To mix or not to mix – compatibilities of parenteral drug solutions

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Summary

Many injectable drugs cannot be mixed together in syringes or infusions. Some cannot be safely diluted in infusion bags. Incompatibility can involve precipitation, ionic reactions, evolution of gas and denaturation of biological molecules. Knowledge of drug compatibility is needed before mixing drugs. Reference texts can provide information, but data are often unavailable for new drugs. If drugs are mixed together, the mixture should be inspected for precipitates, turbidity or changes in colour, however not all incompatibilities are visible.

Key words: diazepam, injections, phenytoin, precipitation.

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Introduction

Mixing solutions of parenteral drugs is generally not recommended because of the potential for incompatibility and consequent loss of activity of one or both drugs. However, in some circumstances there may be compelling reasons for mixing two or more parenteral drug solutions in the same infusion bag, in the same syringe or at a Y-site junction where two or more intravenous lines meet. Such circumstances include:

- difficulties with venous access limiting the number of intravenous lines available for continuous administration of multiple drugs
- multiple drugs requiring parenteral administration within a short time frame such as in a home visit by a general practitioner
- patients at home requiring many drugs by simultaneous continuous infusion where multiple intravenous lines are not feasible, for example, use of a syringe driver during palliative care.

The decision to mix drugs should not be made without knowledge of their compatibility. If intravenous drugs are not mixed but are given consecutively, the infusion line should be flushed through with compatible fluid between each administration.

Mechanisms of incompatibility

Incompatibility problems are more likely to arise when small concentrated volumes are mixed in a syringe rather than in the larger volume of an infusion bag. This is because of higher mutual drug concentrations and potentially greater pH changes in the more concentrated solution. The absence of any visible change to a solution upon mixing does not automatically exclude degradation of either or both components.

Drugs that precipitate upon dilution

Precipitation of a drug from its concentrated injection solution when it is diluted with water or saline is counter-intuitive. However, a small number of injection solutions are formulated in non-aqueous solvents to allow dissolution of a poorly water soluble substance in a small volume. In these formulations, dilution of the non-aqueous injection vehicle with water or saline may precipitate the drug.

The problem is frequently observed when diazepam injection is diluted. Diazepam is very poorly water soluble so it is formulated as an injection solution in a vehicle comprising 50% propylene glycol and 10% ethanol. At first, dilution produces a slight turbidity which clears upon mixing, but dilution beyond fourfold produces an opaque white precipitate which does not clear until substantial further dilution.

Other drugs which demonstrate solubility problems and which are formulated in injection vehicles other than simple aqueous solutions include digoxin, clonazepam, phenytoin, amiodarone and phytomenadione. In some cases, the manufacturer recommends administration of the undiluted drug. In other cases, care needs to be taken to ensure that if the injection solution is diluted, the dilution is adequate to ensure continuing solubility over the duration of the infusion.

Precipitation of drugs due to pH change upon mixing

The water solubility of any drug is enhanced by ionisation of the molecule. For a drug molecule which acts as a proton acceptor (a Lowry-Bronsted base), ionisation is achieved by formulation in a low pH solution usually as a hydrochloride or hydrogen sulfate salt (for example, amiodarone hydrochloride or adrenaline acid tartrate). Conversely, for a drug molecule which can lose a proton or hydrogen ion (a Lowry-Bronsted acid – usually a weak organic acid), ionisation is achieved

Table 1

Examples of drug compatibilities

Drug	Compatible in syringe	Incompatible in syringe	Comments
Benzylpenicillin 600 mg powder for reconstitution	No common drugs listed in published data	Prochlorperazine, promethazine, chlorpromazine, sodium bicarbonate	
Dexamethasone sodium phosphate 4 mg/1 mL	Metoclopramide, ondansetron, ranitidine	Glycopyrrolate, midazolam, prochlorperazine, promethazine	
Diazepam 10 mg/2 mL	Nil	Widely incompatible – do not mix with other drug solutions	Poorly water soluble drug marketed in a complex solvent system
Frusemide 20 mg/2 mL	No common drugs listed in published data	Buprenorphine, chlorpromazine, droperidol, metoclopramide, midazolam, morphine sulfate, prochlorperazine, promethazine	pH of solution is 8.0–9.3. Frusemide is unstable in acidic media which may include glucose 5% solution.
Haloperidol 10 mg/2 mL	Hydromorphone	Benztropine, ketorolac	
Hydrocortisone sodium succinate 100 mg powder for reconstitution	Metoclopramide	Prochlorperazine, promethazine, midazolam	
Lignocaine hydrochloride 2% in 5 mL	Glycopyrrolate, metoclopramide	Ampicillin, sodium bicarbonate solution	
Metoclopramide hydrochloride 10 mg/2 mL	Chlorpromazine, dexamethasone, droperidol, fentanyl, hydrocortisone sodium succinate, lignocaine, midazolam, morphine, pethidine, promethazine	Ampicillin, frusemide, sodium bicarbonate	
Morphine sulfate, morphine tartrate (various strengths)	Stability of at least 15 minutes published for atropine, bupivacaine, droperidol, fentanyl, glycopyrrolate, hyoscine butylbromide, ketamine, prochlorperazine, and up to 24 hours for metoclopramide	Aminophylline, flucloxacillin, frusemide, phenytoin, promethazine, sodium bicarbonate	Is less soluble in alkaline conditions
Prochlorperazine edisylate	Atropine, hydromorphone, hyoscine hydrobromide, morphine sulfate (may vary with brand), pethidine	Aminophylline, amphotericin, ampicillin, benzylpenicillin, calcium gluconate, cephalothin, dexamethasone sodium phosphate, frusemide, heparin, hydrocortisone sodium succinate, midazolam	The bulk of the published data refer to the edisylate salt which is marketed overseas. The salt marketed in Australia is mesylate which is similar, and for which extrapolation of data is considered reasonable.
Promethazine hydrochloride 50 mg/2 mL	Atropine, droperidol, fentanyl, glycopyrrolate, metoclopramide, midazolam, pethidine	Aminophylline, benzylpenicillin, dexamethasone sodium phosphate, frusemide, hydrocortisone sodium succinate, morphine, phenytoin, sodium bicarbonate	Locally irritant and unsuitable for subcutaneous injection. Avoid extravasation in intravascular injection.
Tramadol hydrochloride 100 mg/2 mL	No common drugs listed in published data	Diazepam, midazolam	This is a relatively recently marketed drug on which there is a paucity of published compatibility data

by formulation in a high pH solution, usually as a sodium or potassium salt (for example, benzylpenicillin sodium). Any change in pH towards the other end of the pH scale will reduce the proportion of ionised to un-ionised drug in solution and will therefore reduce the water solubility of the drug.

The most prominent example of a pH-related reduction in solubility is dilution of phenytoin sodium injection. The drug is formulated with non-aqueous solubilising agents and the solution is adjusted to a pH of 12. Dilution of injectable phenytoin by adding it to an infusion bag lowers its pH and therefore reduces its solubility resulting in precipitation of the drug. Glucose 5% infusion solution, which has a pH of 4.3–4.5, will precipitate phenytoin almost immediately. Indeed, phenytoin injection is so incompatible that it should generally not be mixed with any other solution.

Ionic reactions forming insoluble substances

The salts of monovalent cations, such as sodium and potassium, are generally more soluble than those of divalent cations, such as calcium and magnesium. Mixing solutions containing calcium or magnesium ions has a substantial risk of forming an insoluble calcium or magnesium salt. Mixing magnesium sulfate 50% and calcium chloride 10% results in precipitation of insoluble calcium sulfate. The mixing of drug salts of calcium, and to a lesser extent magnesium, with phosphates, carbonates, bicarbonates, tartrates or sulfates should also be avoided. A recent warning has been issued about mixing calcium-containing solutions, including Hartmann's solution, with ceftriaxone causing the formation of the insoluble ceftriaxone calcium salt.[1]

Denaturation of biological molecules

Biological substances including blood products and insulin are prone to denaturation when exposed to variations in pH and osmolality. While published compatibility data exist for insulins and some of the blood products, most recently marketed biological drugs such as infliximab, interferons and recombinant coagulation factors have no such data available and mixing with other drugs is not recommended.

Evolution of gas

Addition of an acidic drug solution to a solution containing a carbonate or bicarbonate may result in production of carbon dioxide gas. However, the evolution of gas is a normal part of the reconstitution of some drugs, notably ceftazidime.

Use reliable reference material

Some incompatibilities are eminently predictable from simple chemical knowledge, but most compatibilities and incompatibilities are not so easily predicted. For this reason, the decision to mix any two injection solutions whether in a syringe, in an infusion bag or at a Y-site should be based on a reliable reference. However, published data are specific to the concentration, solvent, ambient temperature and sometimes the composition of the syringe or infusion bag. A number of references, in addition to the manufacturer's product information, are available. These include the Australian Injectable Drugs Handbook.[2] Table 1 shows some of the compatibility and incompatibility data currently available.

Palliative care

There are a number of drugs that are commonly delivered via syringe driver to patients having palliative care in the community (see box). Combinations of two, three or more of these drugs occasionally need to be co-administered via syringe driver. Specialist references dealing with their mutual compatibilities need to be consulted.[3,4]

Combinations of drugs commonly used in palliative care *

Haloperidol and midazolam
Hydromorphine and clonidine
Metoclopramide and atropine
Metoclopramide and midazolam (and morphine)
Metoclopramide and morphine
Morphine and clonidine
Morphine and glycopyrrolate
Morphine and midazolam

* In palliative care settings and in chronic pain control, combinations of as many as four of these drugs may be mixed in the same syringe for use in a syringe driver over 24 hours.

Conclusion

While some general principles can be applied to the mixing of injection solutions, they are fraught with exception and applicability varies with circumstance. Mixing is best avoided. If circumstances are so compelling as to warrant mixing any two or more solutions, there should be support from published compatibility data. A visual check for precipitation, turbidity or colour change should be carried out before administering the mixture, but does not guarantee compatibility.

References

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3. Compatibilities of drugs in syringes. Appendix 2. Palliative Care. Version 2, 2005. In: eTG complete. Melbourne: Therapeutic Guidelines Limited; 2008 Mar.
4. Syringe driver survey database. http://www.palliativedrugs.com [cited 2008 Jul 10]

Further reading

Trissel LA. Handbook on injectable drugs. 14th ed. Bethesda: American Society of Health-System Pharmacists; 2007.

Australian Prescription Products Guide. Hawthorn, Vic.: Australian Pharmaceutical Publishing Company; 2007.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 111)

5. When two drug solutions are mixed together the absence of a visible reaction does not exclude degradation of either drug.
6. Injectable diazepam should be diluted with four parts water to ensure it does not precipitate in the syringe.

New guidelines for endocarditis prophylaxis

The Australian recommendations for the use of antibiotics in the prevention of endocarditis have been revised by Therapeutic Guidelines. These changes are consistent with new international guidelines for endocarditis prophylaxis, which have generally reduced the indications for using antibiotics.

The revised guidelines are available free of charge on the Therapeutic Guidelines website www.tg.com.au and in the electronic publications eTG complete and miniTG. The booklet versions of Therapeutic Guidelines: Antibiotic and Therapeutic Guidelines: Oral and Dental will be updated when new editions are published.