УДК 612.82: 615.9

# ЭЭГ ПРИ ФАРМАКОЛОГИЧЕСКИМ ВОЗДЕЙСТВИИ У ПАЦИЕНТОВ С БЕССОЗНАТЕЛЬНЫМ СОСТОЯНИЕМ

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РЕЗЮМЕ. Кома является основным синдромом тяжелого отравления. В свою очередь вегетативное состояние представляется вариантом исхода комы. Имеются сведения, что изменение реактивности ЭЭГ на фоне внутривенного введения бензодиазепина позволяет оценивать прогноз для таких пациентов. Известно также, что положительный бензодиазепиновый тест имеет предсказуемость около 50–60%. Целью настоящей работы явилась оценка роли взаимодействия гамма-аминомасляной кислоты (ГАМК) и холинергических систем мозга. В частности, установлено, что последовательные инъекции бензодиазепина и атропина повышают предсказуемость прогноза на 20%. Полученные результаты подтверждают следующую гипотезу. Аномалии ГАМК-холинергического взаимодействия являются одним из механизмов формирования стабильной патологической системы, которая является основой патогенеза вегетативного состояния.

КЛЮЧЕВЫЕ СЛОВА: острое отравление, нейротоксичность, острая мозговая недостаточность, ЭЭГ, биоэлектрическая активность.

# PHARM-EEG IN PATIENTS WITH LONG UNCONSCIOUS STATUS

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ABSTRACT: The main syndrome of severe poisoning is coma. An option of coma outcome is a vegetative state. EEG reactivity due to intravenous benzodiazepines estimates the prognosis for such patients. However, a positive benzodiazepines test has the predictability of about 50–60%. The aim of the work is to assess the role of interaction between gamma amino butyric acid (GABA) and cholinergic systems of the brain. The consequent injections of benzodiazepine and atropine lead to a 20% increase in predictability. The results obtained confirm the following hypothesis. Abnormality of GABA-cholinergic interaction is one of the mechanisms of forming a stable pathological system resulting in the pathogenesis of the vegetative state.

KEY WORDS: acute poisoning, neurotoxicity, acute cerebral insufficiency, EEG, bioelectric activity.

## INTRODUCTION

At the outcome of the comatose period of acute poisoning there may develop so-called vegetative states (VS). In such cases the cerebral deficiency is characterized by restoration of the activity of brain stem structures, but the recovery of consciousness is not observed [1, 2, 4, 10]. For forecasting of the recovery of the central nervous system (CNS) activity of patients in VS authors have used GABA agonists of benzodiazepines [4].

«Vegetative status» is understood as the term a condition described by full absence of comprehension of and surrounding,

accompanied full or partial safety of the vegetative functions adjustable at a level of hypothalamus and brainstem. The VS acts as one of forms of cerebral insufficiency. Pathogenesis ofthis given form of central nervous system (CNS) dysfunction can be most productively described through concept of typical pathological processes in formation of steady pathological systems in CNS. Typical pathological processes in nervous system are the processes which are not having specific the etiological characteristics and carried out at various forms of CNS defeat. Typical processes play a role of base pathogenetic mechanisms at development of cerebral insufficiency.

Pathological changes in nervous system are caused by two typical pathological processes. The first process is an alteration. As a result of this process there is a destruction of anatomic structures of a brain, infringement and break of functional communications. As a result of process of damage there is a decomposition existing in CNS physiological functional systems. Other pathological process is occurrence new integrations from the damaged and again changed formations of nervous system. Arising integration by results of the activity are in overwhelming majority pathological, as not form mechanisms of compensatory-adaptive reactions.

VS formed in an outcome of a sharp poisoning by neurotoxins direct action, have the features of the pathogenesis. At action of straight lines of neurotoxins adamage of «structures-targets» does not occur. So, for example, synaptic poisons contact corresponding ligand. Sharp cerebral insufficiency in which basis loss or on the contrary excessive activation of any transmitter system lays is as a result formed. Except for it there is a failure of mechanisms of inter transmitter interaction. Such decomposition of transmitter systems has been figuratively designated as «transmitter chaos» [9]. Except for direct infringement of transmitter mechanisms undoubtedly important role plays sharp hypoxia as the in the lead mechanism of any sharp poisoning. Presence of the pathogenetic mechanism caused by infringement of transmitter processes allows to allocate VSin an outcome of sharp poisonings by neurotoxinsin separate group. Data of the VShave no in the basis the primary rough organic defect caused or mechanical destruction of a brain, or the diffuse damage caused sharp hypoxiaand an ischemia. As the primary mechanism of formation of a steady pathological condition at a poisoning by neurotoxinsfailure of transmitter mechanisms of regulation acts. It is obvious, that in the further it causes formation new integrations in CNS.

Evaluation of the EEG reactivity at the intravenous injection of benzodiazepines is described as “benzodiazepine test”. The test is considered positive if at the injection of benzodiazepine (e. g., diazepam) the EEG registers an arousal reaction. However, as the experience shows, not all patients with the positive benzodiazepine test demonstrate a recovery of consciousness. The level of wakefulness is to a large extent defined by the functional activity of the ascending reticular activating system [7]. The dominating role in this system is played by the cholinergic mediation. There was formulated a hypothesis that the possibility of consciousness recovery of patients in VS is also defined by the preservation of interaction between GABA-ergic and cholinergic systems.

This research was aimed to make the pharmaco-EEG analysis of interaction between brain GABA-ergic and cholinergic systems of patients in VS at the outcome of acute poisoning.

## METHODS

The research has been performed in the course of treatment of 19 patients with acute poisonings. The criteria of including patients into this study group were as follows: 1) duration of coma for more than 2 days; 2) recovery of spontaneous breathing; 3) absence of consciousness [6].

The monitoring of the brain bioelectric activity was performed on the hardware-software complex “Mitsar-EEG-201” (Russia). EEG was registered in indirect leads by the system “10/20”. The amplitude-frequency parameters of EEG were analyzed in common ranges. The right spectral edge frequency (SEF) is defined as the frequency at which the spectral capacity of EEG reached 50% (SEF-50) or 90% (SEF-90) of total capacity. To evaluate the variability of cardiac rhythm ECG was registered in the second indirect lead along with EEG.

To evaluate the prognosis of consciousness recovery by a patient in VS “the benzodiazepine test” was performed [4]: diazepam in the dose of less than 15 mg was injected under EEG control. The test was considered positive when a reaction of EEG activation (the increase of SEF-90 by more than 4 Hz) appeared. In the absence of any EGG change the result of the test was considered negative.

The estimation of accuracy of changes was performed by the way of calculating the ranged Mann-Whitney T-criterion and the fitting criterion $\chi 2$. To estimate the connectivity of the examined parameters, the Spearman`s rank correlation coefficient was calculated.

The present investigation is approved by local ethical committee.

## RESULTS

The pattern of background EEG of patients in VS was represented by diffuse slow wave activity of delta- and theta-band of average amplitude frequencies. With the prognostic purpose the patients in VS were given diazepam intravenously in the total dose of less than 15 mg with the simultaneous EEG registration (fig. 1). When the reaction of de-synchronization appeared SEF-90 was increased by more than 4 Hz.

Recovery of formally clear consciousness was demonstrated by 12 patients (Table 1). The retrospective analysis demonstrated that the outcome of vegetative state after severe toxic hypoxic encephalopathy was directly correlated to the result of a benzodiazepine test. The Spearman`s rank correlation coefficient between the presence of de-synchronization and the good outcome constituted 0.61.

Therefore, the intravenous injection of benzodiazepine to 18 patients out of 19 in VS caused the distinct reaction of EEG desyncronization: the generalized slow activity was replaced by the

*Table 1*

**Outcomes of vegetative state after severe toxic hypoxic encephalopathy**

| The result of a benzodiazepine test | Outcomes (abs.) | |
|---|---|---|
| | Recovery of consciousness | Permanent VS |
| Positive | 12 | 6 |
| Negative | – | 1 |
| Total | 12 | 7 |

sustainable fast wave activity of alpha- or beta-band of frequencies. However, only in 12 cases out of 18 the recovery of clear consciousness of patients took place. The unicity of the negative benzodiazepine test may be considered a feature of toxic hypoxic encephalopathy. It is shown that even in an unfavorable course of exotoxic coma such patients are characterized by the durable preservation of ECG reactivity as a response to the injection of synaptic-tropic substances [8].

It was noted that the injection of benzodiazepine to a number of patients caused the expressive deceleration of the heart rate (HR). Therefore, in the initial state the average HR was 78±11 beats per minute[1], and after the injection of diazepam — 48±12 beats per minute[1]. This change of reactivity of cardiovascular system is a feature of the somatogenic phase of severe poisoning by neurotoxic substances.

To control the bradycardia, patients got atropine in the dose of 0.5–0.7 ml in 0,1% solution. Depending on the EEG changes, at the injection of atropine there were identified two variants of reactions: 1) the expressed synchronization in theta-band; 2) the absence of reaction (areactivity) and the preservation of beta- and alpha-waves (fig. 2). The data of outcomes of VS in patients are presented in tab. 2.

The received results show that at the preserved reactivity of cholinergic mechanisms, the favorable outcome of VS is not an occasional event. The coefficient of correlation between EEG reactivity at the consecutive injection of benzodiazepine and atropine and the recovery of consciousness constituted 0.73.

Further, probability of consciousness recovery of patients in VS at different variants of pharmacological tests was estimated. With this purpose, the positive predictive value (PPV) of pharmacological tests was calculated as a share (in%) of truly positive results among all positive test values (true-positive and false- positive ones).

The benzodiazepine test was positive in 18 patients out of the 19 who were examined (tab. 1). 12 patients recovered clear consciousness. It means that in 12 cases the benzodiazepine test gave the true-positive result and in 6 observations the result was false-positive. As a result, the positive predictive value of the benzodiazepine test in the observed group constituted 66%.

Injection of atropine to patients with the true-positive benzodiazepine test brought about the following results. In

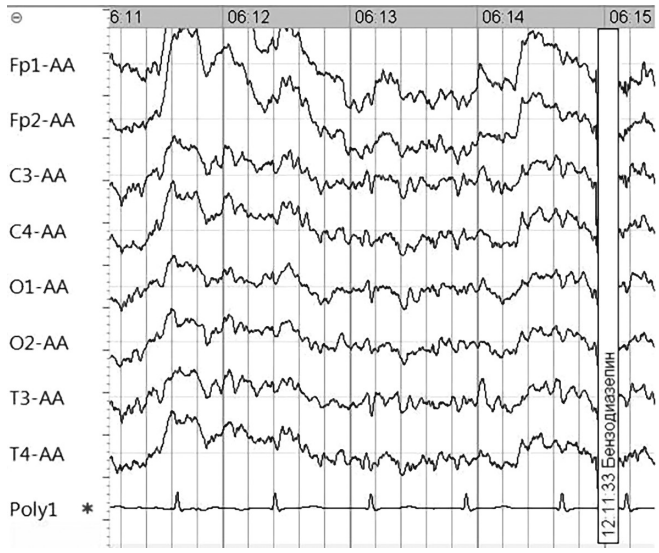


**Fig. 1. EEG of a patient during vegetative state till the injection of diazepam. The vertical mark is the end of intravenous injection. $Fp_1$, $C_3$, ..., $T_4$ — sites on system 10/20; the lower channel is the registration of the electrocardiogram**

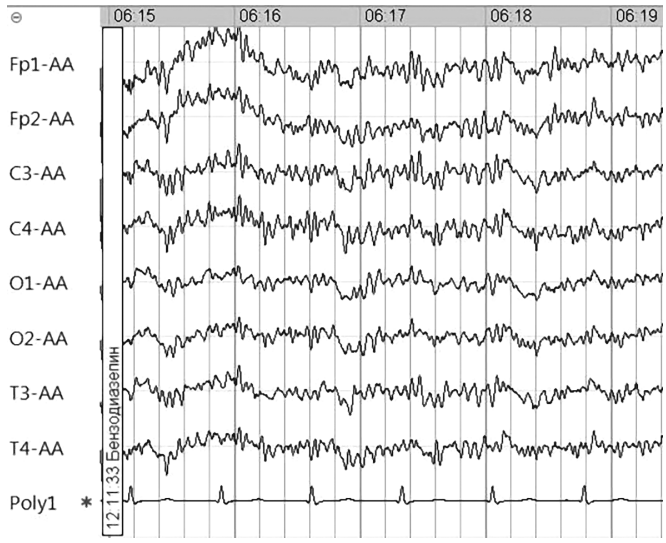


**Fig. 2. EEG of a patient (samecase, see fig. 1) during vegetative state after the injection of diazepam. The vertical mark is the end of intravenous injection. EEG de-synchronization at the end of injecting diazepam. $Fp_1$, $C_3$, ..., $T_4$ — sites on system 10/20; the lower channel is the registration of the electrocardiogram**

12 cases the patients` desynchronization of bioelectric activity was replaced by synchronization in theta-band (tab. 2). In 10 cases such patients demonstrated recovery of consciousness. These facts consider the reaction of synchronization as a response to the injection of atropine to be the positive result of the test. As a result, the prognosis of the criterion “the pres-

*Table 2*

**EEG reactivity of patients in vegetative status with severe toxic encephalopathy**

| A benzodiazepine test | An atropine test | Outcomes (abs.) | |
|---|---|---|---|
| | | Recovery of consciousness | Permanent VS |
| Positive | Synchronization | 10* | 2 |
| | Reactivity | 2 | 4 |
| Negative | | – | 1 |
| Total | | 12 | 7 |

*Note. * — p<0.05.*

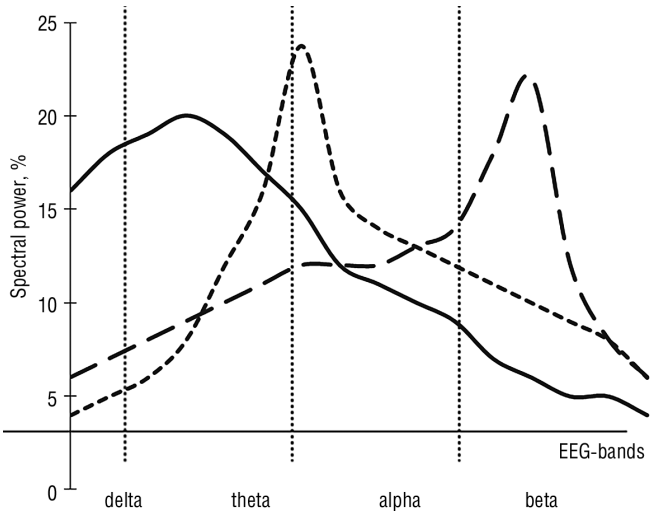


**Fig. 3. The changes of EEG spectral structure of patients in vegetative status at the consecutive injections of diazepam and atropine (scheme)**

ence of the EEG phase reaction at the consecutive injections of benzodiazepine and atropine" in the examined group constituted 85%.

## DISCUSSION

The analysis of EEG-reactivity at patients with long unconsciousnesses at introduction GABA-agonists and cholinergic antagonists allows to estimate a condition of the intracentral attitudes (table 3). During benzodiazepine test positive and negative results are possible. At positive benzodiazepine test introduction of atropine is possible. It supportdichotomic reaction: change of the desynchronization on synchronization in a teta-waves and absence of reaction on cholinergic antagonist (preservation of the benzodiazepine desynchronization). Thus, possible variants of responses reflect changes in mechanisms of EEG generation. Introduction of the GABA-agonist for benzodiazepine in a greater degree changes a condition of thalamic-cortical interactions and pharmacological blockade of the cholinergic system reduces activity of the brainstem reticular formation [6, 10].

Absence of EEG desynchronization at benzodiazepine introduction, most likely, testifies to disintegration cortical departments both with thalamic structures and with brainstem reticular formation. Dissociation of the cortical-reticular circuits, dissociation of the diencephalic structures and cortex does impossible awakening. This assumption, actually, will completely be coordinated with results, that at the negative benzodiazepine test restoration of consciousness at patients with VS practically does not occur [5, 7].

During EEG-activation caused by benzodiazepine introduction, is not stopped by introduction of the atropine's cholinergic antagonists, it is necessary to assume, that functional brainstem — diencephalic dissociation structures takes place also. It is probable, that the leading mechanism of this pathological condition is decomposition of GABA-cholinergic and cholinergic transmitter systems. As a source of the EEG desynchronization, possibly, thus act adrenergic projections of a blue spot of a brainstem rostral part.

*Table 3*

**Variants of the EEG-reactivity during pharmacological tests at patients with long unconsciousnesses**

| | Variants of EEG changes/Pathogeneticmechanisms | | | |
|---|---|---|---|---|
| Benzodiazepine introduction | Desynchronization | | Absence of EEG-activation | |
| Atropine introduction | Synchronization | Absence of synchronization | – * | – * |
| Condition of mechanisms of EEG | Normal integration | Disintegrationof-brainstem — diencephalic structures | Disintegrationof-brainstem — diencephalic structures with cortex departments | |

Note. During negative benzodiazepine test introduction of atropine was not carried out.

In decomposition of transmitter systems can result not so much anatomic damage ascending cholinergic projections, how many decrease in sensitivity of the GABA-ergic neurons to acetylcholine. This reflection of the general process of change of reactance at a chemical trauma has designated as allobiosis condition.

## CONCLUSION

The injection of atropine having the central cholinolytic influence, when a certain level of generated bioelectric activity mechanism is preserved, caused a block of the de-synchronization reaction conditioned by the injection of diazepam. At the basis of the EEG activation phenomenon observed at the injection of benzodiazepine, there is a change of balance between the synchronizing and desynchronizing systems of generated bioelectric activity. The injection of a GABA-agonist diazepam caused suppression of activity of thalamus relay neurons that led to the suppression of synchronizing influences and conditioned a relative prevalence

of the activity of desynchronizing system. Consequently, the EEG activation registered at this point was caused not by the direct action of benzodiazepines, but by a relative increase of the activity of the cholinergic desynchronizing system.

The received results of the pharmacological analysis confirm the hypothesis saying that the probability of the consciousness recovery is to a large extent determined by preservation of intertransmitter interaction, as its abnormality is one of the mechanisms of the formation of the sustainable pathological system.

The usage of the methodology of consecutive injections of benzodiazepine and central anti-cholinergic drug increases the prognostic ability of pharmacological testing of patients with the durable unconsciousness. The results of the pharmacological test with the consecutive injections of benzodiazepines and atropines may be divided into the following variants: 1) positive ones — phase change of bioelectric activity (desynchronization — synchronization); 2) negative ones — absence of response to the injection of benzodiazepine; 3) doubtful ones — desynchronization occurring at the injection of benzodiazepines is preserved at the injection of atropine.

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