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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparison of bromazepam and ibuprofen influence on tooth pulp-evoked potentials in humans

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SUMMARY
Introduction/Objective Somatosensory evoked potentials are a neurophysiological tool for testing the effects of drugs in humans and animals.
The aim of this study was to estimate the way that bromazepam and ibuprofen had on tooth pulp-evoked potentials (TPEPs) after non-painful stimuli, as well as to detect possible differences in this activity.
Methods Sixty young healthy subjects were included in the study. They were arranged into three groups: ibuprofen, bromazepam, and placebo. To record TPEPs response, dental pulp were electrically stimulated through intact enamel with non-painful stimuli. For stimulation and registration we used Xltek Protektor 32 system, software EPWorks, version 5.0 (Natus Medical Incorporated, Oakville, ON, Canada). The experiment consisted of two testing sessions. Five recordings were performed in each session. The first test session was before, and the second was 45 minutes after administration of a single dose of the ibuprofen (400 mg), bromazepam (1.5 mg) or placebo.
Results The results of the present study exhibit that both ibuprofen and bromazepam significantly increased all the latencies; ibuprofen decreased amplitudes of all the waves except the first one ($p < 0.05$), and bromazepam decreased amplitudes of all the waves except the first one ($p < 0.05$); placebo did not modified TPEPs waves ($p > 0.05$). Additionally, there were no significant differences in influence on TPEPs between bromazepam and ibuprofen ($p > 0.05$).
Conclusion Our study showed that both bromazepam and ibuprofen had the same influence on TPEPs after non-painful stimuli. That indicates that anxiolytic dose of bromazepam affects neurotransmission in the same manner as non-opioid analgesics ibuprofen.
Keywords: somatosensory evoked potentials; non-painful stimulus; analgesic; anxiolytic

INTRODUCTION

Somatosensory evoked potentials (SEPs) represent electrical activity changes of the nervous system caused by a somatosensory stimulus. Their waves reflect neural activations along somatosensory pathway with different sensory information processing at subcortical and cortical levels. Contrary to spontaneous electrical activity, evoked response occurs at a specific time after stimulation in a particular cortical region. Although electroencephalography equipment is used to record evoked potentials, only signals from electrodes placed above the region of interest are observed [1]. Therefore, the region of interest for tooth pulp-evoked potentials (TPEPs) is vertex because TPEPs show a bilateral symmetrical scalp distribution with a maximum at the vertex [2].

Since the middle of the previous century, SEPs have been the standard assessment tool for nociception, as well for testing and quantifying the effects of analgesics in humans and animals [3–6]. Various studies have shown specific effects on SEPs characteristics in an experimental pain model after analgesic application [2, 3, 6, 7]. Furthermore, it has also been observed that SEPs were useful neurophysiological tool for assessing the emotional aspects of pain. Examining the effect of sedatives on pain-related SEP components, it was revealed that they also change SEPs characteristics by modifying emotional responses to pain [8–11].

It is widely accepted that ibuprofen, a non-steroidal anti-inflammatory drug, in contrast to opioid analgesics, does not show sedative non-specific side effects [12, 13, 14], as well as that bromazepam, acting via gamma aminobutyric acid (GABA) type A receptors, reduces anxiety and consequently reduces the emotional response to pain, but provide no analgesia [15, 16, 17]. However, recent studies suggest that GABA agonists show anti-nociceptive effects, too [13, 18, 19, 20].

So far known to us, no studies have compared the effect of both anxiolytic and analgesic drugs on TPEPs in humans. Therefore, the aim of this study was to analyze the influence of bromazepam and ibuprofen on TPEPs in healthy subjects. Since SEPs are objective method for assessing neurotransmission, we also included a placebo in the study, assuming it would not cause change of TPEPs. Considering that emotional and cognitive aspect of pain could affect perception and consequently SEPs [10, 21], we decided to use non-painful stimulus.

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METHODS

Ethical approvals

The study was conducted at the Clinic for Oral and Maxillofacial Surgery at the Institute of Faculty of Stomatology, Pančevo, between October 2018 and March 2019. The study was approved by the Ethics Committee of the Institute (1240/1-20-2015) and was in accordance with the Principle of Good Clinical Practice and the Declaration of Helsinki [22]. All subjects gave their written informed consent after a full explanation of the study, focusing on the purpose of the study and the precise procedures.

Subjects

Sixty young healthy male and female participants were included in the study. They were randomly arranged into three equal groups of 20 subjects each. The first group received ibuprofen, the second group received bromazepam, and the third group received placebo.

Regardless of using any drug, exclusion criteria were avital central incisors of the upper jaw, as well as fillings and prosthetics on the same teeth. In addition, exclusion criteria were oral mucosal changes, and fractures, trauma or surgery in the maxillofacial region. All subjects were examined under the same conditions, between 8 a.m. and 2 p.m.

Drugs

Ibuprofen (Brufen®, Galenika AD, Belgrade, Serbia), film coated tablet 400 mg, was used as an analgesic. Bromazepam (Bromazepam HF®, Hemofarm AD, Vršac, Serbia), tablet 1.5 mg, was used as an anxiolytic. As placebo was used Betavitevit Folna 400 (folic acid, 400 μg, and vitamin B12, 3 μg, Esensa d.o.o., Belgrade, Serbia), tablet. All tablets were in same bottles. Subjects were told they were receiving one of the investigated tablets.

Evoked potentials registration and analysis

Before starting the TPEPs registration, stimulus intensity for dental pulp stimulation was determined for each subject based on two criteria: subjective experience of the stimulus intensity and sufficient intensity to evoke characteristic SEPs curve. The stimulus intensity was rated by a 5-level ordinal category scale (1 – no sensation, 2 – barely perceptible, 3 – tingling, 4 – mild pain, 5 – moderate pain). The stimulation of central maxillary incisor began with an intensity of 0.2 mA and increased by 0.2 mA until the subject reported a tingling sensation, level 3 on the scale. The average pulse intensity for dental pulp stimulation was 1 mA.

The cortical somatosensory-evoked responses were recorded from vertex, with reference to inion, after pulp of central maxillary incisor were electrically stimulated through intact enamel (for more information of stimulation parameters and the recording technique see our previous study [23]).

The experiment consisted of two testing sessions; five recordings were performed in each session. The first was before, and the second test session was 45 minutes after the single dose of the drug administered.

Obtained average recordings were numerically, graphically and statistically processed. The peak latency and the peak amplitude of all components were measured. Values of latencies and amplitudes after drug administration were compared with the same values before drugs, as well as with previously standardized values of latencies and amplitudes. Finally, SEP records after administration of ibuprofen, bromazepam and placebo were compared with each other.

Statistical analysis

Data were statistically analyzed with SAS (The SAS System for Windows, release 9.3. Cary, NC, USA) [24]. To determine statistical significance, we used the Wilcoxon signed rank sum test and the Kruskal–Wallis test. Values of $p < 0.05$ were considered significant. Results are expressed as mean ± the standard error of the mean.

RESULTS

TPEPs were successfully recorded in 56 subjects (31 male and 25 female participants mean age 22.5 ± 0.7). Four subjects from the bromazepam group were rejected because the records after drug administration were illegible.

At the beginning of the research, in a pilot study, we have standardized values of latencies (LN1 55 ms, LP1 100 ms, LN2 145 ms, LP2 195 ms) and amplitudes (AN1 7.5 μV, AP1 8.0 μV, AN2 9.5 μV, AP2 8.5 μV), which represented the control group. In this pilot study, no significant differences in TPEPs between the sexes were found (data not shown).

The effect of ibuprofen on tooth pulp-evoked potentials

The results obtained 45 minutes after ibuprofen administration showed significantly longer all latencies compared to the same group pre-drug and to the control group ($p < 0.05$). Furthermore, the amplitudes of the first three waves were significantly decreased post-drug versus pre-drug and control group ($p < 0.05$). The detailed data are shown in Figure 1 and Table 1.

The effect of bromazepam on tooth pulp-evoked potentials

All latencies 45 minutes after bromazepam administration were significantly longer compared to the same group pre-drug and to the control group ($p < 0.05$). Additionally, the amplitudes of the last three waves were significantly decreased post-drug versus pre-drug and control group ($p < 0.05$). The detailed data are shown in Figure 2 and Table 2.

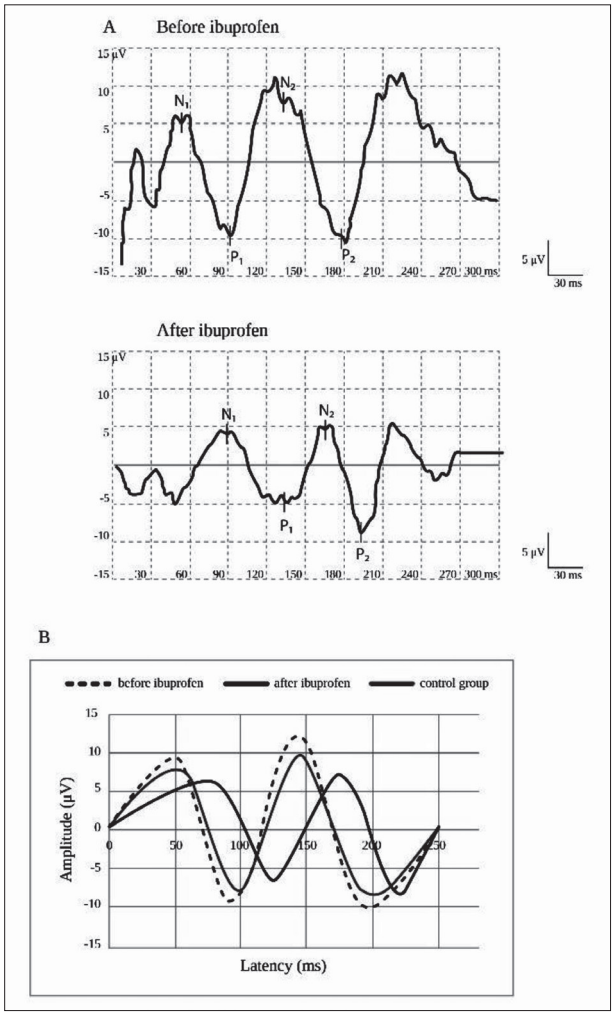


Figure 1. Influence of ibuprofen on tooth pulp-evoked potentials

A) Original waveforms recording from vertex after toot pulp stimulaton before and after ibuprofen administration; B) the pattern of the mean values of evoked potentials before and after ibuprofen administration and control group; all latences were significantly longer ($p < 0.05$) after ibuprofen compared to the same group pre-drug and control group; the amplitudes of the first three waves significantly decreased ($p < 0.05$) after ibuprofen compared to the same group pre-drug and control group

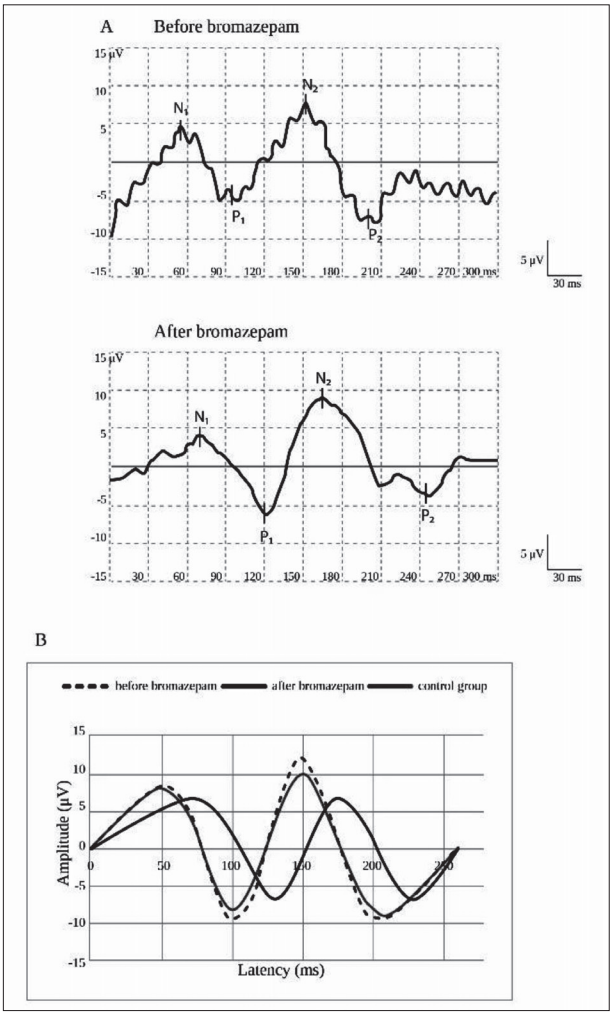


Figure 2. Influence of bromazepam on tooth pulp-evoked potentials

A) Original waveforms recording from vertex after toot pulp stimulaton before and after bromazepam administration; B) the pattern of the mean values of evoked potentials before and after ibuprofen administration and control group; all latences were significantly longer ($p < 0.05$) after bromazepam compared to the same group pre-drug and control group. The amplitudes of the last three waves significantly decreased ($p < 0.05$) after bromazepam compared to the same group pre-drug and control group

Table 1. Comparison of tooth pulp- tooth pulp-evoked potentials parameters before and after ibuprofen administration and control group

Evoked potentials parameters	Pre-drug	Post-drug	Pre-drug *vs.* post-drug p*	Post-drug *vs.* controls p**
Latency (ms)				
N1	52.9 ± 2.2	80.6 ± 4.6	**< 0.0001**	**< 0.0001**
P1	94.5 ± 3.1	127.1 ± 4.5	**< 0.0001**	**< 0.0001**
N2	142.8 ± 3.5	175.7 ± 4.8	**< 0.0001**	**< 0.0001**
P2	191.8 ± 5.9	218.7 ± 6.5	**0.0037**	**< 0.0001**
Amplitude (μV)				
N1	8.9 ± 2.8	5.9 ± 0.8	**0.0153**	**0.0021**
P1	10.4 ± 3.5	6.7 ± 0.2	**0.0056**	**0.0078**
N2	12.2 ± 3.8	7.1 ± 0.7	**< 0.0001**	**0.0078**
P2	9.9 ± 5.3	8.2 ± 0.8	0.0826	0.1502

Pre- and post-drug values are expressed as mean ± standard error;
*Wilcoxon signed rank sum test;
**Wilcoxon–Mann–Whitney test

Table 2. Comparison of tooth pulp-evoked potentials parameters before and after bromazepam administration and control group

Evoked potentials parameters	Pre-drug	Post-drug	Pre-drug *vs.* post-drug p*	Post-drug *vs.* controls p**
Latency (ms)				
N1	57.9 ± 1.1	78.5 ± 1.7	**< 0.0001**	**< 0.0001**
P1	100.6 ± 1.9	125.8 ± 1.3	**< 0.0001**	**< 0.0001**
N2	144.1 ± 2.7	171.1 ± 2.1	**< 0.0001**	**< 0.0001**
P2	190.5 ± 3.1	216.8 ± 2.8	**< 0.0001**	**< 0.0001**
Amplitude (μV)				
N1	7.9 ± 0.7	6.3 ± 0.9	0.4615	0.4839
P1	9.5 ± 0.5	6.5 ± 0.6	**0.0087**	**0.0057**
N2	12.0 ± 1.5	6.8 ± 0.4	**0.0087**	**0.0059**
P2	8.9 ± 0.3	6.7 ± 0.3	**0.0087**	**0.0112**

Pre- and post-drug values are expressed as mean ± standard error;
*Wilcoxon signed rank sum test;
**Wilcoxon–Mann–Whitney test

The effect of placebo on tooth pulp-evoked potentials

After placebo administration, there were no significant differences in the TPEPs components either within the same group pre-drug, or in relation to the control group ($p > 0.05$). The detailed data are shown in Figure 3 and Table 3.

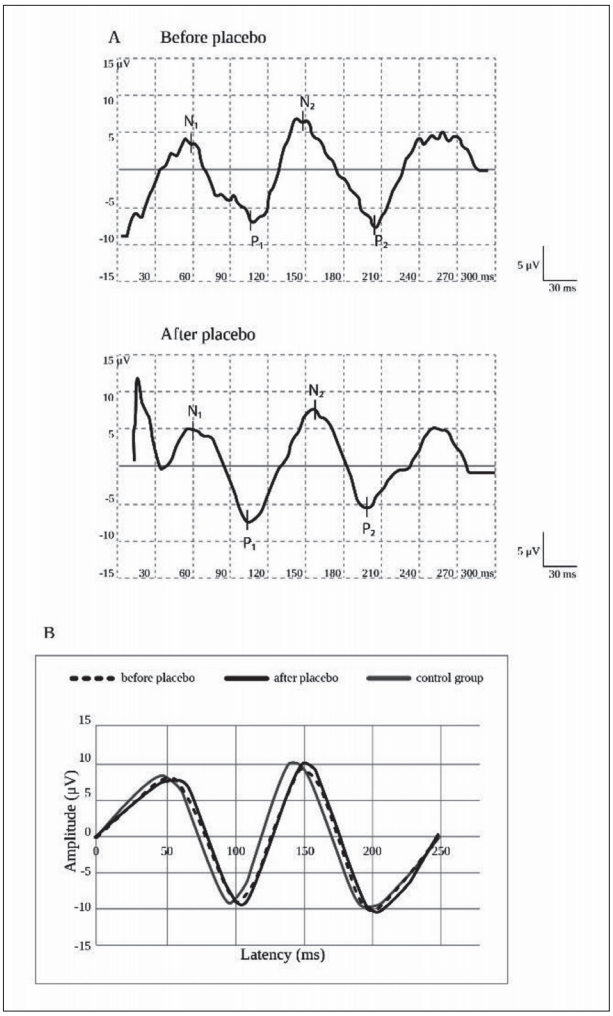


Figure 3. Influence of placebo on tooth pulp-evoked potentials

A) Original waveforms recording from vertex after toot pulp stimulaton before and after placebo administration; B) the pattern of the mean values of evoked potentials before and after placebo administration and control group; there were no significant differences ($p > 0.05$) in the all latencies and amplitudes either within the same group pre-drug or in relation to the control group

Comparison between influence of ibuprofen, bromazepam and placebo on tooth pulp-evoked potentials

Comparing the obtained mean values of wave latencies and amplitudes after ibuprofen administration and the mean values of same parameters after bromazepam administration, no statistically significant differences were found ($p > 0.05$). Contrary, all latencies of both, ibuprofen and bromazepam, were significantly longer than latencies after placebo, while the first three values of amplitudes after ibuprofen, and the last three values of amplitudes after bromazepam were significantly decreased comparing to the same parameters after placebo. The detailed data are shown in Figure 4 and Table 4.

Having in mind that all groups consisted of different subjects, we compared TPEP components between controls

Table 3. Comparison of tooth pulp-evoked potentials parameters before and after placebo administration and control group

Evoked potentials parameters	Pre-drug	Post-drug	Pre-drug *vs.* post-drug p*	Post-drug *vs.* controls p**
Latency (ms)				
N1	58.5 ± 2.1	61.9 ± 1.9	0.1272	0.8858
P1	105.4 ± 2.8	107.1 ± 2.6	0.5879	0.2017
N2	152.9 ± 3.8	154.2 ± 3.6	0.7869	0.0545
P2	199.7 ± 4.7	201.2 ± 4.5	0.7737	0.1078
Amplitude (μV)				
N1	6.8 ± 0.4	7.1 ± 0.5	0.6355	0.3469
P1	7.9 ± 0.5	8.2 ± 0.7	1.0000	0.9700
N2	8.5 ± 0.6	9.5 ± 0.8	0.2439	0.9400
P2	8.9 ± 0.5	9.1 ± 0.6	0.2163	0.1879

Pre- and post-drug values are expressed as mean ± standard error;
*Wilcoxon signed rank sum test;
**Wilcoxon–Mann–Whitney test

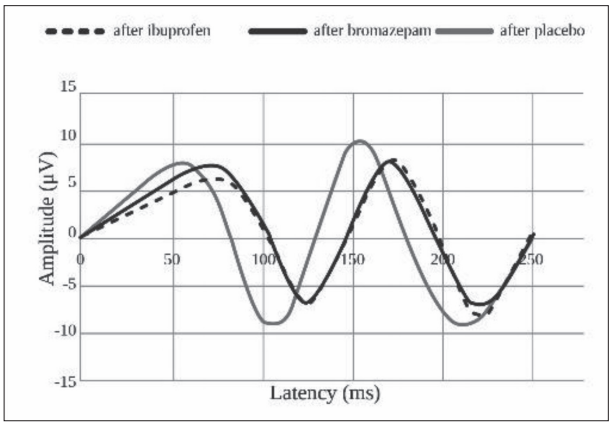


Figure 4. The pattern of the mean values of evoked potentials after ibuprofen, bromazepam and placebo

There were no significant differences ($p > 0.05$) in the all latencies and amplitudes between groups after ibuprofen and after bromazepam; the amplitudes were significantly less comparing to amplitudes after placebo ($p < 0.05$)

Table 4. Comparison of tooth pulp-evoked potentials parameters after drug administration between ibuprofen, bromazepam and placebo groups

Evoked potentials parameters	ibuprofen *vs.* bromazepam p	ibuprofen *vs.* placebo p	bromazepam *vs.* placebo p
Latency (ms)			
N1	0.6327	**< 0.0001**	**< 0.0001**
P1	0.8986	**0.0002**	**< 0.0001**
N2	0.3897	**0.0005**	**0.0006**
P2	0.5664	**0.0128**	**0.0075**
Amplitude (μV)			
N1	0.2141	**0.0024**	0.2141
P1	0.1810	**0.0081**	**0.0018**
N2	0.3724	**0.0072**	**0.0024**
P2	0.5664	0.5664	**0.0014**

Pre- and post-drug values are expressed as mean ± standard error;
Wilcoxon–Mann–Whitney test

and each group before drug administration, as well as between all groups before drug administration. Analysis showed no significant differences in all comparisons ($p > 0.05$) (data not shown). Therefore, post-drug results could be compared between groups.

DISCUSSION

In this study TPEPs modulation by analgesic and anxiolytic was studied. TPEPs are the most appropriate method for assessing orofacial pain, because any supra-threshold stimulus that affects the tooth-pulp is perceived as pain [2, 9, 25]. Each of the four waves is characterized by two components: latency and amplitude. An upward deflection of the TPEPs waveform was defined as N (negative) and downward deflection as P (positive). The latency reflects rate of neurotransmission, and the amplitude stimulus intensity [7, 26]. Amplitudes with peak occurring at a mean latency less than 100 ms (exogenous SEP components) were proportional to stimulus intensity, while amplitudes with peak occurring at a mean latency greater than 100 ms (endogenous SEP components) were proportional to the intensity of perception [26]. Therefore, early waveform components manifest the energy transmission at the first-order synapses in the pons and along trigeminal lemniscus, and the late components reflect the brain processes during stimuli perception at thalamus-cortical and thalamus-limbic levels [7, 8].

The results of the present study, that ibuprofen at a dose of 400 mg significantly increases all latencies and decreases amplitudes of first three waves, are in accordance with the previous studies which examined the influence of different doses of analgesics on SEPs [2, 3, 6, 7]. Moreover, our findings indicate that ibuprofen, as a cyclooxygenase inhibitor that affects transmission at the first-order synapses in the pain pathway [14, 20], slows down neurotransmission along the entire pain pathway and reduces the stimulus intensity perception at the level of the pons and trigeminal lemniscus, despite non-painful stimuli.

The dose-dependent effects of benzodiazepines range from anxiolytic and sedative to loss of consciousness [13, 15]. It is well-known that sedative doses of benzodiazepine, as well as opioid analgesics, affect the emotional aspect of pain, in contrast to non-opioid analgesics which affect the sensory aspect of pain [9]. Gonzalez-Liencres et al. [27] reported that endogenous evoked potentials are associated with attention and stimulus evaluation. Since their components correlate with state of the subject, attention level and meaning of the stimulus [10, 21], they can be affected by centrally acting drugs [10, 20]. Many previous studies showed that sedative drugs modify late SEP waves. In fact, they cause a dose related significant increase in latencies and decrease in amplitudes [8–11]. The same modifications of these SEP components caused by analgesics were actually a consequence of their nonspecific sedative effects [2, 28]. In order to avoid sedative effect of bromazepam, in this study, anxiolytic dose was administered. Furthermore, non-painful stimuli were applied since various studies have shown that intensity of painful stimuli positively correlated with amplitudes and negatively correlated with latencies [2, 3, 7, 11], as well as non-painful stimuli did not affect amplitudes [29]. Moreover, in order to eliminate the influence of fear of pain, the subjects were told that the stimulation of TPEPs would be painless and that the drug they receive is an analgesic. Indeed, our findings exhibit that bromazepam even at a dose of 1.5 mg significantly increased all latencies, and decreased amplitudes of last three waves.

According to other studies, benzodiazepines increase the inhibitory postsynaptic potential via GABA-ergic membrane hyperpolarization, which leads to a decrease in the firing rate of neurons [13, 15, 30]. Our results indicate that anxiolytic dose of benzodiazepines slows down neurotransmission along the entire somatosensory pathway and reduces the stimulus intensity perception from the trigeminal lemniscus, through the thalamus, to the limbic system and cortex, even if non-painful stimuli were applied.

Our results showed that placebo did not modify TPEPs waves, as we assumed. Furthermore, there are significant difference between results of placebo and other drugs, which implies that the drug effects on TPEPs are valid. Cruccu et al. [31] examined whether the late components of TPEPs are a reliable index of pain intensity. They found that changing the experience of expected pain under the influence of placebo reduces the amplitude of TPEP and subjective assessment of pain, while input from the periphery remains unchanged. Because TPEP, instead of being an event specifically related to the nociceptive message, represents the electrical equivalent of an unspecific associative activity which seems to depend more on the novelty and affective correlate of the stimulus than on the stimulus intensity. According to Thürauf et al. [10] and von Mohr et al. [21], emotional and cognitive aspect of pain could affect perception and consequently SEPs. Since we applied non-painful stimulus and our subjects did not expect pain, there was no change in the characteristics of the evoked potential, as we assumed.

Even though we found that bromazepam changed last three TPEPs amplitudes, as well as the ibuprofen changed first three TPEPs amplitudes, there were no significant differences in influence on TPEPs when these two groups are compared. Considering that there are no studies that examined the effect of both anxiolytic and analgesic on TPEPs, and based on the knowledge of all factors that affect the SEPs, which we mentioned earlier, we assume that these findings are outcome of non-painful stimuli application.

It is important to note that this part of our experiment have certain limitation. The second part of our exploration is including the effects on TPEPs after painful stimulation of the dental pulp. Due to the appropriate procedures regarding the selection and consent of patients, it was necessary to include a modified sample of patients in the study. We thought that due to the change in study conditions, participants and sample size, it would be more correct approach to present this part of the study separately after completion, and also to compare these subsequent results with result presented here. Further ongoing research, that involves painful stimulation of the dental pulp, will provide

a more complete insight into the effects on TPEPs of these two drugs with different modes of action.

CONCLUSION

In this study, we showed that both bromazepam and ibuprofen had the same influence on TPEPs after non-painful stimulus. In other words, that indicates that anxiolytic dose of bromazepam affects neurotransmission in the same manner as non-opioid analgesics ibuprofen.

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Conflict of interest: None declared.

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Поређење утицаја бромазепама и ибупрофена на евоциране потенцијале зубне пулпе код људи

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САЖЕТАК

Увод/Циљ Соматосензорни евоцирани потенцијали су неурофизиолошко средство за тестирање ефеката лекова на људе и животиње.

Циљ овог истраживања био је да се процени начин на који бромазепам и ибупрофен утичу на евоциране потенцијале зубне пулпе након примене безболног стимулуса, као и да се открију могуће разлике у овој активности.

Методе У истраживање је укључено 60 младих здравих испитаника, који су сврстани у три групе: ибупрофен, бромазепам и плацебо. У циљу добијања одговора на евоциране потенцијале зубне пулпе, зубна пулпа је стимулисана електричном струјом преко интактне глеђи стимулусима који не изазивају бол. За стимулацију и регистрацију користили смо апарат *Xltek Protektor* 32 систем, софтвер *EPWorks*, верзија 5.0 (*Natus Medical Incorporated*, Оквил, ОН, Канада). На сваком испитанику је урађено два пута по пет снимања евоцираних потенцијала, први пут пре примене лека, а други пут 45 минута након примене појединачне дозе ибупофена (400 *mg*), бромазепама (1,5 *mg*) или плацеба.

Резултати Резултати ове студије су показали следеће: и ибупрофен и бромазепам изазвали су значајно продужење свих латенци; ибупрофен је изазвао снижење амплитуда свих таласа осим првог ($p < 0,05$), а бромазепам је изазвао снижење амплитуда свих таласа осим последњег ($p < 0,05$); плацебо није модификовао таласе евоцираних потенцијала ($p > 0,05$). Такође, нису уочене значајне разлике у променама евоцираних потенцијала под дејством бромазепама у односу на ибупрофен ($p > 0,05$).

Закључак Наша студија је показала да су бромазепам и ибупрофен имали исти утицај на евоциране потенцијале зубне пулпе након примене безболног стимулуса. Добијени резултати указују да бромазепам у малим дозама на исти начин утиче на неуротрансмисију као и ибупрофен, који је неопиоидни аналгетик.

Кључне речи: соматосензорни евоцирани потенцијали; безболни стимулус; аналгетик; анксиолитик