedipinom registruje se u svakodnevoj stomatoškoj praksi. Da bi se utvrdila povezanost nifedipina sa pojavnim hiperplazije gingive korišćen je eksperimentalni model. Pacovima soja Wistar je posebnom kanalom svakodnevno davan vodeni rastvor nifedipina u različitim dozama. Na početku eksperimenta pre davanja nifedipina i u datim vremenskim periodima merena je veličina gingive. Za-preminja centralne interdigitalne papile donjih inciziva predstavljala je pomnožene vrednosti vertikalne visine meziolodistalne širine i bukolingvalne dubine izražene u milimetrima. Rezultati pokazuju da je došlo do izraženije hiperplazije gingive kod pacova koji su dobijali veći dozu leka kroz duži vremenski period. Nifedipin je lek koji na fibroblaste gingive deluje tako da lute povećanu količinu kolagena koja izaziva uvećanje gingive.

K l j u č n e r e č i: nifedipin; gingiva, hiperplazija.

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