PHARMACOLOGY

Bioavailability and distribution

OBJECTIVES:

- Major body fluid compartments
- Concept of compartments.
- Apparent volume of distribution (Vd).
- Plasma protein binding.
- Tissue binding.

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Bioavailability

Bioavailability

Is the amount of unchanged drug that enters systemic circulation after administration and becomes available to produce pharmacological actions.

(rate and extent of active reaching systemic circulation)

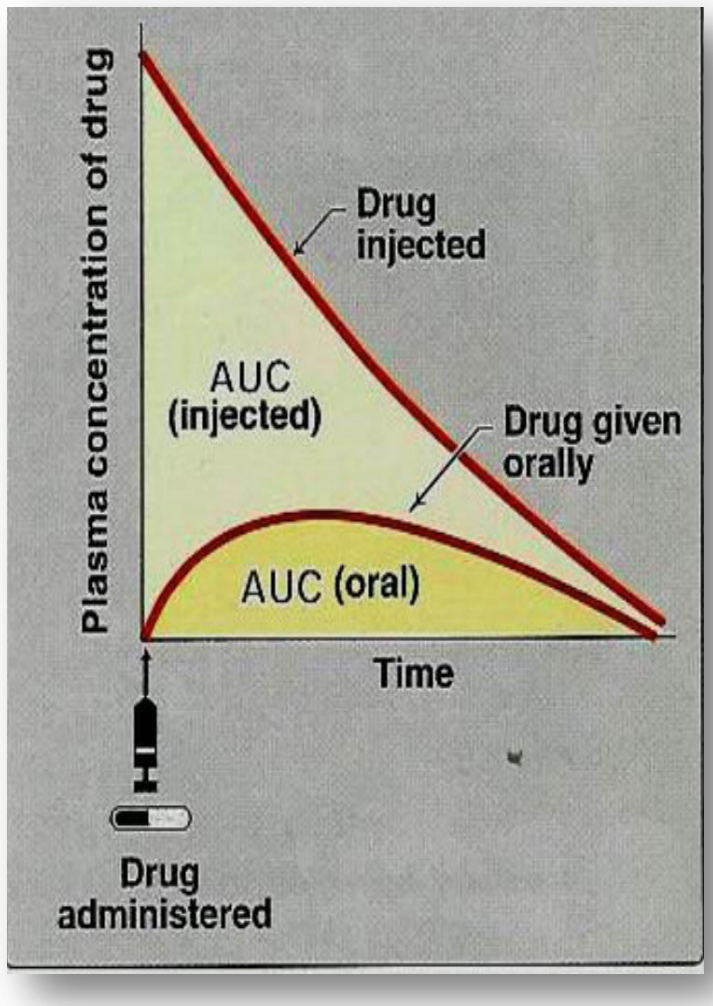
Factors affecting Bioavailability:

1. Same factors affecting Absorption MW, dosage forms, drug solubility, etc.
2. First Pass Metabolism

$$\text{Bioavailability(F)} = \frac{\text{AUC (Oral)}}{\text{AUC (I.V)}} \times 100$$

AUC = Area Under Curve

- I.V. provides 100% bioavailability i.e. F= 1.
- Subcutaneous, intramuscular, oral, rectal, and other extra vascular routes of administration require that the drug be absorbed first, which can reduce bioavailability



Bioavailability

Bioavailability

Absolute (FA)

The bioavailability of a drug after administration by any route is compared to its intravenous standard formulation

Relative (FR)

It is determined when <u>two</u> products are compared to each other (not to an intravenous standard formulation)

Relative Bioavailability:

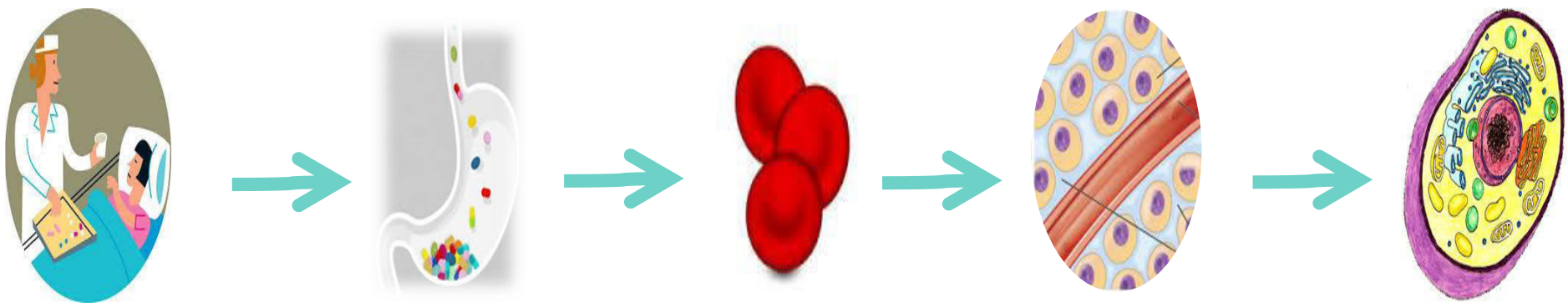
- This is commonly calculated in the drug industry to determine that the generic formulation is bioequivalent to another formulation
- Example: **Tylenol** (500g) compared to **Panadol** (500g)
- It is important to get an idea of how different formulations or routes of administration differ in their bioavailability.
- Dosage adjustment is required when changing formulations or routes of administration.

Bioequivalence

DEFINITION: **Two pharmaceutically products are bioequivalent when the <u>rate</u> and <u>extent</u> of bioavailability of active ingredients in two products are the same.**

Distribution

DEFINITION: Is the process by which drugs leave blood circulation and enter the Interstitium and/or the cells of the tissues.



Drug administration → **Absorption** → **Blood (plasma)** → **Extracellular** → **Intracellular**

Apparent Volume Of Distribution (VD)

DEFINITION: It is the ratio of drug amount in body (dose) to the concen tration of drug in blood.

$$Vd\ (L) = \frac{\text{Dose (mg)}}{\text{Plasma Concentration (mg/L)}}$$

Vd is important to:

1. Calculate the loading dose
2. Predict the duration of action:
   - High Vd means long duration of action.
   - Low Vd means short duration of action.

Major body fluid compartments

Extracellular fluid (21%)

- **Plasma** (5 % of body weight) = 4 L
- **Interstitial fluid** (16 %)= 10 L

Intracellular fluid (35%)

Fluid present inside all cells in the body (28 L).

Cases for drug distribution:

Case 1: The drug stays in the blood. In this case the drug is in one compartment (plasma compartment).

Case 2: It crosses the endothelial cells of the capillaries and the drug reaches th e interstitial fluids surrounding the cell BUT it does not enter the cell yet. It is con sidered two compartments and we say (extracellular) around the cells.

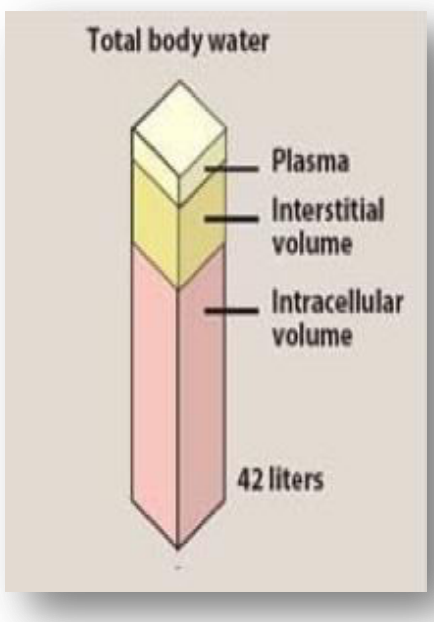
Case 3: It enters the cells and in this case we say intracellular and we say multi compartments.

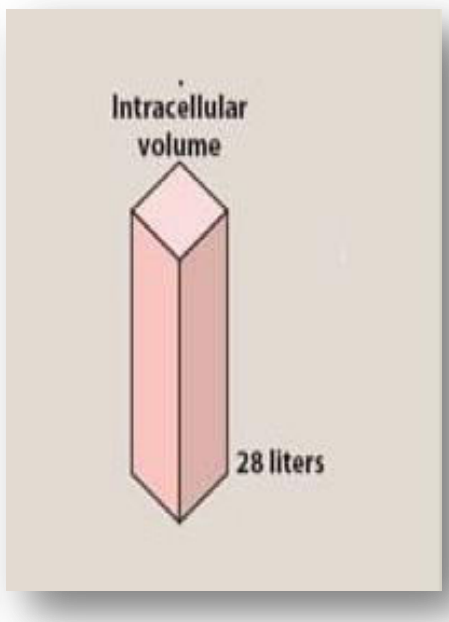
Maximum volume of drug distribution in the Compartments:

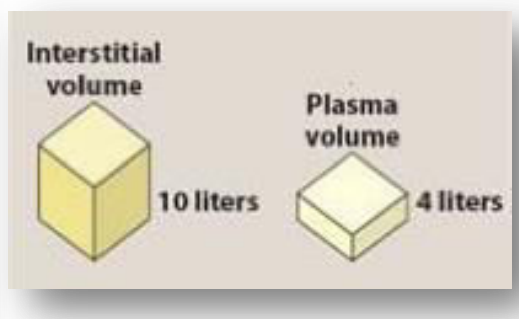
Case 1: If the drug is distributed in only one compartment then the maximum liters that are distributed are about 4L.

Case 2: If the drug is distributed in two compartments then the max L that is distribut ed is 14L (It will first be distributed in the first compartment (Plasma 4L) and then the second one (Interstitial 10L) (4+10)).

Case 3: If it was multi-compartment then the max L is 42L and it CAN exceed the total body fluid and that is if there was drug/tissue binding for a long period of time.







Volumes of some compartments of the adult human body in relation to Vd:

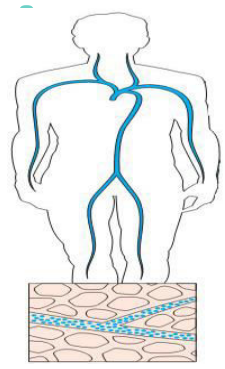
- Total body water 0.6 L/Kg Body Weight
- Intracellular water 0.4 L/Kg Body Weight
- Extracellular water 0.2 L/Kg Body Weight
- Plasma 0.04 L/Kg Body Weight

Total Body Water = 0.6 x Weight

Drug may be distributed through :

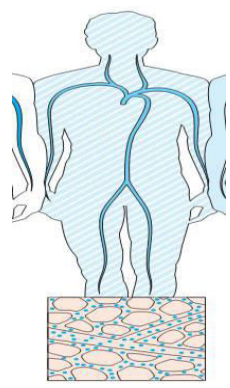
One Compartment

Plasma Compartment



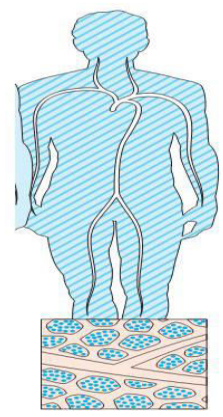
Two Compartments

Extracellular Compartment



Multiple Compartments

Intracellular Compartments



Distribution

	PLASMA COMPARTMENT	EXTRCELLAR COMPARTMENT	INTRACELLULAR COMPARTMENT	
VD	4L	4-14L (4+10)	Equal to total body water	Higher than total body water.
Properties	• high molecular weight drugs • Drug binds to plasma protein	• Low molecular weight drugs but are hydrophilic	Lipid soluble drugs (hydrophobic)	Drug that binds strongly to tissues.
Distribution	Cannot move across endothelial cells of capillaries (trapped in blood)	Pass endothelium into interstitial fluid BUT can not cross cell membrane to intracellular fluids	Pass the cell membrane and enters the cell	
Example	Heparin (4L)	Atracuronium (11L)	Ethanol 38L (34-41)	Digoxin (385L)

Drugs with low Vd:

- **Distributed in extracellular compartments** (plasma & interstitial fluid).
- **Polar Compound or Lipid insoluble drug** e.g. **Gentamycin** and **Atracuruim**
- **High molecular weight drugs** e.g. **heparin – insulin**
- **High plasma protein binding** e.g. **warfarin** (anticoagulant)
- **Do not cross BBB or placental barrier** (BBB = Blood Brain Barrier)

Drugs with high Vd:

- **They have higher concentration in tissue than in plasma**
- **Lipid Soluble**
- **Distributed Intracellularly**
- **Example: Digoxin, Phenytion** and **Morphine.**

Factors affecting Distribution

Factors that mainly affect Distribution:

1. **Cardiac output and blood flow.**
   The greater the blood flow to tissues, the more distribution that occurs from plasma to interstitial fluids.
   (Drugs distribute more rapidly to brain, liver and kidney than skeletal muscles & fat)
2. **Capillary Permeability**
   Endothelial cells of capillaries in tissues other than brain have wide slit junctions allowing easy movement, permeation and distribution. (Brain has tight junctions (Blood Brain Barrier)
3. **Physical & Chemical properties of the drug:**

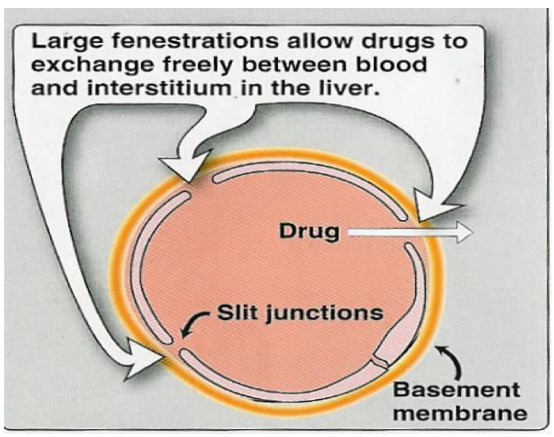
- Molecular weight.
- Pka.
- Lipid solubility.
- Most lipid soluble drugs (unionized, uncharged, nonpolar) cross biological membranes.
- Hydrophilic drugs (ionized, charged, polar) do not readily cross membranes but go through slit junctions in endothelial cells of capillaries.

4. **Plasma protein binding**
5. **Tissue binding.**

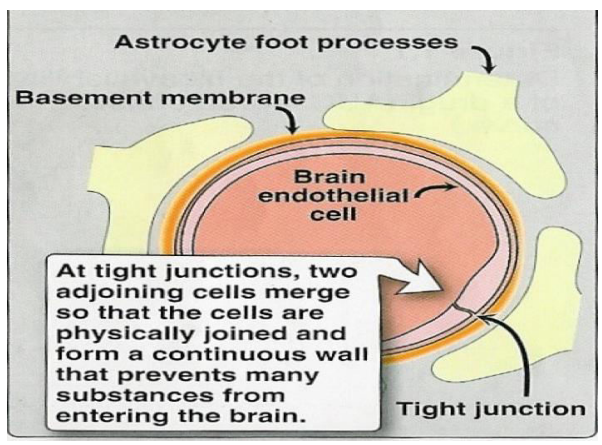
Blood Brain Barrier(BBB):

- Only lipid soluble drugs or actively transported drugs→ can cross BBB.
- Hydrophilic / ionized / polar drugs→ can't cross BBB. However, Inflammation as in meningitis increase their permeability.
  Example: **penicillin & gentamycin.**

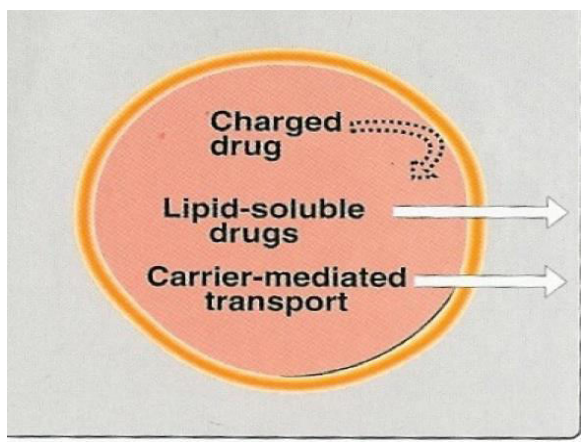
Placental Barriers: **Lipid soluble drugs can cross placental barrier and enter the fetal blood.**



Structure of Endothelial Cells in the Liver



Structure of a Brain Capillary



Permeability of a Brain Capillary

Binding of Drugs:

1- Plasma Protein Binding:

Extensive plasma protein binding will cause more drug to stay in the blood compartment. Therefore, drugs which bind strongly to plasma protein tend to have lower distribution (Vd).

(This is sometimes an intended process)

- In blood, drugs exist in two forms bound and unbound forms in equilibrium .
- Bound drug ⇌ Unbound Drug (free form).

(When the free form of drug is consumed, a portion of the bound drug is converted into free form, so the drug can complete its action. (It interacts with the receptor to give its effect))

Plasma Proteins

Albumin: Has affinity for acidic drugs as **warfarin**, **phenytoin**, **aspirin**.

Alpha 1-acid glycoproteins: Has affinity for basic drugs (cationic) as **diazepam**, **quinidine**.

2- Tissue Binding:

Drugs can bind to specific tissues and will have high volume of distribution (Vd).

Ex. Tetracycline bind to bone

- Drugs binding to Plasma proteins = decrease in its Vd
- Drugs binding to Tissues = increase in its Vd

Bound and Unbound Forms

Bound Form of the Drug	• Non diffusible form • Can not cross endothelial Barrier • Can not combine with Receptors • Inactive (Cannot produce pharmacological action) • Not available for Metabolism & excretion by the liver & kidney • Has long duration of Action (t ½).
Unbound Form of the Drug	• Diffusible form • Cross endothelial barrier • Active (Can produce pharmacological action) • Available for metabolism & Excretion by the liver & kidney • Has short duration of Action (t ½).

Characters & consequences of Binding:

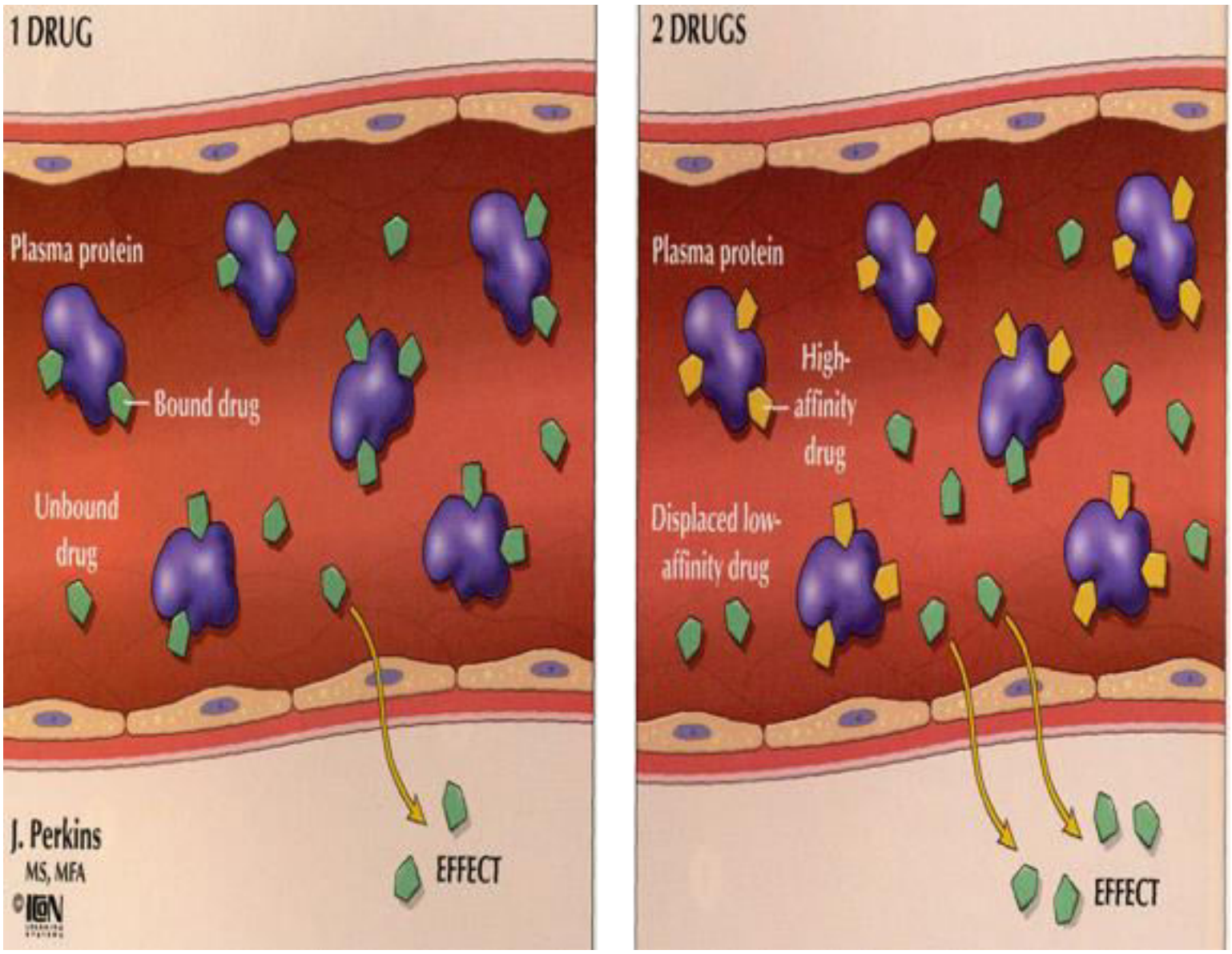
1. Usually reversible.(When unbound form of drug is consumed, bound form is converted or reversed into unbound(free) form)
2. Determines volume of distribution (Vd).
3. Slows drug metabolism & excretion.
4. Prolongs duration of drug action (t ½).
5. Result in clinically important drug interactions.

Displacement:

Competition for the same binding site on the plasma proteins may occur between two drugs ⟶ displacement of one drug & increasing its concentrations & effects.

Aspirin + Albumin-warfarin ⟶ Albumin-aspirin + free warfarin ⟶ bleeding

NOTE:
Aspirin has a higher binding capacity than the **warfarin**.
Free form of the drug is what causes the side effects. (In this case bleeding).



THANK YOU FOR CHECKING OUR WORK

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