Toxicodynamics & Kinetics

frequncy of, matter of the dose اكد الفاصل هو ال, toxic ممكن تصير drugs *①,
exposure (which is renally eliminated) digoxin واعطيته renal failure مثلاً شخص عنده, patient factore
chance of digoxin toxicity عالية

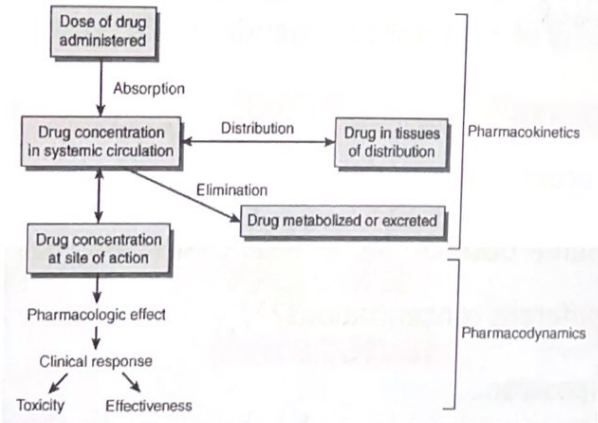
- The toxicity of a substance depends on the dose
- The concentration of a chemical at the site of action is usually proportional to the dose
- But……same dose of two different chemical may lead to vastly different concentrations???
- …….Disposition…..

factors that cause variation *② قد تكون
intraindividual variations
interindividual variations ⑴

Toxicokinetics: Disposition (ADME)

- Toxicokinetics is the quantitation of the time course of toxicants in the body during the processes of **absorption**, **distribution**, **biotransformation**, and **excretion** or clearance of toxicants
- In other words, toxicokinetics reflects how the body handles toxicants as indicated by the plasma concentration of that xenobiotic at various time points
- The end result of these toxicokinetic processes is a **biologically toxic dose** of the toxicant/s

Toxicodynamics & Kinetics



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Toxicokinetics: ADME

- Once a living organism has been exposed to a toxicant, the compound must get into the body and to its target site in an active form in order to cause an adverse effect

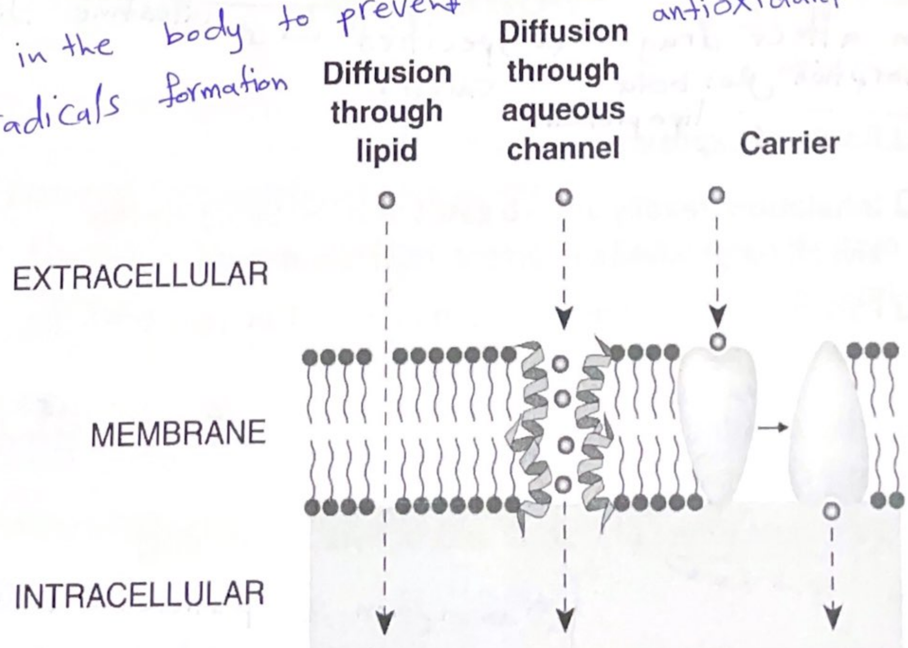
كيف تتعامل living organism مع any expousre to toxicant ؟

- The body has defenses:
  1. Membrane barriers
     - ✓ Passive, simple diffusion (pH, protein-bound??), facilitated (saturable, selective), active (ABC transporters), or special carriers
  2. Biotransformation enzyme, antioxidants
  3. Elimination mechanisms

* يسمح بمرور المواد حسب: ① molecular size, ② lipid solubility, ③ pH of the media, ④ pKa/pKb of the drug ⑤ هل هاد الدوا بحاجة إلى specilized transporter for it's absorption

* احنا العادة بتحول الـ metabolism from active → inactive, toxic → intoxic لكن أحيانًا ممكن يصير العكس

مثلاً: natural antioxidant present in the body to prevent free radicals formation



Absorption

أول step ← Absorption ، موجودة بكل الـ routs ماعدا الـ IV

- Ability of a chemical to enter the blood stream (GI tract, skin, lungs)
- Absorption: RATE & EXTENT ← سرعة: بعدد time to reach peack Concentration ← بعدد الكمية اللي وصلت للدم عند سرعة معينة
- The rate is of toxicological importance coz is the main determinant of the peak plasma concentration
- The extent determines the total body exposure or internal dose

حجم أصغر ← امتصاص أسرع

Absorption

- Route of exposure
  - **Inhalation**: readily absorb gases into the blood via the alveoli (large alveolar surface, high blood flow)
  - Particle size is the main determinant, ≤ 1µm penetrate the alveolar sacs of the lungs (nanoparticles!!)
  - **Enteral administration**: particle size ①, surface area ②, blood flow rate ③, pKa ④, Pgp ⑤, intestinal motility?? ⑥ ← يعتمد الامتصاص على
  - ✓ First-pass effect (intestine and/or liver can modify) ← مثل الدوا exposed to the liver قبل ما يصير له امتصاص ودلا لا

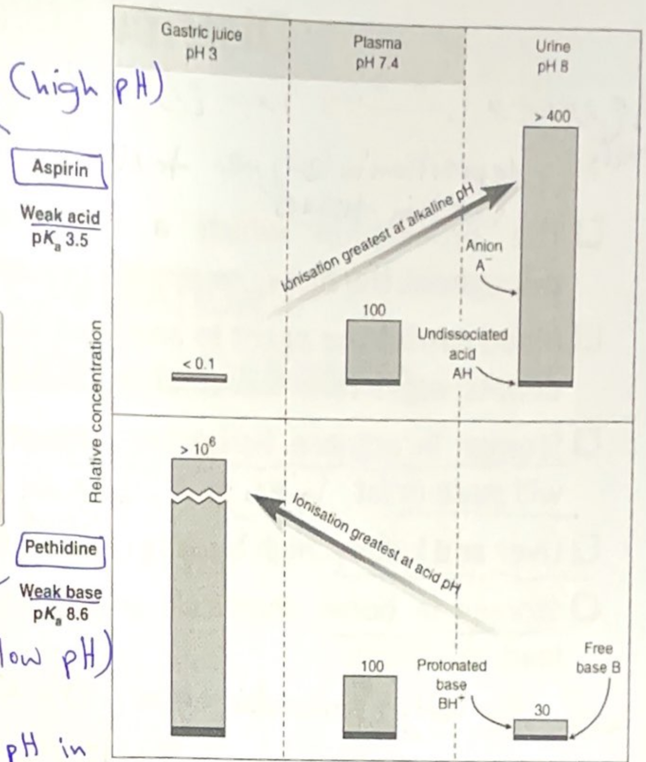
↑absorption ← particle size↓ ①
↑absorption ← lipid solubility↑ ②
(weak acid, weak base) degree of ionization ③

Can affect drug absorption مثل: beta lipoproten ← specified في بعض الـ intestine بال carrier *

this first pass effect make the drug maybe more toxic OR detoxify the drug so help to reduce the chance of toxicity

في بعض الأدوية بتخسر من الـ activity first pass effect تماما ازا بتعرض لـ toxicant الـ

ionized in intestine (high pH)



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ionized in stomach (low pH)

$$pH = pK_a + \log \frac{[\text{nonprotonated species}]}{[\text{protonated species}]}$$

For acids: $pH = pK_a + \log \frac{[A^-]}{[HA]}$

For bases: $pH = pK_a + \log \frac{[B]}{[BH^+]}$

blood	intestine	stomach	pH in urin
neutral 7.35 7.45	alKaline (8)	acidic (1.5)	acidic (6)

* نفرض وا مرمار عند aspirin overdose
شو بعمل كي أزيد ال renal excreation؟
← بدي أزيد ال ionization له
← ارفع ال pH لل urin
← الاسبرين بصير charge ويمنع reabsorption فبزيد خروجه مع ال urin after filtration

Absorption

- **Dermal**: fortunately not very permeable
  - ✓ Absorption through epidermis by passive diffusion (stratum corneum thickness, condition of skin, blood flow, small size) ← لازم يكون lipid soluble حتى يتم امتصاصه
  - ✓ .....then dermis by diffusion....systemic circulation
- **Parenteral**: I.V, I.P, I.M, S.C
  - I.M → absorped throw muscles
  - S.C → subcatanous (absorbed throw adipose tissue)
- **Physicochemical properties of the toxicant..**
  - particle size, lipid soluble إلها دور بال absorption

pithidine overdose → بزيد ال acidity for urine مثلاً بعطي vitamin (C)

زيادة ال excreation للدوا من خلال زيادة ال ionization (polarity) (water solubility) → acid in base OR base in acid meduim

Distribution

*① وصل ال blood stream راح يبدأ ينتشر وين بروح؟؟ it depends
سواء أدوية أو toxicant بصير إلها deposition in certain tissues

- The process in which a chemical agent translocates throughout the body...reversible process
- Blood carries the agent to and from its site of toxicity, storage depots, organ of transformation, and organs of elimination
- Storage in adipose tissue: very lipophilic compounds (DDT) will store in fat ← بتروح مباشرة على lipophilic tissue وتتخزن فيها
- Liver and kidney: high binding capacity for several chemicals
- Storage in bone: chemicals analogues to calcium, fluoride, lead, strontium

*② في بعض CNS medications مثل benzodiazepem إلها long half life because they dispose in fatty layers وبصير إلها slow release

disadvantage: difficult to remove from blood
advantage: can limit further distribution to other tissues

Distribution: storage & binding

*① الانتشار السريع: high volum of distribution (صعب انتخلص منه لأنو توزع في الجسم بحجم كبير)

- The rate of distribution dependent upon
  - ① Blood flow → كل ما زاد ل organ معين تزداد ال distribution
  - ② Characteristics of toxicant (affinity for the tissue, and the partition coefficient) كل ما كان ارتباطه بالدم أكبر ← أقل distribution
- Binding plasma proteins: in equilibrium with the free portion, displacement by another agent
- BBB......tight capillary endothelial cells. → limit drug distribution to the brain [brain damage is irreversible]

*③ liver, Kidney ممكن يرضو يكونو site of distribution لبعض chemicals
*④ في أدوية مثلاً بتروح مباشرة على ال bone فاهمة يلي بتجيب الكالسيوم
*⑤ distribution is limiting factor for drug elimination
يعني كل ما زاد ال distribution بصير صعب يتخلص الجسم من الدوا

ELIMINATION =
EXCRETION + METABOLISM

Elimination

- ❑ Toxicants are eliminated from the body by several routes
- ❑ Urinary excretion (increase drug excretion by change pH of the urin)
  - ✓ Water soluble products are filtered out of the blood by the kidney and excreted into the urine
- ❑ Exhalation
  - ✓ Volatile compound are exhaled by breathing (مثل inhaled anesthetics)
- ❑ Biliary excretion via fecal excretion → high lipid soluble Compound
  - ✓ Compounds can be extracted by the liver and excreted into the bile. The bile drains into the small intestine and is eliminated in the feces
- ❑ Milk, Sweat, Saliva →

في حال كانت الأدوية مرضعة لازم ننتبه لها

Metabolism (biotransformation)

- Toxic response depends on the concentration of active compound at the target site over time
- The process by which the administered chemical (parent compound) are modified by the organsim by enzymatic reactions
- 1st objective – make chemical agents more water soluble and easier to excrete
  - Increase solubility ---- decrease amount at target
  - Increase ionization ---- increase excretion rate ---- decrease toxicity
- **Bioactivation/toxication** ---- biotransformation can result in the formation of reactive metabolites

we will try to increase drug solubility in order to decrease it's amount at target site → we need to increase it's ionization making it more water soluble so increasing the elimination

Metabolism (biotransformation)

مثال على intoxic → toxic هو الميثانول :-

methanol —oxidation→ formaldehyde → acetic acid + formic acid (further severe toxic effect)

- Can drastically affect the rate of clearance of compounds
- Can occur at any point during the compound's journey from absorption to excretion
- Key organs in biotrasnformation
  - Liver (principal) (main) ← بسبب وجود ال hepatic enzymes
  - Lung, kidney, intestine
  - Others

* بالعادة ال metabolism convert from active → inactive

في حالات = أقل inactive → active

- Biotransformation pathways
  - Phase I: make the toxicant more water soluble (action of hepatic enzyme: oxidation, reduction)
  - Phase II: links with a soluble endogenous agent (Conjugation)

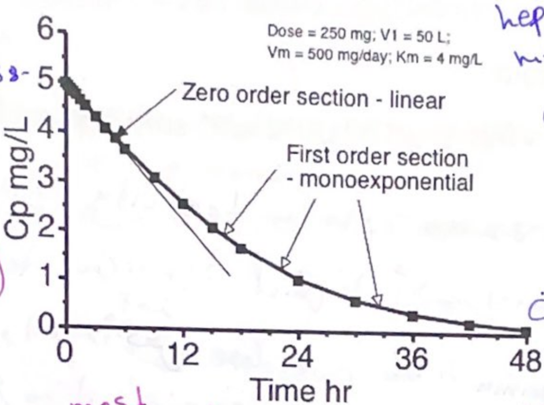
Classical Toxicokinetics

- Drugs highly charged or polar are excreted by the kidney…1st order elimination
- Lipid soluble drugs, first metabolized by liver….if enzymes saturated…zero order elimination

(ما فهمت بس هيك حكى الدكتور)

①* metabolism in the body can go into two Kinetic process - zero order (amount of metabolizm depends on enzyme saturation) / first order

يعني ما توصل الانزيمات لمرحلة الإشباع راح تبطل تعمل metabolizm للدوا لذلك راح يتراكم في الجسم



②* ازا كان الدوا hepatic metabolized وعم نزيد الجرعة ونوصل لوضع الاشباع بتحول إلى zero order(s)

③* zero order : من بتفاوت أكثر شي الدوا ازا كان narrow therapeutic index ↓ even small amount increase in drug conc will cause further increase in drug metabolism

①* most medications can go throw first order except some (zero)

Factors influencing Toxicity

1. COMPOSITION OF THE TOXIC AGENT
2. DOSE & CONCENTRATION
3. ROUTE OF EXPOSURE
4. METABOLISM OF THE TOXICANT
5. STATE OF HEALTH
6. AGE & MATURITY
7. NUTRITIONAL STATE
8. GENETICS
9. GENDER
10. ENVIRONMENTAL FACTORS

Factors influencing Toxicity

1. Composition of the toxic agent:

- A basic fallacy: responsible toxicant is the pure substance
- Physiochemical composition of toxicant: solubility, charge, hydrophobicity, powder/dust
- Solid vs Liquid
- Poisoning is more with liquid and small particles (particle size)

← ممكن تكون toxicity من مادة وحدة أو من أكثر من مادة
← ال toxicity من المواد liquid أكبر أسرع من toxicity from solids (يعني لو واحد أخذ overdose من ال revanin أسرع من لو أخذ نفس dose بس حبوب) شراب بتسمم

Factors influencing Toxicity

* بعض الأدوية تعرضها للضوء بخليها toxic عشان هيك بنحطها ب amber bottel

1. Composition of the toxic agent:

- ① E.g: Cr^{3+} relatively non-toxic, Cr^{6+} causes skin and nasal corrosion and lung cancer
- ② PH: strong acids or bases vs mild acids and basics
- ③ Stability: paraldehyde.....acetaldehyde (بسبب nausea, pulmonary edema) GI tract problems

① أحيانا بعض metals تصير toxic لما يصير إلها oxidation مثل cr
cr^{+3} oxidation → cr^{+6} (more skin toxicity, high chance to cause cancer)
② weak acids ولا strong إيهم أعلى toxicity ? strong أكيد لأنها تذوب tissue
③ paraldehyde → acetaldehyde (بتحول لما يصير oxidation أو تتعرض للضوء)
⑦

Factors influencing Toxicity

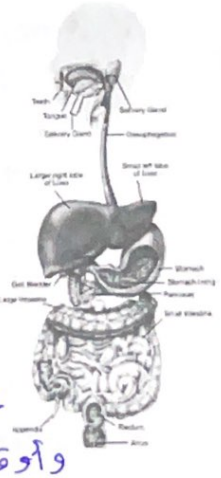
Dose↑ ⟶ ↑ higher chance to develope toxicity

2. **Dose and concentration:**
   - Most important factor: e.g. acute ethanol exposure causes CNS depression, chronic exposure liver cirrhosis
   - Diluted solutions Vs concentrated solution (easily absorbed)
3. **Route of exposure:** oral, inhalation, dermal
   - Affect time of onset, intensity and duration
   - Predict the degree of toxicity and the organ mainly affected

IV/ inhalation > oral/ dermal
(أسرع من)

Factors influencing Toxicity

Oral is related to:



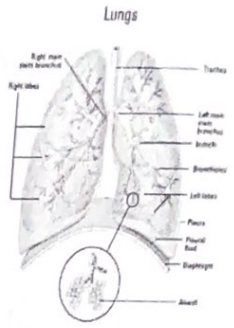
① • Rate of disintegration & dissolution
② • Degree of ionization
③ • Solid forms? Tendency to clump together
④ • Presence of food: protein and fat delay absorption, carbohydrate beverages increase absorption
⑤ • Chance to readily metabolize...and "hoped" detoxify!! 1st pass effect

* مثلاً اذا كان ماخذ دوا fatty meal وأوقات دوا lipid soluble راح يزيد امتصاص الدوا
↳ gastric emptying if fatty meal well delay Chance of (drug or toxicant) to be absorped throw intestine

Factors influencing Toxicity

Inhalation:

- Particle size is a limited factor ≤ 1μm



Dermal:

- Penetration is time dependent
- Skin condition
- Nature of the toxicant (irritant)

Skin Condition + drug lipid تعتمد على solubility

Factors influencing Toxicity

4. **Metabolism of the toxicant**

✓ 1st pass effect

- NOT ALWAYS
- MeOH $\xrightarrow{Ox.}$ Formaldehyde + Formic acid ...serious side effects

5. **State of health:**

- Hepatic, renal insufficiency → ↑ toxicity
- Diarrhea or constipation may decrease or increase the time of contact between chemical and absorptive site
- Hypertension may exacerbate response to chemical with sympathomimetic activity → Blood pressure لانها ترفع

* ممكن المرض يأثر على الدوا أو الدوا يأثر على المرض

Factors influencing Toxicity

6. Age and maturity

- Chloramphenicol....grey baby syndrome (not given for premature baby)
- Geriatric....generalized decrease in blood supply to tissue.....decrease in toxicity....(not always)
  - P.O drugs....absorption decrease
  - Diseases (hepatic, renal, CV)....decrease detoxification, excretion, distribution

تختلف ← muscle mass حسب العمر وهادا الشي بأثر سلبي أو إيجابي على drug disposition

Factors influencing Toxicity

7. Nutritional state

- Empty stomach or food contents (pH, high fat,....)
  - Ca^{2+} in milk and tetracycline (divalent أو trivalent Cation)
  - Fatty food increase absorption of griseofulvin (or Ketokenazole) antifungal
  - Tyramine rich food and MAO inhibitors (ما بتاخدو مع بعض)
  - Hypoalbuminemia: greater amount of free drug

ما بنعطو مع بعض بسبب Hypertension Crises, serotonine syndrome

بقلل plasma drug binding ← تزداد free drug Conc

Factors influencing Toxicity

9. Gender

- Difference in absorption.....
- Difference in metabolism rate....
- Differences in quantities of muscle mass and fat tissue....in i.m injection

* فرق الاختلاف بالكتلة العضلية، كمية الهرمون femal, male

drug toxicity ← disposition ← rate of absorption هاد بأثر على

Factors influencing Toxicity

8. Genetics: *(Genetic toxicology....normal Gaussian curve)*

الشرح في الصفحة السابقة ←

- Species, strain variation, inter-individual variations
- Succinylcholine metabolized by **pseudocholisterenase** into succinylmonocholine + choline then....

Esterase (liver)

↓

Succinic acid + choline

- G6PD deficiency..... may cause hemolytic anemia

Toxicology....summary!

- ❑ All substances can be poison
- ❑ Dose determines the response
- ❑ Pathway, duration, frequency of exposure and chemical determine dose
- ❑ The extend of the effect is dependent upon the concentration of the active compound at its site of action over time
- ❑ Bioactivation.....compounds to reactive metabolites
- ❑ Individual variation of the organism will affect absorption, distribution, metabolism, & excretion

١ في ناس عندهم نقص بإنزيمات معينة بسبب جينات معينة
يلي ممكن يرفع تزييه من drug toxicity

٢ G6PD : glugose-6 phosphate dehydrogenase deficiency
ممن لازم يتعرضو لجموعة من الأدوية وأنواع الأكل
مثل سوي الفول وبعض البقوليات مثلاً

مثل sulfonamide (antimalaria)
↓
بسبب hemolytic anemia (RBC hemolysis)

٣ Succinyl Choline عبارة عن neuromuscular Junction blocker (muscle relaxent)
بتغير metabolism عن طريق (pseudocholisterenase)
بعض الناس يكون عندهم defect بهاد الإنزيم مما يسبب تراكم الـ succinyl choline

تابع ②

succingl cholin ← بالدم لازم يصير metabolism أول بالplasma
بعدين بالLiver ويعطي succinck acid (حمض ستاكرة)
choline

هيا بال neuromuscular Junction ارتباط ال nicotinic recepter بال succingl choline

عليها راح يصل muscle paralysis لكن ما بدنا هاد ال paralysis
يطوّل يعني عند وقت معين بدنا يوقف تأثير succingl choline
فاكرين بالي عندهم defect بعضلات التنفس راح يستمر تأثيره
Causes muscles paralysis including respiratory muscle paralysis which can cause apnea
(يختنق المريض)

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