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아동약물요법 적용의 기본 원리 I

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아동약물요법 적용의 기본원리

- **Pharmacokinetic principles**
- **Drugs used to manage pain**
- **Management of status epilepticus**

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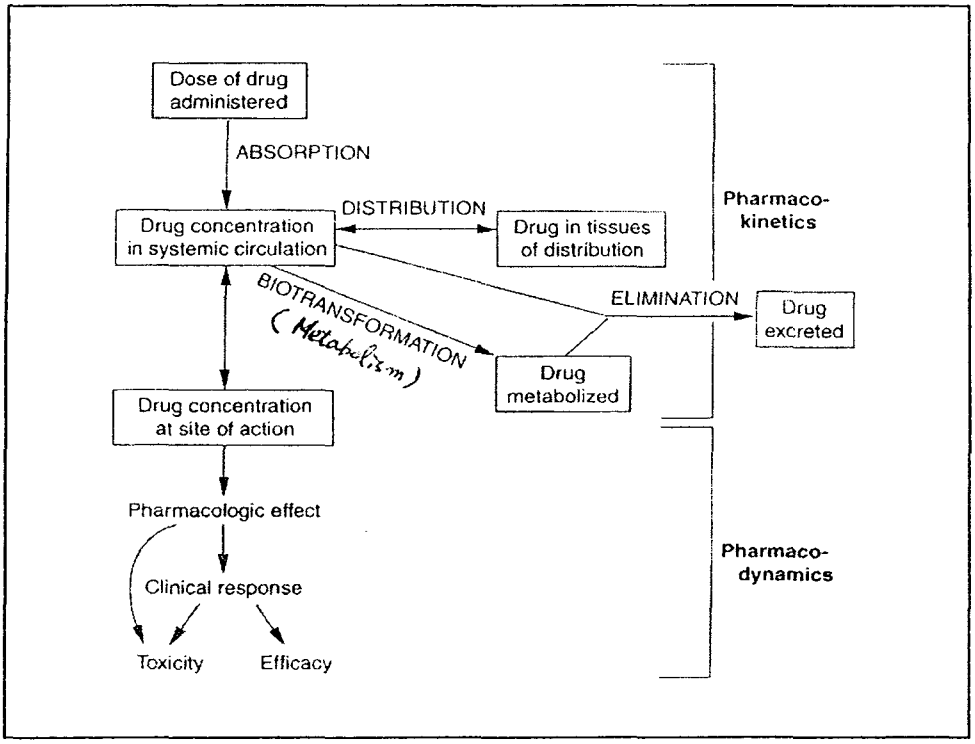
Drug-Body Interactions

- **Pharmacodynamics** (약력학)
  - The actions of a drug on the body
  - Receptor interactions
  - Dose-response phenomena
  - Mechanisms of therapeutic and toxic action
  - Actions, effects, and action mechanism of drugs
- **Pharmacokinetics** (약동학; 약물동태학)
  - The actions of the body on the drug
  - Absorption, Distribution, Metabolism, Excretion (ADME)
  - Bioavailability (생체이용률)
  - Half-life (반감기)

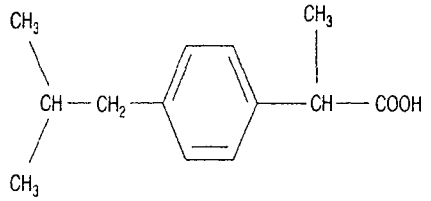


Pediatric Pharmacology

- **Pediatric patients: defined as those younger than 18 years of age**
  - ***Premature***: newborn infants born before 37 weeks of gestational age
  - ***Neonates (newborns):*** 0-28 days
  - ***Infants:*** 1-24 months
  - ***Children:*** 1 year to 12 years of age
  - ***Adolescents:*** 12 to 16 years
- Infants and children are not "small adults" in the way their bodies handle drugs
- Rapid and important age-related physiologic changes in drug metabolism and elimination occur in children, especially during the first year of life.
  - Elimination half-life of phenytoin: initially prolong, gradually shortens during the first few months of life
  - Elimination half-life of furosemide
    - Premature infants: 15-20 hours
    - 3 months old: less than 1 hour

Drug Names

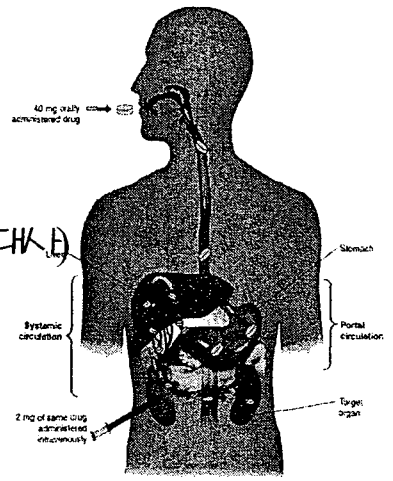
- **Chemical name:** 화학명
  - Exact chemical makeup of the drug and placing of the atoms or molecular structure; it is not capitalized
- **Generic name (nonproprietary name):** 일반명, 성분명
  - Name given to a drug before it becomes official
  - Maybe used in all countries, by all manufacturers; it is not capitalized
- **Trade name (brand name):** 상품명
  - Name that is registered by the manufacturer and is followed by the trademark symbol (enforced by copyright laws worldwide)
  - The name can only be used by the manufacturer
  - A drug may have several trade names
  - The first letter of the name is capitalized.

Chemical name (+/−)-2-(p-isobutylphenyl) propionic acid **Generic name** ibuprofen **Trade name** Motrin	

NSAIDs: nonsteroidal anti-inflammatory drugs (비스테로이드성 항염증약물)

Pharmacokinetics (약동학)

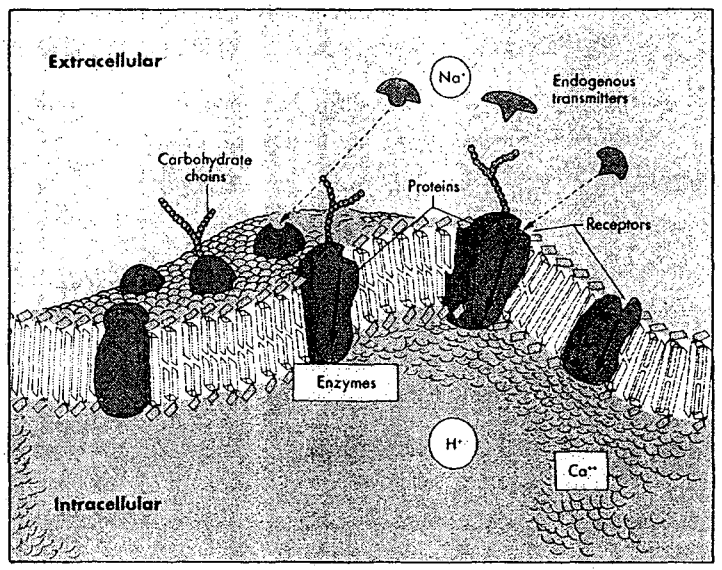
- Absorption (흡수)
- Distribution (분포)
- Metabolism (Biotransformation, 대사)
- Excretion (배설)



Absorption

<Rate and extent of absorption>

- **Route of administration**
  - PO: liquid medications are absorbed faster than tablets or capsules
  - IV, IM, SC
  - Transdermal: adhesive skin patches (clonidine, estrogen, fentanyl, nitroglycerin, scopolamine)
  - Mucosa of the oral cavity, nose, eye, vagina, rectum: systemic absorption
  - Lungs
- **Lipid solubility of the drug**
- **Gastrointestinal function**
  - Gastric emptying time is prolonged (up to 6-8 hours) in the first day or so after delivery
  - Presence of food in the stomach
- **Presence of certain body conditions:**
  - Lipodystropy (atrophy of the subcutaneous tissues)



Absorption

<Absorption from the GI tract>

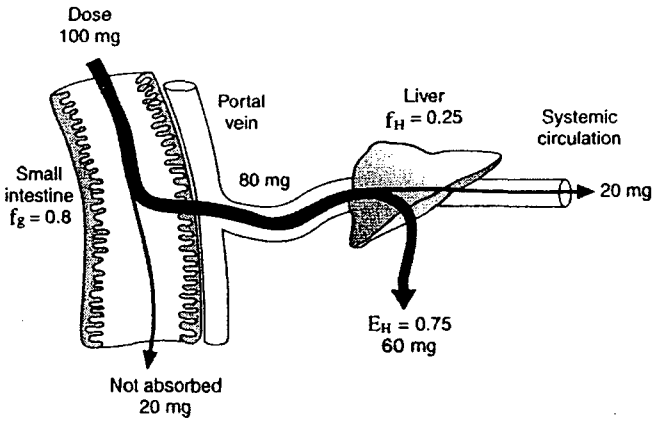
- **Diminished intestinal motility and delayed gastric emptying in neonates and infants:** longer periods of time for a drug to reach therapeutic plasma concentrations after oral administration
  - Acetaminophen, penicillin G, phenobarbital, phenytoin
- **Change of bacterial flora during the newborn period:**
  - Absorption of vitamin K and other lipid-soluble vitamins
  - Hydrolysis of drug conjugates that are excreted in bile
- **Disease conditions:** diarrhea, giardiasis, cystic fibrosis, celiac diseases

<Absorption from intramuscular injection sites>

- **Local factors: blood flow to and from the injected muscles**
  - Low cardiac output, respiratory distress syndrome, and other circulatory disturbances
  - Degree of muscular activity: immobile infants
  - Cardiac glycosides (digoxin, digitoxin), aminoglycosides, anticonvulsants

Bioavailability (생체이용률)

- **Bioavailability:** defined as the fraction of the dose which reaches the systemic circulation as intact drug
  - Expressed as F (%)
- **First-Pass Elimination (First-pass effect):** 초회통과효과
  - Is the extent to which a drug is removed by the liver during its first passage in the portal blood through the liver to the systemic circulation
- **Examples of drugs that undergo substantial first-pass elimination**
  - Aspirin, glyceryl trinitrate, isosorbide dinitrate, levodopa, lidocaine, metoprolol, morphine, propranolol, albuterol (salbutamol), verapamil



Bioavailability (F) = fraction absorbed (f_g) x fraction escaping first-pass clearance (f_H)
F = 0.8 x 0.25 = 0.2 (20%)

Bioavailability of selected drugs (neonates vs. older children)

DRUG	ORAL ABSORPTION
acetaminophen	Decreased
ampicillin	Increased
diazepam	No change
digoxin	No change
penicillin G	Increased
phenobarbital	Decreased
phenytoin	Decreased
sulfonamides	No change

Distribution

- Distribution involves the transport of drug molecules within the body
  - Systemic circulation distributes drugs to various body tissues or target sites.
  - Drug molecules enter and leave the blood stream through the capillaries
  - Depends largely on the adequacy of blood circulation
- Some drugs travel by binding to protein (albumin) in the blood.
  - Drugs interact with specific receptors during distribution.
  - Drugs bound to protein are pharmacologically inactive.
  - Plasma proteins
    - Albumin (4 g/dL): phenytoin, salicylates, dysopyramide
    - α_1-acid glycoprotein: quinidine, lidocaine, propranolol
- Drug distribution into the CNS
  - BBB
- Drug distribution during pregnancy and lactation

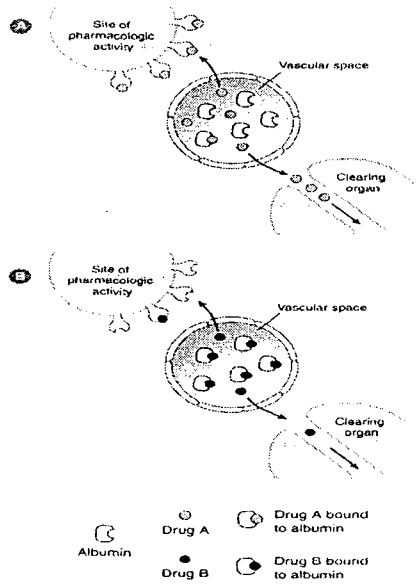
Pregnancy Categories (미국 FDA 최기형성 등급)

- **Teratogen** (기형유발물질): any substance that causes abnormal development of the fetus leading to a severely deformed fetus.
- Five categories suggesting the potential of a drug for causing birth defects [congenital defects; 선천결함, 선천결손(증)]
  - Category A
  - Category B
  - Category C: Risk cannot be ruled out!
  - Category D
  - Category X

Distribution

- **Differences in water compartment**
  - Total body water compartment:
    - Premature neonates: 85% of total body weight
    - Full-term neonates: 70-75% of total body weight
    - Adults: 50-60%
  - Extracellular water compartment
    - Neonate: 40% of body weight
    - Adult: 20%
  - Water-soluble drugs: aminoglycosides
- **Differences in body fat**
  - Premature infants: 1% of total body weight
  - Full-term neonates: 15%
  - Lipid-soluble drugs: digoxin
- **Decreased plasma concentrations of total protein and albumin** in newborns and infants compared with those in adults

Protein Binding & Drug Trapping

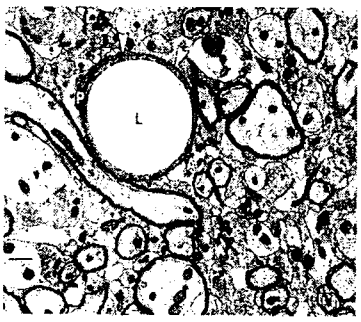


Acetaminophen, acyclovir, nicotine, ranitidine

Amiodarone, fluoxetine, naproxen, warfarin
Phenytoin

Blood-brain barrier (BBB, 혈액뇌장벽)

- Is composed of capillaries with tight walls that regulate diffusion of drug molecules from the bloodstream into brain tissue
- A covering of nerve cells (astrocytes) that encircle the capillary walls of the brain
- Selective passage of substances
  - Only highly lipophilic molecules can diffuse passively thru the barrier
  - Catecholamines (dopamine, norepinephrine, epinephrine) cannot cross the BBB

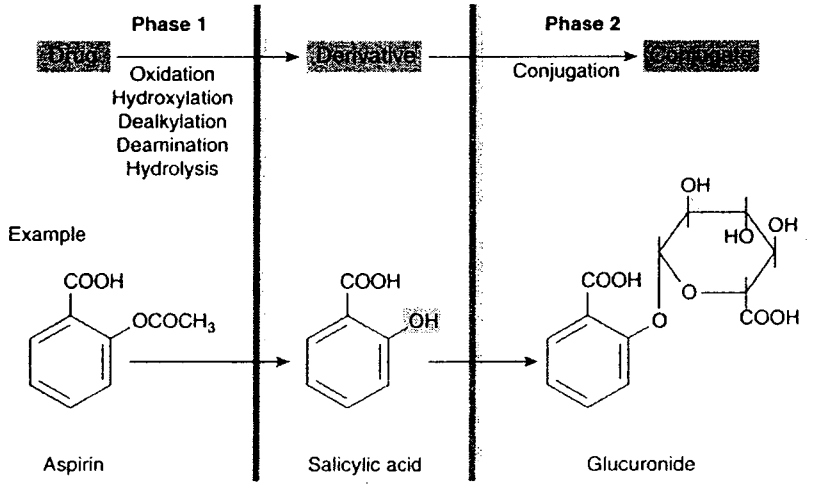


L: lumen, P: pericyte (혈관주위세포)
A: astrocyte foot processes

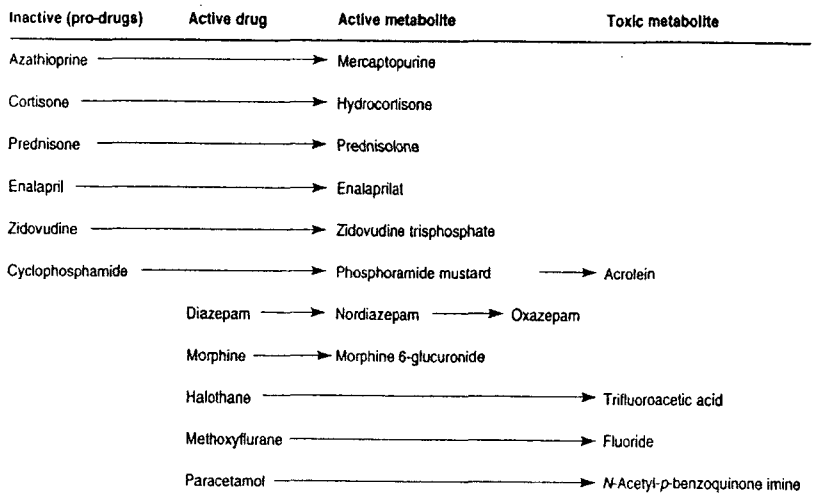
Metabolism

- **Sites of Drug metabolism**: mainly liver
- **Phase I reactions (degradation):** oxidation, reduction, hydrolysis
  - Cytochrome P450 (CYP, P450) system
    - P450 enzymes can be induced or repressed by some drugs ⇒ potential interactions between drugs that are metabolized by P450
    - **Enzyme inducers:** phenobarbital, phenytoin, carbamazepine, rifampin
    - **Enzyme inhibitors:** allopurinol, isoniazid, cimetidine, ethanol, ketoconazole, erythromycin, troleandomycin
  - Phase I reactions achieve maturity by 6 months of age
- **Phase II reactions (conjugation):**
  - Glucuronidation, acetylation, glutathione conjugation, glycine conjugation, sulfate conjugation, methylation, water conjugation
  - Glucuronide formation reaches its full maturity (adult values) between the third and fourth years of life.

The two phases of drug metabolism



Some drugs that produce active or toxic metabolites



Examples of pediatric drugs subject to phase I and phase II reactions

Phase I	Phase II
phenytoin	acetaminophen
ibuprofen	morphine
codeine	corticosteroids
diazepam	dopamine
naloxone	sulfonamides
methylphenidate	isoniazid
indomethacin	digoxin
succinylcholine	diazepam

Excretion

- Refers to elimination of a drug form the body
- The kidney excretes the inactive compounds from the body.
- Some drugs are excreted unchanged by the kidney without liver involvement.
- Patients with kidney disease may require a dosage reduction and careful monitoring of kidney function.
- Children have immature kidney function.
  - Glomerular filtration rate in neonates is 30-40% of the adult value and reaches adult values by 12 months.
  - Aminoglycoside, penicillins, digoxin
- Older adults have diminished kidney function.
- Other drugs are eliminated by sweat, feces, or breath.

Half-life (반감기)

- Refers to the time required for the body to eliminate 50% of the drug
- Knowledge of the half-life of a drug is important in planning the frequency of dosing.
- It takes five to six half-lives to eliminate approximately 98% of drug from the body.

Approximate elimination half-lives of some drugs in neonates and adults

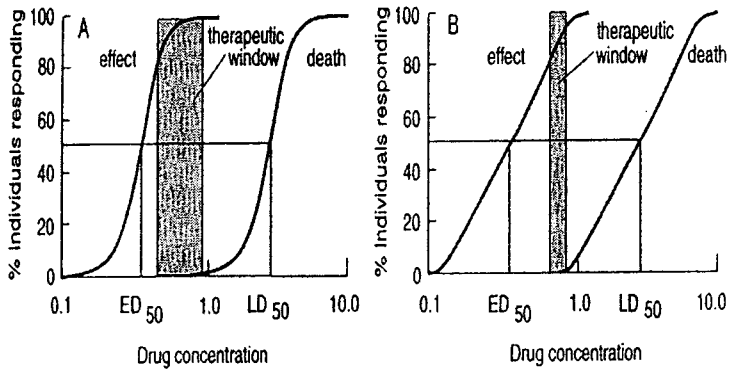
Drug	Neonatal age	Neonates $t_{1/2}$ (hours)	Adults $t_{1/2}$ (hours)
acetaminophen		2.25	0.9-2.2
diazepam		25-100	40-50
digoxin		60-70	30-60
phenobarbital	0-5 days 5-15 days 1-30 months	200 100 50	64-140
phenytoin	0-2 days 3-14 days 14-50 days	80 18 6	12-18
salicylate		4.5-11	10-15
theophylline	Neonate Child	13-26 3-4	10-15

Therapeutic Index (TI, 치료지수)

$$\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}}$$

- A measure of drug safety
- A drug with a higher therapeutic index is safer than one with a lower therapeutic index.
- Median lethal dose (LD_{50}): the dose that kills 50% of the animals that receive it
- Median effective dose (ED_{50}): the dose at which 50% of individuals exhibit the specified quantal effect

- In both graphs, the drugs have the same therapeutic index.
- However, because of the different slopes of the curves the drug in A has a wider **therapeutic window** than the drug in B.



Pediatric drug dosage

- **Dosage based on age or weight**
  - **Age (Young's rule):**
    - Dose = adult dose x $\frac{\text{Age (years)}}{\text{Age + 12}}$
  - **Weight (Clark's rule):**
    - Dose = Adult dose x $\frac{\text{Weight (kg)}}{70}$
    - Dose = Adult dose x $\frac{\text{Weight (lb)}}{150}$
- **Dosage based on surface area**

Determination of drug dosage from surface area

Weight		Approximate Age	Surface Area (m^2)	Percent of Adult Dose
kg	lb			
3	6.6	Newborn	0.2	12
6	13.2	3 months	0.3	18
10	22	1 year	0.45	28
20	44	5.5 years	0.8	48
30	66	9 years	1	60
40	88	12 years	1.3	78
50	110	14 years	1.5	90
60	132	Adult	1.7	102
70	154	Adult	1.76	103

If adult dose is 1 mg/kg,
Dose for 3-month-old infant: 1.8 mg/kg (18% of 60 mg/6 kg)