Acute poisoning with neurotropic drugs (benzodiazepines, barbiturates, neuroleptics, antidepressants) - features of the cerebrodepressive syndrome, clinical course, criteria for diagnosis, differential diagnosis. Principles and methods of treatment.

Neurotoxicity is a form of toxicity in which a biological, chemical or physical agent causes an adverse effect on the structure or function of the central and / or peripheral nervous system. This occurs when exposure to a substance - particularly a neurotoxin or neurotoxicant - alters the normal functioning of the nervous system in such a way as to cause permanent or reversible damage to the nervous tissue. This can eventually disrupt or even kill neurons. Symptoms may appear immediately after exposure or be delayed. These may include weakness or numbness of the limbs, loss of memory, vision and / or intelligence, uncontrollable obsessive and / or compulsive behavior, delusions, headaches, cognitive and behavioral problems.

Neuroleptics

Neuroleptics / antipsychotics are drugs used to control psychosis with their specific symptoms - most often schizophrenia and mania. Schizophrenia is a severe mental illness with a chronic recurrent course. It occurs with a disorder in perceptions, thinking and behavior. "Positive" symptoms dominate in acute episodes of the disease and include hallucinations (mostly threatening auditory), delusions, abnormal behavior. As the disease progresses, the "negative" symptoms deepen - social isolation, lack of motivation, emotional dullness. Gradually, cognitive deficits develop, affecting memory and attention.
Neuroleptics are classified into two main groups - typical and atypical. Typical neuroleptics are phenothiazines (chlorpromazine), thioxanthenes (chlorprothixene), butyrophenones (haloperidol) and diphenylbutylpiperidines. Atypical neuroleptics are clozapine, olanzapine, quetiapine.
All neuroleptics block D2 dopaminergic receptors in the CNS; affect the main dopaminergic systems in the brain and their functions. By blocking D2 receptors, neuroleptics exert their specific effect primarily on 'positive' symptoms. Their action on other dopaminergic pathways is associated with adverse reactions, mainly extrapyramidal.
Atypical neuroleptics are less likely to cause extrapyramidal disorders, have therapeutic activity against "negative" symptoms, favorably affect cognitive symptoms due to higher affinity for 5-HT2A receptors.
Neuroleptics are taken orally and parenterally. Variable resorption through GIT. High lipophilicity - wide distribution in tissues and large volume of distribution. They are metabolized in the liver and some of the metabolites are active substances. They are excreted in urine and faeces. The plasma half-life of neuroleptics is typically long (> 20 hours).
In case of intoxication with neuroleptics, the symptoms are expressed in the strengthening of their clinical effect.
Extrapyramidal disorders - affect the motor area.

They are due to the blocking of dopaminergic receptors in the nigrostatic system. They are improved by cholinolytic antiparkinsonian drugs. Symptoms: muscle spasms affecting the orofacial muscles, inability to remain still. Hypertension, CNS depression - from sedation and confusion to coma and loss of cerebral stem reflexes.
Treatment: CPR, gastric lavage, muscle relaxants / benzodiazepines, Akineton (anticholinergic) to affect EPD symptomatically.
Neuroleptic malignant syndrome: muscle rigidity, hyperthermia, tremor, autonomic instability, altered mental status. Serum creatine kinase and myoglobin levels are elevated.
Treatment: CPR, muscle relaxants, symptomatic.

Antidepressants

Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being.
A major depressive episode is a period characterized by symptoms of major depressive disorder: major depressed mood for two weeks or more and loss of interest or enjoyment of daily activities accompanied by other symptoms such as emptiness, hopelessness, anxiety, uselessness, guilt and / or irritability, changes in appetite, difficulty concentrating, memorizing details or making decisions and thoughts or suicide attempts. Insomnia or hypersomnia, aches, pains or digestive problems that are resistant to treatment may also be present.
Leading imbalance of neurotransmitters - low levels of serotonin / norepinephrine / dopamine in the cortical / limbic areas.
Classification of antidepressants:
-monoamine oxidase inhibitors (MAOIs) (moclobemide, phenelzine)
-tricyclic antidepressants (amitriptyline)
-selective serotonin reuptake inhibitors (fluoxetine)
Antidepressants are lipophilic and cross the blood-brain barrier. They have good absorption after oral administration and reach peak plasma concentrations 1-8 hours after administration. They are metabolized mainly in the liver by oxidation and glucuronidation. Most antidepressants have a high degree of plasma protein binding.
The administration of antidepressants leads to an increase in serotonergic and / or norepinephrine mechanisms by suppressing the reuptake of monoamines and a corresponding increase in the level of monoamines in the synapse.

MAOIs

They inhibit the enzyme monoamine oxidase and thus increase the availability of norepinephrine, serotonin and dopamine in the brain and peripheral tissues. MAOIs increase the concentration of monoamines in the nerve endings, which leads to a rapid increase in motor activity and excitation.
Symptoms include: hypotension, tremor, restlessness, insomnia and convulsions in case of overdose. Cheese syndrome - when eating foods containing tyramine (cheese, wine, beer, nuts) - severe hypertension and throbbing headache.
Treatment: CPR, gastric lavage, symptomatic

Tricyclic antidepressants

They block the uptake of amines by nerve endings, competing for the binding site of the amine transporter. They mainly inhibit the uptake of norepinephrine and serotonin. Other receptors such as M-cholinoreceptors may also be affected.
Symptoms of overdose are due not only to serotonin-like syndrome, but also to their anticholinergic effect.
Cerebrotoxic syndrome: impaired coordination, impaired consciousness to coma, convulsive or equivalent seizures at any attempt to touch the patient, hyperthermia
Cholinolytic syndrome: mydriasis, tachycardia psychomotor agitation to delirium altered consciousness with hallucinations, urinary retention (spasm of the bladder sphincters!)
Cardiotoxic: direct toxic action with heart rhythm disorders, repolarization and conduction with various ECG characteristics: tachyarrhythmia, terminal bradycardia, idioventricular rhythm, atrial fibrillation and oscillation, ventricular extrasystoles, AV block, asystole, exotoxic shock, arterial hypotension.
Treatment: Stabilization of impaired hemodynamics, symptomatic treatment of cardiotoxic lesions (antiarrhythmics, pacemakers, etc.), control of seizures with Diazepam, Phenobarbital, gastric lavage with charcoal solution, circulatory and respiratory resuscitation.
-alakalization with NaHC03 1mmol/kg if symptoms of cardiac toxicity present
*QRS>120ms
*tachycardia>100/min

Selective serotonin reuptake inhibitors

They block the reuptake of serotonin and increase its effect on the synapse.
Symptoms: nausea, headache, sedation.

Serotonin / norepinephrine reuptake inhibitors

Symptoms: convulsions, seizures, cardiac dysrhythmia

Serotonin syndrome

Serotonin syndrome occurs when taking drugs that cause the accumulation of too much serotonin in the body. Symptoms are observed in the brain, muscles and other organs. Milder forms of serotonin syndrome may disappear within a day of stopping the drugs that cause it. However, severe serotonin syndrome can cause death if left untreated.

Symptoms can range from mild to life-threatening. The following complaints are observed:

• confusion, disorientation

• restlessness, irritability

• headache

• myoclonus - muscle contraction

• muscle rigidity

• tremor

• enhanced reflexes

• nausea, vomiting, diarrhea

• sweating

• chills

• increased heart rate

• dilated pupils

In severe serotonin syndrome there is a high temperature above 40 ° C, seizures, arrhythmia, delirium, loss of consciousness.

Treatment: In mild serotonin syndrome, it is sufficient to stop taking the drugs that cause the problem. Symptoms often disappear within 24 to 72 hours.

In severe serotonin syndrome, the patient should be hospitalized. Appointed:

• rehydration - intravenous infusion of fluids

• muscle relaxants - drugs that relieve muscle tension

• benzodiazepines - drugs that affect anxiety, seizures

• medicines that block the production of serotonin - cyproheptadine.

Sedativ/hypnotics

Anxiolytics are drugs that have a calming effect, remove mental tension and feelings of insecurity. They suppress fear, anxiety and sleep disorders, unlike most hypnotics, even in large doses they do not cause anesthesia (the condition in which the body is during anesthesia).

They have no antipsychotic effect and are used mainly for the treatment of neuroses. As they potentiate (enhance) the action of general anesthetics, hypnotics and analgesics, they are used in anesthesiology, neurology and internal medicine.

Barbiturates are CNS depressants that are used as anticonvulsants, sedatives, hypnotics and anesthetics. Barbiturates are derivatives of barbituric acid, which by itself does not have a direct effect on the central nervous system (CNS). In contrast, barbiturates act directly on the brain and CNS.

The strength of the action of barbiturates depends on the individual characteristics of the patient, such as age, body weight, health status, as well as the dose taken. They suppress the respiratory center.

Types of barbiturates

There are many different types of barbiturates. The main difference between them is in the duration of their action. Some of them have a prolonged action and their effect can last up to

two days (the most notable of which is phenobarbital - up to 92 hours), unlike others that have a very short action - only a few minutes (thiopental).

The other significant difference is in the speed of onset of action - some barbiturates have an extremely fast-acting effect, which makes them suitable for emergency surgery.

Mechanism of action - GABA agonists - bind to the GABA receptor and potentiate the influx of chlorine ions - hyperpolarization, enhance the inhibitory effect of GABA.

Barbiturates can be administered by injection - intramuscularly or intravenously, taken in tablet form or administered in the form of suppositories. They are well absorbed when taken orally. Plasma protein binding is different - phenobarbital - 20%, thiopental - 75%. They are metabolized in the liver. Urinary excretion.

Symptoms: Cerebrodepressive - slow / slurred speech, ataxia, from somnolence to coma, miosis, hypotension, tachycardia, shock, respiratory arrest.

Treatment: Barbiturates do not have a specific antidote. Non-specific - Nootropil, Vitanin B complex, Centrophenoxin.

Forced alcaline diurrhesis as they are weak acids

Haemodyalisis

Gastric lavage + activated charcoal. Symptomatic treatment.

Benzodiazepines are widespread and are commonly abused. They can be oral and intravenous - diazepam, midazolam, lorazepam.

They are lipophilic. Rapid absorption, greater volume of distribution - binding to plasma proteins. Metabolism - in the liver. They are eliminated in the urine.

Mechanism of action - bind to the GABA receptor and potentiate the influx of chlorine ions - hyperpolarization, enhance the inhibitory effect of GABA.

Symptoms: Quantitative disturbances of consciousness from somnolence to coma dominate. Ataxia, dystonia, dyskinesia, dyslexia, retrograde amnesia. In more severe cases - hemodynamic instability and respiratory arrest.

Treatment: CPR, gastric lavage + activated charcoal. Symptomatic treatment.

Antidote: flumazenil
Considered in acute BZD poisonings in BZD naïve patients or for reversal of unintentional BZD overdose/oversedation
ampules 0,5mg/5ml

start with 100mcg increments every 30-40secs to reverse the BZD effect, in severe poisonings dose needed might be up to 2mg
If no effect think of other cause of CNS depression

careful in patients on regular treatment with BZD as rapid flumazenil injection could trigger a seizure diffucult to manage