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CLINICAL PHARMACOLOGY OF ANESTHETIC AGENTS AND LOCAL ANESTHETICS

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Abstract: This article provides detailed information about the methods used for anesthesia, their types, mechanism of action, and duration of action. In addition, this article provides detailed information about the procedure, types, mechanism of action and duration of action of local anesthetics.

Key words: narcosis, anesthetics, enteral, parenteral, local anesthetics, blockades, succinylcholine,

Clinical pharmacology of MA.

Currently, ester MAs are not used in our country for neuraxial blockades, therefore, when discussing the advantages and disadvantages of modern MAs, we will talk mainly about amide anesthetics. The intermediate-acting anesthetic lidocaine (Xylocaine), as well as the long-acting MAs bupivacaine (Marcaine) and ropivacaine (Naropine), are available in clinical practice today.

As is known, the main clinical characteristics of MA are:

-power
-speed of development of the effect (latent period)
-duration of action
-toxicity

The physicochemical properties of MA (which, in turn, depend on the chemical structure) largely determine their potency, toxicity and clinical effectiveness.

Systemic absorption of MA

The duration of neuronal blockade, as well as the manifestations of systemic toxicity, largely depend on the rate of systemic absorption of MA from the point of its administration. The degree of vascularization of the area of the body into which the drug is injected affects the rate of its absorption into the systemic circulation, as well as the peak plasma concentration. The value of the latter can be presented in the following order: with intrapleural block > intercostal block > lumbar EA > brachial plexus block from the axillary approach.

Factors influencing the rate of absorption are the degree of ionization of the drug (pK), its lipid solubility, ability to bind to plasma proteins, as well as the nature of vascularization and perfusion of surrounding tissues. In addition, the rate of absorption of MAs is influenced by the

degree of their vasodilating effect. It is generally accepted that all MAs, with the exception of cocaine, are vasodilators. This effect is especially pronounced in lidocaine, which makes it advisable to add adrenaline to prolong its action. It was recently established that ropivacaine has its own vasoconstrictor effect, so the duration of its action does not depend on the addition of external vasoconstrictors.

In late pregnancy, the initial peak plasma concentration of LA may be higher than normal. Due to hormonal changes, increased permeability of tissue membranes to LA, decreased binding of MA to plasma proteins, and their increased cardiotoxicity against the background of increased progesterone synthesis increase the risk of systemic toxic effects of LA (especially bupivacaine).

Metabolism of MA

Amide MAs are destroyed in the liver, with the participation of the cytochrome P450 system, from 1 to 5% of the drug is excreted unchanged in the urine. The half-life of amide MAs is significantly longer than that of ether MAs. Clearance of amide MAs is largely dependent on hepatic blood flow and enzyme activity. It may be impaired by heart failure, liver failure, or taking b-blockers or H2-receptor blockers.

Renal failure does not have a significant effect on the clearance of LA, since the process of their inactivation occurs mainly in the liver. However, accumulation of metabolites is possible.

Differentiated blockade

The ideal LA used for postoperative pain relief should selectively block nociceptive fibers A? and C, without affecting motor fibers A? and A?. It has been established that ropivacaine in low concentrations (0.2%) causes a predominant blockade of A-delta and C-fibers, while it blocks C-fibers faster than A-fibers (Wildsmith J., 1997). Reducing the concentration of anesthetic (0.125%) increases the selectivity of sensory blockade. At higher concentrations (0.5-0.75%), bupivacaine and ropivacaine exhibit similar effects on motor and sensory fibers. The ability of ropivacaine to cause differentiated sensorimotor block is its clinical advantage over bupivacaine.

MA dosing. Is the concept of "maximum recommended dose" acceptable?

The issue of choosing the optimal dose of LA for a particular method of regional anesthesia still remains controversial. The situation with spinal anesthesia is most clear - we have the only anesthetic spinal marcaine 0.5% (simple and heavy), there is a minimum effective dose of 10 mg and a maximum possible dose of 20 mg. Within this framework, we must operate with doses, taking into account the patient's age, his volume status, the volume of surgical intervention, etc.

The situation with the choice of dose of LA for brachial plexus block is more or less clear, since it is known that its effectiveness is determined by the volume of the administered LA solution (35-40 ml). Thus, the total dose depends on the concentration of the drug chosen (lidocaine 1-1.5%, bupivacaine 0.25%-0.5%, ropivacaine 0.75%).

The greatest difficulty is in choosing the optimal dose of MA for EA. At present, the long-standing recommendations on the dosage of LA for EA in milliliters per segment, milligrams per kilogram, etc., have been recognized as completely untenable. What should you be guided by, the maximum dose of the drug recommended by its manufacturer?

The MA maximum recommended dose (MRD), often listed in package inserts or catalog text, is widely used as a simple quantitative measure of the safe use of a drug, usually expressed in

mg/kg body weight. At the same time, none of the recommended doses are scientifically justified. The main goal of all existing recommendations is to avoid the administration of an excessive dose of anesthetic that can have a systemic toxic effect. However, this usually does not take into account the site of drug administration, as well as the factors influencing its metabolism and excretion.

Most experts currently reject the concept of MRD, as they consider it to be misleading due to:

The existence of pronounced individual differences in drug tolerability.

Possibility of a severe toxic reaction in case of unintentional intravenous injection of a dose significantly lower than the MRD.

The MRL concept may create the illusion of safety when doses below the MRL are used, as well as the false impression that higher doses are inherently dangerous.

Allergic potential of MA

In most cases, reports of allergic reactions caused by LA represent a false interpretation of various clinical situations caused by the action of these drugs. Most often they come from dental practice and, upon closer examination, turn out to be the result of accidental intravascular injection of LA (especially adrenaline-containing ones).

True allergic reactions to MA are extremely rare and, in the vast majority of cases, are associated with the use of essential MA. Most often they are caused by para-aminobenzoic acid, which is one of the degradation products of essential MAs.

In the literature there are literally isolated reports of allergic complications caused by amide MAs.

Toxicity of MA

The toxicity of LA manifests itself in the form of systemic (effects on the central nervous system and cardiotoxicity) and local toxic reactions (direct neurotoxic effects). Systemic toxicity occurs mainly with accidental intravascular administration of LA and is characterized by central nervous system stimulation, as well as convulsive activity.

Large doses of LA increase the risk of systemic toxicity, while high anesthetic concentrations and prolonged exposure (to a greater extent than the total dose) determine the direct neurotoxic effect.

Neurotoxicity of MA

Histological criteria for the neurotoxic effect of LA are damage to Schwann cells, as well as axonal degeneration and vacuolization of neonic membranes.

Lidocaine, in comparison with bupivacaine (Marcaine), has a significantly higher direct neurotoxic effect. The extreme degree of neurotoxicity is the development of transient neurological syndrome (TNS). In the vast majority of cases, the development of TNS is caused by the use of lidocaine (regardless of the dose and concentration) in SA and, to a lesser extent, in EA.

Systemic toxicity of LA (effects on the central nervous system)

Depending on the injection site, signs of systemic toxicity may appear immediately or several hours after injection of the drug. Experimental studies have shown that the higher the rate of administration of MA, the lower its dose that causes seizures.

In clinical settings, seizures most often occur due to systemic absorption when large doses of LA are used to block peripheral nerves and plexuses, as well as when LA is inadvertently administered intravenously in doses intended for regional anesthesia. The latter situation is possible when the epidural catheter is inserted into the vertebral vein unrecognized. SA from this point of view seems to be the safest (maximum dose - 20 mg of spinal marcaine).

Manifestations of systemic toxicity are directly related to plasma concentrations of MA. Administration of LA into highly vascularized areas (intercostal nerve block) is associated with a greater increase in plasma concentrations of anesthetic compared with the same dose of drug used for femoral nerve block.

It is important to remember that the systemic toxicity of lidocaine progresses with increasing doses from signs of CNS toxicity to cardiotoxicity. At the same time, the toxic effect of powerful MAs (bupivacaine) can immediately manifest itself as severe cardiovascular failure.

Cardiotoxicity of MA

The cardiotoxic effect of MA is determined by several components. First of all, blockade of Na channels disrupts normal atrioventricular conduction. Another factor determining the cardiotoxicity of LA is their inhibitory effect on ATP synthesis in mitochondria.

In vitro, it was found that the high cardiotoxicity of bupivacaine is associated with its extremely slow dissociation from Na channels. In particular, the period of binding of bupivacaine to the Na channels of the cardiac conduction system is 1000 times longer than that of lidocaine. Na channel blockade caused by bupivacaine is very persistent, which significantly reduces the effectiveness of resuscitation measures for ventricular fibrillation (McClure J.1996). It was later found that the cardiotoxic effect has a pronounced stereospecificity (bupivacaine is a racemic S- and R-rotating isomer), since the S-isomer has significantly less toxicity compared to the R-isomer.

After this, a new amide anesthetic, ropivacaine, was created and introduced into the clinic in 1996, which is a pure S-isomer and is an analogue of bupivacaine, in which the butyl group is replaced by propyl.

Ropivacaine's affinity for Na channels is intermediate between lidocaine, which binds rapidly to an open Na channel and rapidly dissociates during the relative refractory period, and bupivacaine.

It has been established that ropivacaine-induced myocardial depression and arrhythmia are less pronounced than the similar effect of bupivacaine, while a 10-fold increase in the concentration of ropivacaine does not significantly enhance its cardiotoxic effect (Carpenter R., 1997).

Under experimental conditions, it was found that ropivacaine suppresses ATP synthesis in myocardial mitochondria to a lesser extent than bupivacaine (Sztarc, 1998). Similar data were obtained when comparing the effect of these anesthetics on ATP synthesis in the mitochondria of liver cells. The minimal inhibitory effect of ropivacaine on ATP synthesis in mitochondria explains the fairly high effectiveness of resuscitation measures in case of accidental intravascular administration of a toxic dose of this anesthetic.

There are reports of accidental intravenous administration of ropivacaine (up to 150 mg) in 6 patients when attempting to perform EA (Selander., 1997). In no case were cardiotoxic effects or other manifestations of systemic toxicity observed. It is important to note that a similar dose of bupivacaine administered intravenously would be fatal in 100% of cases.
Overall, ropivacaine is » 40% less cardiotoxic and » 30% less neurotoxic than bupivacaine.

Methods for preventing the toxic effects of MA:
The use of techniques that reduce the likelihood of intravenous administration of LA
Mandatory aspiration tests at all stages of manipulation
Administration of anesthetic in small doses with step-by-step assessment of signs of systemic toxicity
Mandatory adherence to the maximum recommended doses, especially when blocking peripheral nerves and plexuses
If it is necessary to administer significant doses of LA into heavily vascularized areas (nerve plexus blockade), it is recommended to use drugs with a low cardiotoxic effect (ropivacaine)
Any regional blockade must be performed in conditions that provide the availability of drugs and equipment for cardiopulmonary resuscitation

Treatment of toxic manifestations of the action of MA.
Treatment of toxic manifestations of the action of MA depends on their intensity. The usual sequence of treatment actions is as follows:
Ensuring patency of the upper respiratory tract, inhalation of 100% oxygen (assisted ventilation in hyperventilation mode). The seizure threshold decreases against the background of metabolic acidosis and increased pCO2. In addition, acidosis enhances the cardiotoxic effect of LA.
If seizures occur, midazolam 0.05-0.1 mg/kg or sodium thiopental 1-1.5 mg/kg
If ineffective - succinylcholine 1-1.5 mg/kg and tracheal intubation
In case of severe hypotension, expand the volume of infusion therapy + adrenaline 0.02-0.2 mcg/kg/min
In case of circulatory arrest - cardiopulmonary resuscitation. In pregnant women >24 weeks' gestation, emergency caesarean section is indicated. This operation is life-saving because it eliminates compression of the inferior vena cava. In addition, uteroplacental blood flow is minimal during CPR, especially when large doses of epinephrine are used.

References:

1. Butterworth J. Local anesthetics: pharmacology and clinical use. // Anesth. Analg.- 2002.-V.94 (3 Suppl S).- P.22-26.
2. Carpenter R. Local anesthetic toxicity: the case for ropivacaine. // Am.J.Anesthesiol.- 1997.- V.24 (5, Suppl).- P.4-7.
3. McClure J. Ropivacaine. // Br. J. Anaesth. –1996. –V.76. – P.300-307.
4. Rosenberg P. Maximum recommended doses of local anaesthetics – need for new recommendations? // Highlights in Regional Anaesthesia and Pain Therapy. XI. – Special Edition World Congress on Regional Anaesthesia and Pain Therapy – Barselona, Spain, 2002. – P.30-34.

5. Turdimuratov B. et al. DIGITALIZATION OF THE MEDICAL FIELD IN UZBEKISTAN //Mejdunarodnaya konferenstiya akademicheskikh nauk. - 2022. - T. 1. – no. 29. - S. 25-27.
6. Asfandyorov J. et al. ON GENERAL CHARACTERISTICS OF ADENOCARCINOMA DISEASE //Current approaches and new research in modern sciences. - 2022. - T. 1. – no. 4. – S. 70-72.
7. Asfandyorov J. et al. SOME CONSIDERATIONS ABOUT PYLOnephritis DISEASE AND ITS CONSEQUENCES //Akademicheskie issledovaniya v sovremennoy nauke. - 2022. - T. 1. – no. 15. - S. 55-57.
8. Choriyeva Z. et al. INFORMATION ON DIABETES DISEASE. THE ORIGIN OF DIABETES DISEASE AND MEASURES APPLIED IN THIS DISEASE //Theoretical aspects in the formation of pedagogical sciences. - 2022. - T. 1. – no. 4. – S. 96-99.
9. Rakhmon oğ A. M. et al. PHYSIOLOGY OF THE HEART, AUTOMATIC HEART, ELECTROCARDIAGRAM //SUSTAINABILITY OF EDUCATION, SOCIO-ECONOMIC SCIENCE THEORY. - 2022. - T. 1. – no. 4. – S. 4-8.
10. Mirzaali son A. J. et al. THE LAST BRAIN, ITS CHANGES DEPENDING ON AGE. RELIEF OF PLASH. LATERAL WHITE MATTER OF THE BRAIN. BASAL STEMS //PEDAGOG. - 2022. - T. 5. – no. 6. - S. 319-326.
11. Tashboltaevna A. S. et al. STUDY OF SEASONAL BIOLOGICAL BACTERIAL INTESTINAL INFECTIONS IN THE EXAMPLE OF ESHERICHIA //Journal of Universal Science Research. - 2023. - T. 1. – no. 3. - S. 110-115.
12. Mirzaali o‘g‘li, A. J., Begzod o‘g‘li, M. M., & To’ramurodovich, H. F. (2023). SCIENTIFIC BASIS OF MORPHOLOGICAL CHANGES IN THE LIVER DUE TO DIABETES DISEASE. *Web of Semantics : Journal of Interdisciplinary Science*, *1*(1), 25–28. Retrieved from https://web.semanticjournals.org/index.php/wos/article/view/6