PHARMACO-THERAPEUTIC ASPECTS OF INTRAVENOUS ADMINISTRATION

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PARENTERAL FORMS OF ADMINISTRATION

Otherwise known as administration by injection, the parenteral route of administration involves administration of drugs by injection into the body to produce a systemic effect or a local effect (for example in treating arthritic pain). The three most common routes include the intravenous route, the intramuscular route and the subcutaneous route. The type of injection depends both on the nature of the drug as well as the condition being treated.

Intramuscular injection: the drug is injected into a muscle, usually on the thigh, the upper arm or the buttock. Since the injection is painful, lignocaine is sometimes added as an analgesic. Oily solutions and presence of lignocaine mean NEVER inject intramuscular preparations intravenously unless specified by the manufacturer.

Subcutaneous injection: The drug is injected directly under the surface of the skin.

Intravenous injection: The drug is injected directly into a vein and therefore directly into the blood stream. Drugs given by this route act more quickly than drugs given by other types of injection.

Other forms of parenteral therapy include:
Intrathecal
Intracardiac

ADVANTAGES OF THE INTRAVENOUS ROUTE OF ADMINISTRATION

1. Some drugs cannot be absorbed by any other route – ex. Heparin and Insulins are unstable in the presence of gastric juices, gentamicin is not absorbed orally.

2. Irritating properties of drugs – can cause higher pain or trauma when given by other parenteral routes (intramuscularly or subcutaneously) such as the cytotoxic drugs.

3. Instant drug action, since drug is being placed directly into the circulation – for ex. Intravenous nitrates

4. Better control over rate of administration – bolus vs infusion

5. Convenient route when patient cannot tolerate fluids or when patient is unconscious.

DISADVANTAGES OF THE INTRAVENOUS ROUTE OF ADMINISTRATION

1. Possibilities of incompatibilities – these can be chemical physical or therapeutic.

2. Local complications

3. Systemic complications

4. Rapid onset of action

5. Irritating properties – risk of damage to surrounding tissues

LOCAL COMPLICATIONS

Local complications are more common than systemic complications but are less severe in nature.

1. **Infiltration**. This is the inadvertent administration of a nonvesicant solution into the surrounding tissues as a result of dislodgement of a cannula. There is increasing oedema at or near the site of venipuncture.

2. **Extravasation**. Inadvertent administration of a vesicant solution into the surrounding tissues. A vesicant solution is a solution or medication that causes the formation of blisters with subsequent sloughing of tissues occurring from tissue necrosis. Examples of vesicant solutions include most chemotherapeutic agents, dopamine, noradrenaline.

3. **Phlebitis**. This is a condition in which inflammation of the intima of the vein occurs. Phlebitis may be:
   - *Chemical* – in response to certain chemicals or as a result of the cannula material. It can be prevented by using filters, adhering to recommendations of the manufacturer with respect to dilutions and reconstitution, and by using irritating solutions in a diluted form.
   - *Mechanical* – due to dislodgement of cannula
   - *Bacterial* – infection of cannula site.

SYSTEMIC COMPLICATIONS

1. **Pyrogenic reactions**. These occur when pyrogens (proteins foreign to the blood) are introduced into the blood stream and produce a febrile reaction. The patient presents with chills and fever, which may be accompanied by general malaise, headache, nausea and vomiting. If the infusion is allowed to continue, the increased presence of pyrogens may induce the more serious symptoms of vascular collapse and shock. In such circumstances:
   - Stop the infusion immediately
   - Monitor vital signs
   - Inform the physician immediately
   - Save the solution for testing.

2. **Pulmonary embolism** occurs when a substance, usually a blood clot, becomes free floating and is propelled by the venous circulation to the right side of the heart and into the pulmonary artery.

3. **Pulmonary oedema**. Overloading the circulation is a hazard to the elderly and patients with renal or cardiac problems – if fluids are infused too rapidly, there could be an increase in

venous pressure with the possibility of cardiac dilatation and subsequent pulmonary oedema. Preventive measures include:

- Maintenance of infusions at the flow rate prescribed.
- Never infuse fluids in excess of the quantity prescribed.

4. **Speed shock**. This is a systemic reaction to a substance injected rapidly into the blood stream – ex. Red man syndrome caused by rapid injection of vancomycin.

5. **Septicaemia** – rarely occurs, normally with massive microbial loads for example with batch defects, contaminated TPN solutions etc.

6. **Drug allergies**. Drug allergies are undesired reactions to a drug which may occur even if a small amount of the drug is administered. An allergy may take various forms including a skin rash, an asthmatic attack, fever and difficulty in breathing. Unfortunately, it is not possible to predict whether or not a patient will develop an allergy to a particular drug. It is therefore very important to:
   - Contact a doctor immediately if a patient develops an unusual reaction such as SOB
   - You may wish to prepare a hydrocortisone injection but do NOT administer without medical consultation. You may think that the patient has an allergic reaction when some other condition is manifesting itself.
   - If a patient tells you that he or she is allergic to one or more drugs, this should be immediately annotated on the treatment chart and in the patient records, and always brought to the attention of the medical officers.

   Sometimes a TESTDOSE is administered to a patient to check whether or not the patient is allergic to a drug. Normally this is carried out with drugs known to be a common cause of allergies. For example, prior to the first administration of asparaginase in a patient, a small test dose is given intradermally. When test doses are administered, it is imperative that the patient is placed under constant watch for any reactions.

WHAT IS CONTAINED IN A FORMULATION FOR INJECTION?

Apart from the drug, or active ingredient, that is the cause of the pharmacological effect of the injection, the formulation would also include other ingredients (known as excipients) that allow the preparation to remain stable:

1. Buffers – these stabilise the pH of the preparation (how acid or alkali the preparation is) and examples of buffers include sodium sulphate, sodium acetate, sodium carbonate.
2. Bactericides (or preservatives) – these limit microbial growth in the solution – examples include benzyl alcohol and phenol
3. Stabilising agents – anti-oxidants in that they limit oxidation and reduction reactions (these are chemical reactions to the water in the solution and to the air that diminish the chemical stability of the drug in the solution).
4. Solvent – the liquid in which the drug is in solution – normally water for injections or normal saline.

These excipients are worth mentioning in view of the fact that they have an important bearing in both the stability of the preparation, as well as the use or route of administration. For example, preparations with a preservative cannot be administered intrathecally and not all preservatives may be used in intravenous injections.

Injections are normally contained in one of the following containers:

Ampoules – glass containers where the top portion is broken to extract the drug solution
Vials – glass or plastic containers with a rubber bung as tip – bung is punctured to extract the drug.
Prefilled syringes – ready to use syringes.

These are worth mentioning due to implications they may have on administration as well as precautions to be taken. Ampoules are for one use only, any remaining portion must be discarded. Care must be taken due to the possibility of glass fragments – these may enter the ampoule when this is broken (risk can be reduced with the filter needle). Vials are normally for one use only unless the manufacturer of the medicine specifies them to be multidose. Care must be taken for any rubber fragments that may deposit in the solution after puncturing.

Vehicle of the injection

The vehicle of the injection is that liquid in which the drug is in solution. The vehicle should be pharmacologically inert and non-toxic, it must maintain the solubility and stability of the drug.

STABILITY

There are three kinds of stability: physical, chemical and microbiological. Physical stability involves the physical maintenance of a solution, instability would result in visual phenomena (normally a drug would precipitate out of solution, exhibit flocculation, change in colour or show turbidity). Chemical instability would result in chemical reactions with the drug (normally these cannot be detected) whereas microbiological stability involves maintenance of the sterility of a solution for injection.

When a drug is manufactured, there is over 95% of the stated active ingredient in the formulation. With time, due to chemical reactions, this amount decreases – once the drug falls below 90% then it is 'expired'. Although chemical stability is the greatest consideration in other formulations, physical and microbial stability are very important aspects of intravenous therapy. The precautions upon reconstitution and preparation of IV solutions emphasise on maintenance of these two criteria. Failure to maintain physical, chemical and microbial stability will lead to incompatibilities.

An incompatibility is an undesirable reaction that occurs between the drug and the solution (diluent added), between the drug and the container or between the drug and a second drug added to the same mix.
Drug – Solution. Drugs may interact with the wrong solution or with the wrong amount of the right solution and give rise to chemical as well as physical incompatibilities. If the solution is conducive

to microbial growth (for example TPN's) then microbial incompatibilities may easily occur if aseptic techniques are not adhered to.

Drug – Container. Drugs may interact with the container (PVC, glass and rubber) and lead to phenomena known as adsorption or absorption. When absorption occurs, the drug binds to the inner surface of the container. If adsorption occurs, the drug binds within the container material. In some instances, leaching may occur where components of the container material leach out into the solution. Permeation is when the drug evaporates through the container, for example normal saline through the PVC bag once the outer cover is removed.

Drug- Drug. Drug- drug incompatibilities arise when two incompatible drugs are mixed in the same infusion fluid. Information on compatibility should be obtained if two drugs are going to be mixed in the same solution, or even if two drugs are administered concurrently through 'Y' connections.

FACTORS AFFECTING THE STABILITY OF A SOLUTION FOR INJECTION

1. Vehicle used for reconstitution – use of an incorrect vehicle may result in incompatibitilies, as well as use of incorrect amounts of the correct vehicle. One should always adhere to the recommendations in type of vehicle as well as amount that the manufacturer defines.

2. Addition of a second drug to a solution must be carried out if there is strong evidence of compatibility. This information may be requested through the Medicines Information Unit at SLH (Ext 2057).

3. Preservatives maintain their action as long as the solution is not diluted. Once the solution is diluted, so will the preservative be diluted rendering it ineffective.

4. Period of time the solution stands – decomposition of drugs in solution as well as microbial contamination are both proportional to the time that the solution is left to stand. Ideally, solutions are prepared immediately prior to administration. When this cannot be achieved, it is recommended that solutions are refrigerated until administration (low temperatures lower the rate of chemical reactions and microbial growth) and allowed to achieve room temperature before injecting into the patient. Be aware that a small number of solutions for injection cannot be refrigerated since they would precipitate out of solution. This must be checked with the product insert.

5. Light may catalyse several reactions – some solutions may require protection from light (some even during administration if by infusion). Again, this must be checked on the product insert.

PREPARATION OF A SOLUTION FOR INJECTION

1. Check the expiry date of the ampoule or vial as well as any diluent or intravenous fluid used. If expired or with no expiry date indicated, remove from the cabinet immediately.

2. Proper dilution of powders or liquids must be ensured. To do this, always refer to the recommendations laid down by the manufacturer with respect to diluent as well as final

concentration, if any is indicated. Check whether the preparation is a concentrate requiring dilution (for example potassium chloride).

3. Double-check the active ingredient and strength Double-check any calculations required for preparation.

4. Always check the licensed route of administration. Intramuscular injections may not be given intravenously due to the presence of analgesics as well as some preservatives. Intravenous injections may not be given intrathecally if they contain preservatives.

5. Use strict aseptic techniques, including the following points:
   - Swab the rubber bung or upper surface of ampoule before puncturing or breaking.
   - Work on a disinfected workbench or tray (disinfect with alcohol before use)
   - Wash hands well and use a fresh pair of gloves
   - Avoid touching the critical points with your fingers (those points in direct contact with the sterile solution – for example the syringe barrel, tips of syringes or needles)
   - Avoid build up of air in the vial
   - Label the final container if there is a delay until it is to be administered to the patient.

6. Always examine the resulting solution in terms of clarity or particulate matter.

7. If there is a considerable time period between preparation of solution and administration, refrigerate (after checking whether this can be done with the product insert). However allow to warm to room temperature before administering to the patient.

8. Protect from light if this is specified in the product insert.

9. Never use infusion bags of saline as a diluent where small volumes are required – esp. if the bag is used repeatedly for more than one dose. Use the small plastic ampoules of 10mls available from the pharmacy.

10. Do not remove outer wrap of infusion bags until administration to the patient since the fluid may evaporate through the PVC.

11. Drugs that are manufactured in liquid form may have an overfill in the vial, which means that there may be actually more than the indicated amount of solution. When this happens, it is important to administer on the recommended amount and to discard the extra amount of solution.

MULTIDOSE VIALS

A few vials (never ampoules) are **multidose**, i.e. they can be used more than once. These vials normally contain a strong preservative that would limit microbial contamination throughout the use of the drug. The manufacturer recommends an ‘in-use’ shelf life for these vials (the manufacturer must always state that the preparation is multidose- this must NEVER be assumed). The in-use

shelf life is the time period after FIRST PUNCTURE during which the vial may be re-used. For example, heparin vials may have an in-use shelf life of 14 days (this may change with changes in brand – always check!!). Therefore after first puncture, the same vial may be utilised for 14 days thereon, after which any remaining solution must be discarded.

In order to operate an in-use shelf life, one must label the vial when it is first punctured. Also, the contents must never be diluted, and strict aseptic techniques must be adhered to at all times. In addition, it is good practice to refrigerate the solution in between withdrawal of doses to limit microbial contamination.

MODES OF INTRAVENOUS ADMINISTRATION

Continuous infusion

Mixing of the drug in a large volume of solution, which is infused continuously over a period of several hours. The solution is connected to an administration set and an electronic device which may be used to deliver the drug accurately at the prescribed rate of flow. For example, isosorbide mononitrate (Isoket) and heparin. Care must be taken due to incompatibilities between the drug and other IV drugs. This route is used when

- The drug must be highly diluted
- Constant plasma concentrations of the drug must be maintained
- Large volumes of fluids and electrolytes must be maintained.

Disadvantages:

- Possible fluid overload
- Potential incompatibilities between the infusion and other i.v. drugs administered through the same venous access device

Intermittent infusion

Drug is added to a small volume of fluid and infused over 15-90 minutes. This method of administration is generally used in the case of antibiotics such as gentamicin and ciprofloxacin.

Advantages:

- The ability of the drug to produce peak plasma concentrations at periodic intervals
- Decreased risk of fluid overload

Disadvantages:

- The increased concentration of the drug in the intermittent solution may cause venous irritation
- The drug may be less effective than if administered by continuous infusion.

Bolus injection

Drug is administered directly into the venous system. Also known as a stat dose. Rate of injection may need to be timed just the same, for example by injection a small volume over 5 minutes.

Venous access must always be flushed before and after IV administration, normally using normal saline.

CALCULATIONS

1Kg = 1000g
1g = 1000mg
1mg = 1000mcg

1 L = 1000ml

% w/v = %g in 100 mls. For example, 5% w/v = 5g in 100mls
% v/v = %ml in 100mls. For example, 5% v/v = 5mls in 100mls

1 in 10 (1 : 10) means there is 1g in 10mls
1 in 100 (1 : 100) means there is 1g in 100mls
1 in 1000 (1 : 1000) means there is 1g in 1000mls
1 in 10,000 (1 : 10,000) means there is 1g in 10,000mls

DISPLACEMENT VALUES

Awareness of displacement values is important when patients require part of a vial. When dry powders are reconstituted prior to injection (antibiotics are good examples of this) they are reconstituted with a recommended volume of diluent. The final volume, however may differ and maybe greater or smaller than the amount of diluent added in view of contraction or expansion of volume. For example, if a vial needs to be reconstituted with 5mls water for injection, the resulting solution may be 5.25ml or 4.8ml. If a patient requires the full strength of the vial, then one must ensure that the entire content is withdrawn. If a paediatric patient requires part of a vial, for example, the entire contents must be withdrawn, the exact volume present must be determined and the volume to be administered to the patient must be calculated based on the actual volume present in the vial.

This information may not always be present on the product insert.