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Pharmacology

Doctor 2018 | Medicine | JU

Sheet ○ Slides

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Bioavailability

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation (it is the study of a drug to know the proper dosage the patient need)

Example: if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%

Why is this important?

Because if the same person takes another drug that has a bioavailability of 40% and you give him 100 mg of that drug, the quantity of the drug reaching the circulation will be 40 mg thus you won't see the same results.

So, to produce the desired clinical effect from a certain drug you need to adjust the dosage according to the bioavailability of that drug.

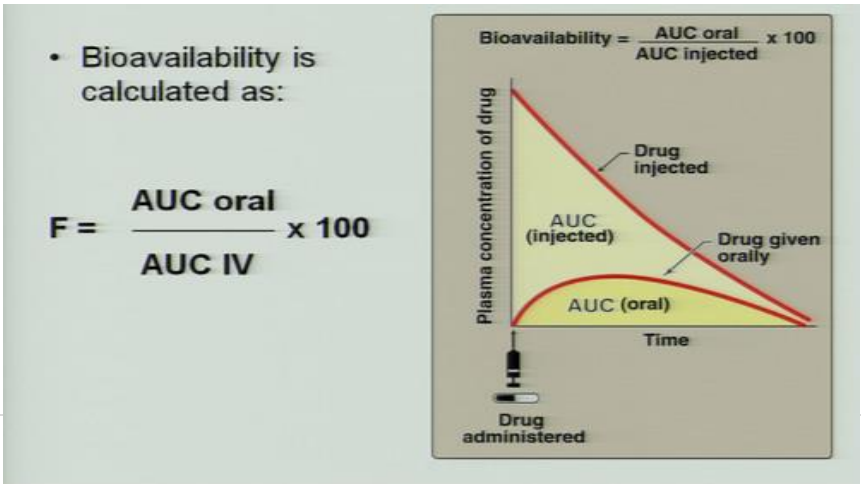
Determination of bioavailability

As we said the bioavailability is important for calculating drug dosages for different routes of administration, so now how do we determine the bioavailability?

Note that the bioavailability of intravenous administration is 100% (since all the drug is injected directly into the blood stream), and all other routes (orally, rectally etc...) will have a bioavailability that is less than 100% (since only part of the administered dose appears in the plasma.)

Bioavailability is determined by comparing plasma levels of a certain drug after a particular route of administration with levels achieved using the same drug but by IV administration.

And by plotting plasma concentrations of the drug (in the circulation) versus time, the area under the curve (AUC) can be measured and it reflects the extent of absorption of that drug, then the bioavailability of a certain drug using a particular route of administration will be the ratio of the AUC following that route to the AUC following IV administration



For clarification, let's see how the bioavailability of oral paracetamol can be calculated.

Note that these tests are made **before** the drug is released to public (in the clinical investigation phases)

we give patient 1 the dose of the drug by using IV administration and patient 2 the same dose by using it orally and then we measure the change in concentration of that drug with time for both patients, until the concentration of the drug in the blood is zero so you will notice the IV curve, it starts at 100% (the peak) then it starts to decline (result of distribution and biotransformation)

While for the oral curve, the curve grows by time as absorbance takes place and the concentration of the drug in the plasma grows then it starts to decline (result of distribution and biotransformation)

To calculate the bioavailability of the oral administration you just have to calculate the area under its concentration curve, and divide it with area under the IV administration, which represents the 100% bioavailability

we can measure bioavailability by measuring AUC (Area Under Curve) for both curves then by the equation:

Bioavailability = AUC oral ÷ AUC IV × 100

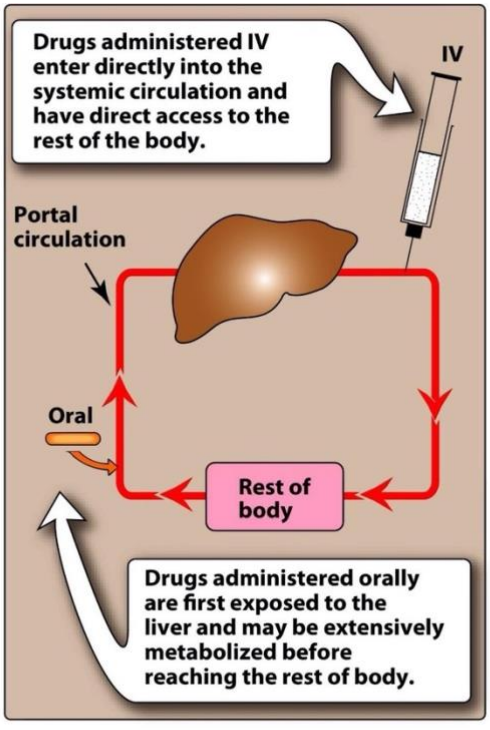
Factors influencing bioavailability

1- First-pass metabolism:

Remember first-pass metabolism is the metabolism of the drug before it reaches the systemic circulation

When a drug is absorbed from the GI tract, it enters the portal circulation (circulation of blood to the liver from the small intestine) before entering the systemic circulation. If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the **amount of unchanged drug entering the systemic circulation is decreased** which is the bioavailability

E.g.: More than 90% of the absorbed nitroglycerin is cleared due to first pass metabolism. So to overcome the first pass effect nitroglycerin is administered sublingually.



First-pass metabolism can occur with orally administered drugs. IV = intravenous.

The Amount metabolized due to first pass metabolism is measured by the extraction ratio of the liver (also known as liver clearance rate) and it depends on the blood flow to the liver and the metabolic rate of the drug.

Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

If we have more first-pass metabolism we have less bioavailability of the drug

By now we have two factors that determine the bioavailability of the drug which are

1- The absorption (we talked about it in the previous lecture)
2- The first-pass metabolism and it's resembled by the extraction ratio of the liver, and is calculated according to this equation
ER= CL liver/Q

ER → extraction ratio
CL liver → liver clearance of the drug (constant for a specific drug)
Q→ hepatic blood flow

So, depending on these factors another way to calculate the systemic bioavailability for orally administered drugs is by using this equation

F= f * (1-ER)

F → systemic bioavailability

f → extent of absorption (depends on the drug)

2- Solubility of the drug

We know that for a drug to pass through the membrane passively it has to be lipophilic, but we'd take into account that our compartments (ICF, ECF (Intravascular, Interstitial)) are aqueous.

Very hydrophilic drugs are poorly absorbed because of their inability to cross lipid-rich cell membranes.

Drugs that are extremely lipophilic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. So, the ideal drug must be **largely lipophilic**, yet have **some solubility in aqueous solution**.

This is one reason why many drugs are either weak acids or weak bases (can exist in lipophilic and hydrophilic states).

How do we determine the solubility of the drug (lipophilic or hydrophilic)?

Using the partitioning coefficient which is the ratio of concentrations of a compound in a mixture of two immiscible phases at equilibrium, and that's by putting my drug in a tube containing both oil and water and shaking it until equilibrium, then I take a sample from both compartments (oil and water) and measure the concentration of the drug in these two compartments then decide how much lipophilic or hydrophilic it is (depending on the concentration), for example 35% hydrophilic , 65% lipophilic

3-Chemical instability:

-Some drugs, such as penicillin G, are unstable in the pH of the gastric content (acid labile).

-Insulin and other peptides and proteins get destroyed in the GIT by proteases and degrading enzymes.

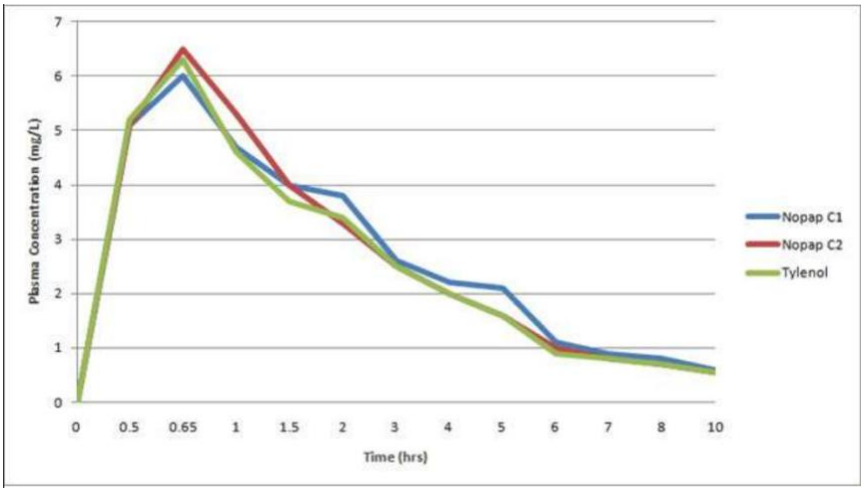
4-Nature of the drug formulation:

Drug absorption may be altered by factors unrelated to the chemistry of the drug.
For example: **particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients** (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

Bioequivalence

One of the important studies that we do in phase 3 of the clinical investigation phases is making sure that this drug is at least as effective or superior to the effectiveness of other drugs
So, Let's say I'm a new drug company and I want to make paracetamol in a certain dosage form, and I want it to be approved and released to the market. what I need to do is to compare my drug to Panadol for example which is already in the market, and that's by comparing the extent of bioavailability of both drugs using a plot like this one:

Drug products are considered to be bioequivalent when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions



The blue and red lines are our drug we are testing, The green line is the drug in the market

Tylenol is the commercial name of paracetamol in the USA

Distribution

We talked about absorption, which was the first step of pharmacokinetics, now the next step is distribution, (what happens to the drug after reaching the systemic circulation).

Distribution depends on many variables, some are related to the **drug itself**, and some are related to **the tissues of the body**.

Depending on drug size and lipid solubility, drugs can distribute to most body compartments. Though **Brain**, **prostate**, and **eye** tissues might be difficult to penetrate because they have a special barrier that won't allow the entry of certain drugs to these organs, example: blood brain barrier.

So, what are **the factors that determine the distribution**

(1) capillary permeability
if the junctions and spaces between epithelial cells are wider this will allow more of the drug to penetrate and reach different tissues of the body and vice versa for example, in the blood brain barrier there are more tight junctions, so it is impermeable for the drug to penetrate through.

(2) blood flow–tissue mass ratio (i.e., perfusion rate)
means how much blood is a particular organ getting, for example, some organs have a higher perfusion rate like the heart, liver and kidneys because they perform more important body functions, so if we have a higher perfusion rate it means a higher chance of the drug reaching that specific organ.

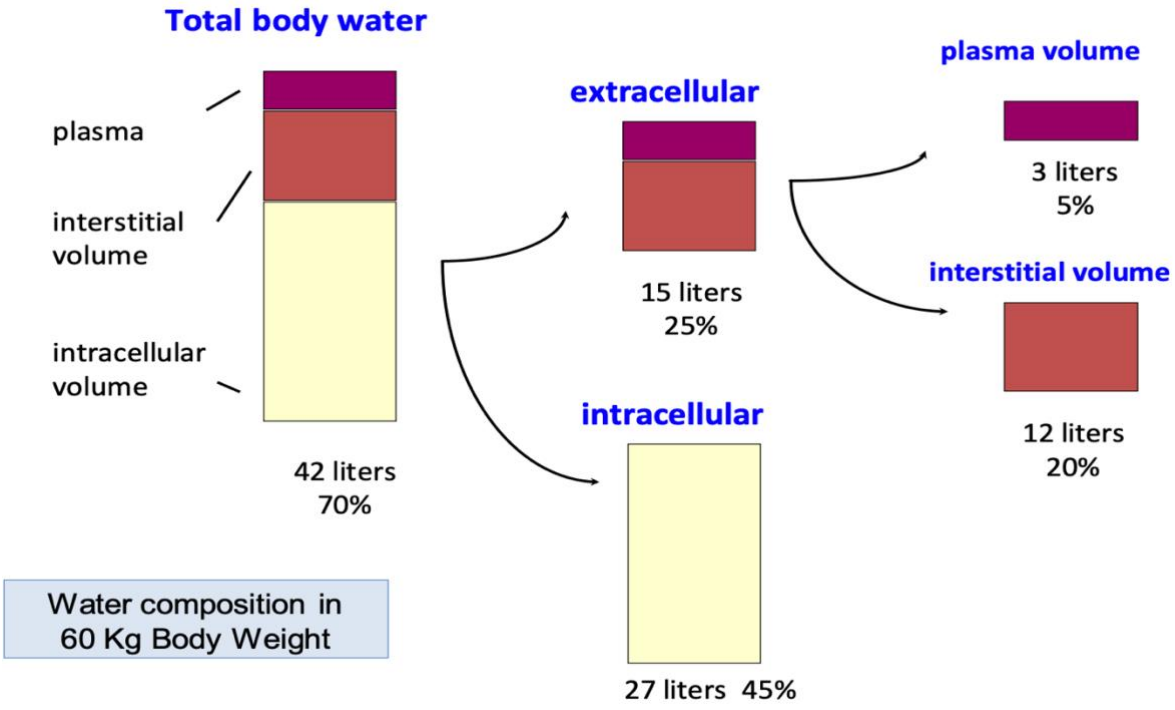
(3) extent of plasma protein and specific organ binding
we know we have plasma proteins swimming in our blood like albumin for example, some drugs such as acidic drugs have affinity for albumin and they tend to bind to it, but albumin can't exit the circulation to surrounding tissues due to its high molecular weight, so any drug that is bound to a plasma protein won't leave the circulation and will not reach the target tissue thus affecting the distribution of the drug. We will talk about this in details shortly.

(4) regional differences in pH
as we took earlier the differences in pH and pka of drugs affect how much of the drug can cross membranes and penetrate inside of the cells (depending on what form charged or uncharged)

(5) transport mechanisms available
for example, in the blood brain barrier we have glucose transporters that allow more glucose to enter the brain, so if transport mechanisms are available for drugs the distribution will be much easier.

(6) the permeability characteristics of specific tissue membranes.

Body distribution and body water



The total volume of the fluid compartments of the body into which drugs may be distributed is approximately 42 L in a 60-kg adult.
These compartments include:

– **Plasma water**
– **The interstitial fluid**
– **The intracellular fluid**

now why is this important?
Because after circulating in the blood for a while the drug will start to distribute to different tissues, mainly in the water of the body according to the specifications of that drug.
now let's see what compartments drugs can be found in depending on their characteristics

A. **plasma**
   A drug that is not lipid soluble and has a **very large molecular weight** or **bind extensively to the plasma proteins** (as we said earlier) will not be able cross the spaces between endothelial cells into the interstitial compartment, So the drug is effectively trapped with the plasma (vascular) compartment. In this case the drug will distribute in a volume that is about 6% of the body weight. for example, in 60 kg individual, agents of this type, such as Heparin, will distribute in 3 L of body fluids.

B. Extracellular

If a drug is **hydrophilic** and has a **low molecular weight**, it can move through the endothelial junctions but cannot cross the membrane to inter the cells (because it is hydrophobic).

So, drugs like aminoglycosides, will distribute into a volume equal the sum of the plasma water and the interstitial fluids but not intracellularly (in a volume that is about 25% of the body weight).

C. Total body water

If a drug is **hydrophobic** and has a **low molecular weight**, then the drug can move through the membranes into the cells. Here the drug will distribute into the total body water (a volume of about 60% of the body weight).

To sum up if the drug

1- Has large molecular weight/binds to plasma proteins → plasma
2- Is hydrophilic and Has low molecular weight → extracellular
3- Is hydrophobic and has low molecular weight → Total body water

-**Important Notes:**

- Some drugs have affinity for particular tissues in the body, so they will accumulate there, for example lipid soluble drugs once they reach the fatty tissue they will accumulate there and wont distribute to other tissues, and there will be some equilibrium between the free form that's not bound to the fatty tissue and the bound form.

- Some areas of the body are not accessible to drugs due to anatomic barriers. for example, the capillary membrane between the plasma and brain cells is much less permeable than is the membrane between plasma and another tissue. Therefore, the transfer of drugs into the brain is regulated by what is called "blood brain barrier" and it is

1. only permeable to lipophilic agents
2. impermeable to ionic hydrophilic agents
3. Amino acids, glucose etc. have specific uptake system (transporters)

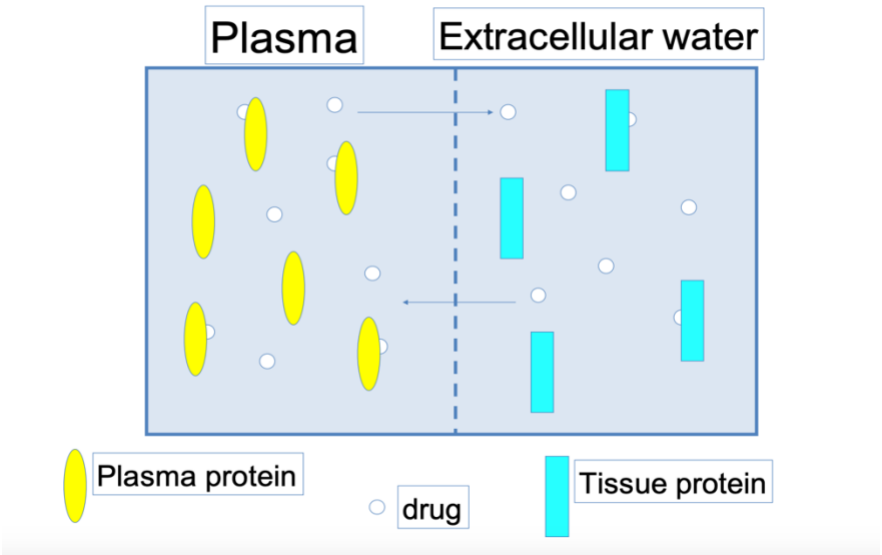
Protein binding

-We have already talked about this topic but let's go through some details
Usually, after absorption, some drugs bind to proteins. And this binding affect drugs by:
1- **making them inactive**
2- **lowering the distribution of the drug**, because now they are larger molecules (can't cross membranes between different compartments).

-So, we conclude that the protein binding limits the distribution of the drug in the body, but this doesn't mean that the whole dosage I give will bind to proteins, there is
A balance (equilibrium) created between bound (inactive) drugs and unbound(active) drugs.

-The fraction of total drug in plasma that is bound is determined by
1- the drug concentration
2-its affinity for the binding sites
3- the number of binding sites.

So, what is the benefit of drugs binding to proteins?
Bound drugs are considered as the depot (a place for storage) inactive forms of the drug, what does this mean?
since the bound and unbound drug are in equilibrium, as the unbound free drug is distributed and used by the tissues, more of the bound drug is released to make up for the loss of the free unbound drug in tissues, and this adds a prolonged effect for the drug.



Free Drug + Protein ™ Bound Drug

As you see only the free form of the drug can cross membranes

DRUG BINDING TO PLASMA ALBUMIN

- Some drugs bind nonspecifically and reversibly to various plasma protein, albumin and globulins, in which the bound and free drug reach equilibrium, and only the free drug exerts a biological effect. (the bound drug doesn't exert a biological event)

- plasma proteins and what drugs are they bound to
  albumin → primarily for acidic drugs
  a1-acid glycoprotein → for basic drugs
  Lipoproteins→ for some lipid soluble drugs

- In general albumin binding reduces pharmacological activity (because it decreases the number of the drug in its free form), but as we said it actually prolongs duration of action in a way dependent on **affinity**, **binding capacity** and **rate of dissociation** (because it acts as a storage unit).

We talked about the benefit of drugs binding to proteins (prolonged duration of action), but on the other hand protein binding is an important area of **drug-drug interactions**.
drug interactions are defined as interactions between drugs and other substances that prevents the drug from performing as expected.

Drug interactions occur on albumin by the displacement of one drug by another and it Can raise the dose of some drugs to toxic levels. How? Take this example
Anticoagulants (Warfarin) can be displaced by the anti-inflammatory agents Phenylbutazone.
Warfarin is an anticoagulant that tend to bind to albumin, so let's say 50% of it will bind to albumin and the other 50% are in the active free form, so when a doctor prescribes warfarin to a patient he already takes into consideration that half of the warfarin will be in the inactive form, now if the patient takes another medication that also bind to albumin like phenylbutazone it will compete and displace warfarin which actually increases the concentration of the free active warfarin meaning it can be toxic and fatal.

Note: Only unbound drugs are capable of crossing the placenta. So, Drugs with low protein binding reach higher concentrations in the fetus compared to the mother.

We have talked about the different factors affecting the distribution like protein binding, permeability of membranes, drugs characteristics, etc.

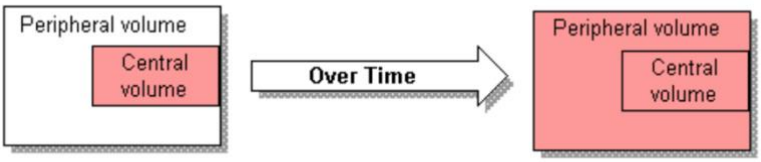
Now how do we determine and compare the distribution of different drugs in our body?

Volume of distribution

We have a concept called the volume of distribution or the apparent volume of distribution, Vd, and it is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C0)

Vd = amount of the drug in the body / C0

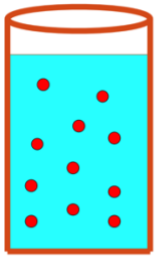
Although Vd has no physiologic or physical basis, it's a measure of the tendency of a drug to move out of the blood plasma to some other site. and it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.



take this simple example

Say you have a beaker containing a known volume of water (2 liters) and you put 50mg of a soluble drug inside, then simply you can find the concentration of the drug using the equation C= amount/volume, which will equal to 25 mg/L.

Now let's say you don't know the volume of the water but you can actually measure the concentration of the drug using a device, now by rearranging the equation to volume= amount/concentration, you can find the volume of water inside the beaker, 50mg/25mg/L = 2L .



What is the volume of water in the beaker?

$$\text{Volume} = \frac{\text{amount}}{\text{concentration}}$$

$$\text{Volume} = \frac{10\ \text{mg}}{10\ \text{mg/L}} = 1L$$

Using the same concept, we can use the volume of distribution as a measure of distribution of drugs.

If you administer a dose of a drug intravenously, you would naturally expect it to have an immediate blood concentration C0 which directly corresponds to the amount of blood contained in the body, Mathematically this would be:

C0= amount of drug /volume of blood

But in reality, this is not the case. Instead you will observe that the drug has distributed into other tissues of the body and the C0 you measured is actually lower than the C0 you precalculated using the previous equation, so probably the first question you may ask is: how much of the drug is no longer in the blood stream?

The volume of distribution (Vd) quantifies just that by specifying how big a volume you would need in order to observe the blood concentration actually measured, so using the equation

Vd = amount of the drug in the body (that you administrate) / C0 (that you measure)

You can actually visualize the extent of distribution for a certain drug even if the numbers are just theoretical and not measuring an actual physical quantity. How is that?

By looking at the equation, If the Vd is a small number that mean that C0 is considerably large(close to the theoretical one) meaning that most of the drug is still in the blood which means that the drug is poorly distributed or has a high degree of plasma protein binding. While on the other hand if Vd is a large number it means that the concentration of the drug in the blood is low, meaning that most of it has distributed to the different tissues of the body.

To sum up

Volumes of distribution (Vd)

(In litres for average 70 Kg adult human)

Warfarin	7
Gentamicin	16
Theophylline	35
Cimetidine	140
Digoxin	510
Mianserin	910
Quinacrine	50,000

Small vol. Mainly stays in plasma little in tissues.

Medium vol. Similar concs in plasma and tissues

Large vol. Mainly in tissues, little in plasma.

Imp Note: the volume of distribution is normally measured in L/kg

Because Vd depends on the body size of the individual, the larger the weight the larger the total body water, meaning more volume for the drug to distribute into. So, Vd would be more accurate if divided by the weight of the person.

e.g.
Theophylline Vd = 0.48 L/kg
For 60 kg adult,
Vd = 0.48 L/kg x 60 kg = 28.8 L

Now just to practice

A dose of analgesic (50mg) is administered i.v. and a blood sample is taken shortly afterwards. The initial concentration of analgesic in the blood sample is 0.85 µg.ml-1 . Calculate the volume of distribution of the analgesic (in Liters).

Model solution
Vd = amount / C0
= 50 mg / 0.85 µg.ml-1
= 50,000 µg / 0.85 µg.ml-1
= 58,824 ml
= 59 Liters

Good luck.