Variability in Drug Dosage Requirements

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Heart failure

- Heart failure is accompanied by a decrease in cardiac output which results in lower liver and renal blood flow.

- Changes in drug pharmacokinetics due to decreased renal blood flow are not widely reported.

- However, declines in hepatic clearance are reported for many drugs.

Heart failure

- Additionally, decreased drug bioavailability has been reported in patients with heart failure.

- The proposed mechanisms for decreased bioavailability are collection of edema fluid in the gastrointestinal tract which makes absorption of drug molecules more difficult and decreased blood flow to the gastrointestinal tract.

Heart failure

- The volume of distribution for some drugs decreases in patients with heart failure.

- Because clearance and volume of distribution may or may not simultaneously change,

The alteration in half-life, if any, is difficult to predict in patients with heart failure

Obesity

- The presence of excessive adipose tissue can alter the pharmacokinetics of drugs by changing the volume of distribution.

$$V = V_B + (f_B/f_T)\, V_T$$

$$V = V_B + (f_B/f_{heart})\, V_{heart} + (f_B/f_{muscle})\, V_{muscle} + (f_B/f_{fat})\, V_{fat} + \ldots + (f_B/f_n)\, V_n$$

Obesity

- If the drug has
  - *a large affinity for adipose tissue (lipophilic)*
  - *a highly tissue binding*

➢ *The free fraction in adipose tissue will be small ($\downarrow f_{fat}$)*

➢ *The volume of distribution in obese patients for these drugs can be dramatically larger than in normal weight patients*

Obesity

- Examples of lipophilic drugs with larger volume of distribution values in obese individuals are diazepam, carbamazepine, and trazodone.

- However, hydrophilic drugs tend to not distribute into adipose tissue so that the volume of distribution for many water-soluble drugs is not significantly different in obese and normal weight patients.

- In that sense, The volumes of distribution for digoxin, cimetidine, and ranitidine are similar in overweight- and normal-weight subjects.

Obesity

- Although the presence of excessive adipose tissue is the most obvious change that occurs in obese individuals, other physiologic changes are present;

1. ↑ *Supportive tissues*
2. ↑ *Extracellular fluid*
3. ↑ *Blood*

In the adipose tissue

4. ↑ *Lean tissue (muscle)*

Obesity

- The net result of these changes is that hydrophilic drugs with small volumes of distribution may experience distribution alterations in obese patients.

- For example, the aminoglycoside antibiotics are water-soluble molecules that have relatively small volumes of distribution.

- Since the volume of distribution is so small, the addition of just a few liters of extracellular fluid can increase the volume of distribution of these antibiotics.

Obesity

- However, if the volume of distribution for a hydrophilic drug is intermediate or large, the additional extracellular fluid contained in adipose tissue may not significantly alter the distribution of the agent.

- Examples of medications with larger and intermediate volumes of distribution are digoxin (V = 500 L) and vancomycin (V = 50 L).

Obesity

- Another change that is found in obese individuals is increased glomerular filtration rates.

- This alteration primarily affects hydrophilic drug compounds that are renally eliminated and will increase the renal clearance of the agent.

- Vancomycin, the aminoglycosides, and cimetidine all have higher clearance rates in obese patients compared to normal weight individuals.

Obesity

- Obesity has variable effects on the metabolism of drugs.
- For many agents, such as carbamazepine and cyclosporine, obesity does not significantly effect hepatic clearance.
- While for other drugs, obesity increases hepatic clearance, as with diazepam, or decreases metabolic clearance, as with methylprednisolone.

Obesity

- Clinicians should be aware of this variability and dose hepatically metabolized drugs cautiously in obese individuals in the absence of specific recommendations.

Obesity

- Half-life changes vary according to the relative alterations in clearance (Cl) and volume of distribution (V):

$$t\ 1/2 = (0.693 \cdot V) / Cl$$

- In the case of the aminoglycoside antibiotics, *clearance and volume of distribution* increases are about the same magnitude in obese patients, so half-life does not change.

Obesity

- If the volume of distribution increases with obesity, but clearance is unaffected, half-life can increase dramatically as with carbamazepine.

- Finally, if clearance changes and volume of distribution remains constant, obesity may also cause a change in the half-life of a drug as is the case for methylprednisolone.

Drug interactions

Inhibition or induction Drug Interactions

- A drug can inhibit or induce the enzymes responsible for the metabolism of other drugs.

- Enzyme inhibition ↓ intrinsic clearance, and enzyme induction ↑ intrinsic clearance.

- If two drugs are eliminated by the same enzyme, they may compete for the metabolic pathway and decrease the clearance of one or both compounds.

Drug interactions

- Two drugs eliminated by the same active renal tubular secretion mechanism can compete for the pathway and decrease the renal clearance of one or both agents.

Drug interactions

Plasma protein binding displacement drug interactions

- A drug may displaces another drug from its plasma protein binding sites when the two compounds share the same binding site.

Drug interactions

Alteration in organ blood flow

- It may be possible for an agent to change liver blood flow.
- For instance, *ß-blockers* can ↓ heart rate and cardiac output which ↓ liver blood flow.
- Since liver blood flow is the predominate factor that determines clearance for high hepatic extraction ratio drugs, this type of interaction is only important for this category of medication.
- ß-blockers decrease lidocaine clearance by decreasing liver blood flow.

Drug interactions

- In general, changes in plasma protein binding also cause alterations in volume of distribution.

- Half-life may change as a result of drug interactions, or, if clearance and volume of distribution alterations are about equal, half-life may remain constant even though a major drug interaction has occurred.

Thank you