Pharmacology

Sheet Slide

number

2

Done by

تسنيم عساف

Tahani Kharoub

Corrected by

Fatma Abu Ghannam

Nora Haj-ali

Doctor

Bilal faiq & Afnan Atallah

Routes of Drug Administration -> طرق ادخال الدواء للجسم

Note: Pharmacokinetics -> Study of the absorption, distribution metabolism and excretion (ADME)

- لكن بعض المدارس بتحكي انهم مش 4 كلمات هم 5 (AADME) وضمت ال (Routes of Drug Administration) ل (Pharmacokinetics) ، طرق ادخال الدواء يعتبر اشي تقني لهيك مش الكل اعتبره ضمنها .

- طبعا لازم نعرف انه طريقة ادخال الدواء بتاثر على امتصاص وفعالية الدواء : The route of administration (ROA) that is chosen may have a profound effect upon the speed and efficiency with which the drug acts .

- كل طريقة من الطرق الها مخاطرها وسلبياتها واكيد ايجابياتها واحنا بنعطي الطريقة حسب المريض وعمرة ومرضة ... الخ ، متلا واحد عامل حادث ما بينفع حبوب لازم (IV or IM) ، رضيع صغير الافضل (rectal) .

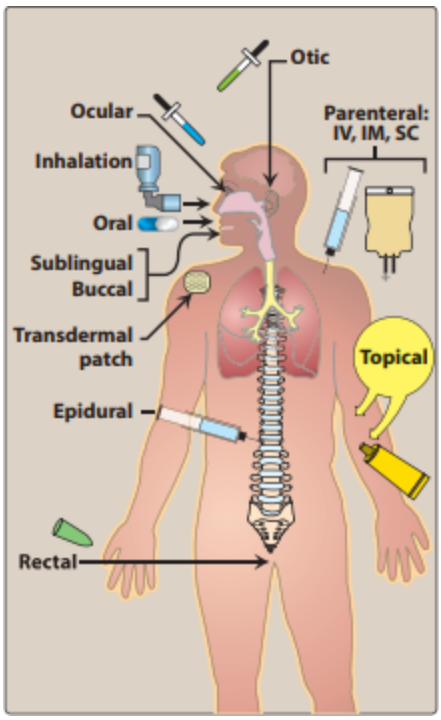
*****

The route of administration is determined by:

- Properties of the drug (for example, water or lipid solubility, ionization)
- Therapeutic objectives (for example, the desirability of a rapid onset of action, the need for long-term treatment, or restriction of delivery to a local site).

*****

Major routes of drug administration include:



- Enteral -> داخلي مثل الحبوب (For certain reasons we can't give the patient the drug by means of the enteral route ,reasons for treatment or circumstances of the patient , here we decide to take parenteral route.)
- Parenteral -> injection
- Others -> transversal, nasal inhalation, oral inhalation, topical (skin cream, eye drops, ear drops), vaginal … etc

Note: the difference between nasal inhalation and oral inhalation :

- nasal inhalation -> the target is the upper respiratory
- oral inhalation -> the target is the lower respiratory

1. Enteral:

-> Drug placed directly in the GI tract:

- Oral.
- Sublingual -> تحت اللسان
- Buccal.
- On the Tongue ->
مثل الدواء الي يستخدم لمرض الشقيقة (Migraine) وهي عبارة عن وجع رأس شديد جدا لازم دوا امتصاصة سريع
- Rectal.

*****

- Oral:

Advantages

- **Convenient -** can be self- administered, pain free, easy to take
- **Absorption** - takes place along the whole length of the GI tract
- **Cheap** - compared to most other parenteral routes
- **Safe -** low risk of infection
- Overdose and toxicities can be overcome by antidotes, such as charcoal (we can reverse and remove the drug from the patient's body by many mechanisms (induce vomiting, or give them aspartame).

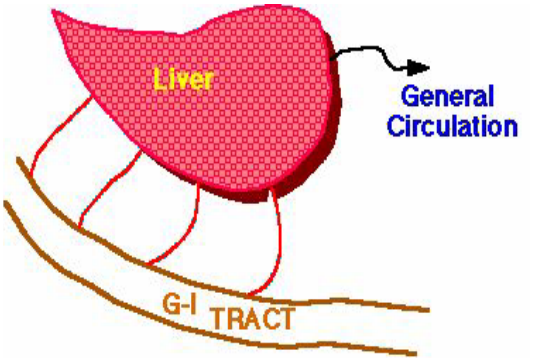
Disadvantages

- Sometimes inefficient - only part of the drug may be absorbed
  - Absorption can be affected by several factors, such as gastric pH
  - First-pass effect - drugs absorbed orally are initially transported to the liver via the portal vein
  - Destruction of drugs by gastric acid and digestive juices
- Irritation to gastric mucosa - nausea and vomiting
- Effect too slow for emergencies
- Unpleasant taste of some drugs
- Unable to use on unconscious patients

First-Pass Effect:

- The first-pass effect is the term used for the intestinal and hepatic degradation or alteration of a drug or substance taken by mouth, after absorption, removing some of the active substance from the blood before it enters the general circulation.

- The greater the first-pass effect, the less the agent will reach the systemic circulation when the agent is administered orally.



Note:

Depending on the physicochemical properties -> الدوا بعاني من (First-pass Effect).

ناخد هالتشبيه علشان نفهم شو يعني : متلا لو عنا مدينة كبيرة فيها مي ، لو اجت قرية صغيرة واخدت منها (سرقة يعني) المدينة الكبيرة ما راح تحس لانه التاثير قليل وغير ملموس ، لكن لو اجت قرية كبيرة التاثير بصير اكبر بالتالي المدينة راح تحس وتتاثر وتعرف وكل ما كبرت القرية المدينة تاثرت اكتر وهيك الدوا كمان كل ما زاد first pass effect بيعاني من مشاكل اكتر ، مثلا عنا portal vein مرات بناءا على physiochemical properties بسحب جزء من الدوا وبوديه على الكبد قبل ما يحصله امتصاص

Other names for first pass effect:

- First pass inactivation.
- First pass degradation.
- First pass error.
- First pass alteration.

Note:

- في حالة كانت extensive يعني في مشكلة بالدوا ولازم ما ينعطى orally اما اذا كان neglected بكون في تاثير بس خفيف فممكن ناخده لانه من الاصل عنا فروقات بين الافراد ومش كلهم بيستجيبوا للادوية بنفس الطريقة ، المورفين متلا مسكن قوي جدا عنده extensive first pass effect ما بنعطيه oral الا في حالات خاصة متلا بعد العمليات او في حالة السرطان ليه لانه اثر قليل احسن من ولا اشي ..

- في حالات الطوارئ وفقدان الوعي ما بقدر اعطي oral .

Wide range of oral tablet preparations including:

- Enteric-coated: Is a chemical envelope that resists the action of fluids and enzymes in the stomach but dissolves readily in the upper intestine.

➔ To protect drug from stomach -> حماية الدواء من حموضة المعدة
➔ To protect stomach from drug -> حماية جدار المعدة من الدواء

Such coat is useful for:

- Drugs that are acid unstable (e.g. Omeprazole)
- Stomach irritating drugs (e.g. Aspirin)

- Extended- release preparations: Have special coating or ingredients that control how fast the drug is released from the pill into the body.

Advantages:

➔ Slower adsorption and prolonged duration.
➔ Better patient compliance.
➔ May maintain concentrations within acceptable therapeutic range over a long period of time.
➔ These preparations are advantageous for drugs with short half lives.

Ex. Morphine:

➔ Its half-life is 2 -4 hours in adults.
➔ Oral morphine has to be administered 6 times in 24 hrs. to obtain continuous analgesic effect.
➔ Controlled-release tablets allow a twice daily dosage.

- Film coated:

➔ To protect the tablet from moisture
➔ To mask the taste

- Normal tablet: حبة دواء عادية مثل الاكامول تم صناعتها تحت الضغط

- Sublingual/ Buccal:

- Placement under the tongue allows a drug to diffuse into the capillary network and enter the systemic circulation directly
- The buccal route: drug is place between cheek and gum

الهدف منه:

- تبعد عن extended circulation وذوب الدواء بالفم قبل ما توصل GI لنبعد عن first pass metabolism .
- فعل / اثر سريع -> rapid action

- ال sublingual كان هاشي بالنص بين ال oral وال IV .

Advantages:

➔ Ease of administration
➔ Rapid absorption
➔ Low risk of infection
➔ Bypass of the harsh GI environment
➔ Avoid the first-pass metabolism

Disadvantages:

➔ Inconvenient
➔ Small doses
➔ Unpleasant taste of some drugs

Note:

الناس الي عندهم angina بصير عندهم partial clotting في الاوعية الدموية ، الحل - > نعمل vasodilation ونفتح الطريق ، ال angina عبارة عن chest pain بعد تعب او تمارين او غضب او ضغط ... الخ .

Example:

- Nitroglycerin -> وهاد الدواء بحقق الهدفين
- B12 -> first pass metabolism بيناخد بالطريقة هذه لهدف الحماية من

- Rectal: Systemic or Local Effect

الطريقة التالة وهي الشرجي ، ممكن يناخد systemic في الدم وممكن local موضعي ، مثلا واحد عنده مشكلة بال rectum مثلا جرح او حتى بواسير وبدو يعالج الألم فبكون استخدام ال rectal -> local .

* The upper part of the rectum is rich in blood supply which includes the portal vein and has fast onset of action, conversely with the lower part of the rectum which includes the general circulation.

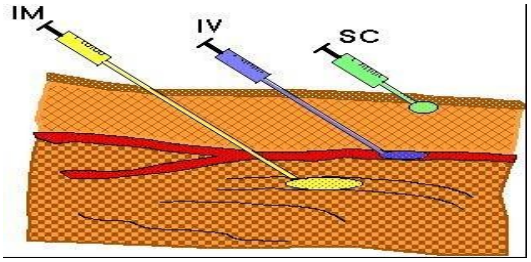
Advantages

➔ Unconscious patients and children.
➔ If patient is nauseous or vomiting.
➔ Good for drugs affecting the bowel such as laxatives.
➔ Easy to terminate exposure.

Disadvantages

➔ Absorption may be variable.
➔ Irritating drugs contraindicated.

2. Parenteral:



Introduces drugs directly across the body's barrier defenses into systemic circulation.
*(absorption process occurs in places that differ from the GI tract).
* The drug is introduced against some barriers:
1- The external barrier is the layer of skin
2- It involves the intestinal barrier

* Uses: الاسباب الي بتخلينا نترك الطرق الداخلية ونتجه لهادي الطريقة

➔ Drugs that are highly/quickly metabolised / poorly absorbed from GI tract (e.g. heparin).
➔ Drugs that are unstable in the GI tract / affected from GI system (PH, enzyme...) (e.g. insulin)
➔ In patients unable to take oral medication (e.g. unconscious patients, infants, elderly, emergencies: seizure, vomiting…)
➔ Circumstances that require a rapid onset of action
➔ Drugs have high molecular weight (if we take the oral route, it will exit as feces without being absorbed, or if it was absorbed –very fast metabolism- then it will be inactivated by the liver's metabolism).

- **Advantages**

➔ Have the highest bioavailability -> نسبة الدواء الي بتوصل للدم

➔ Avoid first-pass metabolism or harsh GI environments.

➔ Provides the most control over the actual dose of drug delivered to the body (dose more accurate- risk of error less than oral {taken with a spoon}).

➔ Usually, the frequency of administration is less than oral.

Note: Bioavailability differs between (IV, IM, SC, ID), the best is IV because the drug immediately enters circulation so the IV route has 100% bioavailability.

- **Disadvantages**

➔ Irreversible

➔ Low convenience, may cause pain, fear…

➔ Local tissue damage, local interaction with the drug- because the tissue doesn't tolerate the dose, infections if we don't clean the needle carefully

➔ In an IV injection cutting the vein will lead to symbiosis or embolism or inflammation at the site of injection in the vein's wall.

- **Strategies to decrease the medication risk error:**

1. If toxicity occurs in the blood, then we can maybe decide to do dialysis.
2. Give the patient drugs to inhibit the unfavourable drug (in some cases, the dangerous effect might not allow any other interference).

- **Three major parenteral routes are:**

➔ Intravascular (IV, IA)- placing a drug directly into the blood stream

➔ Intramuscular (IM) - drug injected into skeletal muscle

➔ Subcutaneous - Absorption of drugs from the subcutaneous tissues

Note:

** العلم بيحاول يبعد عن هذه الطريقة لانها مؤلمة جدا وخاصة لو كان استخدام يومي مثل الانسولين اذا بدي اعطيه orallyبصرله degradationفبضطر اعطيه IV ، طيب الاطفال الصغار الي عندهم سكري النوع الاول العلاج بالنسبة الهم عذاب لهيك العلم بدور عطرق تانية.

عام 2006 تم ايجاد بديل عن ابر الانسولين وهو بخاخ عن طريق الانف تم سحب الدواء عام 2007 لانه سبب مشاكل بالرئتين .

حاليا ومن عام 2017 تم تصنيع انسولين orally ويبدو انه ناجح وحاليا تحت التجريب.

1- Intravenous (IV): Why is it not called intravascular?

Because when we enter the drug to vein it will go to heart and then will be distributed to the whole body not like the artery which goes to a specific organ- in some cases it could be toxic if we decide to give the patient the drug by artery.

In Liver Cancer *chemo therapy– we decide to insert the drug to the artery which feeds the liver, here we decrease the side effects on the body and treat only the tumour.

How do we introduce the drug?

1- **Bolus:** 2cm dose of drug in needle which directly enters the blood within seconds).

2- **Slow intravenous injection:** some drugs if they enter directly, can cause local irritation (need to be diluted- not to be accumulated at the time of injection- which is why we give an IV injection but slowly.

In both of the previous two mechanisms, we can control the rate of insertion only when we have a small dose of drug (like 3-5 ml).

3- **Intravenous infusion –**when we have to insert a large dose such as 10 ml of drug, we can't control the rate of insertion so we decide to use this method.

Advantages

1- Rapidity of onset of action
2- Better bioavailability
3- Less painful

*The largest muscle can tolerate a maximum of 5 ml (IM –the pain continues for minutes-the pain we feel is produced by the accumulation of the drug in tissue and not because of the insertion of the needle).

*In subcutaneous we can tolerate 2ml at most.

*In an IV injection, there is no limit to the volume of drug, the drug is diluted, and there isn't pain like that which is produced in IM.

Disadvantages

1. Irreversible, causes infections of disease between patients

2. Embolism – blood clots/coagulations in a specific place= thrombus which could move to small capillaries, block them, and prevent oxygen from arriving there.
3. High risk of adverse reaction, risk of side effect is higher than others.

2- IM injection: more rapid than oral, slower than IV. Its absorption is faster than oral, better bioavailability than oral.

IM Preparation (according to duration of action):

1- Fast onset of action: If I completely dissolve the drug in an aqueous solution –fast release-fast absorption, high diffusion through capillaries; this causes the drug to reach the maximum concentration in a short time – fast elimination rate of drug.

2- Delay onset of action (slow release preparation): we sometimes need to give the patient an IM injection 3 times daily, this is inconvenient for them (painful, requires the help of people to insert the needle), so we choose this option.

- It is slowly absorbed into muscle-slowly eliminated and this will give long duration of action to reach therapeutic concentration.

- We prepare the IM drug as a suspension –not dissolved in an aqueous solution- the drug particles are suspended in a solution, we obtain a (non-solvent) vehicle (not toxic, doesn't cause irritation for the site of administration, rapid diffusion from administration region) and make this vehicle dissolve the drug and put it in an aqueous media and we inject the 3 components (drug +vehicle + aqu. solution), when it reaches the muscle the aqueous media will diffuse to blood capillaries or..., the vehicle will leave the site of administration, and the drug particles will not directly dissolve. Firstly, the drug particles will have dissolution occur to them on several stages (dissolve in solvent to more easily enter the circulatory system)-this gives us: slow duration of action + slow elimination rate of drug + slow release-slow absorption.

* Vehicle is liquid because if it isn't liquid, then it will be toxic.

3- Subcutaneous injection:

1- Rate of absorption will vary according to site of administration

2- Rates of blood flow vary according to site of administration and difference between patients, which depend on the many components of skin layers + weight + heart function + normal blood circulation + temperature (higher temperatures lead to an increase in the surface of absorption regions)

Ex: Diabetes patients take subcutaneous injections:

The difference between who has good circulation and who has failure (slow circulation): they take fast acting insulin (taken with or shortly before a meal), if the patient not take their dose, they will then have hypoglycaemia, if the patient who has failure takes the dose after eating then they will have hyperglycaemia.

Advantages

1- Slower onset of action than IV, sometimes we can control them- make some fast onset of action which give fast absorption, and make some slow onset of action which gives slow absorption.
2- We can control the onset of action (rapid or slow):

Insulin types: differ according to frequency of administration

A) Rapid insulin: (taken with a meal or shortly before the meal), if the patient does not take their dose what they will then have is hypoglycaemia. (it is taken with each meal).

B) Regular (ultra-rapid) insulin : taken before the meal 15/30 minutes and will not lead to hyperglycaemia. 2 times daily.

3- Other routes:

1- **Oral-inhalation preparation:** in the respiratory system (asthma, inflammation ex: bronchitis), there are two types of drugs that depend on duration and convenience + they give fast local onset of action + minimize systemic side effects.

a- **Inhalable drug –** to the general circulation- faster onset and immersion + faster elimination of drug + patient wakes up faster from operation.
b- **Injectable drug –** to avoid long duration of operation.

***** If we give them topically/locally we minimize side effects and get true treatment, not like if we were to give them systematically.

2- **Intra-nasal preparation:** when the patient has allergy and inflammation بالجيوب we give him decongestant or (anti) drug, if we give him topically we will achieve our purpose but there are systemic side effects.

Decongestant drugs work on the alpha receptor (alpha antagonist= alpha inhibition)

بسبب الاحتقان بيصيرvasodilatation

وبدي اعملvasoconstriction

So we give them alpha agonist which does vasoconstriction in blood capillaries nodes and in systemic blood capillaries, this will lead to hypertension, like cortisone (if we insert locally we will decrease systemic side effects).

Some preparations can be used systematically: injectable drug

*Disorders in the nervous system (blood capillaries around them are called the blood brain barrier, it's permeability is highly selective to the entrance and exit of substances from or to brain).

*Sometimes there is a defect in the central nervous system and there are special drugs to treat them.

*There is no blood brain barrier in the nasal cavity; we can introduce drug to it that affect the CNS and treat its disorders. Some of the drugs to treat diabetes insipidus (has hyper urination + thirst + actually normal sugar levels + insulin in blood) there is defect in antidiuretic hormone in the pituitary, so we give him antidiuretic hormone (exist as inter-nasal preparation) and for the latter there is a receptor in the central nervous system to treat the diabetes insipidus.

There are other routes for administration that affect the central nervous system:

1- Interventricular (in blood stream-CSF)

2- Intrathecal (epidural) in particular vertebra تخدير موضعي

Ex: surgical labor, general anaesthesia…

3- Topical application either on skin–burns, inflammation… or on mucous membrane like eye drops, vaginal/rectal cream.

Ointment مرهم

Cream is faster than ointment.

3- **Transdermal:** we applied the drug topically but we affect systematically- long bioavailability- reaches the general circulation to be absorbed. Prepared as transdermal patches -5cm-as layers-long duration of action- slow release of drug on the skin which starts from the closer layer -> further layer تدريجيا مش بنفس الوقت (لصقة الظهر johnsonبتختلف contain substances that vasodilate capillaries and feel comfortable)

-Example on transdermal:

1- Glycerine subdermal which prevents heart attacks.

2- Subdermal contraceptive patch

Disadvantages:

1- Not every drug can be given transdermally (depends on the amount and potency).

2- Region: where we place it needs to be the same region.