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BENZODIAZEPINES: THE MAJOR REPRESENTATIVES AND THEIR PHARMACOLOGICAL SIGNIFICANCE

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Benzodiazepine tranquilizers, which appeared later than neuroleptics and antidepressants, have undergone both a colossal rise in popularity and an equally large-scale decline in their short time. The first benzodiazepine, chlordiazepoxide, was synthesized in 1955 by Leo Sternbach as a result of the search for methods for the synthesis of tranquilizers. In less than 10 years, this class of drugs has occupied more than 90% of the market, which was previously dominated by barbiturates. Although benzodiazepines have good anxiolytic properties, side effects were discovered quite quickly during therapy with this group of drugs: it was shown that benzodiazepine tranquilizers can enhance the withdrawal syndrome of alcohol and barbiturates. However, the main undesirable effect that prevented the promotion of benzodiazepines not only in the pharmaceutical markets, but also in clinical practice, was the risk of addiction. Currently, benzodiazepine drugs continue to be widely used not only by psychiatrists in the treatment of mental and anxiety disorders and withdrawal syndrome, but also by general practitioners. We conducted a brief review of information on the pharmacological significance of the main representatives of benzodiazepines, their application features and the consequences of their administration.

Keywords: benzodiazepines, tranquilizers, anxiolytics, chlordiazepoxide, diazepam, nitrazepam, oxazepam, alprazolam, flunitrazepam, clonazepam

Introduction. The term “benzodiazepine” means the chemical name of a heterocyclic compound formed by combining a benzene and diazepine ring system. According to the Ganch-Widman nomenclature, diazepine is a heterocycle with two nitrogen atoms, five carbon atoms and the maximum possible number of cumulative double bonds. The prefix “benzo-” denotes a benzene ring connected to a diazepine ring.

Benzodiazepines are drugs that slow down the reaction of the central nervous system, thereby creating a feeling of peace and relaxation.

Commonly known as “benzos”, benzodiazepines discovered by chance in the mid-1950s were adopted by medical professionals as a safer alternative to barbiturates. By the early 1960s, these medications were being used to treat problems such as anxiety, panic disorder, insomnia, muscle spasms and seizures. They are intended only for short-term treatment, as they are extremely addictive [1].

Relevance. Benzodiazepines are a large group of drugs that have anti–anxiety, sedative and hypnotic effects. In addition, drugs from this group promote muscle relaxation, preventing the appearance of muscle cramps. Benzodiazepines are prescribed to eliminate physiological and psychological manifestations of anxiety, to combat the consequences of a violation of the autonomic system (heaviness in the stomach, excessive sweating, blood flushes), alertness, anxious premonitions, fears, pathological manifestations from the muscles.

In recent years, the problem of dealing with stress, anxiety, panic attacks has become a very topical issue. The life of a modern person is very fast and active, so it is almost impossible to avoid stress. Benzodiazepines have proven to be the most effective and safe drugs – they are low-toxic, cause less dependence compared to alcohol or barbiturates, in therapeutic doses does not cause motor disorders or depression [2].

Purpose of research. To study the list of Russian and foreign sources describing the principle of action of benzodiazepines, their pharmacological features, the consequences of their use and effects on the human body.

Materials and methods of research

To study the features of the use of benzodiazepines, we have worked out a list of Russian and foreign sources containing reliable and officially confirmed information about the pharmacological and chemical features of drugs based on benzodiazepines, as well as their most important representatives.

Research results and their discussion

Benzodiazepines have a similar chemical structure, and their effect on the human body is mainly due to allosteric modification of a special type of neurotransmitter receptors, GABA receptors, which increases the conductivity of this inhibitory channel. This leads to both therapeutic and side effects of benzodiazepines. At the same time, the targets of anxiolytics are the limbic system of the hypothalamus, the reticular formation of the brain stem, and the thalamic nuclei. Dependence on benzodiazepines can occur with prolonged use of drugs or with a constant overdose. The patient may feel that the effect of taking it is insufficient, and he will constantly increase the dose in order to get rid of

unpleasant symptoms completely – this is how dependence is formed during overdoses [3].

Symptoms of overdose with benzodiazepine derivatives resemble a picture of barbiturate intoxication. There is lethargy, drowsiness, muscles relax, coordination is disrupted. At the same time, fussiness, activity, mood lifting may sometimes occur, all this is accompanied by inhibition of reactions, difficulties in switching attention. In appearance, drug addicts resemble people in a state of strong alcoholic intoxication. A few hours after taking the drugs, intoxication turns into lethargy, weakness, the patient falls asleep. During the day, all residual effects disappear.

Benzodiazepines and their active metabolites bind to plasma proteins. The degree of binding significantly depends on lipophilicity and ranges from 70% for alprazolam to almost 99% for diazepam. The concentration of free benzodiazepines in the liquor is about the same as in plasma. Benzodiazepines can compete for plasma proteins with other drugs, but clinically significant interactions have not been described [4].

There are a large number of benzodiazepine derivatives, among which chlordiazepoxide, diazepam, nitrazepam, oxazepam, alprazolam, flunitrazepam, clonazepam and others can be distinguished.

1. Chlordiazepoxide. After ingestion on an empty stomach, up to 75% is absorbed in the gastrointestinal tract. The maximum concentration in the blood plasma is reached after 0.5-4 hours. The bond with plasma proteins is 96%. Deposited in adipose tissue. Penetrates through the blood-brain and placental barrier, enters breast milk [5].

Metabolism in the liver is carried out with the formation of four active metabolites: oxazepam (half-elimination period of 5-15 hours), desmethyl chlordiazepoxide (half-elimination period of 8-24 hours), demoxepam (half-elimination period of 14-95 hours) and desmethyldiazepam (half-elimination period of 40-250 hours). Elimination is performed by the kidneys [6].

2. Diazepam. After ingestion on an empty stomach, up to 75% is absorbed in the gastrointestinal tract. The maximum concentration in the blood plasma is reached after 90 minutes. The bond with plasma proteins is 98%. It is deposited in adipose tissue. Penetrates through the blood-brain and placental barrier, enters breast milk. Metabolism in the liver occurs with the formation of active metabolites in the form of desmethyldiazepam with a half-elimination period of 40-250 hours. The half-life is 24-48 hours. Elimination of the drug is carried out by the kidneys [5].

3. Nitrazepam. It is absorbed from the gastrointestinal tract quickly and in full. Bioavailability is 54-98% (depending on the dosage form). When taken simultaneously with food, absorption slows down and the maximum plasma concentration decreases by about 30%. With a single oral administration of 10 mg of nitrazepam, the average maximum concentration is 0.08-0.1 mcg / ml and is reached after 1-4 hours. The bond with plasma proteins is approximately 85-90%. The phase of distribution of the active substance in the body varies greatly and ranges from 1.7 to 3.5 hours. The volume of distribution increases with the age of patients and is 1.3-2.6 l/kg. It penetrates well through histohematic barriers, including blood-brain and placental barriers, and is found in mother's milk. It is metabolized in the liver by reducing the nitro group and subsequent acetylation with the formation of inactive acetyl derivatives. The half–life is 16-48 hours (depends on the age and body weight of patients), from the cerebrospinal fluid – about 68 hours. The main metabolites are 7-aminonitrazepam, 7-acetaminonitrazepam, 2-amino-5-nitrobenzophenone and hydroxy-2-amino-5-nitrobenzophenone, excreted by the kidneys (65-71%) and with feces (14-20%). About 1-5% is excreted unchanged by the kidneys. Accumulation during repeated administration is minimal (refers to benzodiazepines with a short or medium half–life), excretion after discontinuation of treatment is rapid [6].

4. Oxazepam. Absorption after oral administration is achieved within 2 hours in full. Binds to plasma proteins by 97%, biotransformation in the liver is carried out by direct conjugation with glucuronic acid to inactive metabolites, the half-life is 5-15 hours. It is excreted by the kidneys and gastrointestinal tract. The drug passes through the blood-brain barrier, placental barrier and penetrates into breast milk [7].

5. Alprazolam. A derivative of benzodiazepine of medium duration of action, causes central nervous system depression from mild sedation to coma, depending on the dose. Absorption after ingestion is rapid and occurs within 2 hours. It can pass through the placenta, the blood-brain barrier, and penetrate into breast milk. The bond with plasma proteins is 80%. It is metabolized in the liver by hydroxylation to low-activity (≤ 1/2 of alprazolam activity) or inactive metabolites. Elimination by the kidneys (in the form of compounds with glucuronic acid). Accumulation during repeated admin-

istration is minimal (refers to benzodiazepines with an average half-elimination period), elimination after discontinuation of treatment is rapid. After withdrawal, the plasma concentration decreases to subclinical within 24 hours. It is not removed during hemodialysis [8].

6. Flunitrazepam. After oral administration at a dose of 1 mg, the maximum concentration is noted after 0.75-2 hours and is 6-11 ng / ml. Bioavailability reaches 70-90%. Eating reduces the rate and degree of absorption. Binding to blood proteins is approximately 78%. Daily intake is accompanied by moderate plasma accumulation. With repeated administration, the equilibrium concentration of flunitrazepam in plasma is reached after 5 days and at a dose of 2 mg is at least 3-4 ng / ml. The equilibrium concentration of pharmacologically active N-demethylmetabolite is almost identical to that of the starting substance. The volume of distribution in the equilibrium state is 3-5 l/kg. Quickly penetrates into the cerebrospinal fluid. Slowly passes through the placental barrier, penetrates into breast milk. It is metabolized in the liver (10-15% at the first pass). The main metabolites in plasma are 7-aminoflunitrazepam and norflunitrazepam, in urine – 7-aminoflunitrazepam. It is excreted mainly by the kidneys mainly in the form of metabolites and with feces. The half–life of flunitrazepam is 16-35 hours, the half-life of norflunitrazepam is 28 hours. Reduces excitability of subcortical structures of the brain, inhibits polysynaptic spinal reflexes. The hypnotic effect develops quickly and lasts 6-8 hours. It also has a sedative, anxiolytic, muscle relaxant (central) and anticonvulsant effect. Reduces psychomotor activity, causes amnesia [7].

7. Clonazepam. Clonazepam is well absorbed from the digestive tract. Oral bioavailability is 90%. When ingesting a single dose of the drug, the maximum concentration in the blood serum is observed after 1-4 hours. Clonazepam binds approximately 85% to blood proteins. The drug passes through the blood-brain and placental barriers, also penetrates into the mother's milk. The volume of distribution is 1.8-4.4 l/kg. It is metabolized in the liver to pharmacologically inactive metabolites. The half-life is 20-60 hours. It is excreted mainly in the urine in the form of metabolites. Less than 0.5% of the dose of the drug is excreted unchanged by the kidneys [8].

At the moment of reaching the maximum serum concentration, hypnotic doses of benzodiazepines to one degree or another cause nausea, fatigue, impaired coordination of movements, slowing of reaction, deafness, anterograde amnesia. Cognitive functions suffer less than motor functions. If the drugs are taken at night, the preservation of these phenomena after waking up is considered as a side effect. They can greatly interfere with driving and other activities; it is extremely dangerous to drink alcohol at the same time. The severity of these disorders clearly depends on the dose, but a person may not notice them: most patients underestimate how far their condition is from the norm. Daytime drowsiness can also be a side effect, although treatment reduces drowsiness caused by chronic insomnia. The risk and severity of side effects increase with age; age-related changes in both pharmacokinetics and pharmacodynamics play a role here [4, 7].

Despite the listed side effects, benzodiazepines are relatively safe. In the absence of other drugs, even very high doses rarely lead to death or coma. Death from benzodiazepines is often caused by the simultaneous use of alcohol. An overdose of benzodiazepines rarely causes severe respiratory and circulatory disorders, but even normal doses can exacerbate respiratory failure in chronic obstructive pulmonary disease and obstructive sleep apnea.

The differences between the doses of benzodiazepines that cause motor disorders and disinhibition strongly depend on the drug, the type of animal and the scheme of experience. Although these differences may have contributed to the market promotion of some benzodiazepines as selective tranquilizers and hypnotics, they did not predict the sedative activity of benzodiazepines used as anxiolytic drugs [8].

Benzodiazepines suppress epileptic seizures caused by pentetrazole and picrotoxin, but seizures caused by strychnine and high-voltage current are prevented only in doses that sharply disrupt motor activity. In clonazepam, nitrazepam and nordazepam, anticonvulsant activity is more selective than in other drugs. Benzodiazepines also suppress photogenic seizures in baboons and seizures with alcohol withdrawal syndrome in humans. Unfortunately, tolerance to anticonvulsant action limits the use of benzodiazepines in epilepsy.

Benzodiazepines have an analgesic effect in animals, but in humans there is only a transient analgesic effect with intravenous administration of these drugs, which in fact may be due to amnesia. There is no doubt, however, that benzodiazepines, unlike barbiturates, do not cause hyperalgesia [9].

Benzodiazepine drugs are widely used in the treatment of patients with bipolar affective disorder, schizophrenia or other psychotic disorders. They are prescribed mainly as an addi-

tional therapy to neuroleptics or mood stabilizers in order to achieve a short sedative effect to reduce the symptoms of manic or psychotic arousal, aggression, behavioral disorders or sleep problems. Currently, there is insufficient reliable data in the literature on the effectiveness of benzodiazepine derivatives in anxiety and depression in patients with schizophrenia. A number of studies warn of the need for a more scrupulous analysis of the effectiveness of drugs as monotherapy for aggression and agitation caused by psychosis, and indicate that their benefits as an additional therapy are difficult to assess due to the large number of side effects available, as well as the insufficient quality of comparative studies. Despite this, some recommendations allow the use of benzodiazepines with similar symptoms in this group of patients [7].

Using benzodiazepines in old age leads to other side effects, including constipation, urinary retention, an increase in the number of car accidents, especially when benzodiazepines are combined with antidepressants, and earlier death. An atypical reaction to benzodiazepines in the form of psychomotor agitation, hallucinations and delirium is also more typical for the elderly [9].

Conclusion

Analysis of literature sources has shown that long-term use of benzodiazepines can lead to addiction and abuse. At the same time, their risk of occurrence is lower than in the case of barbiturates and narcotic analgesics.

The main side effects of benzodiazepine tranquilizers, manifested against the background of abuse or non-medical use of drugs of this group, include hypersedation (drowsiness, decreased concentration, memory problems), hypermyorelaxation (lethargy, muscle weakness), behavioral toxicity (impaired cognitive functions and psychomotor skills), paradoxical reactions (agitation, aggressiveness, sleep disorders), addiction (mental and physical dependence with manifestations of neurotic anxiety). Constant intake of benzodiazepines leads to the formation of tolerance – in order to achieve the desired state of euphoria, an increasing dose is required each time. Prolonged abuse of benzodiazepines often causes personality disorders – facial expressions become impoverished, memory is impaired, speech and movements slow down, intelligence suffers, a person becomes more selfish, cruel, callous towards others, rude. The longer the patient takes benzodiazepines, the worse he tolerates physical and mental stress, the less he wants to work and observe moral norms.

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