



**MONASH** University  
Pharmacy and Pharmaceutical Sciences

# Adverse reactions linked to pharmaceutical formulations

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# Formulation misadventures

## Biopharmaceutics at the coal face

# Outline

- Biopharmaceutics and the formulation of medicines
- Formulation misadventures
- Pharmacokinetics
- Case studies
- Manufacturing, compounding and dispensing

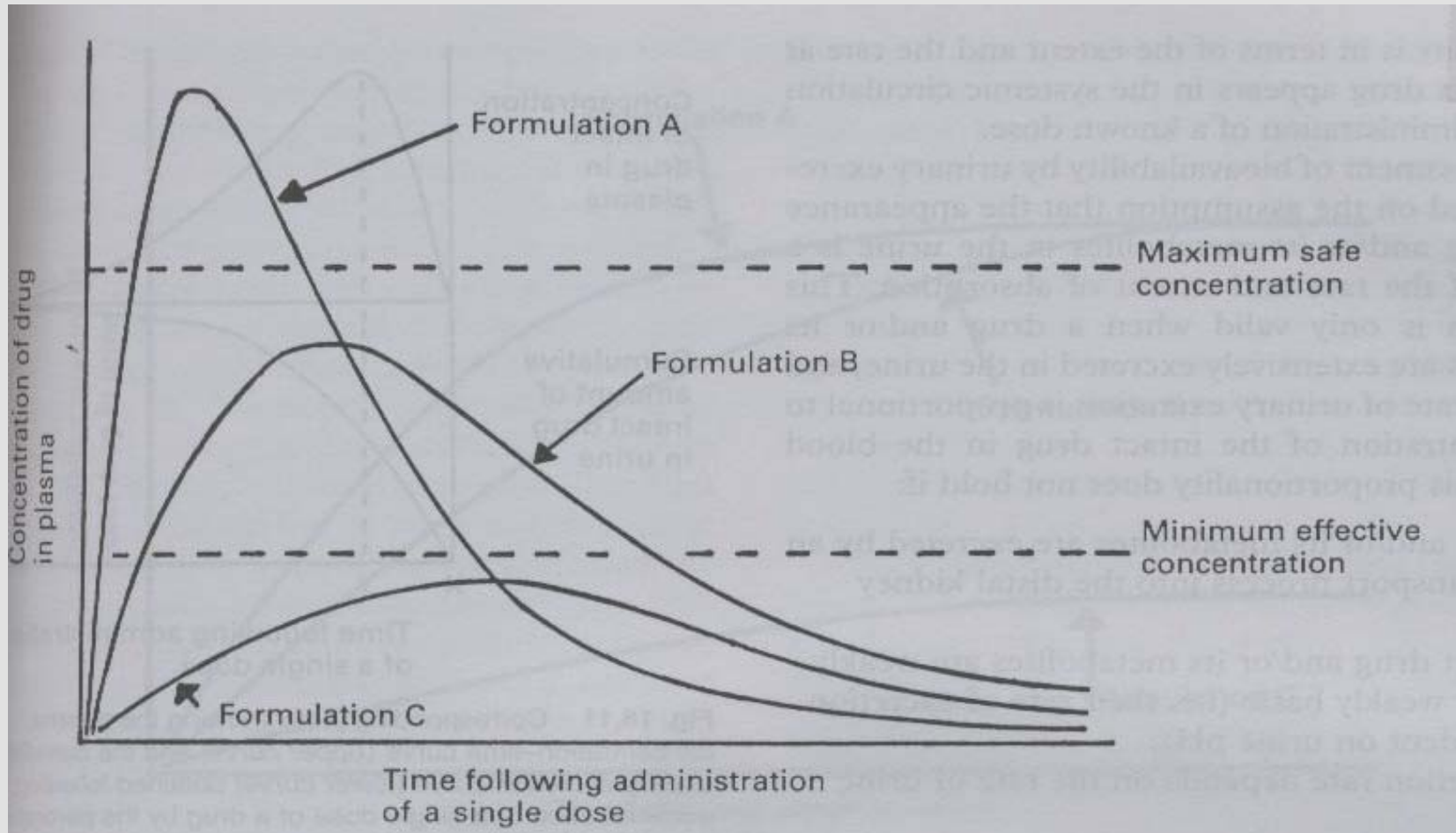
# Terminology

- Conversion of drugs into medicines; the design and manufacture of dose forms is **pharmaceutics**
- Study of how the physicochemical properties of drugs, dosage forms and routes of administration affect the rate and extent of drug absorption is **biopharmaceutics**
- Study and characterization of the time course of drug absorption, distribution metabolism and elimination (ADME) is **pharmacokinetics**

# Bioavailability and bioequivalence

- Compares the bioavailability of several different products containing the same drug:
  - **Time** to max serum concentration ( $t_{max}$ )
  - **Max concentration** achieved ( $C_{max}$ )
  - **Total** amount of drug absorbed (AUC)
- Formulation errors can result in different profiles
- There can be marked interspecies differences in bioavailability

# Bioequivalence



# Medicines

- Medicines are usually drugs plus additives
  - Excipients
  - Formulation is usually necessary
- Three major considerations in dosage form design:
  - Physicochemical properties of the drug\*
  - Biopharmaceutical considerations\*
  - Therapeutic considerations

# Physicochemical properties

- Particle size and surface area\*
- Solubility
- Dissolution rate\*
- Partition co-efficient and  $pK_a$ \*
- Crystal properties: polymorphism\*
- Stability
- Organoleptic properties
- Other drug properties\*

# Particle size and surface area

- Smaller particle size > greater surface area
- Affects dissolution and absorption rate
- Poorly water soluble drugs are more readily bioavailable if small particle size
- Examples – griseofulvin and MBZ
- Excipient and manufacturing process can blunt use of small particles,
- Trade off with stability and content uniformity
- Size important for inhalation aerosols

# Dissolution rate

- Drug must dissolve in fluid at site of absorption
- Correlates with bioavailability
- Physicochemical properties and excipients are important
- Some dose forms have unusual characteristics
  - sustained release
  - enteric coating
- *In vitro* tests can be surrogate for *in vivo*
  - Needs adaptation for species differences and complex dose forms

# Partition coefficient and $pK_a$

- Permeation across biological membranes
  - Membranes act as lipophilic barrier
  - More permeable to un-ionized drugs
- Depends on drug's size, relative aqueous and lipid solubility, and ionic charge
- Most drugs are weak acids or bases
  - Depending on their pH, exist in ionized or un-ionized form

# ...partition coefficient and $pK_a$

- pH at site of absorption and lipid solubility of the un-ionized form significantly determine absorption of weak acids and bases
- Partition coefficient is a measure of a drug's lipophilicity
- $pK_a$  is a measure of a drug's ionization ('dissociation')

# Crystal properties: polymorphism

- Drug properties can vary
  - Amorphous (no regular molecular lattice formation) or crystalline
  - Anhydrous, hydrated, or solvated
  - Varying crystal hardness, shape and size
- Can exist in more than one form
  - Polymorphism
  - Vary in physical properties(affects dissolution etc)

# ...crystal properties: polymorphism

- Amorphous form
  - Minimal “energy” for solubilisation, so solubility and dissolution advantages
  - Bioavailability of poorly-soluble drugs↑
  - Physical stability↓ and chemical reactivity↑
- Transformation of drug properties can occur during formulation
  - Additives/excipients can help control changes

# Other drug properties

- Large-scale manufacture could be an issue
- Need to consider hygroscopicity, flowability and compressibility – for solid dose forms with high drug content
- May need low-moisture manufacturing environment
- May require addition of flow agents (fumed silica);
- Formulations which stick to tablet presses will need re-formulation

# Phenytoin capsules

- Anti-epileptic medication which encountered a re-formulation issue
- Phenytoin sodium (Dilantin®) capsules were originally 100 mg or 300 mg doses
  - Patients were well stabilised on these
- Parke-Davis reformulated the capsules by replacing the calcium sulphate filler with lactose
  - Possibly for economic reasons.

# ...phenytoin

- Clinical overdoses of phenytoin occurred
- Different blood concentration-time profiles for the two formulations
- Area under the drug blood concentration-time curve for the newer formulation shown to be about three-fold larger than that for the old formulation

# ...phenytoin

- Calcium sulphate was poorly water soluble
  - Remained largely intact throughout the length of the GI tract
  - Much of the phenytoin content was adsorbed on the surface of the calcium sulphate particles
  - Impeded absorption across the GI mucosa
- Lactose is water-soluble so nothing there to impede the phenytoin absorption
  - Oral bioavailability was essentially complete.

# ...phenytoin

- two equipotent formulations could be made to have very different efficacy by simply changing from a very slightly water soluble excipient to a much more water soluble excipient.
- As a result, phenytoin sodium capsules were reformulated in doses of 30 mg and 100 mg.

# Levothyroxine tablets

- Levo isomer of thyroxine
- FDA received 58 ADR reports associated with potency
  - 47 suggested sub-potent tablets
  - Nine suggested super-potency
- Two scenarios
  - Brand switching associated with some cases
  - Other ADRs associated with refill prescriptions

# ...levothyroxine

- Scenarios indicated lack of consistency in stability, potency, and bioavailability between different lots of tablets from the same manufacturer
- One manufacturer reformulated levothyroxine by removing two inactive ingredients and changing the physical form of coloring agents
- The reformulated product increased significantly in potency

# ...levothyroxine

- Levothyroxine is unstable in the presence of light, temperature, air, and humidity
- Some excipients used with levothyroxine acted as catalysts to hasten degradation
- To compensate for the initial accelerated degradation, some manufacturers used an overage of active ingredient formulation
  - Can lead to occasional instances of super-potency.

# Mebendazole dose forms

- Three different dose forms of MBZ evaluated against *T hydatigena* and *E,granulosis* in dogs
  - Powder
  - Micronized powder
  - Micronized tablets
- Most active was micronized powder

# Procaine penicillin toxicity

- Unexpectedly, some horses were highly excited, and some died, after routine treatment
  - Sustained release formulation
- Possible causes: anaphylaxis; procaine toxicity; emboli; excipients
- Found that heating resulted in increase in free procaine
  - 1gram in 20mL dose
  - Not all brands affected
  - Unsure of the mechanism

# Carbamazepine tablets

- An epileptic patient was fairly well stabilised on carbamazepine tablets
- Repeatedly noticed that he was more likely to have a seizure if he had taken the tablets with milk rather than with water
- Fat content of milk would be expected to partly dissolve the poorly-water soluble lipophilic carbamazepine, and thus retard its absorption from the GI tract

# ...carbamazepine

- Results in plasma concentration-time profile being lower and broader with milk was used
  - Area under the curve would be the same as when water was used to aid swallowing
  - That portion of the curve above the “minimum effective concentration” was smaller in area > under-dosing
- Seizures could be expected from time to time (“fairly well stabilised”) but more frequently when milk was used

# Phenytoin capsules (again!)

- Epileptic patient stabilised on phenytoin capsules
- Regularly put capsules into a seven-day medication organiser
- Went to Hong Kong for several days
  - Capsules in the organiser
- On returning had one unexplained and severe seizure
  - First in quite a long time.

# ...phenytoin

- Humid environment of Hong Kong meant capsule contents absorbed moisture
- The sodium phenytoin particles retained moisture as a thin alkaline film over the surface
- Alkaline film then absorbed carbon dioxide
  - More acidic than that of phenytoin (pKa 8.3 vs 6.8) liberated phenytoin in the free acid form from the salt form in a thin layer around each particle.

# ...phenytoin

- As phenytoin free acid is far less soluble in water than the salt form, the dissolution rate is about 5000-fold slower
- Hence, the dissolved phenytoin concentration in the GI contents was substantially lower than normal during the time in Hong Kong
  - Lead to progressively lower doses, until the threshold activity level in the blood was not reached, and efficacy was lost

# Sodium nitroprusside

- Sodium nitroprusside infusion can be used after cardiac surgery and to quickly reduce severe hypertension
- Cardiac surgeons prefer to use isotonic glucose in water as the infusion vehicle, rather than normal saline
- A hospital sterile solutions unit had a history of safely providing sodium nitroprusside infusion in D5W during or after cardiac surgery

# ...sodium nitroprusside

- On one occasion patient noticed that the initially-provided pale straw coloured solution had, during the course of the infusion, turned a bright blue colour
- Medical staff removed the infusion from the patient
- Investigation showed that the only difference from previous practice, was that the patient was in a bed beside a large, sunlit window

# ...sodium nitroprusside

- Aqueous solution of glucose and sodium nitroprusside forms a potential redox couple which remains quite stable unless catalysed by exposure to adequate light intensity
- The resulting chemical reaction produces a mixture of nitroprussides constituting the mononitric oxide analogue of the ferricyanide/ferrocyanide complex which is known to artists as Turnbull's Blue or Prussian Blue

# ...sodium nitroprusside

- When very dilute, soon after initiation, get deep blue solution that progresses to a blue colloidal dispersion and ultimately a blue precipitate
- At the last stage, the precipitate could be dangerous, through infusion of particulates
- The final resolution of the problem was:
  - Move the patient away from the sunlight
  - Shield the infusion solution by wrapping the bottle in aluminium foil

# Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Elimination

# Absorption (ADME)

- Absorption is the process by which drugs enter the circulation
- The extent of absorption is referred to as the bioavailability
- The speed of absorption is also important
- Several factors influence absorption:
  - Route of administration
  - Drug properties
  - Formulation of the medicine
  - Disease states

# Phenylbutazone tablets

- An 'old' NSAID formerly in common use
- Many 100mg tablet products on the market
- Potency was satisfactory for each one
- *In vitro* dissolution tests conducted
  - 3 brands satisfactory
  - 1 brand marginal
  - 2 brands did not meet USP requirements

# Antacids

- Antacids were once in common use
  - Calcium or magnesium carbonates, aluminium or magnesium hydroxides, bismuth compounds
  - Before the advent of the proton pump inhibitors and H<sub>2</sub> antagonists,
- Excessive use meant very low acidity > a significant portion of the administered antacid remained as undissolved, high surface area finely divided solid

# ...antacids

- Co-administration of other drugs, especially low dose or poorly absorbed compounds (tetracyclines or folic acid) was likely to lead to surface adsorption of such compounds, thus reducing oral bioavailability
- The reduced bioavailability of the tetracyclines was exacerbated by the reduction in bioavailability that resulted from complexation with calcium or magnesium ions

# Distribution (ADME)

- Distribution is the transfer of drugs to sites of action, storage, metabolism and excretion
- Several factors influence distribution:
  - Cardiac output
  - Tissue perfusion – fat is low, brain is high
  - Plasma and tissue binding
  - Drug properties

# ....distribution

- Distribution of drug through the body is an uneven process
- It takes a while to reach equilibrium between blood and tissues
- Extent of drug distribution into tissues depends on the extent of plasma binding and tissue binding

# Plasma binding

- Drugs can bind to serum proteins
- This is a quick and reversible process
- The importance lies in the influence protein binding has on the distribution of drugs (bound drug isn't filtered and isn't able to enter tissues)
- One drug may displace another off proteins – to result in more free drug than expected

# Tissue binding

- Drugs bind to various substances in tissues
- Chloroquine binds to nucleic acids!
- Several other drugs bind to fat
  - Distribution into fat is slow because of poor perfusion
  - Distribution will be extensive in obese animals

# Loading dose

- Give a large enough initial dose to “fill up” all binding spaces quickly
- With no loading dose, drug accumulates slowly
- Toxicity will limit the usefulness of loading doses

# Digoxin

- Digoxin is used to treat heart failure in dogs
- It distributes slowly to cardiac muscle (and to other parts of the body)
- Without a loading dose it takes many hours to exert its full therapeutic effect
- Digoxin is given in several high doses until toxicity is evident – then reduced to a daily “maintenance” dose

# Thiopentone

- Thiopentone is a highly lipid-soluble anaesthetic
- Distributes quickly to brain following a single IV injection > short-acting anaesthesia
- Distributes more slowly to poorly perfused tissues
  - Initial IV dose of thiopentone rapidly reaches the brain
  - Then redistributes to the viscera, muscles and fat, and is slowly metabolised by the liver

# ...thiopentone

- Recovery from anaesthesia is not dependent on immediate metabolism or excretion
  - When the animal recovers consciousness the full dose of thiopentone is still in the body!
- Top-up doses fill the fatty tissues which then act a reservoir and prolong anaesthesia
  - Repeated doses lead to tissue “saturation” and recovery may be prolonged for many hours

# Metabolism (ADME)

- The major site of metabolism is the liver
  - Liver microsomes
- There are two phases of metabolism:
  - Phase 1 – oxidation/reduction/hydrolysis
  - Phase 2 – “synthetic” acetylation, conjugation and glucuronidation
- The resulting metabolites are usually more water soluble and easier to excrete
- Some metabolites are pharmacologically active

# Paracetamol

- Paracetamol is very toxic in cats because there is defective Phase 2 metabolism
- Paracetamol undergoes Phase 1 metabolism
  - Yields toxic metabolites which are not 'mopped up' by glutathione
- Results in hepatic necrosis and methaemoglobinaemia

# First pass metabolism

- Most drugs go to the liver after being absorbed from the upper gastrointestinal tract
- The liver is the major site of drug metabolism in the body
- There is also cytochrome P450 in the gut wall
- The ‘destruction’ of drugs soon after absorption is called “first pass metabolism”

# Prodrugs

- Not all drugs are destroyed by metabolism
- Some may be activated from inactive compounds (“prodrugs”)
- This situation can be exploited to get drugs into the body that are difficult to handle or are poorly absorbed
- Recent development of highly water-soluble pro-drugs of benzimidazole

# Ketamine in harness racing

- Recent case involving detection of minute amounts of ketamine in post-race urine sample
- Possible source of ketamine:
  - Metabolites if from the horse
  - No metabolites if a contaminant
- No attempt made to detect metabolites
- Possible urine collection issues
  - Two gelding operations earlier in the day
  - Special K

# Elimination (ADME)

- Major sites are the kidneys
  - Also lungs, sweat, saliva, hair, bile *etc*
- In the kidneys the process begins with filtration through the glomerulus
- Followed by transcellular and paracellular re-absorption
- Several factors influence excretion:
  - Glomerular filtration rate
  - Protein drug binding
  - Water solubility of the drug
  - Ionisation state of the drug (effect of urine pH)

# Phenylbutazone (again!)

- PBZ used orally and IV in horses
- Distributed throughout the body
- Plasma protein binding exceeds 98%
- Serum half-life about 6 hours (dose dependent)
  - Efficacious for 24 hours + (irreversible binding to COO)
- Metabolized to oxyphenbutazone (OPZ) *et al*
- BPZ and OPZ more rapidly excreted in alkaline than acidic urine

# Manufacture of pharmaceutical products

- **Industrial manufacturing**
  - Complete with code of GMP
  - Registration of pharmaceutical products
- **Dispensing and compounding**
  - One-off preparation from a prescription
  - Single course of treatment
  - Integral part of pharmacy practice
  - Usually follow established formularies
  - Compounding pharmacies pushing the boundaries

# Compounding

- Now a 'twilight zone' between industrial manufacturing and dispensing
- Allows dose forms and some drugs to be made available when there are no other alternatives
- Fine line between manufacturing and dispensing
- Compounding beyond established formularies can be associated with formulation misadventurers
- TGA and APVMA guidelines

# Venezuelan polo horses

- Team unable to legally bring Biodyl into the USA “to make their horses more resilient”
- Decided to get a compounding pharmacy to make an equivalent
- All 21 horses injected with the product died
- Too much selenium
- Causes:
  - Incorrect prescription?
  - Incorrect amount used?
  - Incorrect formulation?

