The Use of Intravenous Valproic Acid in Patients with Epileptic Seizures Developing during Radiation Therapy Following Glial Tumor Surgery

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Abstract

Objective: To study the effect of Valproic acid on epileptic seizures developing during radiation therapy (RT) following glioma surgery in patients taking antiepileptic drugs (AED).

Materials and Methods: This prospective observational study involved 879 patients aged 18 - 78 with glioblastomas (GM) who were receiving RT. The patients underwent clinical and neurological examination, electroencephalography (EEG), and neuroimaging tests. After the examination and surgical treatment, patients were prescribed RT. During an RT procedure, the patient has to stay in a steady non-moving position for 30 min. To prevent the patient from developing sporadic or serial seizures during RT, we used Valproic acid administered via the intravenous route. The efficacy and safety of Valproic acid were evaluated together with the outcomes of RT.

Results: Of 879 participants, symptomatic epilepsy was detected in 147 patients (16.7%). An increase in epileptic seizures (even under basic AED therapy) after surgery for GM was noted on days 14 - 21 after the start of RT (i.e. between the 7 and 11th RT session) in 65 of 147 patients (44.2%). The IV administration of Valproic acid allowed all 65 patients to complete the course of RT. No adverse Events associated with the use of Valproic acid were reported.

Conclusion: This observation from our clinical practice allows us to recommend Valproic acid for the treatment of epileptic seizures (focal and generalized) developing during radiotherapy after surgery for GM. The treatment should be accompanied by clinical, neurological and EEG monitoring.

Keywords: Valproic Acid; Valproate; Antiepileptic Drug; AED; Glioblastoma; Serial Seizures; Status Epilepticus; Radiation Therapy

Introduction

Glioblastoma (GM) is the most common and aggressive type of primary brain neoplasm. GM therapy consists of the maximum surgical resection within safe limits, followed by the use of radiation therapy (RT) and chemotherapy (CT) with stemotomy-house.

Epileptic seizures are one of the most common symptoms of hypertensive patients. The appearance, frequency of seizures, their serial status are often observed after surgery on the basis of RT and ICT [1,2]. Valproic acid is used as an antiepileptic drug (AED) in patients with brain neoplasms, since it has low toxicity due to its efficacy and profile [3,4]. Several in vivo and in vitro studies have shown that valproic acid has a radio sensitizing effect in gliomas, and the radioprotective effect of nano-normal brain tissue hippocampal neurons [5]. The results of several retrospective studies have also shown the potential advantage of valproic acid to increase the survival of patients.

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with hypertrophic hypertension [5]. In the literature there are no reports on how to conduct RT in the background of increased EP, which determined the need for this clinical observation. In this work, we studied the use of valproic acid for the intravenous administration of CGM patients after surgical treatment with an increase in EP and the appearance of epileptiform activity (EA) in the background of RT and ICT.

Aim of the Study

The goal is to study the effect of valproic acid in patients with cerebral gliomas of the cerebral hemispheres after surgical treatment and a sharp increase in epileptic seizures on the background of AEP administration during radiation therapy.

Materials and Methods

In the period from 2014 to 2018, a prospective clinical observation was carried out with the participation of 879 patients of 18-78 years old with hypertrophic hypertension who received radiation therapy.

All manipulations in the framework of this work were performed with the informed consent of the patients and in accordance with the ethical standards of the Helsinki Declaration (2000).

The main group consisted of patients in whom the release of RT showed a serial status flow of seizures.

Clinical and neurological examination

A comprehensive examination of patients was performed in the RT department. Clinical and neurological examination consisted of a detailed collection of anamnestic information, an exhaustive description of the structure of epileptic seizures, the dynamics of the development of the disease, beginning with the history of the first paroxysms in accordance with the Classification of the International Antiepileptic League [6].

Attention was drawn to the peculiarities of the main clinical manifestations of epilepsy, the field of surgical treatment for the removal of GM. Their frequency and periodicity were also evaluated. Epileptic seizures are divided into:

1) Frequent - More than two attacks of delay;
2) Daily - From three to five seizures, for it is in vain.

Neurological examination was aimed at the identification of focal neurological disorders, evidence of cerebral dysfunction. The severity of the idioms of focal signs of central nervous system damage was studied in detail.

Electroencephalography

EEG was recorded for all patients at the beginning of RT. Record was made of surface cup electrodes (Fp1; Fp2; F5; F6; F7; F8; C3; C4; P3; P4; O1; O2) established by standard, bipolar methods in the international system “10 × 20”, which was multifunctional neurophysiological complex Nicolet, Bravo program (Nicolet Biomedical, USA). Then the EEG was repeated every three days. With increasing frequency of EP or before their occurrence, as well as with the detection of EA, EEG was performed every other day, throughout the entire subsequent course of radiotherapy. In order to increase the efficiency of the neurophysiological examination, standard or special functional tests (single or rhythmic photo stimulation, 3-5-minute hyperventilation).

The analysis of EEG activity between seizures (interictal EEG) and the time of attack (ictal EEG) was carried out to prove the true focus of bioelectric brain dysfunction. The localization of the epileptic focus and its lateralization was determined.

The analysis of the amplitude-frequency characteristics of the biopotentials of the brain, the state of its excitability, the parameters of the main alpha and beta rhythms, as well as the features of pathological forms of activity was carried out. Convulsive forms of activity (acute waves, “acute-slow wave”, “peak-wave” complexes), slow-wave activity was distinguished. Taking into account the incompleteness

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of the processes of formation of normal rhythms, the main attention was paid to features of epileptic activity, changes in brain excitability, structure and spatial distribution of slow-wave activity taking into account the patient’s age. In the general assessment of EEG, classification was used [7].

**Therapy**

Considering the fact that radiotherapy during the serial course of EP is impossible, since the patient must be within 30 minutes, is in a stationary state, we used valproic acid for intravenous administration. The administration of valproic acid for intravenous administration is safely and well tolerated at an infusion rate of up to 10 mg/kg/min. doses up to 30 mg/kg [8-11]. Transient local irritation due to the rapid administration of undiluted shock doses can cause transient, lacking clinical significance, changes in blood pressure in some patients. The absence of serious side effects from the side of the cardiovascular, nervous systems, liver, side effects and the rapid achievement of therapeutic concentration justify the use of valproic acid for intravenous administration in emergency situations.

**Statistical analysis**

Statistical studies of this work were carried out on the basis of standard methods of boots. We used parametric (Student t) and non-parametric (Kolmogorov-Smirnov, Pearson) information analysis criteria. We used methods for assessing the reliability of differences in indicators of average values, and correlation analysis. The results were considered reliable at p < 0.05. For statistical processing, we used the Excel editor (Microsoft, USA), a statistical analysis software package Statistical 5.0 for Windows (Stat Soft, Inc, USA).

**Results and Discussion**

The duration of RT was 5 - 6 weeks. It should be noted that the increased frequency of EP or their appearance, even in the context of the use of basic AEDs, was noted on the 10 - 21st day from the beginning of RT between 7 - 11 sessions of radiation therapy). On admission, patients received benzodiazepines, valproates, carbamazepine, seizer, topiramate, and becampanel. Anticonvulsants in the post-operative period were prescribed systematically to patients with epileptic seizures or signs of epileptiform activity on EEG [12].

EPs were noted in 147 (16.7%) of 879 (100%) patients who underwent surgery with a GM populator and received RT during the period 2014 - 2018. Of the 147 (100%) patients, in 65 (63.1%), due to the rapid increase in EP, it was impossible to perform RT, since seizures could develop during the RT session. To prevent seizures at the beginning or during the RT session, valproic acid was administered. The duration of the course of radiation therapy was 5 - 6 weeks. It should be noted that the increased frequency of EP or their appearance, even in the context of the application of basic AEDs, was noted on the 10 - 21st day from the beginning of RT. Patients who began to complain of unpleasant sensations noted the appearance of focal neurological symptoms (between the 7th and 9th sessions of RT). EAEG revealed EA.

To reduce perifocal edema and improved nervous system function, defamed zones from 8 - 20 mg/day were prescribed, since it has low mineralocorticoid activity and is actively used in RT. On admission, patients received benzodiazepines, valproate, carbamazepine, seizer, topiramate, paraspinal. Our task was to enable the patient to undergo a course of radiation therapy in the background of a sharp increase in EP. For this purpose, valproic acid for injection was used.

**Clinical example**

Patient A, 36 years old. She considers herself to be a sick person in 2017, when an epileptic aura appeared - a short focal sensory epileptic seizure, proceeding with a preserved consciousness and accompanied by subjective sensations - numbness, tingling, weakness and twitching of the left limbs, 2 - 3 times. The patient lives in the oblast; In October 2017, the frequency of seizures reached 4 - 5 times to the implementer, there was a “contusion” of speech with secondary generalization and the subsequent development of Todd’s paralysis. When contacting a medical institution, the place of residence was assigned valproic acid 500 mg + lamotrigine 200 mg - there was no effect. After 30 days, state changes were not noted. Therapy was corrected: valproic acid 1000 mg + lamotrigine 200 mg, seizure frequency 3 - 4. After five months of treatment, the patient was consulted by a neurologist to clarify the diagnosis. The patient’s EEG is shown in figure 1.
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Brain MRI of the patient is presented in figure 2.

**Figure 1:** EEG record of patient A., 36 years old. Tumour in the posterior parts of the right frontal lobe; Symptomatic epilepsy. Slow activity of the theta range 5\(^\circ\)A with an amplitude of 50 - 70 μV is dominating, bilaterally synchronous bursts with an amplitude higher than 200 μV are recorded throughout the frontal-central-parietal regions without distinct lateralization.

**Figure 2:** MRI scan of patient A, 36 years old. Tumour in the posterior parts of the right frontal lobe.

On September 24, 2017, an operation was performed to remove a tumor of the right frontal lobe. Histological examination revealed anaplastic oligodendroglioma of the III degree. Anaplastic oligodendroglioma are characterized by rapid growth, their cells are significantly different from abnormal cells. Upon admission, isolation of the patient's RT revealed a moderately pronounced left-sided hemiparesis, EPs generalized by the Stood paresis, up to 4 times to the introducer. Considering that the administration of radiotherapy during EC is impossible, since the patient must be within 30 minutes be “immobile” to complete a radiation therapy session (Figure 3 and 4).

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In urgent convulsive conditions, valproic acid was used for blood serum valproic acid for intravenous administration of shock doses - 1500-2000-3000 mg, for 30 - 60 minutes to quickly achieve the appropriate level of AED. the beginning of the RT or during the RT to stop or stop EP. Significant changes in blood pressure, respiratory disorders, electrocardiograms were not noted.

After completing the RT course, valproic acid 2500 mg is recommended.
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Currently, the evidence base for the effectiveness and safety of AEDs, submitted by large-scale controlled studies of patients with focal seizures associated with brain tumors, is limited [9]. Symptomatic treatment, for example, is the same as for focal seizures, taking into account the assumption that the cause is focal brain damage. AED treatment can be started after the first attack. There is no convincing evidence of the effectiveness of preventive treatment. When treating seizures associated with tumors, some important points need to be considered, including the following:

- High relapse rate after the first seizure.
- Hypersensitivity to undesirable effects of AED;
- Disease progression and associated changes in the clinical response;
- Possible interactions between AEDs and anticancer drugs.

As a rule, complete control of seizures is rarely possible. There is no evidence of effective the effectiveness and safety of the AED for a given category of patients, submitted by large controlled studies.

According to scientific sources, the use of valproic acid for intravenous administration seems to be a highly effective and safe method of treating many emergency situations of patients with brain tumors [10-12]. In our study, the use of valproic acid for intravenous administration allowed in 2014 - 2018. complete the course of radiation therapy to all 65 patients in whom an increase in EP was noted.

Conclusion

The observation in the conditions of real clinical practice allows us to recommend valproic acid for the treatment of patients with hypertrophic hypertension and focal epithelium, both focal and generalized, in the context of adjuvant radiation therapy under the control of clinical and neurological examination and EEG.

Conflict of Interests

The authors declare about the absence of conflict of interest with respect to this publication. All authors contributed equally to this article.

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