Injection compatibility

After completing this tutorial, you will be able to:

- Define physical and chemical incompatibility.
- Know where to look for, and interpret, information about the compatibility of injectable medicines.
- Be able to predict injection compatibility if data are lacking.
- Advise ward staff how to avoid compatibility problems with injectable medicines, and be able to recommend the safest course of action.

Why this subject matters...

Injections and infusions are common in hospitals, and in high care areas particularly. However, some patients have restricted intravenous access and in these situations pharmacists need to be able to advise nursing and medical staff about safe ways to continue to give all the medicines required. Mixing injections may be part of the solution, but if approached incorrectly this might cause patient harm, so pharmacists must know how to do it safely. It is a common subject to be asked about when on-call.

Definition

An incompatibility occurs after mixing parenteral drugs if at least one of them becomes less effective (or more toxic, although this is rare). Changes that can occur include:

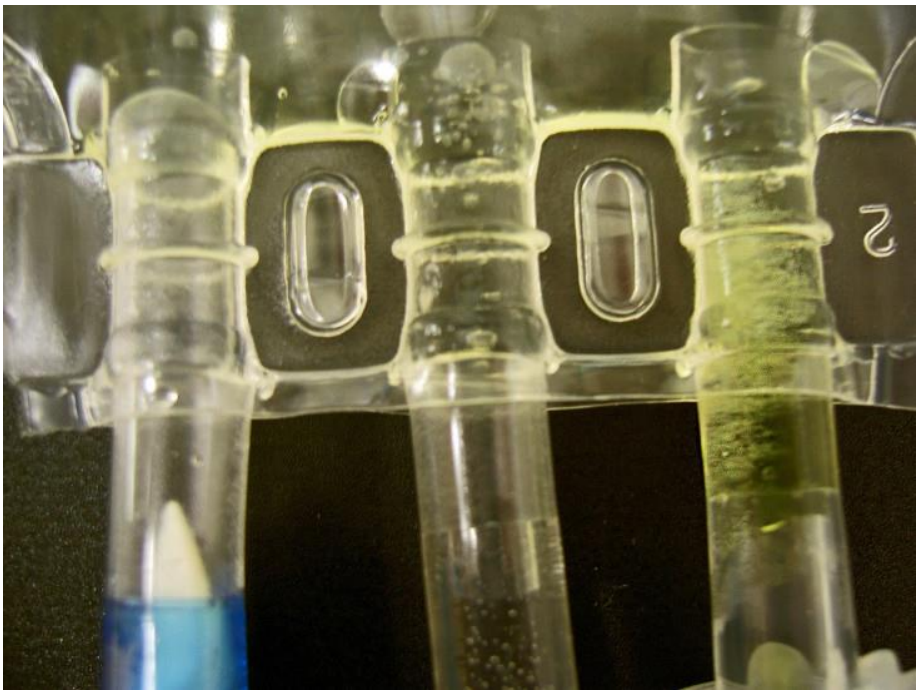
- **Physical incompatibility** (e.g. precipitation, haziness, crystallisation, or emulsions 'cracking'). This is a visible change largely determined by the pH and formulation of the injections concerned.

- **Chemical incompatibility** (e.g. degradation, inactivation, or a new compound formed). This is a chemical reaction between the drugs after mixing.

Note that many published studies of compatibility only examine physical incompatibility – i.e. there is a visual inspection of the mixture only, without chemical analysis. Chemical incompatibility must be determined by assay of the mixture (e.g. by HPLC).

Physical incompatibility, particularly precipitation, is also the only incompatibility that might be easily detected at ward level. So, just because a mixture 'looks okay' does not necessarily mean that the drugs are compatible!

Precipitation – an example of physical incompatibility



This neonatal TPN was formulated incorrectly and calcium has crystallized out in the far right port
Courtesy of Peter Rhodes

Implications for patients

Physical or chemical incompatibility may make one or both drugs unavailable to the patient because they are no longer in solution or are destroyed. This means that a patient may not receive all or part of a dose, despite it being prescribed and administered. The small particles generated as a result of physical incompatibility can cause other problems: they may block intravenous administration lines, and might cause vasculitis, small emboli or even death.

Reducing risk

Injectable medicines can be mixed in a variety of ways such as:

- In the same bag of intravenous fluid (sometimes called 'admixture').
- In the same syringe, diluted, for a subcutaneous infusion.
- In the same syringe, neat, for intramuscular injection.
- In the same intravenous line, or cannula.

Avoiding the need for mixing

The easiest way to solve an incompatibility problem is to think about ways to avoid mixing. You can remember these with the acronym: NATO (**N**ecessary? **A**lternative route? **T**iming? **O**ther drugs?):

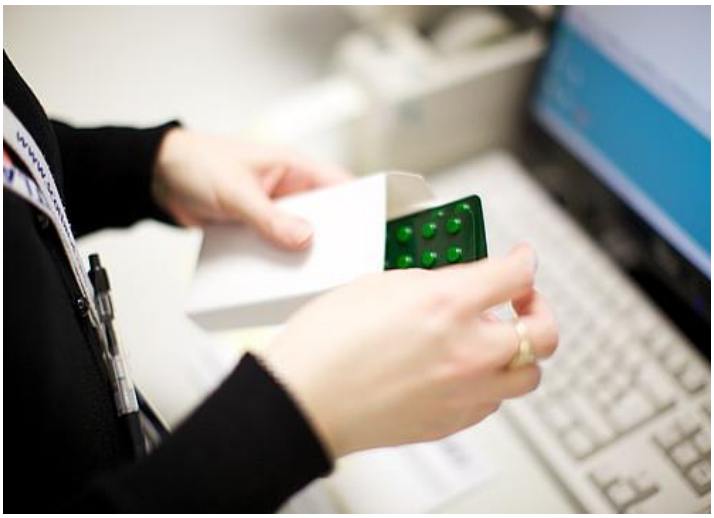
Necessary?

Can some non-essential drugs be stopped? Is there any unnecessary duplication (e.g. you should not need to mix co-amoxiclav and metronidazole because their antibacterial spectrums overlap).

Alternative routes?

Can an alternative route be used to avoid IV administration? For example:

- Insulin may be given *subcutaneously* instead of IV.
- Metronidazole can be given *rectally* instead of IV.
- Cefuroxime can be given by *IM injection* instead of IV.



Is the oral route an option?

- Fluconazole has excellent bioavailability *orally* compared to IV.
- If the patient has a nasogastric tube, many drugs are available as *oral syrups or solutions*.
- Many drugs can be given by IV *injection* as well as by infusion. Since IV injections are quicker, this may avoid the need for mixing.

Timing?

Changing the timing of drug administration may avoid the need for mixing.

- Can short IV infusions be given sequentially (i.e. one after the other) to avoid mixing? This can often be done with antibiotics. Remember to flush between each drug.
- Can a less urgent continuous infusion (e.g. pantoprazole) be interrupted temporarily to allow administration of a short infusion of a second drug?

Can you choose a different medicine?

Other drugs?

Can a different drug be used to overcome a compatibility problem? For example:

- An IV injection of teicoplanin instead of a long IV infusion of vancomycin.
- Subcutaneous tinzaparin can be given instead of an IV infusion of heparin to treat PE.
- Sublingual lorazepam instead of IV midazolam or diazepam for anxiety.
- Sublingual buprenorphine instead of a parenteral opioid for pain.
- Buccal prochlorperazine instead of a parenteral antiemetic.

Inserting another intravenous line

If these strategies are not practical or clinically inappropriate, then it may be necessary to attempt to gain additional intravenous access by inserting another line into the patient in order to administer potentially incompatible medicines. However this is not without risk or discomfort for the patient, and some individuals may be more difficult to cannulate (e.g. children, those who have undergone previous multiple cannulations, patients who are dehydrated).

Predicting incompatibility

Often there are little published data available to help with compatibility decisions. If there is inadequate information you must always inform the enquirer of this. When no information at all is available, mixing should be avoided. However, sometimes it is important to at least offer some guidance to ward staff if a certain number of drugs will have to be mixed despite a lack of knowledge of their compatibility.

The **questions below** may help if the points in the Reducing risk section do not help you to avoid mixing injectable medicines:

- **Do the drugs have a similar pH?** Drug solutions with very different pH values are less likely to be compatible than those with similar pH values. There is a table of common injections showing their pH below.

- **Are other chemically similar drugs compatible?** For example, if a study showed that morphine was compatible with ondansetron, you would have more confidence that diamorphine might be compatible with ondansetron.

Courtesy of Norden.org

- **Do the injections have a similar formulation?** Drugs with very different formulations are unlikely to be compatible. For example, oil-based injections such as Depixol are unlikely to be compatible with aqueous injections.

- **Are individual drugs or formulations intrinsically stable?** Drugs that are naturally very unstable, or which require very precise formulation to ensure stability, may be more likely to be incompatible with other drugs (e.g. Diazemuls).

- **Are any of the injections new products?** There are often very little data on compatibilities for drugs that are completely new chemical entities or very novel formulations. You should be extremely careful about mixing these drugs with anything.

- **What concentrations are being used?** Most information sources give compatibility data

based on specific concentrations of the drugs involved. If the concentrations you encounter are different from these, you need to interpret the published data with caution. The stability of some drugs varies significantly depending upon concentration (e.g. co-trimoxazole, phenytoin).

- **What diluents are being used?** Sometimes incompatibilities arise because a drug is not compatible with the diluent used for the second drug. If the diluent can be changed, then the problem might be avoided. For example amiodarone is incompatible with sodium chloride 0.9%.

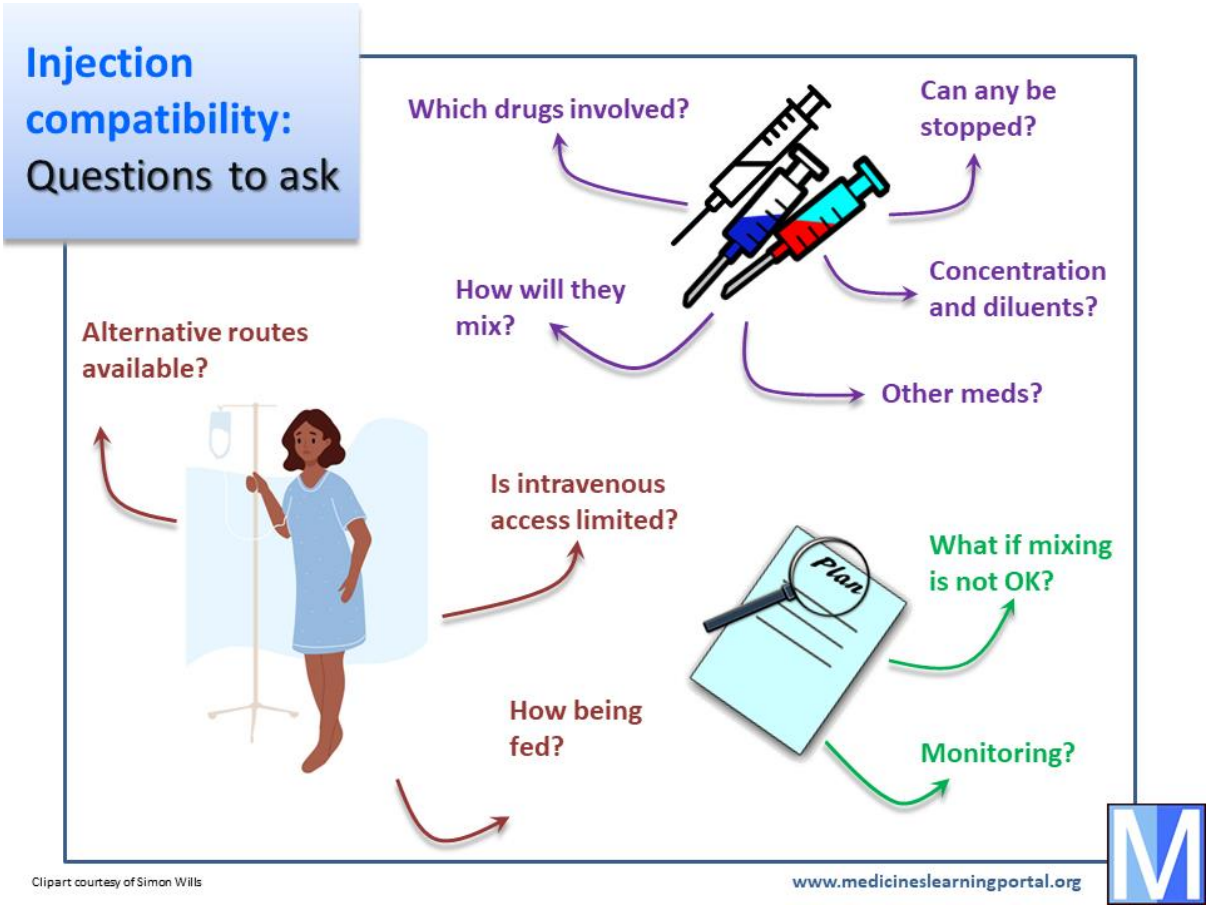
Acidic and alkaline injections

As mentioned in the section on predicting incompatibility, the acidity or alkalinity of injection solutions is a particularly important factor in determining compatibility. The table below gives examples of pH values for common injections:

Acidic: pH<6	Neutral: pH 6–8	Alkaline: pH>8
Morphine	Insulin	Phenytoin
Dopamine and Dobutamine	Ranitidine	Dantrolene
Vecuronium	Benzylpenicillin	Furosemide
Cyclizine	Ceftriaxone	Aminophylline
Hyoscine hydrobromide	Hydrocortisone	Co-trimoxazole
Midazolam	Albumin	Ganciclovir
Amiodarone	Sodium chloride 0.9%	Iron sucrose
5% glucose (pH 3.5-6.5)	Heparin	Sodium bicarbonate (pH 7.4 to 8.5)

Suggested questions

They may not apply to every situation you come across, but there are some questions you should be thinking about in practice.



The medicine

- Which drugs are involved? *Which ones are currently being mixed? Which drugs are you planning to mix? Although you may be asked about a specific combination, finding out what other injectable drugs are being given may highlight safe combinations to mix or identify opportunities to free up IV lines.*
- How will the drugs be mixed? *You need precise information. Will they mix in a bag, syringe or a line? What types of IV lines are in place? How long will the drugs be in contact for?*
- What are the concentrations of the drugs, and what diluents are being used? *You need this information because the concentration and the diluent can affect compatibility. You may be able to advise using a lower concentration or a different diluent to ensure stability.*

- Can any IV medicines be stopped? *Often it is obvious that the answer to this question is 'no'. But you may find that an IV antibiotic is due to stop today, or that one IV medicine is not proving beneficial and could be stopped so freeing up IV access.*
- What other medication is the patient receiving? *This gives you an overview of other potential ways to administer medicines – parenterally and by other routes.*

The patient

- Are the number of intravenous access points limited? *You should ask if additional IV access could be provided, and if not, why?*
- Can alternative routes of administration be considered? *It will help you to know if the patient is completely nil-by-mouth, or if they cannot receive rectal medicines for example.*
- How is the patient being fed? *If there is an enteral feeding tube this may offer a potential alternative administration route; if PN is being used this can create additional compatibility problems.*

Going forward

- What will happen if the drugs can't be mixed? *It helps to know how critical the situation is so that you can offer guidance on least-worst options. For example, it's not helpful to simply explain that drug A and drug B can't be mixed if both are essential: what can they do instead?*
- Who will monitor the treatment? *It's important that any injectable drugs that mix are regularly monitored for signs of incompatibility, and that the patient responds to treatment as expected.*

Information sources

American Society of Health-System Pharmacists (ASHP) **Injectable Drug Information** is a good starting point if you are asked about mixing drugs. Remember that medicines will be listed under their US names and not all UK drugs are included. A key disadvantage is that the concentrations do not always represent what is used in clinical practice here in the UK. This may mean you have to make a judgement about their relevance.

If this isn't helpful then try the Injectable Medicines Guide monographs. Compatibility data may also be found in the Document library on the left-hand side of the home page. This database will also tell you about the pH of injections.

If you have access, then Micromedex has an IV medicines compatibility checker. As a US resource, the same limitations of the ASHP apply as above.

SmPCs are rarely helpful if you are asked about mixing drugs, but can help you with questions around the choice of diluent to use. Alternatively consider contacting the product manufacturers for any in-house data they may have.

For enquiries about mixing drugs in **syringe drivers**, especially in the palliative care context, Andrew Dickman's The Syringe Driver is an excellent resource (Oxford University Press). You can read some general information about syringe drivers on this page of the palliative care tutorial.

Be careful about conducting a general internet search on this subject. If you do, you may like to look at our brief guide to evaluating websites about medicines.

Presenting your answer

Once you've asked sufficient questions, gathered the information required and assessed it, you'll need to provide an **answer**. As a reminder, we offer some general guidance on answering clinical problems. You might like to refresh your memory if you've not looked at

this recently.