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1 Characteristics of IV Therapy

1.1 Concentration – time profiles

Describe mathematically or in words the concentration – time profile that occurs after an IV bolus?

\[ C_p^t = C_p^0 \times e^{-kt} \]

What is special about this curve?

It is exponential so it has a constant decay factor, where a fixed proportion of the amount remaining is eliminated in unit time.

Described by a constant decay factor or:

Half-life \( t_{1/2} \)
1.2 Half-Life?

What is the Half-life and what does it tell you?

Half-Life is defined as:
The time taken, for the concentration of a drug, in the blood, to halve is called the half-life. It varies from drug to drug and is an average figure for a ‘healthy-patient’ population for an individual drug.

A After 5 half-lives the drug has completely disappeared from the blood. So the half-life tells you the (pharmacokinetic) duration of action of the drug. It changes when the eliminating organ (kidneys or liver) is dysfunctional. It therefore varies from patient to patient. Note rarely a drug (e.g. steroids) may have a pharmacological duration of action that differs from the blood profile.

B If the half-life tells you how quickly the effects of an IV decrease and we usually dose at the half-life one can see that if a drug has a half-life about 24 hours then we usually administer it daily.

<table>
<thead>
<tr>
<th>Half-life</th>
<th>Prescribed frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two weeks or more</td>
<td>Monthly depot injection</td>
<td>Pharmacological effects may be longer than plasma profile</td>
</tr>
<tr>
<td>One week</td>
<td>Weekly depot injections</td>
<td></td>
</tr>
<tr>
<td>Two days</td>
<td>Daily injection</td>
<td></td>
</tr>
<tr>
<td>One day</td>
<td>Daily injection</td>
<td></td>
</tr>
<tr>
<td>18 hours</td>
<td>Daily injection</td>
<td></td>
</tr>
<tr>
<td>12 hours</td>
<td>Twice a day</td>
<td></td>
</tr>
<tr>
<td>8 hours</td>
<td>TDS</td>
<td></td>
</tr>
<tr>
<td>6 hours</td>
<td>QDS</td>
<td></td>
</tr>
<tr>
<td>4 hours</td>
<td>4 hourly</td>
<td>Consider simplicity of infusion</td>
</tr>
<tr>
<td>2 hours</td>
<td>Continuous infusion</td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>Continuous infusion</td>
<td>Consider syringe driver for accuracy</td>
</tr>
</tbody>
</table>

C If the half-life is less than 4 hours then the medicine is usually administered by infusion.

To ask a nurse to administer a drug every 4 hours may be challenging on a medical ward with a few nurses and many patients. It may be readily delivered in High Care, and 2 hours may be achievable on Intensive Care. However a drug with a half-life of 4 hours or less is usually administered by infusion.

D When dosing at the Half-life, 5 half-lives also gives you the time to steady state (see later).

E All Infusions should clearly indicate a concentration (e.g. 500mg/500ml). Continuous infusions should be prescribed with a volume rate (ml/hr) and a dose rate (mg/kg/hr) to facilitate checking of the calculation and early detection of errors. It is useful to prescribe in mg/kg/hr for drugs that have a half-life of 1 hour or more and in µg/kg/min for drugs that have a half-life of less than one hour. This may indicate to staff the extent of response delays after dose adjustments.

1.3 What Dose?

Posology – the science of dosing is a complicated process where the peak response of a dose must exceed the minimum effective concentration but not usually the minimum toxic level (where side-effects may exceed benefits). Thankfully this usually takes place before the product becomes licensed, but will be an issue in clinical trials and possible early licensed usage. The electronic medicines compendium (www.medicines.org) lists the Specific Product Characteristics (SPC) that includes the dose, frequency and method of administration. The BNF is also a useful guide for common doses and a few moments reading can avoid significant prescribing errors.
1.4 Intermittent Infusion?

Sometimes individual doses may produce peak concentrations in the toxic range and intermittent infusions may be required to avoid this. For example, Vancomycin as a bolus is hazardous producing toxic peak-related effects in addition to histamine release (red man syndrome). Converting this to 1G delivered over 1-2 hours eliminates these problems.

Magnesium 2G bolus may produce profound Bradycardia and Vasodilatation mediated hypotension, whereas over 2 hours these effects are absent.

In the USA Gentamicin is delivered in minibags over 20 minutes to avoid tinnitus related litigation, whereas in the UK the same dose as a bolus over 2-5 minutes is perceived as achieving good tissue penetration and therefore better cure rates. Note this applies to 1-2mg/kg dosing not Extended Interval Dosing (EID) using 5-7mg/kg). EID utilises 100ml minibags over 20 minutes and still achieve a 10 fold peaks to MIC ratio.

Rifampicin IV is administered as a 2-hour infusion to reduce liver related toxicity.

1.5 How Often?

An intermittent bolus is when the previous dose has been completely eliminated before another dose is administered. There may be a gap between zero concentration and the next dose of hours, days or years (i.e. the doses are completely unconnected). This may be appropriate for acute pain management, diuretics for flash oedema, vaccines and even antibiotics.

An adjacent bolus is when the previous dose has been completely eliminated before another dose is administered but any gap is less than one hour. (The doses are semi-connected). This might be used for fluid bolus or stat Frusemide boluses where fluid balance is being assessed. Also pain killers where dose titration is being undertaken.

The most common form of bolus administration is with accumulating bolus where accumulation does not cause blood levels to rise above the minimum toxic concentration. Thus there is some residual drug remaining in the blood before the next dose is administered. Conventionally this continues until a steady
state is achieved, where input rate is equal to the output rate (elimination rate). The variation from peak to trough concentrations is within the therapeutic range (TR = MEC to MTC)

Accumulating bolus –
with Loading Dose or not?

1.6 With Loading Dose?

A loading dose is only required if the time to steady state (5 x Half-life) is not rapid enough for the required clinical response.

For example to achieve steady state with digoxin would take about two weeks in an average patient with good renal function. This may not be clinically appropriate if you want to achieve rate control today.

Phenytoin has a half-life of 1-2 days in adults so steady state would arise in 7-10 days. If resuming prophylactic therapy no loading dose (LD) may be required. However if you want to treat status epilepticus a LD would be required to achieve control more rapidly.

Fluconazole has a Half-life of about 24 hours, but you may wish to achieve high tissue levels and rapid onset with a 400mg LD before starting the usual maintenance dose (MD) of 200mg daily.

A half-life of 12 hours or less implies that an LD is unlikely to be required. Analgesics may be an exception to this, but multiple adjacent boluses may be preferable to a large LD to avoid side effects.

1.7 Continuous Infusion?

Short Half-life = Infusion
1.8 Effect of organ dysfunction?

If the drug is not eliminated by the failing organ, no modification is usually required. E.g. liver failure in a drug usually eliminated by the kidneys.

However, if the drug is eliminated by the failing organ then adjustment of the dosing frequency is usually required. This can be illustrated by a stretched concentration – time profile:

As can be seen above, if the standard dosing frequency is used in this scenario, blood levels will accumulate, possibly to toxic levels.

2 Why give drugs parenterally

Parenteral administration is desirable when a rapid onset of action is required, such as for the relief of acute pain.

Parenteral administration is desirable when achieving high blood or tissue concentrations is important, such as with antibiotics.

Parenteral administration is desirable when it is important to be reassured that the drug is entering the bloodstream, such as in the treatment of acute, life-threatening arrhythmias.

Parenteral administration is desirable when giving an initial loading dose such as when trying to control convulsions.

These are all positive selection criteria.

2.1 Whether to consider alternative routes

These are where parenteral administration is associated with negative connotations.

Injections are hazardous and the oral route must always be considered as a first option. If the oral route is unavailable, then Intramuscular or subcutaneous injections may represent safer alternatives. However
they IM/SC have their own limitations; such as maximum volumes, they may be painful or have erratic and slow absorption.

If the oral route is unavailable, but enteral tube administration may be possible naso-gastrically or naso-jejunally. Alternatively it may be appropriate to endoscopically place a percutaneous enterogastric or entero-jejunal tube for drug administration. Care in both tube and medicinal product selection is important.

Nausea, vomiting, diarrhoea, ileostomy, and recent gut surgery may make the options above inappropriate and rectal administration should be considered but again there are clinical cautions and pharmaceutical considerations.

Transdermal administration is a growing area, currently limited by technology advances and availability of suitable medicinal products.

Parenteral administration is also expensive, but can be justified where positive selection criteria are clinically warranted or alternative routes contra-indicated.

2.2 What route

IV usually means administration via peripherally inserted cannulae, but sometimes-Central line administration is required. What does Central mean?

Why would you consider Central Administration?
Are you competent to place a Central Line? Or
If the patient has one already do you know how to use it safely?

Central line administration may be necessary because you need to measure a central blood pressure such as CVP or PAWP (pulmonary artery wedge pressure).

You may want to give minimal fluid volumes with drug administration and that can be possible centrally because the venous return dilutes the drug coming out of the catheter tip.

The drug you want to give may only be licensed for Central administration (this is rare) or the concentration you want to use is too irritant to be given peripherally.

If the patient has not got a Central line currently inserting one may pose additional unjustifiable hazards including lack of recent practice, training or expertise. Additionally the time taken to prepare for and insert a Central line may delay urgent treatment (see potassium), but consider the acute trauma scenario where access is a priority despite the hazards.

Finally Peripheral line insertion is easier, les hazardous and more familiar to most junior doctors. Most patients can cope with the volumes.

2.3 What IV Fluid – 1

Crystalloids or colloids

Colloids are special IV fluids that have a large molecular weight and size so they tend to stay in the plasma. They will leak out but very slowly. They are therefore specific treatments for fluid restricted and oedematous patients. They may be used as fluid challenges to produce rapid increases in CVP and to redistribute fluid in the wrong place. They are usually restricted to high care & intensive Care and expensive.

Crystalloids are solutions of electrolytes like sodium chloride, dextrose they will pass through vascular membranes so they tend to move into the tissues fairly quickly. Therefore large volumes may need to be given to sustain Central venous pressure and urine output. They are therefore often referred to as maintenance fluids. They are commonly used on surgical and medical wards and relatively cheap.
Remember if you give a non-diabetic dextrose, they will activate their own insulin secretion and move the dextrose into the tissues and carry with this potassium, magnesium, calcium and phosphate. So fluids alone not only dilute but also redistribute electrolytes.

Fluids kept at Southampton can be found in appendix 1

3 Practicalities

3.1 Where to prepare – consider your environment

Ok so it’s got to be IV, but you have to make it up. What environment do you select – ward treatment room, theatres because that’s even cleaner or the toilet cubicle?

No seriously studies have shown lower contamination when products have been prepared in the toilet. This was because researchers took more care because they knew it was a dirty environment. So, consider how busy are you and, will you rush and make a mistake or contaminate the IV product. Alternatively you may be able to persuade pharmacy to prepare the IV product as part of Central IntraVenous Additive Service (CIVAS). This is an aseptic room with sterile filtered air that makes theatres look dirty. The staff wear gowns and hoods as if it were a major outbreak of a highly infections virus.

If it’s Epidural or Intrathecal you must filter the product, but seek expert advice before you start or get pharmacy to make as CIVAS. There are NPSA alerts about this so alarm bells should ring if you ever consider these routes. Also don’t make the mistake of giving an IV by these routes

3.2 When to prepare IVs

The obvious answer is immediately before you administer. However going to theatres presents some challenges. Pre-operative antibiotics are usually given in the anaesthetic room as part of the induction sequence. These prophylactic antibiotics should be administered so that when the surgeon puts knife to skin there the blood has peak antibiotic levels. Some drugs like vancomycin need to be given as intermittent infusions that may take some time to run in (1G should be given over 2 hours). This may present problems

There is a compromise between starting vancomycin 2 hours before knife to skin and the logistics of getting the patient there. Some anaesthetists will choose to give vancomycin as the first IV in the anaesthetic room. Evidence shows that as long as the infusion has been running for more than 30 minutes then adequate blood levels will be present at knife to skin. Those who have seen red-man syndrome will know this hypotensive crisis can be traumatic for all, especially if you need to give anaesthetics with vasodilating side-effects.

Injectables prepared on the ward must be administered before 24hours have elapsed due to the risks of microbial contamination. Many reconstituted drugs are less stable than this and either chemically degrade or physically precipitate in less than 24 hours. The latest NPSA alert advises that to avoid all these risks all injectables should be made as CIVAS or bought as ready to use commercial products. This is not yet possible, but is an aim to strive for.

There is a huge saving in time if a particular course of injections are prepared all together, so preparing all the antibiotics for the weekend is not as stupid as it initially sounds. However logistically if you are due to stop the antibiotics on Sunday morning, communicating this to the CIVAS part of pharmacy will avoid significant wastage of resources.

Many injectables such as antibiotics or cytotoxics can be made for a whole week in CIVAS because of the laminated airflow environment. If we can rationalise product ands strengths used we may be able to prepare your common injectables so they sit on the shelf ready-to-go. This would eliminate calculation and preparation and huge amounts of nursing and doctors’ time.
3.3 How to prepare

Do you know how to prepare the common injectables that you will prescribe or administer yourself? Do you know how to find out this information?
Take some time to familiarise yourself with www.medicines.org, if you can’t remember the site go through the SUHTranet useful links to pharmacy and you will find it saved there.
Always select the SPC option. PIL (patient information leaflet) will be unhelpful to you.
The BNF has dosage and frequency details in the main text and appendix 6 at the back lists the products and their appropriate diluents (but not always the volume and strengths).

How do you prepare Cefuroxime 750mg dry powder vial?
How do you administer Metronidazole IV 500mg?
(Please note that IVs converting to oral often requires a dose change)
Could these drugs be given through a ‘Y’ site connection?
How would you find out about incompatibilities?
How would you prepare IV Rifampicin 600mg?
What is Propofol and what problems would you encounter if you were asked to dilute it?
What is piggybacking? – When would you use it?
Why would you ‘Y’; site into a fast running infusion? – What do you need to consider?

Please note when issuing instructions for dilutions it is important to clearly describe the item. For example Fentanyl is a 50microgram/ml injection in 2ml and 10ml sizes. This is best described as 100microgram in 2ml and 500microgram in 10ml. Thus:
100µg/2ml + 48ml bupivacaine 0.25% to give 100 µg Fentanyl in 50ml.

Now write this out if you only have the 0.5% Bupivacaine available.

If you know all the above, what problems might you encounter inserting a central line, when the nurse has helpful put ampoules of Lignocaine, Saline, Water and Potassium on the sterile tray behind you?

Please read the Potassium policy on SUHTranet

When adding an ampoule of any drug to an IV bag it is very important to mix thoroughly. Potassium is denser than the fluids into which it is injected and will settle at the base of the bag near the exit port. Without mixing this will be administered as a bolus when the infusion is run. There are cardiovascular consequences of a rapid potassium bolus. If it’s through a peripheral vein it will also cause pain, thrombophlebitis and necrosis. So make sure you know how to mix this properly. Better yet always prescribe the ready-made bags so nurses you work with cannot make this mistake. There are many drugs where good mixing is important

Drugs are prepared in a variety of formulations to enable a stable medicinal product to be prepared. This varies from simple solutions in water or saline, to complex emulsions and lipid solutions. They may be presented as freeze dried powders for reconstitution with water or saline or they may require reconstitution with special pH buffers that then require further dilution.

Reconstitution and dilution instructions must be carefully followed in order to avoid a product that is degraded, inactivated or precipitating. Details of this are available in the BNF, the electronic medicines compendium (on the internet) or in specific information folders on your ward

3.4 Phenytoin

This drug has a number of problems with its use. Ask your pharmacists about its pharmacokinetics, therapeutic drug monitoring and interpretation of blood levels.

The injection of phenytoin presents a number of problems. (Link to SUHTranet guidelines)
This is a special formulation requiring co-solvents, stabilisers and a pH adjustment. The ampoule has a pH of 10 so administered directly it's like intravenous bleach – likely to cause pain and vein irritation. However if you dilute it becomes unstable and may precipitate.

There are two answers to this riddle
A – It can be administered undiluted (neat) but must be into a well perfused vein (preferably central, but can be peripheral) followed by a flush solution of at least 20ml. Note this should be saline and not dextrose. (Dextrose is an acidic solution).
B it can be diluted in sodium chloride 0.9% 100mg or 500mg /100ml but it is unstable and must be administered within one hour of preparation (time related precipitation)

3.5 How to administer

Make sure you know how to administer the drugs you prescribe – If the nurses don’t like what you have written they are entitled to ask you to do it!

Medicines.org, BNF

Rifampicin is a drug that comes as a freeze-dried powder with a special solvent for reconstitution before further dilution. Only use this as it contains special co-solvents
Make sure you know the correct diluents or the preparation may precipitate
E.g. Propofol is an emulsion and is usually used neat, if you flush the line of dilute it with saline it will cream out of solution and block lines

3.6 What IV Fluid – 2

Sodium Chloride 0.9% or isotonic saline is a common intravenous fluid used to maintain a patient’s hydration, urine output, capillary refill time, and blood pressure. However constantly administering IV sodium ions is not without problems and the clinician should be alert to risk of hypernatraemia. Constantly administering Chloride ions may also alter acid-base status due to strong ion difference. Dextrose 5% or isotonic glucose is a common intravenous fluid used to maintain a patient’s hydration, urine output, capillary refill time, and blood pressure. However constantly administering IV glucose contributes calories and alters the balance of blood sugar, insulin secretion and potassium distribution. Also constantly administering water without balancing electrolytes can cause problems as tissues consume the glucose. The clinician should be alert to the risk of pseudo hyponatraemia (i.e. excess water).

Dextrose saline is commonly available in two forms:
Glucose 4% and sodium chloride 0.18%, hypotonic Dex/saline
Glucose 5% and sodium chloride 0.45% isotonic Dex/saline
Maintenance fluid is commonly either dextrose saline or a combination of bags of isotonic saline and dextrose 5%
Compound sodium lactate (Hartman’s is commonly used by anaesthetists
Sodium bicarbonate is a specific correction of acid-base imbalance Fluid Balance

4 Fluid Balance

A simple question of input equal to output
A straight question of 3L in, and 3L out
A question of giving sufficient fluid to achieve 1mg/kg/hr urine output
A complex balance of forces to achieve a urine output of about 1mg/kg/hr (assuming normal renal function) without causing heart failure, pulmonary or peripheral oedema
Achieving an adequate urine output (accounting for other losses) with a maintenance dose, and giving treatment doses to sustain BP&CO
Giving a fluid challenge is a therapeutic manoeuvre to assess any rise in BP, CRT and UO as well as a diagnostic test to determine if the patient is adequately filled.

A decreasing Urine output could be an infra-renal problem but is commonly pre-renal failure secondary to hypovolaemia. So has your patient sufficient intravascular volume to pee?
So has your patient sufficient blood pressure to pee?
5 Problems with Infusions and fluids

The problem with IV maintenance fluid is that it is perceived as boring and staff forget it is running or forget to review it regularly and prescribe appropriately. This is not the same as writing up the fluid for the weekend on Friday night.

The problem with drug infusions is that they mentally blur into the background and are forgotten particularly the volume being administered to the patient each 2q4 hours. Note that parenteral nutrition (TPN) contributes both volume calories and electrolytes. It should be prescribed by experts and not adjusted like a maintenance fluid. Do not add drugs or electrolytes to TPN without first consulting your lawyer!

Drug infusions are associated with a high risk of calculation error. Even if this is done carefully setting up the pump or syringe driver needs education about the device and experience of its safe operation. In hospital circumstances change but rapid adjustments without rechecking the calculation are regretted at leisure by clinicians and patients – but welcomed by the legal profession.

The simplest error is to double the concentration and the volume infused so quadrupling the dose – yes this does happen.

Fluids and Frusemide – it seems logical to propose that a patient either needs fluid – because you have assessed them as under filled, or Frusemide because you think they are over filled. So is there logic to prescribing fluids & Frusemide?

Adjusting the maintenance fluid should be considered before adding Frusemide.

If your instructions (& prescriptions) are safe, nurses are unlikely to make mistakes and patients will receive fewer iatrogenic injuries. If you are unsafe you will put your registration, and that of others, on the line and patients will pay the price for this.

6 Appendix 1 - Composition of intravenous fluids at SUHT

7 Appendix 2 - Peri-operative Drugs