LOCAL ANESTHETICS MECHANISM OF ACTION pdf

1: Local anesthetic - Wikipedia

This explains why local anesthetics are slower in onset of action and less effective in the presence of inflammation, which creates a more acidic environment with lower pH. Contrastingly, the addition of sodium bicarbonate is used clinically to increase the pH of local anesthetic solutions thereby enhancing onset of action.

Diagnostic Tests[edit] Diagnostic tests such as bone marrow aspiration, lumbar puncture spinal tap and aspiration of cysts or other structures are made to be less painful upon administration of local anesthetic before insertion of larger needles. It may also be suitable for other kinds of punctures such as ascites drainage and amniocentesis. Surface anesthesia also facilitates some endoscopic procedures such as bronchoscopy visualization of the lower airways or cystoscopy visualization of the inner surface of the bladder. Properties of Ideal Anesthetic[edit] It should not irritate the tissue to which it is applied. It should not make any long-lasting changes on nerve structure. Its systemic toxicity should be minimal. It must be effective regardless of whether it is injected into tissue or applied locally on mucous membranes. The time of onset of anesthesia should be minimal. Duration of action must be sufficiently long to allow the procedure to be completed but not so long as to necessitate extended recovery. It should have enough potency to administer full anesthesia without supplementing additional concentrated solutions that are potentially damaging. It should not produce allergic reaction. It should be stable in solution and should spontaneously undergo biotransformation in the body. It should be sterile or capable of being sterilized by heat without deterioration. This could be caused by a variety of reasons including trauma during injection, infection, an allergic reaction, haematoma or injection of irritating solutions such as cold-sterilisation solutions. Usually there is tissue swelling at the point of injection. This is due to puncturing of the vein which allows the blood to flow into loose tissues in the surrounding area. Blanching of the tissues in the area where the local anaesthetic is deposited is also common. This gives the area a white appearance as the blood flow is prevented due to vasoconstriction of arteries in the area. The vasoconstriction stimulus gradually wears off and subsequently the tissue returns to normal in less than 2 hours. The density of tissues surrounding the injured vessels is an important factor for Haematoma. There is greatest chance of this occurring in a posterior superior alveolar nerve block or in a pterygomandibular block. Giving local anaesthesia to patients with liver disease can have significant consequences. Thorough evaluation of the disease should be carried out to assess potential risk to the patient as in significant liver dysfunction, the half-life of amide local anaesthetic agents may be drastically increased thus increasing the risk of overdose. Local anaesthetics and vasoconstrictors may be administered to pregnant patients however it is very important to be extra cautious when giving a pregnant patient any type of drug. Lidocaine can be safely used but bupivacaine and mepivacaine should be avoided. Consultation with the obstetrician is vital before administrating any type of local anaesthetic to a pregnant patient. Symptoms are likely to resolve within a few weeks. An estimated one in 5, to 30, nerve blocks results in some degree of permanent persistent nerve damage. Potential side effects[edit] General systemic adverse effects are due to the pharmacological effects of the anesthetic agents used. The conduction of electric impulses follows a similar mechanism in peripheral nerves , the central nervous system , and the heart. The effects of local anesthetics are, therefore, not specific for the signal conduction in peripheral nerves. Side effects on the central nervous system and the heart may be severe and potentially fatal. However, toxicity usually occurs only at plasma levels which are rarely reached if proper anesthetic techniques are adhered to. High plasma levels might arise, for example, when doses intended for epidural or intrasupport tissue administration are accidentally delivered as intravascular injection. This is the anticipation of pain during administration that activates the parasympathetic nervous system while inhibiting the orthosympathetic nervous system. Notable symptoms include restlessness, visibly looking pale, perspiration and possible the loss of consciousness. In severe cases, clonic cramps resembling an epileptic insult may occur. The patient may feel a tingling sensation in hands and feet or a sense of light-headedness and increased chest pressure. Hence, it is crucial for the medical professional administrating the local anaesthesia, especially in the form of an injection, to ensure that the patient is in a comfortable setting and has any potential fears alleviated in order to avoid these possible

complications. Central nervous system[edit] Depending on local tissue concentrations of local anesthetics, excitatory or depressant effects on the central nervous system may occur. At higher concentrations, a relatively selective depression of inhibitory neurons results in cerebral excitation, which may lead to more advanced symptoms include motor twitching in the periphery followed by grand mal seizures. It is reported that seizures are more likely to occur when bupivacaine is used, particularly in combination with chloroprocaine. Another possibility is direct exposure of the central nervous system through the cerebrospinal fluid , i. Cardiovascular system[edit] Cardiac toxicity can result from improper injection of agent into a vessel. Even with proper administration, it is inevitable for some diffusion of agent into the body from the site of application due to unforeseeable anatomical idiosyncrasies of the patient. However, infections are very seldom transmitted. Cardiac toxicity associated with overdose of intravascular injection of local anesthetic is characterized by hypotension , atrioventricular conduction delay, idioventricular rhythms, and eventual cardiovascular collapse. Although all local anesthetics potentially shorten the myocardial refractory period, bupivacaine blocks the cardiac sodium channels, thereby making it most likely to precipitate malignant arrhythmias. Even levobupivacaine and ropivacaine single-enantiomer derivatives , developed to ameliorate cardiovascular side effects, still harbor the potential to disrupt cardiac function. Allergic reactions to the esters is usually due to a sensitivity to their metabolite, para-aminobenzoic acid , and does not result in cross-allergy to amides. Nonallergic reactions may resemble allergy in their manifestations. In some cases, skin tests and provocative challenge may be necessary to establish a diagnosis of allergy. Also cases of allergy to paraben derivatives occur, which are often added as preservatives to local anesthetic solutions. Methemoglobinemia[edit] Methemoglobinemia is a process where iron in hemoglobin is altered, reducing its oxygen-carrying capability, which produces cyanosis and symptoms of hypoxia. Exposure to aniline group chemicals such as benzocaine , lidocaine , and prilocaine can produce this effect, especially benzocaine. Second-generation effects[edit] Application of local anesthetics during oocyte removal during in vitro fertilisation has been up to debate. Pharmacological concentrations of anesthetic agents have been found in follicular fluid. However, there is some concern with the behavioral effects of lidocaine on offspring in rats. Despite this, risks of toxicity may be higher in pregnancy due to an increase in unbound fraction of local anesthetic and physiological changes increase the transfer of local anesthetic into the central nervous system. Guy Weinberg in , and was not widely used until after the first published successful rescue in Evidence indicates Intralipid , a commonly available intravenous lipid emulsion, can be effective in treating severe cardiotoxicity secondary to local anesthetic overdose, including human case reports of successful use in this way lipid rescue. Ample supporting animal evidence [15] [16] and human case reports show successful use in this way. This theory is compatible with two studies on lipid rescue for clomipramine toxicity in rabbits [24] [25] and with a clinical report on the use of lipid rescue in veterinary medicine to treat a puppy with moxidectin toxicosis. Though many other drugs also have membrane-stabilizing properties, not all are used as LAs propranolol , for example. LA drugs act mainly by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane , in particular the so-called voltage-gated sodium channels. When the influx of sodium is interrupted, an action potential cannot arise and signal conduction is inhibited. The receptor site is thought to be located at the cytoplasmic inner portion of the sodium channel. Local anesthetic drugs bind more readily to sodium channels in an activated state, thus onset of neuronal blockade is faster in rapidly firing neurons. This is referred to as state-dependent blockade. LAs are weak bases and are usually formulated as the hydrochloride salt to render them water-soluble. Once inside the cell, the local anesthetic will be in equilibrium, with the formation of the protonated ionized form, which does not readily pass back out of the cell. This is referred to as "ion-trapping". In the protonated form, the molecule binds to the LA binding site on the inside of the ion channel near the cytoplasmic end. Most LAs work on the internal surface of the membrane - the drug has to penetrate the cell membrane, which is achieved best in the nonionised form. Acidosis such as caused by inflammation at a wound partly reduces the action of LAs. This is partly because most of the anesthetic is ionized and therefore unable to cross the cell membrane to reach its cytoplasmic-facing site of action on the sodium channel. All nerve fibers are sensitive to LAs, but due to a combination of diameter and myelination, fibers have different sensitivities to LA blockade, termed differential blockade. Type B fibers sympathetic tone are the most

sensitive followed by type C pain , type A delta temperature , type A gamma proprioception , type A beta sensory touch and pressure , and type A alpha motor. Although type B fibers are thicker than type C fibers, they are myelinated, thus are blocked before the unmyelinated, thin C fiber. The most peripheral technique is topical anesthesia to the skin or other body surface. Small and large peripheral nerves can be anesthetized individually peripheral nerve block or in anatomic nerve bundles plexus anesthesia. Spinal anesthesia and epidural anesthesia merge into the central nervous system. Injection of LAs is often painful. A number of methods can be used to decrease this pain, including buffering of the solution with bicarbonate and warming. Surface anesthesia is the application of an LA spray, solution, or cream to the skin or a mucous membrane; the effect is short lasting and is limited to the area of contact. Infiltration anesthesia is infiltration of LA into the tissue to be anesthetized; surface and infiltration anesthesia are collectively topical anesthesia Field block is subcutaneous injection of an LA in an area bordering on the field to be anesthetized. Plexus anesthesia is injection of LA in the vicinity of a nerve plexus , often inside a tissue compartment that limits the diffusion of the drug away from the intended site of action. The anesthetic effect extends to the innervation areas of several or all nerves stemming from the plexus. Epidural anesthesia is an LA injected into the epidural space , where it acts primarily on the spinal nerve roots; depending on the site of injection and the volume injected, the anesthetized area varies from limited areas of the abdomen or chest to large regions of the body. Spinal anesthesia is an LA injected into the cerebrospinal fluid , usually at the lumbar spine in the lower back , where it acts on spinal nerve roots and part of the spinal cord ; the resulting anesthesia usually extends from the legs to the abdomen or chest. The anesthetic effect is limited to the area that is excluded from blood circulation and resolves quickly once circulation is restored. Local anesthesia of body cavities includes intrapleural anesthesia and intra-articular anesthesia. Transincision or transwound catheter anesthesia uses a multilumen catheter inserted through an insicion or wound and aligned across it on the inside as the incision or wound is closed, providing continuous administration of local anesthetic along the incision or wounds [29] Dental-specific techniques include: Vazirani-Alkinosi Technique[edit] The Vazirani-alkinosi technique is also known as the closed-mouth mandibular nerve block. It is mostly used in patients who have limited opening of the mandible or in those that have trismus; spasm of the muscles of mastication. The nerves which are anesthetised in this technique are the inferior alveolar, incisive, mental, lingual and mylohyoid nerves. Dental needles are available in 2 lengths; short and long. As Vazirani-akinosi is a local anaesthetic technique which requires penetration of a significant thickness of soft tissues, a long needle is used. The needle is inserted into the soft tissue which covers the medial border of the mandibular ramus, in region of the inferior alveolar, lingual and mylohyoid nerves.

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2: Anaesthesia UK : Local Anaesthetic Pharmacology

Full text Full text is available as a scanned copy of the original print version. Get a printable copy (PDF file) of the complete article (K), or click on a page image below to browse page by page.

Lipid solubility-anaesthetic potency correlation the Meyer-Overton correlation [edit] The Meyer-Overton correlation for anaesthetics The nonspecific mechanism of general anaesthetic action was first proposed by Von Bibra and Harless in In Hans Horst Meyer published the first experimental evidence of the fact that anaesthetic potency is related to lipid solubility in his article entitled "Zur Theorie der Alkoholnarkose". He found a nearly linear relationship between potency and the partition coefficient for many types of anaesthetic molecules such as alcohols , aldehydes , ketones , ethers , and esters. It was noted also that volatile anaesthetics are additive in their effects a mixture of a half dose of two different volatile anaesthetics gave the same anaesthetic effect as a full dose of either drug alone. Outdated lipid hypotheses of general anaesthetic action[edit] Bulky and hydrophobic anaesthetic molecules accumulate inside the neuronal cell membrane causing its distortion and expansion thickening due to volume displacement. Membrane thickening reversibly alters function of membrane ion channels thus providing anaesthetic effect. Actual chemical structure of the anaesthetic agent per se was not important, but its molecular volume plays the major role: From the correlation between lipid solubility and anaesthetic potency, both Meyer and Overton had surmised a unitary mechanism of general anaesthesia. They assumed that solubilization of lipophilic general anaesthetic in lipid bilayer of the neuron causes its malfunction and anaesthetic effect when critical concentration of anaesthetic is reached. Later in Miller and Smith suggested the critical volume hypothesis also called lipid bilayer expansion hypothesis. Accumulation of critical amounts of anaesthetic causes membrane thickening sufficient to reversibly alter function of membrane ion channels thus providing anaesthetic effect. Actual chemical structure of the anaesthetic agent per se is not important, but its molecular volume plays the major role: Based on this theory, in Mullins suggested that the Meyer-Overton correlation with potency can be improved if molecular volumes of anaesthetic molecules are taken into account. Several types of bilayer perturbations were proposed to cause anaesthetic effect reviews [15] [16] [17]: This anaesthetic-induced fluidization makes membranes less able to facilitate the conformational changes in proteins that may be the basis for such membrane events as ion gating, synaptic transmitter release, and transmitter binding to receptors. All these outdated lipid theories generally suffer from four weaknesses [1] full description see in sections below: A small increase in body temperature affects membrane density and fluidity as much as general anaesthetics, yet it does not cause anaesthesia. Increasing the chain length in a homologous series of straight-chain alcohols or alkanes increases their lipid solubility, but their anaesthetic potency stops increasing beyond a certain cutoff length. Therefore, the correlation between lipid solubility and potency of general anaesthetics is a necessary but not sufficient condition for inferring a lipid target site. General anaesthetics could equally well be binding to hydrophobic target sites on proteins in the brain. The main reason that more polar general anaesthetics are less potent is that they have to cross the bloodâ€”brain barrier to exert their effect on neurons in the brain. Objections to the outdated lipid hypotheses[edit] 1. However, in vivo enantiomers of many general anaesthetics e. This objection provides a compelling evidence that the primary target for anaesthetics is not the achiral lipid bilayer itself but rather stereoselective binding sites on membrane proteins that provide a chiral environment for specific anaesthetic-protein docking interactions. Nonimmobilizers[edit] All general anaesthetics induce immobilization absence of movement in response to noxious stimuli through depression of spinal cord functions, whereas their amnesic actions are exerted within the brain. According to the Meyer-Overton correlation the anaesthetic potency of the drug is directly proportional to its lipid solubility, however, there are many compounds that do not satisfy this rule. These drugs are strikingly similar to potent general anaesthetics and are predicted to be potent anaesthetics based on their lipid solubility, but they exert only one constituent of the anaesthetic action amnesia and do not suppress movement i. The existence of nonimmobilizers suggests that anaesthetics induce different components of anaesthetic effect amnesia and immobility by affecting different molecular targets and not just the one target neuronal bilayer as it was

believed earlier. Temperature increases do not have anaesthetic effect[edit] Experimental studies have shown that general anaesthetics including ethanol are potent fluidizers of natural and artificial membranes. Thus membranes are fluidized only by large quantities of anaesthetics, but there are no changes in membrane fluidity when concentrations of anaesthetics are small and restricted to pharmacologically relevant. Effect vanishes beyond a certain chain length[edit] According to the Meyer-Overton correlation, in a homologous series of any general anaesthetic e. However, beyond a certain chain length the anaesthetic effect disappears. For the n-alcohols, this cutoff occurs at a carbon chain length of about 13 [27] and for the n-alkanes at a chain length of between 6 and 10, depending on the species. However, above certain length the potency vanishes. If general anaesthetics disrupt ion channels by partitioning into and perturbing the lipid bilayer, then one would expect that their solubility in lipid bilayers would also display the cutoff effect. However, partitioning of alcohols into lipid bilayers does not display a cutoff for long-chain alcohols from n- decanol to n-pentadecanol. A plot of chain length vs. The cutoff effect was first interpreted as evidence that anaesthetics exert their effect not by acting globally on membrane lipids but rather by binding directly to hydrophobic pockets of well-defined volumes in proteins. As the alkyl chain grows, the anaesthetic fills more of the hydrophobic pocket and binds with greater affinity. When the molecule is too large to be entirely accommodated by the hydrophobic pocket, the binding affinity no longer increases with increasing chain length. Thus the volume of the n-alkanol chain at the cutoff length provides an estimate of the binding site volume. This objection provided the basis for protein hypothesis of anaesthetic effect see below. This makes short chain alkanols efficient mediators that redistribute lateral stress from membrane interior to its interface. B This ability decreases in the row of n-alkanols since longer chains are more flexible and are not so tightly tethered to the hydroxyl group. C Polyhydroxyalkanes 1,6,11,hexadecanetetraol and 2,7,12,octadecanetetraol exhibit significant anaesthetic potency as was predicted by cutoff effect because the length of the hydrocarbon chain between hydroxyl groups is smaller than the cutoff. However, cutoff effect can still be explained in the frame of lipid hypothesis. Consequently, these segments efficiently redistribute lateral stresses from the bilayer interior toward the interface. In long-chain alkanols B hydrocarbon chain segments are located further from hydroxyl group and are more flexible than in short-chain alkanols. Efficiency of pressure redistribution decreases as the length of hydrocarbon chain increases until anaesthetic potency is lost at some point. It was proposed that polyalkanols C will have anaesthetic effect similar to short-chain 1-alkanols if the chain length between two neighbouring hydroxyl groups is smaller than the cutoff. Most membrane proteins especially ion channels are sensitive to changes in this lateral pressure distribution profile. These lateral stresses are rather large and vary with depth within the membrane. According to the modern lipid hypothesis a change in the membrane lateral pressure profile shifts the conformational equilibrium of certain membrane proteins known to be affected by clinical concentrations of anaesthetics such as ligand-gated ion channels. This mechanism is also nonspecific because the potency of the anaesthetic is determined not by its actual chemical structure, but by the positional and orientational distribution of its segments and bonds within the bilayer. However, it is still not obvious what the exact molecular mechanism is. In , Cantor suggested a detailed mechanism of general anesthesia based on lattice statistical thermodynamics. Calculations showed that general anaesthesia likely involves inhibition of the opening of the ion channel in a postsynaptic ligand-gated membrane protein [32] by the following mechanism: A channel tries to open in response to a nerve impulse thus increasing the cross-sectional area of the protein more near the aqueous interface than in the middle of the bilayer; Then the anaesthetic-induced increase in lateral pressure near the interface shifts the protein conformational equilibrium back to the closed state, since channel opening will require greater work against the higher pressure at interface. This is the first hypothesis that provided not just correlations of potency with structural or thermodynamic properties, but a detailed mechanistic and thermodynamic understanding of anaesthesia. Thus, according to the modern lipid hypothesis anaesthetics do not act directly on their membrane protein targets, but rather perturb specialized lipid matrices at the protein-lipid interface, which act as mediators. This is a new kind of transduction mechanism, different from the usual key-lock interaction of ligand and receptor, where the anaesthetic ligand affects the function of membrane proteins by binding to the specific site on the protein. Thus, some membrane proteins are proposed to be sensitive to their lipid environment. A slightly different

detailed molecular mechanism of how bilayer perturbation can influence the ion-channel was proposed in the same year. This decreases brain activity and induces lethargy and anaesthetic effect. Recently super resolution imaging showed direct experimental evidence that volatile anesthetic disrupt the ordered lipid domains as predicted [34]. In the same study, a related mechanism emerged where the anesthetics released the enzyme phospholipase D PLD from lipid domains and the enzyme bound to and activated TREK-1 channel by the production of phosphatidic acid. These results showed experimentally that the membrane is a physiologically relevant target of general anesthetics. In the early s, Franks and Lieb [35] demonstrated that the Meyer-Overton correlation can be reproduced using a soluble protein. They found that two classes of proteins are inactivated by clinical doses of anaesthetic in the total absence of lipids. These are luciferases , which are used by bioluminescent animals and bacteria to produce light, [36] and cytochrome P , [37] which is a group of heme proteins that hydroxylate a diverse group of compounds, including fatty acids , steroids , and xenobiotics such as phenobarbital. Remarkably, inhibition of these proteins by general anaesthetics was directly correlated with their anaesthetic potencies. Luciferase inhibition also exhibits a long-chain alcohol cutoff, which is related to the size of the anaesthetic-binding pocket. According to this theory general anaesthetics are much more selective than in the frame of lipid hypothesis and they bind directly only to small number of targets in CNS mostly ligand neurotransmitter -gated ion channels in synapse and G-protein coupled receptors altering their ion flux. Particularly Cys-loop receptors [42] are plausible targets for general anaesthetics that bind at the interface between the subunits. General anaesthetics can inhibit the channel functions of excitatory receptors or potentiate functions of inhibitory receptors, respectively. Although protein targets for anaesthetics have been partly identified the exact nature of general anaesthetic-protein interactions still remains a mystery. It was initially hypothesized that general anaesthetic binds to its target ion channel by a key-lock mechanism and changes its structure dramatically from open to closed conformation or vice versa. However, there is a significant amount of evidence against direct key-lock interaction of membrane proteins with general anaesthetics [43] [44] [45] [46] Various studies have shown that low affinity drugs including inhaled general anaesthetics do not usually interact with their target proteins via specific lock-and-key binding mechanism because they do not change molecular structures of transmembrane receptors, ion channels and globular proteins. Based on these experimental facts and some computer simulations modern version of protein hypothesis was proposed. It is a well known fact that dynamics of protein in microsecond-millisecond timescale is often coupled with functions of the protein. Normal interactions between residues in protein regions loops at the water-lipid interface that play critical roles in protein functions and agonist binding may be disrupted by general anaesthetic. Interactions within the same loop or between different loops may be disrupted by anaesthetics and ultimately functions of Cys-loop receptors may be altered.

LOCAL ANESTHETICS MECHANISM OF ACTION pdf

3: Local Anaesthetics | Pain Community Centre

A local anesthetic (LA) is a medication that causes reversible absence of pain sensation. When it is used on specific nerve pathways (local anesthetic nerve block), paralysis (loss of muscle power) also can be achieved.

It is a white crystalline, odorless powder that is freely soluble in water, but less soluble in alcohol. Each mL contains mg procaine hydrochloride and 4 mg acetone sodium bisulfite as antioxidant. Novocain - Clinical Pharmacology Novocain stabilizes the neuronal membrane and prevents the initiation and transmission of nerve impulses, thereby effecting local anesthesia. Novocain lacks surface anesthetic activity. Novocain is readily absorbed following parenteral administration and is rapidly hydrolyzed by plasma cholinesterase to aminobenzoic acid and diethylaminoethanol. A vasoconstrictor may be added to the solution of Novocain to promote local hemostasis, delay systemic absorption, and increase duration of anesthesia. Indications and Usage for Novocain Novocain is indicated for spinal anesthesia. Contraindications Spinal anesthesia with Novocain is contraindicated in patients with generalized septicemia: The decision as to whether or not spinal anesthesia should be used in an individual case should be made by the physician after weighing the advantages with the risks and possible complications. Spinal anesthesia should only be administered by those qualified to do so. Large doses of local anesthetics should not be used in patients with heartblock. Reactions resulting in fatality have occurred on rare occasions with the use of local anesthetics, even in the absence of a history of hypersensitivity. Safe use of Novocain has not been established with respect to adverse effects on fetal development. Careful consideration should be given to this fact before administering this drug to women of childbearing potential particularly during early pregnancy. This does not exclude the use of the drug at term for obstetrical analgesia. Vasopressor agents administered for the treatment of hypotension or added to the anesthetic solution for vasoconstriction should be used with extreme caution in the presence of oxytocic drugs as they may produce severe, persistent hypertension with possible rupture of a cerebral blood vessel. Solutions which contain a vasoconstrictor should be used with extreme caution in patients receiving drugs known to produce alterations in blood pressure i. Contains acetone sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. Precautions Standard textbooks should be consulted for specific techniques and precautions for various spinal anesthetic procedures. The safety and effectiveness of a spinal anesthetic depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies. The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and possible adverse effects. Tolerance varies with the status of the patient. Debilitated, elderly patients, or acutely ill patients should be given reduced doses commensurate with their weight and physical status. Reduced dosages are also indicated for obstetric delivery and patients with increased intra-abdominal pressure. Novocain should not be used in any condition in which a sulfonamide drug is being employed since aminobenzoic acid inhibits the action of sulfonamides. Solutions containing a vasopressor should be used with caution in the presence of diseases which may adversely affect the cardiovascular system. Novocain should be used with caution in patients with severe disturbances of cardiac rhythm, shock or heartblock. Adverse Reactions Systemic adverse reactions involving the central nervous system and the cardiovascular system usually result from high plasma levels due to excessive dosage, rapid absorption, or inadvertent intravascular injection. In addition, use of inappropriate doses or techniques may result in extensive spinal blockade leading to hypotension and respiratory arrest. A small number of reactions may result from hypersensitivity, idiosyncrasy, or diminished tolerance to normal dosage. Excitatory CNS effects nervousness, dizziness, blurred vision, tremors commonly represent the initial signs of local anesthetic systemic toxicity. However, these reactions may be very brief or absent in some patients in which case the first manifestation of toxicity may be drowsiness or convulsions merging into unconsciousness and respiratory arrest. Cardiovascular system reactions include depression of the myocardium, hypotension or sometimes hypertension , bradycardia, and even cardiac arrest. Allergic reactions are characterized by

cutaneous lesions of delayed onset, or urticaria, edema, and other manifestations of allergy. The detection of sensitivity by skin testing is of limited value. As with other local anesthetics, hypersensitivity, idiosyncrasy and anaphylactoid reactions have occurred rarely. The reaction may be abrupt and severe and is not usually dose related. The following adverse reactions may occur with spinal anesthesia: Toxic effects of local anesthetics require symptomatic treatment: The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors preferably those that stimulate the myocardium, such as ephedrine. Convulsions may be controlled with oxygen and by the intravenous administration of diazepam or ultrashort-acting barbiturates or a short-acting muscle relaxant succinylcholine. Intravenous anticonvulsant agents and muscle relaxants should only be administered by those familiar with their use and only when ventilation and oxygenation are assured. In spinal and epidural anesthesia, sympathetic blockade also occurs as a pharmacological reaction, resulting in peripheral vasodilation and often hypotension. The extent of the hypotension will usually depend on the number of dermatomes blocked. The blood pressure should therefore be monitored in the early phases of anesthesia. If hypotension occurs, it is readily controlled by vasoconstrictors administered either by the intramuscular or the intravenous route, the dosage of which would depend on the severity of the hypotension and the response to treatment. Novocain Dosage and Administration As with all local anesthetics, the dose of Novocain varies and depends upon the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance, and the technique of anesthesia. The lowest dose needed to provide effective anesthesia should be administered. For specific techniques and procedures, refer to standard textbooks.

LOCAL ANESTHETICS MECHANISM OF ACTION pdf

4: Novocain - FDA prescribing information, side effects and uses

Mechanism of Action Local anesthetics bind to the open form of the Na+ channel from the cytoplasmic side of the neuronal membrane.

Explain and identify ester hydrolysis. Explain and identify amide hydrolysis. Explain and identify N-dealkylation. Explain and identify aromatic hydroxylation. Clinical anesthesia 5th ed. Clinical Anesthesia 4th ed. Atlas of regional anesthesia 2nd ed. Basic clinical pharmacology 8th ed. The chemistry of drugs for nurse anesthetists. Fundamentals of general, organic, and biological chemistry 4th ed. Clinical anesthesiology 3rd ed. Pharmacology physiology in anesthetic practice 3rd ed. Basics of anesthesia 4th ed. Philadelphia, PA Churchill Livingstone. Whether your application is business, how-to, education, medicine, school, church, sales, marketing, online training or just for fun, PowerShow. And, best of all, most of its cool features are free and easy to use. You can use PowerShow. Or use it to find and download high-quality how-to PowerPoint ppt presentations with illustrated or animated slides that will teach you how to do something new, also for free. Or use it to upload your own PowerPoint slides so you can share them with your teachers, class, students, bosses, employees, customers, potential investors or the world. Most of the presentations and slideshows on PowerShow. You can choose whether to allow people to download your original PowerPoint presentations and photo slideshows for a fee or free or not at all. There is truly something for everyone!

LOCAL ANESTHETICS MECHANISM OF ACTION pdf

5: Local Anesthetics | Clinical Gate

This video explains the Mechanism of Action of Local Anesthetics.

Understanding the pharmacology of these agents as a group, as well as the differences between specific drugs, enables the anaesthetist to use them safely to maximum effect. This tutorial focuses on the basic structure and function of local anaesthetics. Learning will be improved by trying to answer the questions posed in the text before moving on. Definition of a local anaesthetic A local anaesthetic can be defined as a drug which reversibly prevents transmission of the nerve impulse in the region to which it is applied, without affecting consciousness. There are many drugs which exert local anaesthetic activity in addition to their main clinical uses, but this tutorial will focus on those drugs which are principally used for their local anaesthetic properties. The structural classification of local anaesthetics Local anaesthetics generally have a lipid-soluble hydrophobic aromatic group and a charged, hydrophilic amide group. The bond between these two groups determines the class of the drug, and may be amide or ester. Examples of amides include lignocaine, bupivacaine and prilocaine. Examples of esters include cocaine and amethocaine. The clinically significant differences between esters and amides The ester linkage is more easily broken than the amide bond so the ester drugs are less stable in solution and cannot be stored for as long as amides. Amide anaesthetics are also heat-stable and can therefore be autoclaved; esters cannot. The metabolism of most esters results in the production of para-aminobenzoate PABA which is associated with allergic reaction. Amides, in contrast, very rarely cause allergic phenomena. For these reasons amides are now more commonly used than esters. Local anaesthetics as isomers Local anaesthetics may also be considered in terms of their stereoisomerism. This term describes the existence of molecules with the same molecular and structural formula, but different spatial orientation around a particular atom, the chiral centre. This is like the right and left foot being mirror images of each other. Stereoisomerism occurs in the case of bupivacaine which has two stereoisomers, known as R and S forms, and also in the case of prilocaine. The combination of equal amounts of the two stereoisomers of a particular drug is known as a racemic mixture. Why might this isomerism be important? The different arrangements of the R and S forms of bupivacaine are thought to be associated with differences in potency and side-effect profile. This is the reason why more drugs are being prepared as a single stereoisomer such as levobupivacaine. Another familiar example of this is ketamine. In contrast amethocaine an ester and lignocaine are achiral, ie they have no stereoisomers. The mechanism of action of local anaesthetics Local anaesthetics disrupt ion channel function within the neurone cell membrane preventing the transmission of the neuronal action potential. This is thought to occur via specific binding of the local anaesthetic molecules in their ionised form to sodium channels, holding them in an inactive state so that no further depolarisation can occur. This effect is mediated from within the cell; therefore the local anaesthetic must cross the cell membrane before it can exert its effect. A second mechanism is also thought to operate, involving the disruption of ion channel function by the incorporation of local anaesthetic molecules into the cell membrane the membrane expansion theory. This is thought to be mediated mainly by the unionised form acting from outside the neuron. Nerve fibres differ in their sensitivity to local anaesthetics. Small nerve fibres are more sensitive than large nerve fibres while myelinated fibres are blocked before non-myelinated fibres of the same diameter. Thus the loss of nerve function proceeds as loss of pain, temperature, touch, proprioception, and then skeletal muscle tone. This is why people may still feel touch but not pain when using local anaesthesia. The importance of the pKa of a local anaesthetic drug All local anaesthetic agents are weak bases, meaning that they exist in two forms: The pKa of a weak base defines the pH at which both forms exist in equal amounts. As the pH of the tissues differs from the pKa of the specific drug, more of the drug exists either in its charged or uncharged form. This is expressed in the Henderson-Hasselbalch equation: How may the pKa of a local anaesthetic influence its speed of onset? The pKa of a local anaesthetic determines the amount which exists in an ionised form at any given pH. At physiological pH 7. However the proportions vary between the drugs: Bupivacaine has a pKa of 8. As the drug must enter the cell in order to have its effect it must pass through the lipid cell membrane. Unionised drug will do this more readily than ionised drug. Therefore the

drug which is more unionised at physiological pH will reach its target site more quickly than the drug which is less so. This explains why lignocaine has a faster onset of action than bupivacaine. The relevant feature of infected tissue is that it tends to be a more acidic environment than usual. As the pH is reduced the fraction of unionised local anaesthetic is reduced and consequently the effect is delayed and reduced. Infected tissue may also have an increased blood supply and hence more anaesthetic may be removed from the area before it can affect the neurone. How else may the physicochemical characteristics of a local anaesthetic affect its function? Physicochemical features such as the aromatic ring structure and hydrocarbon chain length of a particular local anaesthetic determine the lipid solubility of the drug and hence its potency. This makes sense since the more lipid soluble drug penetrates the cell membrane more easily to exert its effect. The more potent the drug, the smaller the amount required to produce a given effect. Thus bupivacaine â€" which is highly lipid soluble â€" is approximately four times more potent than lignocaine. This is reflected in the different preparations available of these two drugs; bupivacaine being more potent is prepared as a 0. The duration of action of the drug is also related to its structure, primarily to the length of the intermediate chain joining the aromatic and amine groups. However it should be noted that protein binding is probably at least as important a determinant of duration of action. Clearly the molecular structure of the drug also affects protein binding ability and therefore all local anaesthetics differ in the extent to which they are protein-bound. Therefore one can predict that bupivacaine will have a longer duration of action than lignocaine â€" which is in fact the case. Differences in protein binding also result in differing duration of unwanted side effects and is one of the reasons that bupivacaine is considered more toxic than lignocaine. Pharmacokinetics of local anaesthetics Absorption and distribution Local anaesthetic drugs are administered to the areas around the nerves to be blocked â€" which include skin, subcutaneous tissues, intrathecal and epidural spaces. Some of the drug will be absorbed into the systemic circulation: Some local anaesthetics have vasodilatory effects at low concentrations, increasing their systemic absorption. This is countered in some preparations which include a vasoconstrictor such as adrenaline or felypressin. Cocaine, in contrast, has a vasoconstrictive effect. The distribution of the drug is influenced by the degree of tissue and plasma protein binding of the drug. As discussed above, the more protein bound the agent, the longer the duration of action as free drug is more slowly made available for metabolism. Metabolism and excretion Ester and amide anaesthetics differ in their metabolism. Esters except cocaine are broken down rapidly by plasma esterases to inactive compounds and consequently have a short half life. Cocaine is hydrolysed in the liver. Ester metabolite excretion is renal. Amides are metabolised hepatically by amidases. This is a slower process, hence their half-life is longer and they can accumulate if given in repeated doses or by infusion. Prilocaine is also metabolised extra-hepatically. Which local anaesthetic drugs are more likely to affect the foetus when given in pregnancy and why? How does the situation change if the foetus is compromised? The esters are metabolised sufficiently rapidly to have minimal effects on the foetus so little remains in the maternal circulation to cross the placenta. Amide local anaesthetics are more likely to cross the placenta. Of these, placental transfer is greater in those which are less protein-bound such as lignocaine. If the foetus is compromised it may become acidotic. In this situation more of the foetal local anaesthetic will be ionised and hence unable to return to the maternal circulation. This phenomenon is known as ion trapping and can result in foetal toxicity. These effects are not likely to be important when small amounts of drug are used during spinal anaesthesia, but may become so when larger amount are used for epidural anaesthesia or other nerve blocks around the time of delivery. Clinical uses of local anaesthetics Preparations Local anaesthetics are available as solutions for injection, sprays, creams and gels. They are prepared as the hydrochloride salt to enable them to be dissolved in water resulting in an acidic solution. Of note, due to new legislation, some of the newer local anaesthetics are described in terms of the quantity of free base present alone, in contrast to the older drugs which are described in terms of the quantity of total hydrochloride salt present. This is why, for example, 10ml of 0. Most local anaesthetic preparations contain a preservative agent such as 0. The drug may also be combined by the manufacturer or in some cases the clinician with other local anaesthetics e. EMLA cream - eutectic mixture of local anaesthetics or additives designed to enhance their effects. How might adrenaline, bicarbonate and glucose variously affect the action of local anaesthetics? Adrenaline acts as a vasoconstrictor. The result is to minimise the vasodilator effect of

for example lignocaine and decrease the rate at which drug is removed from the site of action by absorption into the systemic circulation. It also reduces traumatic surgical blood loss from the site by the same mechanism. Bicarbonate added to a local anaesthetic increases the pH of the environment when administered. Consequently more drug is present in its unionised form and speed of onset of anaesthesia is increased. Too much bicarbonate however may result in precipitation of the local anaesthetic as the unionised form is much less soluble in water than the hydrochloride salt. Glucose is added to bupivacaine in order to increase the baricity of the solution to greater than that of CSF. When administered as a spinal anaesthetic this results in more controlled spread of solution within the intrathecal space.

LOCAL ANESTHETICS MECHANISM OF ACTION pdf

6: Block 15 Local Anesthetics MCQ's - ProProfs Quiz

Explain the factors influencing the onset and duration of action and potency of local anesthetics the onset will be determined by how close the pka is because the ionized form will then predominate Describe the causes of local anesthetic-associated toxicity, how to prevent it and how to reat it.

Oliver Wendell Holmes coined the term "anesthesia" in to describe drug-induced insensibility to sensation particularly pain , shortly after the first publicized demonstration of inhaled ether rendered a patient unresponsive during a surgical procedure. Two broad classes of pharmacologic agents, local and general, can result in anesthesia. Local anesthetics, such as Novocain, block nerve transmission to pain centers in the central nervous system by binding to and inhibiting the function of an ion channel in the cell membrane of nerve cells known as the sodium channel. This action obstructs the movement of nerve impulses near the site of injection, but there are no changes in awareness and sense perception in other areas. In contrast, general anesthetics induce a different sort of anesthetic state, one of general insensibility to pain. The patient loses awareness yet his vital physiologic functions, such as breathing and maintenance of blood pressure, continue to function. Less is known about the mechanism of action of general anesthetics compared to locals, despite their use for more than years. The most commonly used general anesthetic agents are administered by breathing and are thus termed inhalational or volatile anesthetics. They are structurally related to ether, the original anesthetic. Their primary site of action is in the central nervous system, where they inhibit nerve transmission by a mechanism distinct from that of local anesthetics. The general anesthetics cause a reduction in nerve transmission at synapses, the sites at which neurotransmitters are released and exert their initial action in the body. But precisely how inhalational anesthetics inhibit synaptic neurotransmission is not yet fully understood. It is clear, however, that volatile anesthetics, which are more soluble in lipids than in water, primarily affect the function of ion channel and neurotransmitter receptor proteins in the membranes of nerve cells, which are lipid environments. Two factors make obtaining a detailed description of how these agents act difficult. The first is that volatile anesthetics, unlike most of the drugs used in medicine, bind only very weakly to their site s of action. As a result, high concentrations, often more than 1, times greater than for typical receptor- or protein-targeting drugs, are needed to achieve an anesthetic state. This makes it tricky to obtain structural details of anesthetics bound in a specific manner to a protein. It also affects the function of many proteins in nerve cell membranes, making it challenging to ascertain which of them are the key mediators of anesthetic action. A second problem is that volatile anesthetics tend to partition into lipids and exert their primary effects on synaptic neurotransmission by interacting with proteins in a lipid environment. It is harder to gain detailed structural information for membrane proteins than it is for water-soluble proteins. Such structural data are essential for understanding how anesthetics interact with proteins and, more importantly, alter their function. Because of the lack of structural data for membrane proteins both in the presence and absence of anesthetics, it remains unclear whether anesthetics exert their primary effects by direct interaction with these proteins, or indirectly via interaction with the lipids surrounding them. Despite these limitations, researchers are taking advantage of a variety of methods to better discern how anesthetic agents induce an anesthetic "state" at the molecular level. The term state is in quotes, because a wide variety of agents--ranging from single atoms such as xenon to polycyclic hydrocarbons--can produce insensibility to pain and loss of awareness. The molecular targets for these different agents do not appear to be the same. Thus the notion that there is a single molecular mechanism of action for all anesthetic agents is probably an oversimplification. Genetic tools are providing promising results regarding the molecular mechanism of anesthetic action. For example, researchers can alter specific protein function and then determine whether this protein can be linked to sensitivity or resistance to anesthetic action in lower organisms. These approaches identify what proteins are involved in anesthetic action and can be thought of as a way to better define relevant anesthetic targets, which investigators can then focus on for structural studies. Other approaches, including sophisticated structural modeling of anesthetic binding to protein targets in a lipid environment and detailed structural determinations of anesthetic binding to soluble proteins, are also showing promise in further

revealing the how of anesthetic action at the molecular level. Thus the simple answer to the question "How does anesthesia work? Many of the tools necessary to answer these questions now exist and we can look forward to new insights into how this great boon to humanity works at the molecular level.

LOCAL ANESTHETICS MECHANISM OF ACTION pdf

7: IV Regional: Mechanism

Neosaxitoxin has poor affinity for the cardiac isoform of the sodium channel and does not cross the blood-brain barrier, thus this compound is virtually devoid of cardiac and central nervous system toxicityâ€"the limiting toxicities of traditional local anesthetics.

To understand the mechanism of action of local anaesthetics To understand their contribution to the management of acute pain To be aware of the inherent risks of using such drugs and to implement strategies reduce such risk Local Anaesthetics Koller introduced the ester cocaine into clinical practice for eye surgery in because the conditions provided by general anaesthesia were poor. It is interesting that the use of local anaesthesia for eye surgery has once more become very popular, although much safer drugs than cocaine are now employed. Local anaesthetics are either aminoesters e. Mechanisms of action Local anaesthetics inhibit nerve conduction by interfering with the physiological changes in ionic permeability during an action potential. Nerve cells are selective in their permeability to ions and consequently have an electrical potential across their membrane; at rest this is of the order of minus 50 to minus 80 mV, with the inside being negative. Cell membranes are composed mainly of lipids and do not permit ions to pass through them, but they are crossed by specialised protein ion channels, which allow potassium, sodium and other ions to pass through. At rest, the potassium channels in nerve cell membranes are open and the sodium gates are closed; when a nerve cell is excited, the membrane suddenly becomes transiently permeable to sodium as that ionic channel opens. The membrane potential is reversed so that it has a positive charge inside, and a propagated action potential is passed along the fibre. Local anaesthetics block sodium channels, prevent the evolution of the action potential and so prevent or decrease sensation arising in the affected area. It is thought that most local anaesthetics work by blocking the sodium channel from the inside of the cell into which they must first diffuse before they can act. In infected tissues, acidic conditions prevent this diffusion and thus local anaesthetics then tend to be less effective. Pain Management Local anaesthetics are used on their own and combination with opioids for epidural and spinal blocks. Local anaesthetics are also used for local blocks and are used extensively for day case surgery, limb surgery and hand surgery. Local anaesthetics can also be used systemically for pain management. Sodium channel blockers can be used to reduce pain due to nerve damage and intravenous lignocaine and oral mexiletine an oral analogue can both reduce neuropathic pain in nonmalignant and cancer pain [1]. Toxic reactions to local anaesthetics can be reduced by slow administration, and intravenous access should always be secured before a block is performed in case of untoward events occurring. Resuscitation equipment and drugs should be immediately available. The effects of local anaesthetics are as follows: Early signs of toxicity are shivering, confusion, and twitching and tremors followed by generalised seizures. Eventually, with large doses, generalised central nervous system depression ensues with cessation of seizures, respiratory arrest and hypoxia. Treatment comprises the administration of anticonvulsants thiopentone or diazepam and oxygenation, with tracheal intubation and respiratory support if necessary. Cardiovascular system - is more resistant to local anaesthetics, but vasodilatation, myocardial depression and disorders of rhythm occur and can lead to cardiac arrest and circulatory collapse. Cardiovascular toxicity may be precipitated and worsened by hypoxia, hypercarbia and acidosis consequent to inadequate treatment of the convulsions and respiratory arrest described above. In particular, hypoxia and acidosis potentiate the cardiodepressant effects and arrhythmias associated with bupivacaine toxicity. Cardiac massage, ventricular defibrillation, intravenous fluids and inotropic support are indicated and resuscitation may be prolonged, especially with bupivacaine. There is also cross-sensitivity between the para-aminobenzoic acid derivatives and methylparaben, a preservative commonly used in local anaesthetic preparations. Allergy to amide local anaesthetics is rare, and almost all have been related to methylparaben. Lignocaine also produces methaemoglobin, but a clinical problem rarely presents. Prilocaine may be a problem if EMLA is used in large quantities on premature babies. Specific drugs Lignocaine This is the most commonly used agent in the U. The effect of lignocaine is prolonged considerably by the addition of the vasoconstrictor adrenaline. Bupivacaine Bupivacaine is more potent than lignocaine; 0. It is available in 0. It is more cardiotoxic than

other local anaesthetics and is not recommended for intravenous regional analgesia. The duration of action is from 4 to 16 hours, and bupivacaine produces more sensory than motor block. Levo-bupivacaine is also available and while the concentrations and usage are the same as bupivacaine, evidence suggests that it may be less cardiotoxic. Prilocaine The potency of prilocaine is similar to lignocaine but as it is metabolised in the lung as well as the liver it is cleared from the body more quickly than the other amides this makes it particularly useful for intravenous regional analgesia. Methaemoglobinaemia is associated with the use of high doses and it is unsuitable for use in obstetrics because of this risk to the unborn child. You may like to examine some of the protocols or guidelines you have in practice that deal with problems associated with epidurals and spinals. Are they valid, reliable and evidence based? Ropivacaine Ropivacaine is a long acting local anaesthetics like bupivacaine but is associated with less cardiovascular toxicity. It is one of the newer local anaesthetics [2].

8: Local Anesthetics and Opioids | Clinical Gate

Mechanism of action of local anesthetics â€" LAs reversibly inhibit nerve transmission by binding voltage-gated sodium channels (Na v) in the nerve plasma membrane. Na v channels are integral membrane proteins, anchored in the plasma membrane.

9: PPT â€“ Local Anesthetics PowerPoint presentation | free to view - id: 95d6b-N2ZjN

is that, although we know a great deal about the physiologic effects and macroscopic sites of action, we don't yet know the molecular mechanism(s) of action for general anesthetics.

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