Odesa National Medical University
Department of General and Clinical Pharmacology and Pharmacognosy

PHARMACOTOXICO-DYNAMICS

STATISTICS

In hospitals – side effects occurs in 4-29% of patients; responsible for 0,24-2,9 % of lethal outcomes (5 position) and 0,3-5 % cases of admitting to hospitals

HISTORICAL NOTES

- **1870-1890 –first commission for investigation of sudden death cases at chloform usage**
- **1922 - jaundice at salvarsan use (syphilis treatment)**
- **1937 – death of 107 individuals after sulfanilamide usage because of presence of diethylen glycol as solvent**
- **1961 – «thalidomide disasaster», phocomely in 10000 kids**

DEFINITIONS

Side effects SE – any unfavorable reaction determined by pharmacological properties of medicine and appeared at therapeutic doses

Side reaction SR – unfavorable hazard for health reaction, when the link between reaction appearance and medicine application can not be excluded

Types of SR - possible, reliable, unforeseen, foreseen etc.

Side phenomenon - any unfavorable medical manifestation that not necessarily connected with medicine's application (alteration of lab indexes, symptoms, disease that coincide with medicine's application)

DEFINITIONS

Predicted SE – has certain clinical symptoms (parkinsonism in case of aminazin usage; hypertension in case of glucocorticoids usage)

Unpredicted SE – appear rarely, not necessarily connected with pharmacologic action of drug, not described in literature

According to character of SE development – direct and indirect

According to localization — local and systemic

CLASSIFICTION

According to severity of clinical course of SE –

- **mild** – there are no necessity of drug's withdrawal of special treatment, side action disappear at dropping of drug's dosage
- **intermediate** – drug's withdrawal and special treatment are needed
- **severe** [live-threatening syndromes, for example complete atrio-ventricular blockage], fatal.

SAFETY OF MEDICINES

- Lethal outcomes because of SE are on the 5-th place (after cardiovascular diseases, pulmonary diseases, cancer and traumas)
- economical losses in result of SE in USA are estimated in 76.6 millions per year
- Around 8000 medicines are registered in Ukraine
- In UK – in result of NSAIDs usage 2000 patients with GI bleeding and 200 lethal outcomes are registered per year

SAFETY OF MEDICINES

- **Frequency of drugs' complications**
  - **Aged patients 14,2 %**
  - **Kids 12,7 %, out of them under 3 years – 29,2%**
  - **In hospitalized kids 23 %**
  - **The reason of hospital admission in kids 3,4%**
- **One-third of SE potentially can be prevented (rational usage of medicines – physician's mistake or non-compliance of patients)**
- **13,6 % patients with SE die (equal to number lethal outcome from car accident, HIV, breast cancer)**

REASONS OF SE

Frequency SE appearance depend on

- **individual peculiarities**
- **gender, age of patient**
- **severity of main and associated disease**
- **pharmacodynamics and pharmacokinetis**
- **dosage, duration of treatment**
- **ways of drugs' administration, drugs' interactions**

More common SE in cardiac glycosides, aspirin, glucocorticoids, diuretics, hypotensive agents indirect anticoagulants, antibiotics, potassium-containing agents, analgesics, tranquilizers, anti-diabetics agents

ANALYSIS OF MISTAKES

- mistakes of choice and dosage of medicines – 56 %
- polypragmasia – 53,2 %
- underestimation of anamnesis – 47,7 %
- incorrect duration and dosage alteration – 34%
- Iatrogenic reactions (fault of nurses and pharmacists) 10 %
- inappropriate spreading of information pharmaceutical companies – 28 % physician mistakes
- mismatch with standards of instructions 42% medicines
- 30 % of drugs are falsificated

DRUGS FALSIFICATION

- 12 620 names of medicines, out of them 70,1% imported and 29,9 % — ukrainian
- Analysis of 122 000 samples – 4 000 are not matching standards, 408 – falsification
- 25 series are rejected - omez, nisoral, levomycetin, biseptol, essentiale, no-spa, brilliant green.
- 60 % of falsifications in the world do not contain active substance, in Ukraine – active substance is present
- Common falsifications – biseptol, no-spa, antibiotics, viagra

DRUGS FALSIFICATION

- Falsification — intentional alteration of drugs making – substitution of expensive components by more cheap ones, decreasing of content or absence of essential component, violation of time and technological processes, depreciation of purification, low-quality package materials etc
- Third-world countries - 50%
- USA - 10-20%, Europe - 2-5%, Ukraine - 1,5—1,8% of market capacity (more low quality drugs – 30-40%)
- According to Ministry of health of Ukraine - 0,3%, substandard - 3,2% (that have lost therapeutic action in result of incorrect storage)

DRUGS FALSIFICATION

- counterfeit - medicines, that have been produced without permission of patent-holder (company-creator), percentage of counterfeit medicines in Ukraine is higher, than falsificated agents from total volume of market
- Brand (INN – international non-appropriate names) – original medicines
- Generics – reproduced medicines
- Ukraine – 14 000 medicines are registered out of which 90%– generics, (official copies of original medicines)
- generics are cheaper than original medicines
- 132 fluconazol variatons, 114 - ceftriaxon

MEDICINES THAT OFTENLY CAUSE SR

- ☹ ANTIBIOTICS – 42 %
- ☹ NSAIDS
- ☹ Cardiovascular agents
- ☹ Hormones – 20 %
- ☹ Metronidazol, co-trimoxazol, viagra, no-spa

Countries: Poland, Bulgaria, India, Russia

MANIFISTATIONS OF SR

SR are manifistated as

- **GIT disturbances**
- **skin problems**
- **changing of potassium level in blood**
- **disturbances of haemopoiesis and blood hemostasis**
- **allergic reactions**
- **psychical disturbances**
- **toxicity of liver, kidney, cardiovascular system**
- **endocrine disturbances**
- **sexual problems**
- **respiratory disturbances**

STATISTICS

Reasons of lethal outcomes SR of medicines

- GIT bleeding and peptic ulcer (glucocorticoids, NSAIDs, anticoagulants)
- other types of bleeding (anticoagulants, cytostatics)
- aplastic anemia (levomycetin, phenylbutazon, aurum-containng agents, cytostatics)
- liver injury (chlorpromazin, isoniazid, tetracyclin)
- kidney injury (NSAID, aminoglycosides)
- decreasing of resistance to infections (cytostatics, glucocorticoids)
- allergic reactions (penicillins, novocain).

REASONS OF SR

Reasons of SR

- Not linked with medicine
  - Connected with peculiarities of patient's organism (age, gender, genetic peculiarities, predisposition to allergic reactions, peculiarities of disease, harmful habits)
  - Connected with environmental factors (for instance, iatrogenic)
- That depend on medicine
  - Choice of medicine
  - Pharmacodynamic and pharmacokinetics peculiarities
  - Ways of drug's administration
  - Drugs interaction

CLASSIFICATION OF SR

- ✓ **Dose-dependent, organotoxic – A:**
  - **linked with pharmacologic activity**
  - **at absolute or relative overdosing of medicine**
  - **in result of drugs interaction**
- ✓ **Dose-independent (unpredictable) B:**
  - **immunologic reactions**
  - **pseudoallergic reaction**
  - **pharmacological variability**
  - **at local application**

CLASSIFICATION OF SR

- ✓ In case of prolong use:
  - adaptation changes
  - at drug's withdrawal («rebound» and «withdrawal» phenomenon)
  - organotoxicity
- ✓ delayed actions:
  - blastomogenic (cancerogenic)
  - action, related to reproductive system

  infertility, mutagenic, teratogenic, embryotoxicity, penetration into breast milk

SIDE REACTIONS TYPE A

- ✓ **Linked with pharmacologic activity – determined by:**
  - ❖ ***pharmacologic* actions of medicine (atropine, neuroleptics)**
  - ❖ ***pharmaceutical* (pyrogenic, changes of ingredients)**
  - ❖ ***pharmacokinetics* (modification of absorption, biotransformation)**
  - ❖ ***pharmacodynamics* (liver diseases, water-salt disbalance)**
  - ❖ ***pharmacogenetic* abnormality (slow and rapid «acetylators»)**
  - ❖ ***usage of large doses or overdosing of medicines, drugs interaction***

Drugs with narrow wideness of therapeutic action: heparin, cardiac glycosides, lidocain, gentamicin

SIDE REACTIONS TYPE A

- ✓ Caused by relative or absolute overdosing of medicines
- absolute – intake of larger dosage (vasodilators - collapse, analeptics – seizers, hypnotic – general anesthesia)
- relative –dose is therapeutic, but concentration in blood and in cells to much high because of peculiarities of drug's pharmacokinetics in the patient (diseases of liver, kidney, genetic profile)

Digoxin – hypoproteinemia

SIDE REACTIONS TYPE B

✓ **Include:**

- ***immunobiological disturbances*** **(drug-induced dysbacteriosis, glucocorticoid-caused immunodeficience)**
- ***immune disturbances*** **(allergy- skin rash caused by antibiotics, tetracyclin-induced photosensitivity, novocainamid-caused SLE)**
- ***pseudoallergy*** **(aspirin asthma and rash, ampicillin - erythema)**
- ***pharmacogenetic determined reactions*** **(idiosyncrasy), clinked with enzymopathy (usage of sulfanilamided in persons with G-6-6-PDG – hemolytic anemia, drugs of addiction – malignant hyperthermia)**

SIDE REACTIONS TYPE 3 and 4

✓**Linked with dose and duration of drug's usage:**

- ***Adaptation changes*** **(long usage of β-adrenomimetics for bronchial asthma – declining of receptors sensitivity, long-time usage of psychotropic agents – tolerance and addiction)**
- ***«Rebound» (hypnotics) and «withdrawal»*** **(glucocorticoids)** ***phenomenon***
- ***organotoxicity and systemic toxicity effects*** **(chloroquin – keratopathy, amiodarone – pulmonary fiborisis)**

✓**Cancerogenic (oral contraceptives- hepatic cancer), mutagenic (anti-cancer), decreasing of fertility – impotency, infertility (MAO inhibitors, sulfasalazin, chlorbutin, cyclophosphan)**

AGENTS WITH TERATOGENIC EFFECTS

- **Tetracyclin – hypoplasia of teeth enamel**
- **Lithium – inborn diseases of heart, goiter, hypotension**
- **Diazepam – hypothermia, hypotonia, abnormalities of extremities**
- **Aspirin – neonatal bleeding**
- **Indomethacin – neonatal hypertension of pulmonary vessels, death of fetus**
- **Warfarin – atrophy of nervous optics, convulsions, bleeding, death of fetus**
- **Phenobarbital – CNS inhibition, impairment of hearing, anemia, tremor, withdraw syndrome, hypertension**

TERATOGENIC MEDICINES

- **Phenytoin – abnormalities of extremities and facial cranium, bleeding**
- **Valproate sodium – spina bifida**
- **Chlorthiazide – cholestasis, pancreatitis**
- **Reserpine – lethargy, hypothermia, bradycardia**
- **Methotrexate – absence of lobe bone**
- **Chlorpropamide – abnormalities of development, hypoglycemia**
- **Vitamin A (10000 IU) – defects of cardiovascular system**

MEDICINES BANNED DURING PREGNANCY

- **Androgens – shortening of extremities, defects and anomaly of cardiovascular and GIT**
- **Streptomycin – deafness**
- **Ergotamin, disulfiram – spontaneous abortion**
- **Quinin – ototoxicity, inborn glaucoma, abnormalities of urogenital tract, death of fetus**
- **Iodide131 – cretinism, hypothyreoidism**
- **Trimethadon – cardiac and ophthalmic abnormalities**

MEDICINES THAT ARE PROHIBITED DURING PREGNANCY

- **Alcohol – growth retardation, decreasing of lactation, dizziness**
- **Amphetamines – insomnia, nervousness**
- **Bromcriptin – decreasing of lactation**
- **Levomycetin – bone marrow depression**
- **Cocaine – withdrawal syndrome**
- **Metronidazol – cancerogenic and mutagenic effects**
- **Salicylates – rashes, metabolic acidosis**
- **Iodide121 – risk of thyroid gland cancer**

MEDICINES THAT NEED CAREFUL PRESCRIPTION DURING PREGNANCY

- Amantadin – urine retention, nausea, skin rash
- Diazepam – sedative effect, cummulation in children
- Indomethacin – convulsions
- Estrogens – feminization
- Isoniazid – pyridoxine deficiency
- Sulfanilamides – jaundice of newborns

DATA RELATIVELY HERBAL DRUGS SAFETY

- Hepatotoxicity – foalfoot, sena, valeriana, magnolia
- Acute renal failure – Chinese plants (magnolia, stephania)
- Hepatotoxicity, mutagenic and cancerogenic actions – asters, beans, foalfoot (containing pyrazidon derivatives)

Are prohibited in many countries (Germany, France, Belgium etc.)