PHARMACODYNAMIC EFFECT OF GABAPENTIN ON CENTRAL NERVOUS SYSTEM IN PATIENTS WITH CHRONIC LOW BACK PAIN: A [99mTc]Tc-ECD SPECT STUDY.

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ABSTRACT

BACKGROUND: Gabapentin is an effective therapeutic alternative for chronic low back pain, indicated in several guidelines for treating neuropathic pain as first-line medication. This study aimed to describe the pharmacodynamics of gabapentin in the central nervous system of patients with chronic low back pain (CLBP) by using single-photon emission computed tomography (SPECT) with [99mTc]Tc-ECD. **METHODS**: We selected 13 patients with CLBP due to lumbar disc herniation. They underwent SPECT before and after using gabapentin, compared to a SPECT database of healthy volunteers. A second analysis compared regional cerebral blood flow (rCBF) changes between responders and non-responders to gabapentin and the healthy controls. **RESULTS**: The mean age of patients was 41 years, and the mean pain intensity was 5.92 points, measured by the Numeric Rating Scale. After using gabapentin, SPECT showed an increase of rCBF in the bilateral anterior cingulate gyrus and a decrease of rCBF in periaqueductal gray matter. Non-responder patients with gabapentin showed a post-treatment decrease of rCBF in the paracentral lobule of the brain. **CONCLUSIONS**: A lack of improvement in some patients with gabapentin may be associated with an activated affective circuit of pain, evidenced by the increase of rCBF of the anterior cingulate cortex. A maladaptive brain state in chronic pain can explain the decrease of rCBF in the default mode network structures. Gabapentin acts directly or indirectly on neurons of periaqueductal gray substance by increasing the pain threshold and decreasing the rCBF of this structure.

KEY MESSAGES

What is already known on this topic: Patients with CLBP have activation of the mPFC and greater functional connectivity of this region with the nucleus accumbens, which is related to the intensity of pain. Study of these patients using gabapentin has never been performed using SPECT.

What this study adds: the effect of gabapentin to treat neuropathic CLBP led to an increase in rCBF of bilateral limbic lobe (anterior cingulate) and a decrease in rCBF in the midbrain and right pons (corresponding to the area of the PAG), involving the culmen of the right cerebellum. These findings suggest a reduction in firing of PAG neurons, probably related to the effect of gabapentin over the spinal and supraspinal antinociceptive circuits.

How this study might affect research, practice or policy: This study opens a new perspective for correlations between the clinical response to gabapentin and rCBF in patients with neuropathic CLBP as an indirect measure of the pharmacodynamic effects of this drugs on CNS. More studies are needed to deepen the understanding of the effects of drugs on the pain matrix, so that, in the future, physicians may be able to decide whether to titrate their doses or replace the drug based on functional aspects of neuroimaging.

INTRODUCTION

Chronic low back pain (CLBP) is one of the main reasons for disability at work, and its prevalence is estimated at 9.4% of the general population [1,2]. Gabapentin (GBP) is considered the first-line treatment in different neuropathic pain guidelines [3]. Voltage-gated Ca2+ channels are directly blocked by GBP binding to its α2δ1 subunit, which is the receptor of GBP and certain thrombospondins (TSPs). The α2δ1 subunit is expressed in neurons and their axonal terminals and dendrites throughout the central and peripheral nervous system, leading to the reduction of presynaptic Ca2+ influx and decreasing synaptic release of glutamate, which is the major excitatory neurotransmitter of the brain [4]. Functional neuroimaging techniques, such as single-photon emission computed tomography (SPECT), evaluate regional cerebral blood flow (rCBF) and can be used to obtain task-free information from ongoing brain activity and may reflect spontaneous characteristics of chronic pain as in patients with cLBP [5]. These functional neuroimaging studies have been employed to understand the mechanism of action and the site of action of drugs that act on the central nervous system. SPECT with 99mTc-ethylene dicysteine [99mTc]TC-ECD has been used to evaluate the distribution of drugs in the brain. Previous studies have reported the use of SPECT to assess the effect of lamotrigine on cerebral blood flow in patients with generalized idiopathic epilepsy and suggest that the drug decreases rCBF in the cortico-thalamic-limbic orbitofrontal cortex and brainstem [6]. SPECT also showed that the anxiolytic properties of cannabidiol in healthy volunteers are mediated by action in the limbic and paralimbic areas of the brain [7].

This study proposes to evaluate the rCBF changes of patients with CLBP secondary to lumbar disc herniation (LDH) after treatment with gabapentin, using brain perfusion SPECT with [99mTc]Tc-ECD. We aimed to identify differences in rCBF associated with the use of gabapentin and its effect on CLBP. The hypothesis is that gabapentin promotes rCBF changes

and may be related to drug efficacy in terms of improvement in pain intensity. Although investigating CLBP by brain SPECT is not new, the study of these patients using gabapentin has never been performed using SPECT, and the responders vs non-responders model seems to be appropriate to assess the brain pharmacodynamics of gabapentin. Identifying the cerebral neurobiological substrate associated with pain may aid in the optimization of treatment with drugs such as gabapentin. It can assist in the titration of this drug based on functional neuroimaging. This study opens a new perspective in the search for correlations between the clinical response to gabapentin and rCBF in patients with CLBP as an indirect measure of the pharmacodynamic effects of drugs on CNS.

PATIENTS AND METHODS

Casuistic

Thirteen patients with CLBP of both sexes were recruited at a tertiary hospital's Neuropathic Pain Outpatient Clinic. The Medical Ethics Committee approved the study of this institution (No.1.190.720), and all patients signed the informed consent form. The inclusion criteria were: individuals aged 18 years or more; neuropathic pain according to NeuPsig criteria (DN4 scale $\geq$ 4); the presence of lumbar disc herniated by MRI; not being treated previously with gabapentin; duration of pain greater than three months; and intensity of pain equal to or greater than 4 in NRS (Numeric Rating Scale). NRS is an 11-point scale, from 0 (no pain) to 10 (worst pain). Exclusion Criteria were: uncontrolled systemic arterial hypertension; diabetes mellitus; anemia; chronic alcoholism; obesity; smokers; changes in hepatic, cardiac, and renal function and evidence of another cause of pain.

Patients and Methods

At the first visit, we applied NRS, and volunteers underwent biochemical tests (blood count, renal and liver function, bilirubin, and glycemia) and an electrocardiogram (ECG). We referred patients to the first brain SPECT before the use of gabapentin if biochemical tests were regular.

Gabapentin was initiated at 300 mg b.i.d. for seven days when patients returned to the second evaluation. Patients who decreased at least 4 points in the NRS from the initial score were considered responsive to gabapentin and underwent the second SPECT.

For non-responders, the dose of gabapentin was increased to 300 mg t.i.d., with a new scheduled reassessment in 7 days and a second SPECT scan. Finally, if the patient was not responsive to 900 mg daily after seven days, a 600 mg b.i.d was prescribed for more than seven days. All volunteers who used gabapentin 1,200 mg daily for seven days, responders and non-responders, underwent the second SPECT. That was the maximum dose of gabapentin stipulated in this protocol. Figure 1 is a flowchart of the protocol.

Insert FIGURE 1 about here

SPECT Protocol

Patients underwent the brain SPECT examination after intravenous injection of the [99mTc]Tc-ECD radiopharmaceutical in a dose of 1,295 MBq (35 mCi). The injection occurred with the patient resting for 30 minutes, with eyes open, in a quiet and low-light environment, refraining from talking and listening.

The SPECT were acquired on hybrid equipment, SPECT/CT, BrightView XCT (Philips Medical Systems Inc., Cleveland, OH, USA) equipped with a double detector, using a high resolution, low energy collimator (LEHR), with 20% symmetrical acceptance energy,

140 keV centered photopeak, using a 128 x 128 matrix, a zoom factor of 1.0 and a pixel size of 2.13 mm. The data were collected in 360-degree step-and-shoot mode, with a total of 128 projections (64 per detector), a total acquisition time of 30 min, and about 100,000 counts/projection/head.

The tomographic images were processed in the EBW workstation (Philips Medical Systems Inc., Cleveland, OH, USA), reconstructed in transaxial sections parallel to the orbitomeatal line, and using the ordered subset maximization (OSEM) algorithm and a Butterworth Filter (order 2, cutoff frequency 0.3). The Chang method was applied to transaxial slices to correct the attenuation of photon effects ($\mu = 0.12$ cm -1).
On the day of the completion visit, the second SPECT was acquired 6 hours after oral intake of the gabapentin morning dose.

Statistical analysis

The comparative analysis of cerebral SPECT between baseline and under gabapentin was performed using the Statistical Parametric Mapping Software (SPM8) in MATLAB 13 (MathWorks, MA): 1. Paired analysis of 13 individuals in two different moments, before and after using gabapentin: first SPECT was compared to the second one. SPM8 generated both the individual analysis of each patient and a group-based comparison of pre and post-treatment images. Each patient with pain, or group of patients with pain, before treatment, was compared voxel-based with the brain SPECT database of healthy volunteers. The same procedure was performed after the treatment. The SPM software highlighted the difference in rCBF between the two individual SPECTs or group of SPECTs; 2. Two subgroups differences: the changes on rCBF after using gabapentin were analyzed separately in the subgroups with and without clinical improvement; 3. Two subgroup differences: individual and intergroup rCBF differences between patients responders and non-responders with

gabapentin were mapped. The reference database included ten healthy volunteers without clinical comorbidities and neurological or psychiatric disorders aged between 30 and 50 years.

The results are shown in P values less than 0.05, corrected for multiple comparisons (FWE). The cluster peak coordinates were determined using "Automated Talairach Atlas for Functional Cerebral Mapping" [8], and results are shown in the three-dimensional planes of a standard MRI sequence T1 model.

RESULTS

The group was composed of 13 patients, seven women (53.8%) with a mean age of 41 ± 9.62 years (25-62 years). The mean duration of pain at the time of inclusion in the study was 4.29 ± 3.95 years (range from 3 months to 12 years). The mean pain intensity assessed at the beginning of the protocol through NRS was 5.92 (± 1.93), and the mean value of the DN4 scale was 4.54 (± 2.63) points. The predominant site of lumbar disc herniation was between the 4th and 5th lumbar vertebrae (L4-L5) in more than 50% of the patients. Some patients included in the study used previous medications, and they were not discontinued or had their doses modified.

Pain assessment

Among the 13 patients, six (46.2%) presented clinical improvement with the proposed gabapentin treatment, evaluated through a decrease of at least 4 points on the NRS. Among the six responders, one improved at 600 mg/day of gabapentin, four at 900 mg/day, and one reached the maximum dose of 1,200 mg/day of gabapentin. All seven patients who did not show clinical improvement got the 1,200 mg/day dose of gabapentin.

Volunteers reported adverse effects of using gabapentin: eight patients complained of dizziness (61.5%), eight presented somnolence (61.5%), and three participants reported headache (23%). Less frequent adverse events were hyperphagia and weakness (7.7%), epigastralgia (15.4%), insomnia (15,4%), and slowing of mental activity. (7.7%).

Regional cerebral blood flow (rCBF)

Changing on rCBF after the use of gabapentin in the group of 13 patients

Table 1 describes rCBF differences between pre and post-treatment with gabapentin, evaluated within two clusters, increasing and decreasing rCBF.

TABLE 1 - Cluster volume of rCBF changes in 13 CLBP patients after using gabapentin.

Patient	Cluster volume * (increase of rCBF)	SD	Cluster volume * (decrease of rCBF)	SD
1	2.577	4.372	-6.043	2.901
2	4.969	2.752	-0,497	3.565
3	0,336	3.339	-3.134	3.856
4	0,873	3.009	-6.155	2.607
5	2.696	4.965	-5.199	2.117
6	6.501	4.157	-5.723	3.131
7	4.245	3.384	-4.104	3.221
8	3.797	4.524	-3.829	2.975
9	6.924	3.077	-1.288	2.046
10	3.386	4.102	-3.586	2.342
11	4.032	5.121	-1.068	3.348
12	2.941	2.917	-1.070	2.042
13	7.088	4.284	-4.316	3.212

ABBREVIATIONS: rCBF, regional cerebral blood flow; SD, standard deviation. * Cluster volume (k) is given by the number of $1mm^3$ x $1mm^3$ x $1mm^3$ voxels found within the cluster. .

A single functional map of the difference between the moments, seen in Figure 2, was generated, overlapping clusters on the T1-weighted magnetic resonance of the SPM model. Changes on rCBF of the 13 patients after using gabapentin: (a) an increase trend of rCBF in bilateral limbic lobe (anterior cingulate; p = 0.05, FWE corrected; cluster volume (k) = 565; Talairach coordinates = (x) 4, (y) 26, (z) 14; maximum voxel Z score = 4.73) (See Figure 2A); (b) decrease of rCBF in posterior regions of the midbrain, pons, and culmen of the cerebellum (p = 0.04, FWE corrected; cluster volume = 319; Talairach coordinates = (x) 2, (y) -30, (z) -20; maximum voxel Z score = 4.14) (See Figure 2B). In Figure 2, color bars signify Z-scores of the intensity of increase or decrease of rCBF.

Insert FIGURE 2 about here

Pos-treatment rCBF changes in responders and non-responders.

We analyzed the rCBF changes of six responders and seven non-responders patients before and after gabapentin, looking for the brain areas associated with therapeutic success and failure.

The statistical analysis showed rCBF increase only in the group of non-responders in the left limbic lobe (anterior cingulate gyrus; p = 0.013, FWE corrected; cluster volume(k) = 260; Talairach coordinates = (X) -2, (y) 26, (z) 12; maximum voxel Z score = 3.96).
The 13 patients were divided into two groups, responders (n=6) and non-responders (n=7) to gabapentin, to explore the neurobiological substrates associated with the therapeutic response. The individual results were quite heterogeneous compared to the database of healthy volunteers (see Table 2).

TABLE 2 - rCBF changes on responders and non-responders patients to gabapentin compared to healthy controls.

Patient # (brain regions)	*P* *	Cluster volume (*k*)	Talairach coordinates x, y, z	Maximum voxel *Z* score
Responders				
Increased rCBF				
#8 R temporal, medium gyrus	0.04	386	60, -30, -6	4.38
L frontal, superior, medial e medium gyrus	0.01	514	-22, 48, 12	4.26
#11 R frontal (superior and medium gyrus)	0.05	362	20, 34, 34	4.28
R temporal (medium gyrus) and	0.05	347	40, -74, 14	4.15
R occipital medium gyrus)				
Decreased rCBF				
#4 R temporal, medium gyrus	0.00	640	30, -80, -24	4.41
Non-responders				
Increased rCBF				
#5 R occipital (fusiform and lingual gyrus), R posterior cerebellum (declive)	0.00	644	10, -68, -16	4.21
#7 Bilateral limbic lobe (anterior cingulate)	0.02	464	-6, 38, 14	4.19
#13 Bifrontal lobe (superior, medial e medium gyrus) e bilateral limbic lobe (anterior cingulate)	0.00	6435	20, 34, 34	5.31
Decreased rCBF				
#7 L parietal (postcentral gyrus, paracentral lobule)	0.05	345	-26, 40, 64	3.55

The number in # indicates the volunteer. Abbreviations: P * value of cluster significance; R, right; L, left.

The rCBF comparison between responders and non-responders did not show differences. When compared with healthy volunteers, responders also did not present rCBF differences. But non-responders presented rCBF decrease over frontal (motor area) and parietal lobes (paracentral, postcentral, and precuneus regions) as compared to healthy volunteers ($p < 0.01$, FWE corrected; Cluster volume (k) = 2,837; Talairach coordinates = (x) -8, (y) -30,(z) 66; and maximum voxel Z score = 0.0724) (See Figure 2C).

DISCUSSION

This study evaluated patients with CLBP secondary to LDH through functional neuroimaging to analyze which brain regions have their rCBF changed by the effect of gabapentin on pain. SPECT images showed increased rCBF in the bilateral limbic lobe (anterior cingulate) after using gabapentin. The anterior cingulate cortex (ACC) seems to be the cortical region most frequently associated with pain experience, involving the emotional reaction to pain and not the painful perception itself [9]. The connections between the dorsal portion of the ACC and the prefrontal cortex (PFC) play a substantial role in pain-related cognitive functions. Previous studies have found abnormal activity in the medial prefrontal cortex (mPFC) and ACC in CLBP. Patients with CLBP had activation of the mPFC and greater functional connectivity of this region with the nucleus accumbens, related to the intensity of pain [10]. A study using arterial spin-labeling (ASL) found that increases in the intensity of CLBP have been associated with an increase of rCBF in mPFC and other areas related to the pain matrix [11]. The prefrontal cortex seems to exert active control over pain perception, modulating interactions with the midbrain, thalamic, striatal, and cingulate structures. The evidence is that chronic pain states show more involvement of PFC, whereas

in normal individuals, the perception of experimental pain most often involves S1, S2, thalamus, and ACC [12].

After using gabapentin, there was a decreasing rCBF in the midbrain and right pons, corresponding to the area of the PAG, involving the culmen of the right cerebellum. PAG is the primary downward modulating center of pain through the production of enkephalins. PAG is a collection of separate functional entities with different ascending and descending connections with systems related to the control of the sensory, motor, autonomic, and limbic responses, including ACC, insula, and amygdala. PAG is activated during exposure to acute noxious stimuli and chronic pain states, such as CLBP. It exerts a dual inhibitory or excitatory control on the modulation of nociceptive impulses [13,14]. The decreasing rCBF after using gabapentin suggests a change in antinociceptive circuits of PAG. Glutamate is the primary excitatory neurotransmitter of PAG projection and afferent neurons, and local GABAergic neurons cause tonic inhibition of these projections [15]. Gabapentin inhibits the release of neurotransmitters from the presynaptic terminal, which explains its analgesic effects. The decrease in excitability of vlPAG neurons might be due to gabapentin effects on spinal or supraspinal components of the pain pathway [16]. Otherwise, the interpolation of PAG voxels during SPM processing of SPECT images must have decreased rCBF in the cerebellar culmen.

We also found an increase of rCBF in the left ACC in those patients without improvement after using gabapentin. This increase in ACC probably reaffirms that chronic pain patients have a strong involvement of affective-motivational circuits related to pain.

Subsequently, the SPECTs of the 13 patients were divided into two small subgroups, responders and non-responders to gabapentin, compared to a database of healthy volunteers. Non-responders presented decreased rCBF in bilateral frontal (pre-central) and parietal lobes (paracentral, postcentral, and precuneus). The primary somatosensory cortex (S1) is located

in the postcentral gyrus and is responsible for processing sensory-discriminative pain information. S1 is one of the regions that compose the pain matrix, a fluid system consisting of several interacting networks. Pain matrix is activated by painful stimuli sparking cortical nociception (first-order), pain perception (second-order), passing through attention, modulation, neurovegetative control, and which can be modified by beliefs, emotions, and expectations (third-order) [17]. Previous neuroimaging studies showed that this region is activated during acute painful stimuli and chronic pain states such as CLBP [11,18,19]. Kong et al. found enhanced functional connectivity in bilateral S1, M1, and left superior frontal cortex in CLBP patients. They also showed an increased cortical thickness of S1 in CLBP patients compared to healthy controls, which could represent the mechanism of central sensitization and compensation for the constant state of pain [20].

There are many activated and deactivated regions in pain [18],[21]. Interestingly, more areas are deactivated than activated during intense pain [22],[23]. The decreasing rCBF found in the current study involves structures from the DMN, a diffuse network of brain structures activated when individuals are in mental rest and reduce their activity when they concentrate on executing a specific task. The DMN covers the PFC, ACC, precuneus, hippocampus, para-hippocampus, and lateral temporal cortex [24]. Possibly, decreasing rCBF on pre-central regions of frontal and parietal lobes is partially justified by a maladaptive cerebral state during chronic pain, which generates a constant alert and leads to the inactivation of DMN central structures.

Some limitations of this study were the small sample of patients (n=13), even smaller when split into two groups (responders and non-responders). This limitation was partially overcome by the use of multiple voxels for each SPECT image and corrected for multiple comparisons (FWE) on SPM software. The heterogeneity of used previous medications, and our study's short duration are also some points that could be improved. As strong points, we

highlight the homogeneity of the sample regarding the clinical characteristics of pain, the topography of the lesion, and neuroimaging findings. In the literature, we did not find any functional neuroimaging studies that assessed only patients with CLBP caused exclusively by LDH. Most of the available studies evaluated patients with nonspecific low back pain of undetermined etiology, making our study a pioneer in this theme.

CONCLUSIONS

The cerebral SPECT of patients with CLBP secondary to LDH showed an increase of rCBF in the bilateral limbic lobes (anterior cingulate cortex) after using gabapentin. These areas are associated with cognitive modulation and reflect poor pain control due to greater pain intensity. There was a post-treatment decrease of rCBF in PAG that may reflect a reduced firing threshold of PAG neurons, probably related to the effect of gabapentin over the spinal and supraspinal antinociceptive circuits. Non-responders to gabapentin presented a decrease of rCBF in frontal (precentral) and parietal lobes (paracentral, postcentral, and precuneus). These findings could represent a maladaptive state of the brain in patients with chronic pain, which generates a constant alert and leads to the inactivation of DMN central structures. Non-responders also presented an increase of rCBF in the left anterior cingulate, suggesting that CLBP pain patients have a strong involvement of affective-motivational circuits related to pain.

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CONFLICT OF INTEREST/DISCLOSURE

The authors report no conflicts of interest.

AVAILABILITY OF DATA AND MATERIALS

The data sets generated and/or analyzed during the current study are not publicly available due to patient confidentiality reasons but are available from the corresponding author on reasonable request and pending approval from the Ethics Committee of our University Clinical Hospital.

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Contributions

PCP, FD, LWA and ODP contributed to the study conception and design. ACT and LAS contributed to the data processing. PCP, FD, ENL, EBC, VLL and LWA contributed to the data presentation and writing of the manuscript. PCP and LWA contributed to the figures. All authors read and approved the final manuscript.

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ETHICS DECLARATIONS

Ethics approval and consent to participate

Informed consent was obtained from all individual participants included in the study. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Committee of our University Clinical Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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FIGURE TITLES

Figure 1 - Flowchart of the study.

Figure 2 - Effect of gabapentin on rCBF in CLBP patients and in non-responders.

FIGURE LEGENDS

Figure 1 - Flowchart showing the study design of clinical assessment of volunteers, criteria used to define therapeutic response, and referral to SPECT or increased dose of gabapentin.

Figure 2 - Statistical parametric mapping showing rCBF changes in 13 patients under gabapentin treatment for CLBP. Gabapentin increased rCBF in the anterior cingulate in A (coronal, transverse and sagittal planes), and decreased rCBF in posterior regions of the midbrain, pons, and culmen of the cerebellum in B. Comparison between non-responders to gabapentin and healthy volunteers database showed rCBF decrease in non-responders over frontal (pre-central) and parietal lobes (paracentral, postcentral, precuneus regions) in C. Color bars signify Z-scores of the intensity of increase or decrease of rCBF. The results are shown in P values less than 0.05, corrected for multiple comparisons (FWE). Abbreviations: R, right; L, left; A, anterior; P, posterior.