

PHARMACOKINETIC, AND PHARMACODYNAMIC PRINCIPLES OF RATIONAL USING OF GENERAL AND LOCAL ANESTHETICS, OPIOID ANALGESICS AND ANTIPYRETICS

A. Actuality

Acute and chronic pain therapy is and will be one of the most important problems of medicine. To now the pharmacokinetics and pharmacodynamics of drugs from different groups used in the treatment of acute or chronic pain, allows a rational selection of anesthetics, adequate associations of different drugs, and establishment of the best dosing regimen.

The study of anaesthetic drugs as well as of those that mitigate the pain, modify psychic state, functional activity of vital organs and presents a great importance for anesthesiology. Anaesthesia assures pain abolition, good functioning of vital important organs and systems, facilitates the operations' performance and post anaesthetic and postoperative recuperation.

B. Training aim

To study the pharmacological and clinical principles underlying the use of analgesics and anesthetics : suitable selection of drugs for pain treatment, dosing adjustment and estimation of general and local anaesthetics, opioids analgesics and antipyretics effectiveness.

C. Teaching objectives:

The student must have the skills to:

- a) Select the investigation methods in assessing the pharmacodynamic effect of local and general anaesthetic, opioid analgesic and antipyretic drugs.
- b) Analyze and appreciate the results of pharmacodynamic study of drugs used in pain therapy, obtained through laboratory and instrumental methods.
- c) Predict the possible complications and side – effects of anaesthetic and analgesic drugs.
- d) Predict the dependence of side – effects to the dosage regimen and the functional state of the body organs and systems;

D. Knowledge from previous studied disciplines and related subjects

Histology, morphopathology, physiology and microbiology.

Vertebral column, peripheral and central nervous system anatomy. Nervous fibers classification, conduction trough the nervous fibers. Notion of pain and pain reception. Notion and classification of nociceptors. Superior integration of pain, modification of nociceptive messages in nervous system. The role of P - substance and bradykinin in pain modulation. Role of endorphins in pain transmission.

Clinical disciplines. Acute and chronic pain pharmacotherapy in internal medicine, surgery, anesthesia, and reanimation. Preanaesthetic examination, preoperative and preanaesthetic sedation. Notion of surgery and anaesthetic risk, fundamental criteria of anaesthesia. Preoperative preparations of patients with broncho – pulmonary affections, cardiac failure, diabetes, hemophilia, obesity, nervous and muscles affections. Signs and stages of general anaesthesia.

Pharmacology. Classifications of general and local anaesthetics, opioid analgesics and antipyretics. Mechanisms of action, clinical effects, indications, side-effects: prevention and treatment.

F. Questions for self training:

1. General anaesthetics. Classification. Mechanisms of action.

2. Pharmacokinetics and pharmacodynamics of inhalational general anaesthetics (desflurane, halothane, enflurane, nitrous oxide, etc.). Clinical uses, contraindications and side-effect.

3. Peculiarities of inhalational general anaesthetics usage in pediatric, in patients with cardiac and hepatic disorders, in obese patients. Dosage regimen and efficiency control.

4. Pharmacodynamic and pharmacokinetic peculiarities of inhalational general anaesthetics used for general anaesthesia in patients with septic and hypovolemic shock.

5. Clinical pharmacology of intravenous general anaesthetics:

a) barbiturates (hexenal, thiopental);

b) benzodiazepines (diazepam, flunitrazepam, midazolam, lorazepam);

c) fenciclidins (ketamine). Dissociative anesthesia.

6. Pharmacokinetic and pharmacodynamic peculiarities of intravenous general anaesthetics used in septic patients with hypovolemic (traumatic, hemorrhagic etc.) shock.

7. Interaction of intravenous and inhalational general anaesthetics with drugs from other groups: adrenoceptor activating drugs, cardiac glycosides, antibiotics, myorelaxants, antihypertensive, anticoagulants, hypoglycemic drugs.

8. Side-effect in intravenous and inhalational general anaesthetic use. Clinical symptoms, prophylaxis and control measures.

9. Clinical pharmacology of local anaesthetics: classification according to activity, toxicity, duration and latency of action. Pharmacokinetic and pharmacodynamic properties of local anaesthetics.

10. Clinical uses of local anaesthetics. Side effects, their prophylaxis and treatment.

11. Clinical pharmacology of opioid analgesics and their antagonists.

12. Peculiarities of opioid analgesic use in children, old people, cardiac, hepatic, obese patients, diabetics, drug addicts. prophylaxis and treatment of side – effects produced by opioids. Non-opioid analgesics with central action.

13. Clinical pharmacology of opioid analgesics antagonists.

14. Clinical pharmacology of non-opioid analgesics with central action.

15. Antipyretic analgesics, classification, role in pain control, mechanism of action, their association with other analgesics. Side – effects, their prophylaxis and treatment.

16. Peculiarities of anaesthetics and analgesics use in pregnant women.

D. Supplement for students

of stomatological faculty

1. Peculiarities of general and local anaesthetics use in stomatological diseases.

2. Pharmacodynamic and pharmacokinetic aspects of opioid analgesics and antipyretics use in stomatological disorders.

General medicine

1. Peculiarities of anaesthetics and analgesics use in infants and children.

E. Short characteristic of main drugs

Vertically: drugs' names

Horizontally: synonyms, delivering forms, administration routes, and doses (therapeutic, maximum), indications, contraindications, side-effect.

1. Diethyl ether

2. Halotane

3. Cyclopropane

4. Nitrous oxide

5. Enflurane

6. Methoxyflurane

7. Procaine

11. Midazolam

12. Diazepam

13. Ketamine

14. Propanidide

15. Morphine clorhidratum

16. Fentanyl

17. Pentazocine

8. Lidocaine
9. Bupivacaine
10. Thiopental

18. Naloxone
19. Diclofenac
20. Paracetamol
21. Baralgine

F. Exercises on medical prescription

Indicate medicines for:

- 1) Painful acute myocardial infarction
- 2) Traumas and burns
- 3) Acute toothaches
- 4) Contact anaesthesia
- 5) Conducting anaesthesia
- 6) Epidural anaesthesia
- 7) Infiltrative anaesthesia
- 8) Analgesic potentiation of anaesthesia
- 9) Traumatic shock, combustions
- 10) Incurable cancer
- 11) Biliary colic
- 12) Induction of general inhalational anaesthesia
- 13) Overdosage of opioid agonist analgesics
- 14) Anaesthesia for short surgery.

I. General and local anaesthetics, opioid analgesics and antipyretics selection according to efficiency, innocuousness, acceptability and cost criterions in order to include them in personal form (P - medicines)

PHARMACOKINETIC AND PHARMACODYNAMIC PRINCIPLES OF RATIONAL USING OF ANTI-INFLAMMATORY, ANTI-ALLERGIC AND INFLUENCING IMMUNE PROCESSES DRUGS

A. Actuality

Inflammation is an universal reaction of organisms to the action of different endogenous and exogenous harmful factors. Doctors' interest for inflammatory process has increased at the same time with the inflammation mediators' discovery, especially of prostaglandins.

Technical and scientific progress modified significantly the environment, this favoring the vertiginous growth of allergic affections incidence and weakening of immunity.

Nowadays, a large arsenal of anti-inflammatory, antiallergic and immunomodulatory drugs are available. For an efficient and rational using of those drugs it is important to know their pharmacokinetic and pharmacodynamic peculiarities.

B. Training aim

The studying and applying of pharmacokinetic and pharmacodynamic principles for individualization and optimization of anti-inflammatory, immunomodulatory and antiallergic drugs administration.

C. Teaching objectives:

The student must be able to:

- a) Select the minimum complex of investigational methods concerning pharmacodynamic effect estimation of anti-inflammatory antiallergic, immunomodulatory drugs.

- b) Analyze and estimate the pharmacodynamic study results of anti-inflammatory, antiallergic, immunomodulatory drugs, obtained by laboratory and instrumental methods.
- c) Prognose possible side-effect reactions and complications.
- d) Prognose the dependence of side - effect by dosing regimen and functional state of body organs and systems.
- e) Apply contemporary methods of pharmacological and non- pharmacological correction of adverse reactions produced by drugs from these groups.

D. Knowledge from previousy studied disciplines and related subjects

Biological subjects. Inflammation. Basis components of inflammatory process: alteration, vascular reactions with exudation and phagocytosis, proliferation. Classification of inflammation mediators. Interdependence of alteration and protection and adaptation reactions within inflammatory process.

Pharmacology. Classification of anti-inflammatory remedies according to their pharmacological effect and chemical structure. Mechanism of action. Pharmacodynamics. Pharmacokinetics.

Classification of anti-allergic and affecting immune system drugs. Mechanism of action, pharmacological effects, indications, side - effects.

E. Questions for self training

1. Anti – inflammatory drugs classification
 - a) steroid anti – inflammatory drugs
 - b) non-steroidal anti – inflammatory drugs
 - with immediate effect (short duration)
 - slow- acting (basic, antirheumatic) agents
2. Modern concept about mechanisms of action of anti – inflammatory and immunomodulatory drugs.
3. Steroid anti – inflammatory drugs. Corticosteroids. Classification. Division in natural and synthetic steroids. Anti – inflammatory, immunosuppressive and anti-allergic marked possessions.
4. Glucocorticoids. Pharmacokinetics. Important metabolic actions. Indication for glucocorticoid medication. Dosing principles, selection of dose, treatment cure duration depending on disease character and severity, functional state of liver, kidneys, adrenal cortex.
5. Drug interactions in case of associated administration of glucocorticoids with other remedies. Rational associations of glucocorticoids with non-steroidal anti-inflammatory drugs.
6. Side - effects in glucocorticoid medication. Corticoid dependence. Adrenal suppression, clinical manifestations. Prophylactic, control methods.
7. Non - steroidal anti-inflammatory drugs with immediate effect. Their division according to duration of action, activity, tolerance. Salicylic acid derivates: acetylsalicylic acid, salicylamidum, benorilate, diflunisal, sodium salicylate, aloxiprinum, salsalate. Mechanism of action, indications, contraindications, side – effects, analgesic, antiplatelet and antipyretic properties.
8. Pyrazolone derivatives: phenylbutazone, phenazone, oxiphenbutazone, azapropazone, pheprozone, benetazone, their usage in rheumatoid affections. Side-effect reactions and their prophylaxis. Pharmacokinetic aspects.
9. Indole acid derivatives indomethacin, sulindac. Pharmacokinetic and pharmacodynamic peculiarities, clinical use, possible complications, their prophylaxis.
10. Phenylacetic acid derivatives: diclofenac, alclofenac, tolmetin. Pharmacokinetic and pharmacodynamic, peculiarities of administration. Side – effects.

11. Propionic acid derivatives: ibuprofen, ketoprofen, flurbiprofen, fenoprofen, naproxen, carprofen. Mechanisms of action, pharmacokinetic aspects. Anti-inflammatory, analgesic and antipyretic properties.

12. Oxicams used as anti-inflammatory drugs: piroxicam, tenoxicam, izoxicam. Their pharmacokinetics. Indications, side-effects.

13. Fenamates and N-aryl-antranilic derivatives: flufenamic acid, mefenamic acid, niflumic acid. Anti-inflammatory and antipyretic potency. Clinical use. Side-effects.

14. Disease modifying, slow-acting antirheumatic (DMARDs). Classification. Gold compounds: aurothiomalate sodium, aurothioglucose, aurothiosulfate sodium, auranofin. Mechanism of action, pharmacokinetics and pharmacodynamics. Peculiarities of clinical use, dosing regimen, adverse reactions.

15. 4-aminoquinoline derivatives (antimalarial drugs): chloroquine and hydroxychloroquine. Therapeutic benefits of antimalarial drugs in rheumatic affections. Mechanism of action, pharmacokinetic and pharmacodynamic peculiarities. Possible complications at a durable treatment.

16. Penicillamine, action on cell immunity. Indications and usage methods. Drug properties. Administration peculiarities and contraindications. Tiopronine drug-recently introduced in therapy, penicillamine analog. Usage peculiarities.

17. Sulfasalazine and levamisole. Mechanism of action. Action peculiarities and their efficiency in rheumatoid arthritis.

18. New DMARDs - leflunomide, infliximab, etanercept. Mechanism of action, pharmacokinetic and pharmacodynamic peculiarities. Adverse reaction.

19. Classification of drugs used in immediate and delayed allergic reactions. Pharmacokinetics and pharmacodynamics aspects.

20. Immunosuppressive drugs. Classification. Glucocorticoids, cytotoxic-alkylating agents (cyclophosphamide, doxorubicin, chlorambucil) and antimetabolites (mercaptopurine, azathioprine, methotrexate). Mechanism of action. Action on immune mechanisms.

21. Clinical usage of immunosuppressive drugs. Their role in suppression of autoimmune process in allergic and infectious diseases, in transplantation tissue incompatibility. Complications that appear during treatment with immunosuppressive drugs.

22. Other drugs with immunosuppressive action: cyclosporine, anti-lymphocyte globulins. Peculiarities of usage in rheumatic diseases and transplantation.

23. Drugs with immunostimulatory effect: levamisole, thalidomide, pirogenol, prodigiosin, sodium nucleate. Classification, mechanisms of action. Patient's selection for immunostimulatory treatment. Using of immunostimulatory drugs in treatment of collagenosis. Treatment and efficiency control. Side-effect reactions.

24. Antihistaminic drugs. Classification. H₁-receptor blockings, pharmacodynamics and pharmacokinetics. Clinical usage and dosing tactics. Side-effects.

25. Remedies blocking the histamine secretion. Mechanism of action. Peculiarities of pharmacokinetic and clinical using.

F. Supplement for students of stomatological faculty

1. Non-steroidal anti-inflammatory drugs used in stomatology (salicylates, pyrazolidinone derivatives, antranilic, phenylacetic acid derivatives etc.) for treating rheumatoid arthritis, temporomandibular joint arthritis, myalgias, neuralgias and other inflammatory affections of maxillo-facial region, lupus erythematosus and other collagenosis.

2. Use of antranilic acid derivatives (mefenamic acid) in local therapy of ulcerous affections of buccal mucosa for improving regeneration processes.

3. Stomatological complications in non-steroid anti-inflammatory drugs medication. Stomatitis developed after a long period of pyrazolidinone derivatives usage.

4. Glucocorticoids use in stomatology (enteral and local) for treating maxillo-facial inflammations, infection-allergic diseases: paradontosis, cheilitis, lupus erithematosus, arthritis and arthrosis of temporo - mandibular articulation.

5. Anti-inflammatory steroids using in make-up of drugs used for treating pulpits (biological method). Stomatological complications in cortizonic medication (osteoporosis and osteomalacia, dental email necrosis and multiple caries development), calcium and potassium drugs usage for their prophylaxis.

G. General medicine

Pharmacokinetic and pharmacodynamic disposition of non-steroidal, steroidal anti - inflammatory, antiallergic and immunomodulating agents in infants and children.

H. Short characteristic of main drugs

Down: drugs names

Across: synonyms, delivering forms, administration roads, doses
(therapeutic, maximum), indications, contraindications, side-effect reactions.

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|--------------------------------|------------------------------|
| 1. <u>Acetylsalicylic acid</u> | 28. Chlorambucil |
| 2. Lazine acetylsalicylat | 29. Mercaptopurine |
| 3. Diflunisal | 30. <u>Azathioprine</u> |
| 4. Salicylamide | 31. Methotrexat |
| 5. Sodium salicylate | 32. <u>Cyclosporine</u> |
| 6. Methyl salicylate | 33. Antilymfocytis globuline |
| 7. Phenylbutasone | 34. <u>Levamisol</u> |
| 8. Oxyphenylbutasone | 35. <u>Timaline</u> |
| 9. Benethasone | 36. <u>Acetaminophen</u> |
| 10. <u>Indomethacin</u> | 37. <u>Prednizolon</u> |
| 11. Sulindac | 38. Methylprednizolon |
| 12. <u>Diclofenac</u> | 39. Triamcinolone |
| 13. Tolmetin | 40. <u>Dexamethasone</u> |
| 14. <u>Ibuprofen</u> | 41. Betamethasone |
| 15. Ketoprofen | 42. Hydrocortisone |
| 16. <u>Naproxen</u> | 43. <u>Difenhidramine</u> |
| 17. <u>Piroxicam</u> | 44. Prometazine |
| 18. <u>Mephenamic acid</u> | 45. Chloropiramine |
| 19. Flufenamic acid | 46. <u>Clemastine</u> |
| 20. Sodium aurotiomalat | 47. Quifenadine |
| 21. Aurotioglucose | 48. Chlorfenamine |
| 22. <u>Auronafine</u> | 49. Astemizole |
| 23. <u>Chlorochine</u> | 50. Terfenadine |
| 24. Hydrochlorochine | 51. <u>Loratadine</u> |
| 25. <u>Penicilamine</u> | 52. <u>Ketotifenum</u> |
| 26. <u>Sulfasalazine</u> | 53. Disodoc cromoglicat |
| 27. <u>Cyclofosfamide</u> | |

I. Exercises on medical prescription

Indicate drugs for

1. Rheumatism
2. Rheumatoid arthritis

3. Primary degenerate arthrosis
4. Lupus erithematosus
5. Sclerodermia
6. Dermatomyositis
7. Ankylosic spondilarthritis
8. Gout
8. Glomerulonephritis
9. Anaphylactic shock
10. Bronchial asthma accesses
11. Urticaria
12. Contact dermatitis
13. Quincke's edema
14. Recovery period after infections.