Semester II.

Pharmacology

Laboratory 7

CNS Narcotics, Anaesthetics and Excitatory substances

CNS modifying substances

1. Narcotics. Pharmacodynamics
2. Anesthetics. Pharmacodynamics
3. Pharmaceutical technique
4. Pharmacography
5. Classification

Volatile general anesthetics

Narcosis compared to chloroform and ether

The phases of narcosis are compared:

a) **Cortical phase:** hyperexcitation due to asynchronous inhibition of various cortical centers. The excitation remain free and manifest in various forms. Thus, anxiety is observable, walking rapidly all directions, severe itching, especially in the head region, disturbances of equilibrium, at the end of cortical phase, narcotic sleep occurs.

b) **Subcortical phase** - disappearance of sensitivity starting from limbs, towards the trunk and the back part of the body.

c) **The medullary-protuberance phase** - reflexes disappear, is the surgical phase, that is the real narcosis phase in which the surgery is performed.

d) **Bulbar phase** - the toxic phenomena occur. By the action of the narcotic on the bulb, the respiratory and vaso-motory centers are affected. This phase appears visible by altering the breathing that becomes dyspnoea and gradually narrows to apnea. Animals intoxicated with volatile narcotics can be resuscitated by artificial respiration

By making a comparative consideration of the action of chloroform and ether, we will see that in the case of first substance, narcosis occurs more rapidly and the elimination is slower. This is due to its higher liposolubility, the partition coefficient being **263**, compared to **50** in ether's case. This is also the reason for the higher toxicity of chloroform to ether.

Comparative lipoidotropic property of chloroform and ether

***In vitro* test**

In two tubes, add 15 ml of distilled water and add 1ml of chloroform in the first and 1ml of ether in the second. It is found that while the ether mixes well with water, the chloroform separates its solubility in water being only 1/150, so 10 times lower than that of the ether.

In two other tubes, add 1ml of vegetable oil and 2ml of chloroform (first tube) and ether (in the second tube). It is mixed and it is found that both substances are solubilized in the fatty oil. However, the solubility of chloroform is higher.

In vivo (discussion of the model only)

Under four glass bells, a mouse is placedeach, each having a similar body weight. Under the bells 1 and 2 a Petri dish containing fatty vegetable oil is covered, covered with a wire mesh. Under the bells no. 1 and 3 a buffer with chloroform is placed, and below the bells no. 2 and 4 a buffer with ether.

Looking at the effect comparatively, we will see that narcosis occurs **more quickly** under bells 3 and 4, where there is no fatty oil, instead it appears **slowly** under bells 1 and 2 where the fatty oil absorbs some of the substance.

Further comparing the affinity for oil of the two substances, we will see that the ether is **less** absorbed by the oil than the chloroform. This causes the induction period of chloroform to **extend longer** than for ether, and the effects are **weaker** compared to the usual action of the two substances.

Substance characteristics	Chloroform	Ether
Molecular weight	1.470	0.715
Flammable or explosive	no	Yes
Induction period	short	long - unpleaseant
Mucosal irritation	fair	hard (cough & lot of secretion)
Safety limit	low (1,3-1,5%)	high (3-6%)
Circulation (blood pressure)	Dercreases	Normal
Heart	Toxic (aritmia)	Normal
Breath	Deprimated	Normal
Muscle relaxation	fair	slight curarrisant
Liver	Toxic	Non-influnced
Capillary bleeding	Unmodified	Raises
Stimulation of the sympathetic system	no	yes
elimination	Lent	Rapid
Contraindications	cardiace, hepatic, renal affections	Respiratory affections, diabetes
Fatal accident (max om)	1/3.000	1/10.000
Postoperative condition (man)	nosea, vomiting	nosea, vomiting
risks	liver	pulmon

Demonstration of respiratory and cardiac reflex action of volatile narcotics (discussion of the model only)

There will be followed the breathing respectively the heart beats in the. The frequency and amplitude of the movements are noted.

Approaching with chloroform or ether will reflexly slow the breathing and cardiac movements or even stop them. After the buffer is removed, breathing begins to start, as does heartbeat. The effect is all the more powerful as the concentration of narcotic is higher. Ether, acts **more strongly** than chloroform.

If a surface anesthetic (e.g. cocaine) is applied to the nasal mucosa after anesthesia is installed, the approach of an ether or chloroform buffer will no longer affect the respiration and heart.

It can be deduced from here that these substances produce an irritation of the nasal mucosa which has the effect of stopping reflex and breathing. The nerve endings of the trigeminal nerve in the nasal mucosa appear to be responsible for this mechanism.

General anesthesia with Baytinal in the rabbit (only discussion of the model)

Baytinal is a barbiturate derivative that has sulfur in its molecule. The chemical formula is 5,5-allyl -(2,-methyl-propyl) sodium thiobarbiturate. The narcotic action is good but short duration.

To track the narcotic and hypnotic effect of Baytinal, 1ml solution is injected into a rabbit. 10% of this substance. We will find that the animal falls asleep immediately, sometimes even before the injection is completed. The sleep is not particularly profound.

The action of narcosis is quite short and therefore only minor surgery can be performed. It is a depressant of the respiratory center, therefore it must be taken care of in its dosage.

Hypnotic comparative action of barbiturates in mice (model discution only)

In four mice, placed separately, sodium solutions of phenobarbital, amobarbital, hexobarbital and pentobarbital injected 0.5ml i.p.

By comparing the duration of the latency period until the first signs of depression of the CNS, as well as the duration of induced sleep, we will observe that the decreasing order is as follows: phenobarbital, amobarbital, pentobarbital and hexobarbital.

Longest sleep occurs after the administration of phenobarbital, and the shortest is produced by hexobarbital. It can be noted that between the duration of the latency period and that of the hypnotic sleep, there is a directly proportional relation.

Substance	Action time	s.c. dose to rats (g)	
Barbital	Long 6-8h	0,22	0,31
Fenobarbital	Long 6-8 h	0,10	0,15
Amobarbital	Middle 4-6h	0,06	0,12
Ciclobarbital	Short 2-3h	0,07	0,18
Hexobarbital	Very short	0,06	0,23

Narcosis with chloralhydrate in the rabbit

Determine the dose of chloralhydrate to be administered (0.10 g/kgbw i.v and 0.15-0.20 g/kgbw orally and rectally). A 10% solution of this substance is injected i.v.

The effect of chloralhydrate, appears rapidly after a short latency period. The excitation phase is completely absent. A good state of anesthesia appears, favorable to the interventions. It's good hypnotic, analgesic and anticonvulsant. It has the disadvantage that therapeutic doses are quite close to the toxic. It has depressing actions on: respiratory, cardiac and vaso-motor centers. Decreases activity of the major functions and produces hypothermia.

Narcosis produced by chloralhydrate lasts 1-2 hours, followed by a long-lasting post-narcotic sleep. Animal awakening is usually done by injecting an exciting substance. Administration can be done well p.o. or as rectal enema. In both cases it must be embedded in a mucilage, to prevent the mucosa from its irritating action. The dose is up to double compared to i.v. administration. Administration of chloralhydrate in the form of an enema is one of the main means of antidotism in strychnine intoxication.

The sensitivity to the toxic action in descending order: dogs, ruminants, pigs, horses. This is the reason why the substance is not used in ruminants and dogs

Narcosis with urethane in the rabbit (model discussion)

A 10% urethane solution is injected to a rabbit i.v.: 0.3-0.8g/kgbw.

Following the effect of urethane, we find that narcosis occurs shortly after injection and is not preceded by the excitation phase. Narcosis is deep and long lasting and is followed by prolonged postnarcotic sleep.

Urethane is used in laboratory animals for long-term general anesthesia in experiments and demonstrations.

Also, based on the prolonged narcosis it produces, it is an excellent antidote for strychnine poisoning.

However, due to the fact that its effect does not appear immediately, it must be preceded by a rapidly acting CNS depressant.

The antagonistic effect between calcium and magnesium

In a rabbit under the hypnotic effect of magnesium sulfate, calcium chloride 0.1-0.2g/kgbw is i.v. injected into 10%.

Immediately the animal awakes from sleep and returns to normal behavior.

We will discuss the antagonizing effect of Ca++ ions against those of Mg++, that it substitutes at the cell membranes.

It will also be shown that in cases of magnesium sulphate overdose, the poisoning can be counteracted by the administration of calcium chloride.

3. Pharmaceutical technique

Preparation of enema with chloral hydrate

Prepare a smooth seed mucilage of 10g of flax seed in 200 ml of water. Tie the flax seeds in a gauze bag and boil in water for 5 minutes. The resulting mucilage is filled to 200ml with water.

In this mucilage is included chloralhydrate in a concentration of 10%.

Thus, in a 10 kg dog, 1.5-2g of chloral hydrate (dose 0.15-0.20/kgbw) will be administered rectally, as an enema, embedded in 15-20ml of mucilage.

Sedatives, tranquilizers, analgesics and antipyretics substances

1. Pharmacognosy:

- general and motor sedatives substances
- tranquilizing and neuroleptic substances
- analgesic substances
- analgesic and antipyretic substances
- standardized drug forms

2. Pharmacodynamics

Sedative action of bromides

- The administration of bromide leads to a diminished and delayed response to the action of external excitatory factors, which is due to the depressing action of bromides on S.N.C.
- The inhibitory effects of bromine salts extend to the reflex activity of the spinal cord.

Sedative action of valerianae

- The administration of valerian to animals leads to the appearance of lazy, slow movements until the impossibility of returning from the dorsal decubitus.
- Depressive action of valerian occurs by increasing the inhibition processes of the central nervous system, which extends even to the peripheral nervous system.

The action of major tranquilizers

On spontaneous mobility

Administration of Plegomazine (chlorpromazine, chlordelazine) 0.05% solution results in decreased spontaneous motor activity in animals.

On the hyperactivity caused

Administration of amphetamine (a substance with excitatory effects on CNS) leads to increased motor activity. After the administration of the Plegomazin 0.05% solution, it will be observed that the administration of this neuroleptic substance the motor hyperactivity disappears, and the motility returns to the initial level or decreases below the normal level.

So conclusions are drawn on the application of major tranquilizers in hyperexcitability in animals.

- **On agility**

The rotation axis test can be used, which consists of putting the animals on a cylindrical axis, compartmentalized using discs, which rotates continuously, at a slow rate. After a one-minute test, during which the animals become accustomed to the rotation, the agility is tested, specifically the ability to continue to the axis by stepping movements in the rhythm of axis rotation.

After the administration of Plegomazin 0.2-0.5 ml 0.05% solution, those who received the neuroleptic, become heavy and have lazy movements, are sleepy, and can not be maintained on the axis of rotation.

To demonstrate the effect of major tranquilizers on agility, also the rectification test can be used. It consists of laying on a wire stretched horizontally at a height of 20-30 cm above the table. Those who have received a neuroleptic have a low capacity to maintain the position, and repeatedly fall.

It will be widely discussed in the lab about the mechanism of action of major and minor tranquilizers and their multiple uses in veterinary medicine.

The action of morphine

I.V. injection of morphine 10 mg/kgbw in a 1% solution results in drowsiness, decreased frequency and amplitude of respiratory movements, myosis, and muscular hypotonia.

The pain is no longer perceived, and a state of analgesia appears. The cord is also slightly modified.

The analgesic effect of morphine is strong and is more pronounced in the case of pre-existing pain. It is the result of the increase of the excitation threshold in the thalamus.

The depressing effect on CNS induces a state of drowsiness or even sleeps, from which one can return through some external stimuli. Depression of the cerebral cortex, however, is accompanied in some animal species by the excitation of other brain areas, which results in phenomena of strong excitation (ruminant, cat and in the initial phase in the dog).

Side effects such as respiratory depression, myosis are removed by atropine administration. The use in veterinary medicine and its effects on various species will be discussed in the lab.

2. Pharmacodynamics

The analgesic effect of morphine and potentiation of the effect by major tranquilizers

Morphine alone acts as a powerful analgesic that raises the threshold of pain perception in the diencephalon, and cerebral cortex for several times.

If hydrochloric morphine in 1% solution, and Plegomazin, is administered concomitantly, this combination of neuroleptics enhances this action, producing complete analgesia in the appropriate dose.

This phenomenon called neuroleptanalgesia is today used in surgery for operative interventions. They are conducted without narcotic sleep.

Exciting effects on the central nervous system of morphine

By morphine administration, an increase in the tonus of the paravertebral muscles and of the tail is observed. This manifestation is called the Straub phenomenon and is used as a test to detect the presence of morphine in biological fluids.

The medullary excitation effect produced by morphine is one of the aspects that the phenomena of excitation have depending on the species. Extremely strong agitation occurs in the cat, and in ruminants are rabiform manifestations.

The multiple aspects of the use of morphine in veterinary therapy, its indications and contraindications will be discussed.

4. Pharmacography

Rp./

Chlorali hydrati 30,0
Aq distill q.s.ad 300,0
M.f sol. Sterilisetur
D.S ext. i.v. to horse

Rp./

Chlorali hydrati 20.0
Alcholi dil 80.0
Sol natrii chlorati izotonici 200.0
M.f sol.
D.S. ext. i.v. to horse

Rp./

Alcholi 1000 ml
Aquae 2000 ml
M.f. sol.
D.S. int to cow of 500 kg

Rp./

Chloralosi 2.0
Aq. Distill q.s.ad 100.0
M.S. ext. i.v. to a 40 kg sheep

Rp./

Urethani 3.0
Aq. Distill ad. 100.0
M.f. sol.
D.S ext. i.v. to a rabbit as 3 mL/kgbw

Rp./

Phenobarbitali 10% 2 ml fiole III
D.S .ext. i.v. to dog

5. Classification

CNS modifiers		
Group	**Subgroup**	**Representatives**
Depressing substances	**Central anesthetics**	**Inhaling**: Clorophorm, Ether, Ethylchlorine, Halotan
		Fix And Hypnotic: Chloralhidrate, Chloralose, Avertine, Ethylic Alcohol, Urethane
		Barbiturates: Fenobarbital, Barbital, Dormital, Baytinal, Pentotal, Magnesium Sulphate
		Motor Sedatives **Natural:** Bromures, Valeriane **Major:** (Neuroplegics) Largactil, Romtiazin **Minor** (Tranquilizers) Meprobamate
Analgezics & Antipyretics	Opiates	Morfine, Dionin, Heroin, Codenal, Papaverine, Hidromorphone
	Synthetics	Polamivet, Mialgin
	Antithermic	**Salicilates:** Na Salicylate, Aspirin Methyl salicilate, Anilinics, Acetanilide, Fenacetine **Pyrazolonics:** Antipirina, Amidopirin, Algocalmin **Quinoleinics:** Quinine
Local anesthesics	Cocaine	Cocaine
	APAB derivatives	Anesthesine, Procain, Tutocain
	Acetanilides	Xiline (Lidocaine)
	miorelaxants	Currara
Excitant substancs		Cafein, Camphor, Pentetrazol, Nicetamide, Stricnine, Veratrin, Lobellin