

Section A

1 Introduction

The use of injectable products is fundamental to modern healthcare. Almost every patient admitted to hospital will be prescribed intravenous fluids, or an intravenous medicine. It is essential that healthcare workers who prepare and administer injectables have access to concise information to ensure they use the products appropriately. This need has prompted the publication of the *UCL Hospitals Injectable Medicines Administration Guide*.

The *Guide* includes information to support the prescribing, dispensing and administration of medicines given via the intravenous, subcutaneous and intramuscular routes. It includes a wealth of background information, including descriptions of the various methods of administration, the relative merits of each method, the devices used to give injectables, and pharmaceutical issues that may influence therapy. The *Guide* incorporates both local practice advice and some nationally accepted best practice guidance, including a summary of aseptic non-touch technique.

2 Overview

2.1 Organisation of information in the *Guide*

The *Guide* comprises two sections:

Section A outlines the responsibilities of the various professionals involved in the prescribing, dispensing and administering of injectables. Full descriptions of the methods of intravenous administration are given, while the infusion devices used to deliver medicines and fluids are discussed. Practical guidance on flushing lines and cannulae, management of extravasation, and drug compatibility is provided. The use of drugs in a syringe for subcutaneous infusion and pharmaceutical aspects of intravenous therapy are also detailed.

Section B starts with a user guide which fully explains the information in the drug monographs. New users can work their way through a tutorial to aid interpretation of the monograph content. The remainder of section B contains the individual medicine monographs in tabular form. Medicines are arranged in alphabetical order and include the following information:

- Formulation.
- Injectable method of administration and recommended infusion device.
- National Patient Safety Agency (NPSA) risk rating.
- Preparatory instructions for the medicine.
- Administration details.
- Recommended flush fluid.
- A list of adverse effects that may result from administration.
- Pragmatic 'in use' advice from clinicians at UCL Hospitals.
- Compatibility data for the medicine with fluids and other drugs for both intravenous and subcutaneous use.
- Pharmaceutical particulars, including pH, tonicity, sodium content and displacement value.

Cytotoxic medicines are beyond the scope of the *Guide*.

2.2 Sources of information and disclaimer

The majority of information in the *Guide* is based on the best available published data at the time of writing. However, some of the advice given is representative of practice at UCL Hospitals and may not be consistent with licensed information found on the manufacturers' summary of product characteristics (SPC). Each monograph has been carefully constructed to give pragmatic preparatory instructions to support those administering the drug. For example, the preparatory instructions from the manufacturers of some medicines, such as abatacept, phytomenadione and ertapenem, have been simplified to reduce the number of steps required to get the medicine ready to administer to the patient. At UCL Hospitals we believe that the simplest methods are the safest. All deviations from manufacturer's advice are supported by literature.

Administration advice for certain patient groups, including children, neonates and the critically ill, has been verified by specialist pharmacists and nurses with first-hand experience of using the medicine. All the advice is given with patient safety at the fore.

Published compatibility data are **not** available for all the combinations and situations covered in this *Guide*. Some of the advice and information therefore reflects local practice and experience only. Readers are reminded that slight variation in the exact combination and concentrations of medicines can adversely affect compatibility. Readers are referred to their local hospital pharmacy department for more specific information and advice.

Neither the authors nor the publisher can accept any legal responsibility or liability for any errors or omissions that may be made within the *Guide*. Readers should take their own precautions to ensure that new information published after the *Guide* was written is followed wherever possible. Readers are referred to the SPCs produced by the pharmaceutical companies for further or more up-to-date information. SPCs are periodically updated and thus the recommendation(s) for administering the medicines included in this *Guide* may alter from time to time.

3 UCLH policies

3.1 Responsibilities of professional staff at UCLH

3.1.1 Nurses' and midwives' responsibilities for injectable medicines (including blood products, IV fluids and IV medicines)

Nurses are referred to the *Standards for Medicines Management* of the Nursing and Midwifery Council and the *Standards for Infusion Therapy* published by the Royal College of Nursing. These provide a comprehensive description of the responsibilities of a practitioner when administering a medicine. Other healthcare professionals will find these documents useful as these standards are universally applicable.

At UCL Hospitals, injectable medicines may be prepared and administered by a registered nurse/midwife as described in UCL Hospitals *Administration of Medicines by Nurses/Midwives Policy and Procedure* document. This document is available from UCL Hospitals.

3.1.2 Pharmacists' responsibilities for injectable medicines

- Pharmacists should provide appropriate information and advice to medical, nursing and other health professionals on pharmaceutical aspects of parenteral medicines, e.g. choice of medical therapy, compatibility, stability, dosage and administration details.
- Pharmacists should monitor prescriptions for parenteral medicines and alert medical and/or nursing staff to any potential problems. Pharmacists should annotate prescriptions for parenteral medicines where appropriate.
- Pharmacists should ensure patients are switched at the earliest opportunity to oral therapy, to minimise risk from IV therapy.
- Pharmacists should provide education and training to healthcare professionals involved in the administration of parenteral medicines.
- Pharmacists will monitor medication errors in local clinical areas, provide targeted training to those involved in the incident and formally report the error. Lessons learned from the incident should be disseminated to colleagues to ensure best practice in all areas.
- Pharmacy will prepare some medicines to be administered by the parenteral route as locally agreed. This centralised intravenous additive service (CIVAS) prepares cytotoxic medicines, intravenous nutrition, monoclonal antibody infusions and a selected group of high-risk medicines such as foscarnet and ganciclovir.

3.2 Preparation of injectable medicines on wards, clinics and departments at UCLH

Injectable medicines:

- **Must not** be prepared in advance of their immediate use
- **Must not** be prepared by anyone other than the registered nurse/midwife or doctor who is going to administer them, unless they are prepared in his or her presence.

All medicines prepared must be appropriately labelled. Additive labels should be completed and attached to the infusion container.

Exceptions:

Injectable medicines may be prepared in advance if covered by a specific protocol agreed by relevant pharmacy and nursing staff. In emergencies practitioners are not required to label medicines, but if several medicines are prepared at the same time, individuals should ensure they are able to identify each separate medicine, and any pre-prepared flushes.

4 An overview of intravenous therapy

There are multiple routes of drug administration including oral, topical, rectal, inhalation, intravenous, intramuscular, subcutaneous and intrathecal injection. A prescriber must decide which is the most appropriate route of administration for a medicine according to the clinical condition of the patient. Intravenous injection is defined as the introduction of medicine or infusion fluid into a vein.

4.1 When is intravenous therapy appropriate?

Intravenous therapy may be the most appropriate option when:

- High plasma levels of a drug are required rapidly. Unlike other routes, the drug is introduced directly into the bloodstream and is available to exert its pharmacological effect as soon as it enters the body. Medicines given by other routes need to be absorbed into the bloodstream first, which can take considerable time. Oral medicines are usually absorbed from the small intestine, while medicines administered intramuscularly must be absorbed from muscle fibres into the bloodstream. The intravenous route is usually the route of choice in emergencies because it is usually the fastest way to achieve a therapeutic effect.
- Tight control of drug levels is required, with the need for small adjustments to the rate of administration, according to the patient's response. This can be achieved by giving the drug as a continuous infusion. Examples of such infusions include insulin for blood glucose control and the infusion of anaesthetic agents during surgery to maintain unconsciousness.
- Patients are unable to take oral medication. This may be because they are vomiting or unconscious, or because they have had recent gastrointestinal surgery.
- Patients are unable to absorb medicine orally, for example those who have severe diarrhoea, active Crohn's or coeliac disease.
- Rapid correction of fluid or electrolytes is required, for example after haemorrhage.
- Other routes are not available. For example, the intramuscular route may not be appropriate in the very young or the very old as they tend to have a reduced muscle mass, which is not ideal for the administration of medicines. Those receiving anticoagulant medicines or patients with clotting diseases such as haemophilia may bleed from the IM injection site.
- Other routes are not acceptable to the patient. IM injections can be painful, and may be refused, even by healthy individuals. Many UK patients refuse suppositories.

4.2 Drug factors that influence the choice of route

Some medicines must be given by the intravenous route because of their chemical or pharmacological properties.

4.2.1 Absorption

Some drugs are broken down by gastric secretions, which prevents them from being given orally. Proteins such as insulin and infliximab are inactivated in the gut so must be injected. Other drugs do not possess the chemical properties to cross the gut wall so cannot be given orally to cause a systemic effect. However, these drugs may still be useful for treating diseases of the gastrointestinal tract, e.g. vancomycin cannot be given orally to treat a systemic infection as it is not absorbed, but can be used to treat *Clostridium difficile* infection of the intestine.

Some drugs may be given by subcutaneous, intramuscular or rectal routes, but the absorption from these sites may be erratic and unreliable. Gentamicin may be given by IM injection, but to treat serious infection the intravenous route is used in preference as therapeutic levels are more likely to be achieved.

4.2.2 The first-pass effect

Medicines given orally are usually absorbed in the small intestine. They are then transported in the blood, via the portal system, to the liver where they may be metabolised. For some medicines, metabolism in the liver occurs to such a great extent that little medicine reaches the target organ – this is called the first-pass effect (or first-pass metabolism). The intravenous route avoids the first-pass effect as the drug is introduced directly into the systemic circulation. It is precisely for this reason that some drugs, e.g. verapamil and propranolol, need to be given at much higher doses orally, than by intravenous injection, to produce a similar therapeutic effect. For some medicines, such as lidocaine, it is not possible to make an oral formulation because the metabolism is so great.

4.2.3 Impact of half-life

The elimination half-life ($t_{1/2}$) is the time taken for the concentration of medicine in the blood to fall to half its original value, e.g. if a medicine has a half-life of 4 hours, this means that it will take 4 hours for the concentration of the medicine in the blood to fall from 10 mg/L to 5 mg/L. Medicines can have half-lives that are measured in seconds, minutes, hours or days.

Medicines with very short half-lives disappear from the bloodstream very quickly and may need to be administered by a continuous infusion to maintain a

clinical effect on tissues, e.g. dopamine has a half-life of 1–2 minutes and so has to be given as a continuous infusion. When the infusion is stopped its effects will be lost within minutes.

If a medicine has a longer half-life, it means that it may be given as a bolus injection or intermittent infusion instead of a continuous infusion, and its effects on the body tissues will last for several hours before another dose is needed. Knowledge of half-life alone is not, however, sufficient in determining the method of administration because many other factors need to be taken into consideration, e.g. drug distribution into tissues.

4.3 Disadvantages of intravenous administration

- A vascular access device (VAD) such as a cannula or catheter must be placed before any intravenous medicine can be given. This requires specially trained personnel and specific equipment.
- Obtaining vascular access can be difficult. Patients who have been regularly cannulated in the past, are in shock, are dehydrated or have fragile veins may be difficult to cannulate. Insertion of a central venous catheter requires specialist training and is an invasive procedure.
- When medicines are given by the intravenous route there is an increased risk of toxicity. Side effects may occur immediately and can be severe.
- Preparation of some intravenous medicines is complicated and can be time consuming. It may require complex calculations, multiple steps in reconstitution and dilution, competence in the aseptic non-touch technique and the use of infusion devices.
- Contamination of medicines and infusion fluids during preparation, or contamination of the VAD during administration, may result in infection as microbes are introduced directly into the bloodstream.
- There is a risk of embolism each time an intravenous medicine is given, from blood clots from the VAD or from inadvertent injection of air or particulate matter.
- There is a risk of fluid overload from the administration of multiple medicines diluted in large volume infusion bags, or through the overzealous use of intravenous infusion fluids.
- There is a risk of pain, irritation and extravasation at the injection site.
- Some patients are afraid of needles and injections and will object to their use.

4.4 Routes of intravenous administration

Intravenous administration can be divided into peripheral and central administration. Catheters and cannulae are described as 'vascular access devices' or 'venous access devices' (VADs), although in everyday language they are called 'lines'.

4.4.1 *Peripheral administration*

Peripheral administration is introduction of fluid into a peripheral vein. Veins are accessed via a cannula, which is most often placed in the veins of the lower portion of the arm because they are located just below the skin. Veins used for cannulation include the cephalic, basilic and metacarpal veins. Antecubital and dorsal veins may also be used. Each site has its advantages and disadvantages, which are beyond the scope of the *Guide*.

4.4.2 *Central administration*

Central administration is introduction of fluid into a large central vein, through a central venous catheter (CVC). The tip of a CVC terminates in the superior vena cava, right atrium or inferior vena cava. Infused fluids are rapidly diluted in the fast flow of blood in the vessel. There are a variety of CVCs – the choice of device will depend on the intended use and multiple patient factors. Refer to local CVC guidelines for a description of the devices available and their relative merits. UCLH has a central venous catheter care guideline which may be accessed via the hospital intranet.

4.4.3 *Peripheral versus central vein administration*

Peripheral vein administration

Advantages

- Simple to insert a cannula.
- Less traumatic compared with central line.
- Cheap.
- Cannula easy to manage for clinical staff.

Disadvantages

- Limited time period of use.
- Blocks more easily.
- Risk of infection.

- Greater risk of extravasation/phlebitis compared to a central line.
- Single lumen.
- Not suitable for certain medicines.

Central vein administration

Advantages

- Allows the administration of irritant solutions, e.g. concentrated potassium solutions or vasoactive medicines.
- Allows rapid administration of large volumes of fluid, e.g. in shock.
- Provides long-term venous access, which is useful for patients requiring intravenous therapy over extended periods, such as those having chemotherapy in cycles or intravenous nutrition (TPN) at home.
- To enable administration of concentrated solutions of medicines, which would normally need further dilution as a result of their irritancy. This is particularly useful in fluid-/sodium-restricted patients.
- Allows the co-administration of multiple medicines without the risk of incompatibility. Most CVCs have more than one lumen, which terminate at slightly different points so that medicines do not mix on infusion.

Disadvantages

- Catheters require a short procedure to be inserted, which takes more skill and time than inserting a cannula.
- Healthcare staff must be specially trained to care for the catheter.
- Insertion can be painful/traumatic.
- There is a risk of serious infection. The exit site (where the catheter comes out of the skin), the outer surface of the catheter and the inside lumen may all be colonised by microbes. This can lead to septicaemia and removal of the catheter.
- Overall more expensive to insert and manage than a cannula.

Section B of the *Guide* advises which medicines should be administered by a central line.

5 Factors affecting patency of intravenous sites

Peripheral cannulae are generally used for around 72 hours before they need to be removed and resited. The vein can become irritated and flow through the cannulae is reduced or stops. CVCs may be used for days, weeks or months depending on the type of catheter inserted. Some factors that influence how long a VAD will remain patent are common to both types of device and are described below.

5.1 Factors increasing failure of intravenous sites

- Infection.
- Irritation:
 - Movement, particularly of cannulae in areas of flexion.
 - Cannula material (steel is more irritant than Teflon).
 - Infusion of particulate matter, which physically blocks cannulae.
 - Infusion of irritant medicines.

5.2 Factors decreasing failure of intravenous sites

- In-line filters help reduce the number of particles infused. Administration sets with 15 micron filters are standard at UCLH. Smaller pore filters may be provided with some medicines that have a tendency to precipitate.
- Good practice/aseptic technique when the VAD is first inserted and each time it is accessed.
- Infusion of dilute solutions of medicines or electrolytes, which tend to be less irritant.

5.3 Occlusion of central venous catheters

Central venous catheters may be occluded by clotted blood, a fibrin sheath, precipitated medicines or the components of intravenous nutrition. Local catheter care guidelines should give advice on how to manage such events. Catheters occluded with a fibrin sheath may be unblocked using urokinase 5000 unit/mL instilled into the catheter lumen using a 'rocking technique' between two syringes attached to the lumen with a three-way tap.

6 Methods of intravenous administration

Medicines are given using a variety of methods which are outlined below. The choice of method may depend on the pharmaceutical properties of the drug, the clinical condition of the patient, the desired therapeutic outcome, and the type of venous access the patient has. It should be noted that there is no consensus regarding the definitions of bolus injection and intermittent and continuous infusion. Definitions in the literature and manufacturers' SPCs may differ slightly from those given here. However, the descriptions below are consistent with the administration methods given in Section B of the *Guide*.

6.1 Intravenous bolus

Introduction of a small volume of medicine solution into a vascular access device is referred to as a bolus injection. A bolus injection is usually administered over 3–5 minutes to minimise vein irritation and the risk of extravasation. Drugs typically given by bolus injection include penicillin antibiotics, such as amoxicillin, and antiemetics, such as cyclizine.

During cardiac resuscitation and other emergencies a bolus may be given over a few seconds as the risk of rapid administration is outweighed by the clinical need for immediate therapeutic effect. Adenosine, used for cardiac arrhythmias, is administered as quickly as possible as it is rapidly inactivated in the blood and would not reach the heart otherwise.

At UCLH a bolus is defined as any injection given in 5 minutes or less, and is less than 50 mL in volume. It is considered impractical to administer a bolus over longer than 5 minutes. The *Guide* recommends that medicines that need to be given over a time period of greater than 5 minutes or that are greater than 50 mL are prepared as an intermittent infusion.

Advantages

- Achieves immediate and high medicine levels.
- Easy and more convenient for the practitioner. There are much fewer steps required to prepare and give a bolus compared to an infusion. Bolus injections do not require dilution to large volumes of infusion fluid, priming of an administration set or programming of an infusion device.
- After giving the dose the practitioner can be sure the patient has received the dose and does not need to monitor an infusion bag/device (c.f. intermittent and continuous infusions).

Disadvantages

- Increased potential for adverse effects, particularly if the dose is given too rapidly, e.g. cyclizine.
- Damage to the veins, e.g. phlebitis or extravasation, especially with potentially irritant medicines.

6.2 Intermittent intravenous infusion

Administration of an infusion over a set time period, either as a one-off dose or repeated at specific time intervals, is referred to as an intermittent infusion. An intermittent infusion of medicine is often a compromise between a bolus injection and continuous infusion. It achieves high plasma concentrations rapidly to ensure clinical efficacy yet reduces the risks of adverse reactions associated with rapid administration.

Many medicines are given as intermittent infusions, including gentamicin, metronidazole and Pabrinex.

At UCLH intermittent infusions are defined as any infusion given over longer than 5 minutes but less than 24 hours. Most infusions are given over an hour, although large-volume fluids, e.g. 1 L compound sodium lactate, are usually given over 8 hours.

6.3 Continuous intravenous infusion

Intravenous administration of a fluid or medicines over 24 hours is referred to as a continuous infusion. The infusion may be repeated over a period of days. Large volumes (i.e. 250–1000 mL) or small-volume infusions (e.g. 50 mL) may be delivered continuously.

Advantages

- May be used to maintain a constant therapeutic concentration of a medicine. For example, some centres may use constant infusions of antibiotics to maintain high blood levels.
- Allows the infusion rate of a medicine to be accurately titrated according to patient response. Morphine infusions for pain control may be adjusted according to the patient's pain and also their level of sedation and respiratory rate. Insulin infusions are titrated according to blood glucose.
- Allows administration of medicines with a short elimination half-life to be given, e.g. adrenaline infusions are used to improve the strength of cardiac contraction in critical care.
- If the solutions are dilute they may be less irritating than bolus administration.

Disadvantages

- May be complicated to prepare. May require complex calculations and multiple transfers of medicine/fluids to produce a solution with the correct concentration.
- Requires the practitioner to be competent in the use of infusion equipment including syringe and volumetric pumps and administration sets.
- During administration the practitioner will need to monitor the infusion to ensure it is running into the patient. This can be very time consuming if an infusion regularly stops.
- Greater risk of microbial and particulate contamination (compared to bolus administration) because of the complexity of preparation.
- Greater risk of infection (compared to bolus administration) as the solutions are used for up to 24 hours, in which time microbes may grow in infusion fluids (particularly those containing glucose or fats, e.g. intravenous nutrition).
- The infusion occupies the VAD continuously. If the patient requires multiple medicines or fluids, more than one infusion may need to be given down the same lumen of a VAD leading to compatibility issues: before two infusions are given via the same lumen it must be confirmed they are compatible.
- Large volumes of fluid may cause fluid overload in some patients.
- Greater risk of pharmaceutical problems, such as drug degradation in solution and drug interaction with the infusion equipment.

6.4 Preparation and administration of intravenous medicines

The following checklist describes the process for preparation and administration of an intravenous medicine. The National Patient Safety Agency (www.npsa.nhs.uk) has produced an excellent and comprehensive standard operating procedure for the prescribing, preparing and administering of injectable medicines. Each item in the checklist below may be comprised of multiple processes itself. Practitioners should refer to the NPSA's document for a breakdown of the full process. Note the Nursing and Midwifery Council now advises that the preparation and administration of all injectable medicines should be second checked by another practitioner in order to minimise error.

- Check the prescription – check that the dose, time and route are correct.
- Understand what the medicine is for and how it works.

- Be aware of any local protocols for preparing and administering the medicine.
- Plan drawing up doses.
- Know how to administer each medicine, including:
 - Calculation of concentration and rate.
 - Reconstitution.
 - Addition of medicines to recommended diluents.
- Use aseptic non-touch technique to prepare the medicine.
- Thoroughly mix any additions, checking for precipitation or particles.
- Complete yellow infusion additive label and attach to infusion.
- Go to patient and check patient identification.
- Explain what you are doing to the patient, when appropriate.
- Check vascular access device.
- Check that any equipment required is working.
- Administer.
- Monitor patient for response and adverse effects.
- Monitor any infusion equipment to ensure it is functional throughout the administration. Monitor the drug solution for signs of precipitation.

6.5 Aseptic non-touch technique (ANTT)

ANTT is fundamental to the safe administration of injectables. Infection, as a result of poor aseptic technique when preparing injectables, or when handling a vascular access device, places a huge burden on healthcare systems. Infection from this route can be severe as microbes are introduced directly into the patient's bloodstream, quickly leading to systemic infection, significant morbidity and high rates of mortality. All practitioners must use ANTT every time an injectable is administered to a patient.

ANTT is an evidence-based method for standardising the aseptic technique of healthcare workers. It is a simple, efficient and logical approach which is the same for peripheral and central line access and for all patients. In IV therapy the focus is on avoiding microbial contamination of the 'key parts' at all the preparation and administration stages.

Key parts are those parts of the equipment that come into direct or indirect contact with the liquid infusion.

Healthcare workers should identify all key parts and then protect them at all times using a non-touch technique. On top of this fundamental principle, the ANTT guideline, importantly, standardises all the equipment to be used and the order in which the procedure is performed. Standardisation is paramount.

ANTT guidelines and resources can be found at www.antt.co.uk.

Here is a simple written overview of the ANTT guideline for IV therapy:

- 1** Clean hands with soap and water or alcohol gel.
- 2** Clean a plastic tray with an alcohol-based surface cleaner. Whilst drying ...
- 3** Gather equipment, including medication, diluents, syringes, needles, etc.
- 4** Clean hands with alcohol gel or soap and water.
- 5** Put on non-sterile gloves (sterile gloves should be used if key parts must be touched).
- 6** Assemble equipment and prepare medicines, protecting key parts at all times by a non-touch technique. Prime the pump and expose the patient's IV port. If this is already done move on to step 7. Otherwise:
 - 6.1** Prime the pump
 - 6.2** Expose the IV port
 - 6.3** Dispose of gloves
 - 6.4** Clean hands with alcohol gel or soap and water
 - 6.5** Put on new non-sterile gloves.
- 7** Clean the key parts with a chlorhexidine gluconate 2% and alcohol 70% wipe. Scrub the port tip with different parts of the wipe, then allow to dry for 30 seconds.
- 8** Administer drugs using a non-touch technique.
- 9** Dispose of sharps and equipment, then dispose of gloves.
- 10** Clean tray with alcoholic wipes.
- 11** Clean hands with alcohol gel or soap and water.

For a pictorial flow chart of the above steps refer to the ANTT website.

7 Extravasation of injectables: overview and management advice

Extravasation is the infiltration of irritant fluids into the subcutaneous tissue. It may lead to an inflammatory response in the affected tissue, which may be immediate or delayed. *The potential for a delayed reaction should be remembered when the initial assessment of a suspected extravasation site is made.* The incidence of infiltration varies widely within the literature but is estimated to occur in 25% of peripheral vascular access devices (VADs, e.g. cannulae) but less than 5% of central lines.

It has been shown that a patient's risk of extravasation depends on several factors.

7.1 Patient factors affecting extravasation

Certain groups of patients are more likely to develop problems after extravasation and should therefore be monitored closely.

7.1.1 Neonates

Neonates, particularly pre-term neonates, possess less subcutaneous tissue than adults, and their veins are smaller and in some cases more fragile. In addition, any extravasated material is more concentrated in the affected area. They are also much less able to vocalise their pain (see below).

7.1.2 Patients unable to vocalise/communicate their pain

Comatose or anaesthetised patients, or those being resuscitated, are not able to provide clear vocalisation of the pain caused by extravasation of a substance. They (and the neonates mentioned above) form perhaps the group of patients at greatest risk from extravasation.

7.1.3 Patients unable to sense pain

Special care should also be taken when administering injectables to patients who have an impaired ability to detect pain. Patients who suffer from peripheral neuropathy (e.g. people with diabetes) are one such group.

7.2 Medicine factors affecting extravasation

The pharmacological properties of a drug influence its ability to induce tissue damage.

7.2.1 Cytotoxic medicines

Several cytotoxic agents will cause extensive tissue damage if extravasated because they are directly toxic to the cells that they come into contact with. Centres that administer cytotoxic agents must have local extravasation guidelines, which should stipulate how to manage the incident according to the type of agent extravasated.

7.2.2 Vasoactive medicines

When vasoconstrictor medicines are administered peripherally, extravasation can produce local vasoconstriction, leading to severe tissue hypoxia and ischaemia. Vasoconstrictors include adrenaline (epinephrine), noradrenaline (norepinephrine), dopamine and vasopressin.

7.2.3 Irritant medicines

The chemical properties of the drug may influence its propensity to cause tissue damage.

i pH

Drug solutions with a pH less than 5.5 or greater than 8.5 may cause tissue damage if they infiltrate subcutaneous tissue as they disturb the normal cellular environment. Blood and tissue fluid have a pH of 7.4 and deviation from this pH will cause damage to cellular structures, particularly by disturbing the function of proteins. The table below shows examples of medicines that have particularly high or low pHs. The reader should note pH values may vary slightly between different preparations of medicine, according to the manufacturer's formulation.

ii Tonicity

All solutions exert an osmotic pressure, dependent on the amount of substance dissolved in the solution. The tonicity of a solution is measured relative to water, which has an osmolarity of 0 mOsmol/L. Solutions with an osmolarity more or less than that of plasma (~290 mOsmol/L) may cause tissue damage. The presence of these solutions can lead to an osmotic imbalance across the cell membrane, leading to the movement of water into or out of the cell, a breakdown of cellular transport mechanisms and cell death. Most injectables are formulated to have the same osmotic pressure as plasma so that the solution to be injected into the patient is unlikely to cause vein irritation. The table below lists a selection of medicines that have high osmolarity and may potentially cause a problem if extravasated. Extra care should be taken when administering these medicines.

Medicines with high or low pH values

Intravenous medicine	pH	Intravenous medicine	pH
Acetazolamide	9.1	Labetalol	3.5–4.2
Aciclovir	11.3	Lidocaine	3.5–6
Adrenaline (epinephrine)	2.8–3.6	Liothyronine	9.8–11.2
Aminophylline	8.8–10	Methyldopa	3–4.2
Amiodarone	3–5	Metoclopramide	3–7
Argipressin	3–5	Midazolam	3
Atracurium	3.5	Morphine	3–6
Atropine	2.8–4.5	Naloxone	3–4.5
Azathioprine	10–12	Noradrenaline (norepinephrine) acid tartrate	3–4.5
Buprenorphine	3.5–5.5	Octreotide	3.9–4.5
Clonazepam	3.5–4.5	Omeprazole	9–10
Co-trimoxazole	9–10.5	Ondansetron	3.3–4
Cyclizine	3.3–3.7	Oxytocin	3.7–4.3
Dantrolene	9.5	Pancuronium	3.8–4.2
Dobutamine	2.5–5.5	Papaveretum	2.5–4
Dopamine	2.5–5.5	Phenobarbital (phenobarbitone)	9–10.5
Doxapram	3–5	Phenoxybenzamine	2.5–3.1
Ergometrine	2.7–3.5	Phenytoin sodium	12
Fentanyl	4–7.5	Potassium canrenoate	10.7–11.2
Folic acid	8–11	Prochlorperazine	5.5–6.6
Furosemide	8–9.5	Propranolol	3
Ganciclovir	10–11	Protamine sulphate	2.5–3.5
Gentamicin	3–5	Quinine dihydrochloride	1.5–3
Glucagon	2.5–3.5	Salbutamol	3.5
Glucose (pH dependent on concentration of solution)	3.5–6.5	Secretin	2.5–5
Glyceryl trinitrate	3.5–6.5	Sodium nitroprusside	3.5–6
Glycopyrronium	2.3–4.3	Terbutaline	3–5
Haloperidol	3–3.8	Tetracosactide	3.8–4.5
Hydralazine	3.5–4.2	Thiopental	10.5
Hyoscine butylbromide	3.7–5.5	Tobramycin	3.5–6
Ketamine	3.5–5.5	Vancomycin	2.8–4.5

Few medicines have an osmotic pressure less than plasma; however, if a medicine is made up with greater than the recommended volume of water for injections, the medicine is likely to be hypotonic and may cause tissue irritation. In practice, this tends to be much less of an issue than injection of hypertonic solutions. Where available, the monographs in Section B list the tonicity of a medicine.

Osmolarity or osmolality? What is the difference?

Tonicity is stated using two different conventions: osmolarity is the theoretical tonicity and is derived through calculation. Osmolality is the measured tonicity and is derived through laboratory testing, such as freezing point depression. Both values are usually similar, with some notable exceptions, such as calcium gluconate. This has an osmolarity of 670 mOsmol/L and an osmolality of 276 mOsmol/kg. It is beyond the scope of the *Guide* to discuss the complex chemistry behind this difference, but it is important to understand that some medicines may be less irritating to tissues than expected, based on their osmolarity. Where possible the osmolality of a solution is stated in the *Guide*, as this is a better indicator of whether a medicine will cause tissue damage. If a medicine has an osmolality of greater than 500 mOsmol/kg (or an osmolarity of greater than 500 mOsmol/L) it is more likely to cause problems if it infiltrates a tissue.

Medicines with a high tonicity may be diluted to a larger volume of infusion fluid in order to reduce the tonicity and thus reduce the irritancy of the medicine. The monographs in Section B give advice on recommended dilutions of medicines.

Medicines with high osmolarity

Intravenous medicine	Osmolarity (mOsmol/L)	Intravenous medicine	Osmolarity (mOsmol/L)
Glucose 10%	535	Mannitol 10%	550
Glucose 20%	1110	Mannitol 20%	1100
Glucose 50%	2775	Magnesium sulphate 50%	4060
Calcium gluconate 10%	670	Potassium chloride 20 mmol/10 mL	4000
Calcium chloride 5 mmol/10 mL	1500	Sodium bicarbonate 4.2%	1004
Intravenous nutrition (TPN)	(variable with bag contents)	Sodium bicarbonate 8.4%	2008

iii Presence of excipients

Some drugs are formulated with substances such as polyethylene glycol and ethanol (alcohol) to improve their solubility, e.g. nimodipine. Such medicines are known

to be more irritating than those formulated in aqueous solutions. If a medicine is known to contain irritating excipients, this is stated in the monograph in Section B of the *Guide*.

7.3 Administration factors affecting extravasation

7.3.1 Site of administration

The selection of the site is a very important factor when placing a VAD. Areas that have small amounts of subcutaneous tissue are the most likely to be problematic should the medicine extravasate. The antecubital fossa and the dorsum of the hand and foot are most often implicated in extravasation injury and should be avoided when administering irritant or vasoactive medicines.

7.3.2 Method of venepuncture

This method of venepuncture is probably as important as the site of injection. The repeated use of any single vein for venepuncture increases the risk of the medicine extravasating into the surrounding tissues. *Venepuncture is a skill that should not be attempted by anybody who has not completed an approved training course.* Inexperience increases the risk of problems arising from venepuncture.

7.4 Overall risk for extravasation

The multiple patient and pharmaceutical risk factors interact to influence whether an extravasated medicine causes tissue damage. A medicine with a normal pH and tonicity may cause tissue damage in a particularly sensitive individual. Before administering medicine or infusion fluid a practitioner should be aware of the possible risks of the product and take into consideration the patient factors that may influence the risk.

7.5 Treatment of extravasation

Extravasation should be suspected if:

- The patient complains of burning, stinging or discomfort at the injection site.
- Swelling or leakage is observed around the VAD.
- Blanching or erythema of the skin occurs at the site.
- Resistance is felt on the plunger of the syringe if the medicine is being given as a bolus.

- The infusion rate slows or stops (regardless of the position of the patient) when administering fluid from a bag.

Extravasation from a central VAD is more difficult to detect. Local guidelines for the management of central venous catheter problems should be consulted.

7.5.1 Immediate action

- **STOP** the administration of the medicine, **leaving the cannula in place.**
- Aspirate the residual medicine through the cannula.
- Elevate the limb.
- Inform the medical staff immediately.

At UCLH the medical/surgical team refers all cases to the plastic surgery team for assessment and advice on treatment at the *earliest opportunity*. The plastic surgery team has several techniques available to limit the likelihood of extensive tissue damage after extravasation. The sooner these measures are started, the more successful they are likely to be.

In areas where irritant injectables are routinely administered, such as haematology and oncology wards, extravasation kits are held. Such kits contain the essential equipment necessary for the immediate treatment of an extravasation, including syringes, needles, a hot and cold pack, gauze, hyaluronidase and dimethylsulfoxide.

7.5.2 Subsequent action

Careful recording of the following in the medical notes is recommended:

- Medicine(s) involved.
- Appearance of site.
- Date and time of the incident.
- Administration technique.
- Needle size, type and insertion site.
- Patient's symptoms and statements.
- Approximate amount of medicine extravasated.
- Name and signature of nurse/doctor administering the medicine.
- Doctor notified.

- Time and date of referral to plastic surgery team.
- Follow-up procedure.

The doctor/nurse administering the medicine should complete an incident form. Further information about risk factors and management advice for extravasation, including a database of incident reports, can be found at www.extravasation.org.

8 Flushing cannulae, catheters and administration sets

8.1 Flushing between medicines

Flushing is simply the introduction of a small amount of fluid into a cannula, catheter or administration set to deliver the contents of the lumen into the patient. Flushing ensures the full dose of a medicine is given to the patient and prevents incompatible substances mixing in the devices. It is standard practice to flush *before* and *after* the administration of a medicine. If giving multiple medicines one after the other, a flush must be given between the individual medicines to avoid interaction between potentially incompatible drugs. Flushes are administered using ANTT, as described above.

Cannulae are usually flushed with 5–10 mL of sodium chloride 0.9% or glucose 5%. Check the individual monograph in Section B to ascertain which fluid is suitable as a flush for a particular medicine. The majority of medicines are compatible with sodium chloride, but there are a few notable exceptions, including amiodarone and phytomenadione, which should be flushed with glucose 5%. Cannulae in neonates and young children require less than 1 mL of flush fluid.

Adult **central venous catheters** should be flushed with 10 mL sodium chloride 0.9% as the volume of the lumen is much larger than in a cannula. Paediatric catheters generally require a smaller volume, while a neonatal catheter may require just 2 mL to be flushed.

Administration sets are flushed by connecting a bag of infusion fluid to the set. The fluid must be compatible with the medicine inside the set, and should be administered at the rate recommended for administration of the original medicine. The volume of an administration set is printed on the package it is supplied in and is usually around 20 mL. Once the set has been flushed the bag can be disconnected and discarded: there is no need to administer the whole bag. Neonatal administration sets usually require 1–2 mL to flush. It is very important to flush an administration set after giving a medicine as the set may contain a considerable proportion of a dose: if the original medicine was in a 100 mL bag, then approximately 10% of the dose will be contained in the administration set prior to flushing.

8.2 When not to flush

When an infusion has been stopped and a medicine's effect is no longer required it may not be appropriate to flush an administration set or catheter. Such medicines tend to be administered via a syringe pump and are used for short-term control of a clinical parameter, for example blood glucose control with insulin. Flushing the medicine through the administration set will deliver a large dose of the drug to the patient, as the drugs are often used in a concentrated form. This would result in a

large and undesirable therapeutic effect – hypoglycaemia may result from flushing an administration set containing insulin, for example.

A small number of medicines are incompatible with all infusion fluids, e.g. some brands of immunoglobulin. These medicines should not be flushed as the flush fluid may cause precipitation of the medicine in the administration set/catheter.

Before taking down an infusion the practitioner should establish whether it is appropriate to flush the medicine. Section B of the *Guide* gives flush advice for each medicine. If it is not appropriate to flush, at the end of an infusion the administration set should be disconnected and discarded and the catheter aspirated so that any medicine in the lumen is removed. The catheter should then be flushed with 10 mL sodium chloride 0.9%.

NB if the medicine is administered via a peripheral cannula the volume of drug inside the cannula prior to flushing is miniscule. Peripheral cannulae do not usually need to be aspirated at the end of an infusion; they may be flushed with 10 mL sodium chloride 0.9%.

8.3 Flushing catheters and cannulae not in use

Peripheral cannulae that are not being used for the administration of fluids or medicines should be flushed with 5 mL sodium chloride 0.9% at 8-hourly intervals to maintain their patency. Neonates require between 0.5 and 1 mL.

Central venous catheters (CVCs) – flush volumes of CVCs will depend on the type of catheter used. If a lumen is not in use, most catheters should be flushed with 10 mL sodium chloride 0.9% at least once or twice weekly. Implantable ports (Portacaths) should be flushed every 4 weeks with 10 mL sodium chloride 0.9%. Paediatric and neonatal catheters generally require a smaller volume to be flushed. Refer to local CVC care guidelines for full advice.

8.4 Flushing with heparin

Until recently flushing with heparin 10 unit/mL or heparin 100 unit/mL was relatively common practice. However, heparin flushes are no longer used at UCLH in response to the National Patient Safety Agency rapid response report *Risks with Intravenous Heparin Solutions*. The report outlined several incidents in which concentrated heparin solutions or drugs other than heparin were inadvertently used to flush venous access devices, resulting in patient harm. There is little evidence that heparin flushes are advantageous over sodium chloride flushes – it is the movement of fluid that maintains the patency of the device, rather than any property of the fluid itself.

In all instances, heparin solutions should not be used to flush venous access devices. However, heparin 100 unit/mL may be used to *lock* an implantable port.

9 Infusion pumps

Fatal errors have been reported after the incorrect administration of medicines via infusion pumps. It is the responsibility of the person administering an injectable to ensure that an appropriate pump is being used, that it is in good working order and that he or she knows how to operate it correctly. Alterations to the pump settings must be made by a person authorised to administer intravenous medicines. The volume of fluid administered should be recorded on the fluid chart. All pumps should be checked at least hourly during the infusion.

9.1 Pumps used at UCLH

In addition to the generic pumps described below, there is a number of special purpose pumps in use in specific clinical areas (e.g. the Cane ApoGo pump used for the administration of apomorphine in Parkinson's disease). These specialised pumps must be used **only** for their intended application; they must **not** be used as general purpose devices.

9.2 Volumetric pumps

These are the preferred pumps for medium- and large-volume infusions, although some are designed specifically to operate at low flow rates for neonatal use. The rate is selected in millilitres per hour (usual range 1–999 mL/hour). Typically, most volumetric pumps are accurate to $\pm 5\%$ at rates down to 5 mL/hour. A syringe pump should be used for rates lower than 5 mL/hour. Volumetric pumps require the use of an administration set matched to the pump.

Volumetric pumps are used to administer a wide range of fluids and medicines, including standard hydration fluids such as sodium chloride 0.9%, medicines that need administration at a controlled rate, such as iron sucrose complex (Venofer), and intravenous nutrition.

9.3 Syringe pumps

These are low-volume, high-accuracy devices designed to infuse at low flow rates and are typically calibrated for delivery in millilitres per hour (usual range 0.1–99 mL/hour). Many pumps will accept different sizes and different brands of syringe, but the pumps must be set up for the particular type and size of syringe in use, unless the pump detects the syringe size and type automatically. The Medicines and Healthcare Products Regulatory Agency (MHRA) recommends that rates less than 0.5 mL/hour should not be used unless the pump is specially designed for

this purpose, because an increase in the occlusion response time occurs. Where the response time to occlusion or the size of the post-occlusion bolus is important (e.g. in neonatal applications), syringe pumps allowing finer control over occlusion pressure should be used. These will generally require the use of a dedicated administration set incorporating a pressure cell.

In general clinical areas at UCLH syringe pumps are used to deliver heparin and insulin infusions, but in critical care they are used to give a large range of medicines, often in a concentrated form. This has the advantage of delivering a medicine in a small volume of fluid, thus minimising the risk of fluid overload. It also allows fine control of the rate of administration so that therapy can be rapidly adjusted according to patient response. Refer to the monographs in Section B for further details. Examples include adrenaline, dobutamine and epoprostenol.

9.4 Pumps for ambulatory use

9.4.1 *Miniature syringe pumps (syringe drivers)*

These pumps typically accept syringes between 2 and 10 mL and are able to achieve very low flow rates. They may require the rate to be set in **millimetres per hour** or **millimetres per day**, i.e. linear travel of syringe plunger against time. Calculations that depend on the syringe size used are required to convert from flow rate to linear travel per unit time.

These pumps are commonly used to deliver analgesics, antiemetics and medicines to reduce respiratory secretions in palliative care. One or more compatible medicines may be mixed in the same syringe, depending on patient need. These syringes are most commonly set to 48 mm and run at 2 mm/hour. The drugs in the syringe must therefore be diluted in a volume of fluid that corresponds to the syringe barrel being drawn up to 48 mm. Refer to Section A15 for further details.

9.4.2 *Miniature volumetric pumps*

These pumps use reservoirs that contain the solution within the pump. Some offer a variety of programming options. These are used to deliver a range of medicines including analgesia, insulin or iron chelating agents. The reservoirs may contain concentrated solutions of drugs which are changed relatively infrequently, e.g. weekly.

9.5 Patient-controlled analgesia (PCA) pumps

These are typically syringe pumps, but they have the facility to enable patients to administer a bolus dose themselves. A PCA pump has several programming options, which may be set by specified clinical staff; access to the programming

controls is usually restricted, typically by a key that disables the programming buttons. The syringe is generally contained inside a lockable cover, to prevent unauthorised access. With PCA pumps, protection against free flow is important because the patient may be unsupervised for some of the time.

A different type of PCA device involves the use of an elastomeric reservoir (Baxter PCA) or syringe reservoir (Vygon PCA). Unlike electronic PCA pumps they have no programming features.

Where there is a clinical need, PCA pumps may be operated by a nurse, in which case the pump is referred to as a nurse-controlled analgesia (NCA) pump. This may be required in children or patients unable to operate the device to give themselves a bolus. PCA pumps give patients the freedom to control their own pain when required. The pumps may be set to deliver boluses only, or may be used to infuse a continuous background dose, supplemented by bolus doses as required by the patient. PCAs are generally used to deliver strong opioids such as morphine, fentanyl, oxycodone or pethidine. Typical drug concentrations, bolus doses and background infusion rates are listed in the individual drug monographs in Section B.

9.6 Target-controlled anaesthesia (TCI or TIVA) pumps

These are syringe pumps incorporating specialised software to control the delivery of specific anaesthetic agents, such as propofol (Diprivan). The pumps share most properties with syringe pumps, but, instead of specifying a fixed infusion rate and volume directly, the user either sets an induction rate and volume, and a maintenance rate, or enters patient information such as gender and weight, from which the pump computes the required rates. The calculation is based on a pharmacokinetic model of the medicine's behaviour in the patient, and is intended to deliver the correct concentration in the patient. Note that some TCI/TIVA pumps require the medicine to be contained in a special, pre-filled syringe.

10 Administration of injectables in primary care

Increasingly, patients are discharged on IV therapy for use at home. Often the task of administration falls to a community (or district) nurse. Although community nurses may have access to their own IV administration policies and training, they often work in isolation and may not be familiar with the injectables they are asked to administer.

Community nurses may therefore require information and advice on the IV medicine(s) before visiting the patient at home. Some may wish to visit the patient on the ward before discharge to familiarise themselves with the medicine, the type of equipment and/or the skills required for care. The information required by the community nurse will include:

- Name of medication.
- Indication for use.
- Dose.
- Patient weight/body surface area/clinical status (as appropriate).
- Method of administration.
- For IV infusions – diluent and volume/concentrations/rate/duration of infusion.
- Method of rate control.
- Frequency of administration (community nurse schedules and patient convenience may need consideration).
- Storage requirements.
- Arrangements for ongoing prescription and supply of medicines.
- Arrangements for disposal of clinical waste.
- Side effects.
- Clinically significant interactions.
- Monitoring.

Reconstitution in the patient's home may pose additional training needs, and COSHH (Control of Substances Hazardous to Health) implications must be considered.

For licensed products the above information will usually be available from the British National Formulary (BNF), SPCs and package inserts. Where medicines are prescribed outside the recommendations of the product licence, community

nurses require access to sufficient information to satisfy themselves that the prescription is appropriate in the context of the condition of the patient. The necessary information should be made available at the time of discharge from the ward. Prescribing guidelines, shared care guidelines and pharmacy discharge plans are useful sources of information.

10.1 Self-caring patients

Some patients may be sufficiently independent to manage their own injectable therapy. There is a growing body of patients requiring long-term intravenous nutrition (IVN) and fluids. During hospital admission these patients are taught how to manage their CVC, including ANTT, how to use administration equipment and devices and to administer nutrition to themselves. The IVN may be compounded in batches and delivered to the patient weekly, or every 2 weeks, depending on the stability of the formulation and the patient's capacity to store the bags. These individuals are taught to recognise administration problems, as well as CVC-related problems, and may be given supplies of drugs or fluids used in such situations, e.g. a small supply of antibiotics for patients who are prone to catheter-related infection, or an additional supply of fluids for those who may become dehydrated.

There are great advantages to self administration: patients take control and responsibility for their own care, which gives them freedom and independence. It also takes some burden away from the healthcare system as daily nursing visits are unnecessary. However, setting up such a system requires patients to be motivated and capable of intensive training to ensure they will be safe at home, as well as a great deal of organisation within a hospital multidisciplinary team to co-ordinate training and install a homecare package. At UCLH this team is formed by specialist nutrition nurses, doctors and pharmacists.

11 Formulation and presentation of injectables

Injectables are available in a range of presentations, as described here.

11.1 Medicines that require reconstitution

These include medicines, e.g. amoxicillin, that are presented as a dry powder and therefore need to be reconstituted before use. Further dilution may be necessary. The advantage of this type of formulation is that it enables prolonged storage of products that are unstable in solution.

There are a number of disadvantages, including the following:

- They need to be reconstituted, which is time consuming, particularly if the preparation is difficult to dissolve.
- All manipulations pose the risk of environmental and microbial contamination of the solution.
- They may be complex to prepare, particularly if they require special diluents or multiple transfers of fluid. The greater the complexity, the greater the chance of an error being made during preparation.
- Some medicines are susceptible to 'foaming', e.g. teicoplanin and asparaginase. If doses are drawn up from foam, part of the dose may be left in the vial. Foaming of protein drugs sometimes inactivates them.
- If the product is presented as glass ampoules that require snapping, there is a danger of glass particles getting into the preparation, staff injuries and the risk of medicine droplets polluting the environment.
- Pressure differentials in vials with a rubber septum may be difficult to manage (see below).

11.1.1 Equalising pressure in the vial

Some vials are manufactured with a vacuum inside, and it is important that the effects of this are corrected during reconstitution. If the vial has a vacuum inside it will be obvious when trying to add diluent because the diluent will be 'sucked' into the vial.

If no vacuum is present in the vial, air needs to be removed. The amount of air drawn back into the syringe should be equal to the volume of diluent added. Before withdrawing the reconstituted medicine from the vial, again pressure differences have to be accounted for. Air needs to be added to the vial equal to the amount of medicine to be withdrawn.

11.2 Preparations in solution requiring further dilution before use

Examples of such preparations are amiodarone and aminophylline.

Advantage

- They are already in a liquid form, so reconstitution is unnecessary.

Disadvantages

- They may need to be further diluted before administration, so the drug may still require multiple complex manipulations before it is ready to administer to the patient.
- Vials may have a pressure differential (as above).
- Glass ampoules are easily broken if stored incorrectly, leading to environmental contamination.

11.3 Preparations available 'ready to use' without further dilution

These preparations may come in bags or small-volume ampoules that can be administered without further dilution, but still require the solution to be drawn up into a syringe for administration, e.g. ondansetron and ranitidine. These are convenient to use but still have disadvantages.

Disadvantages

- Hazards associated with microbial contamination.
- Prone to vacuum/pressure problems (if vials).
- Can cause glass breakage problems (if ampoules).

11.4 Preparations available 'ready to administer'

These preparations include infusion bags, e.g. 500 mL sodium chloride 0.9%, pre-filled syringes, e.g. adrenaline, and pre-filled bags/bottles of medicines, e.g. ciprofloxacin and metronidazole.

Advantages

- Easy to use and prepare so there is minimal risk that dosing errors may occur.
- Minimal risk of microbial contamination during preparation – usually the practitioner just needs to attach an administration set or, in the case of a pre-filled syringe, simply remove the sheath from the needle.
- Lower risk of environmental contamination.

Disadvantages

- They are bulky to store and transport. This may be a significant problem if many doses are used in a clinical area. If all drugs were presented as ready to use preparations most healthcare providers would need to find additional storage space for medicines.
- The packaging and containers must be disposed of after use. The drugs tend to come with large amounts of cardboard and are often presented in large glass bottles, for which disposal facilities must be provided. The carbon footprint of such preparations is likely to be much greater than small-volume, minimally packaged presentations.
- The drugs tend to be presented in a limited range of doses. In certain patient groups, e.g. children and neonates, it may be difficult to give the correct dose of a medicine without withdrawing fluid from the preparation, or using an infusion device to accurately measure the amount of fluid delivered, then stopping the infusion part of the way through in order to give a part bottle or bag.
- The drug may be diluted in a large volume of fluid, which may be unsuitable for some patients, e.g. fluid-restricted patients and neonates.

12 Pharmaceutical aspects of injectable administration

The preparation and administration of some drugs is influenced by the physicochemical properties of the formulation.

12.1 Displacement values

When a solid is dissolved in a fluid, the volume of the fluid increases. The volume of this increase is called the displacement value. It is important to consider this when preparing medicines, since many medicines are presented as dry powders, to which diluent must be added. For example: amoxicillin 250 mg vial has a displacement value of 0.2 mL. Usually amoxicillin is reconstituted with 5 mL water for injections. After reconstitution the total volume of the solution is 5 mL + 0.2 mL = 5.2 mL. If the prescribed dose is 250 mg, then the practitioner should administer the full 5.2 mL to the patient. The concentration of amoxicillin in the solution is 48 mg/mL.

Perhaps a practitioner is working on a paediatric ward and the dose prescribed is 50 mg. To reconstitute the vial the practitioner should take into account the displacement value. The practitioner should add 4.8 mL water for injections to the vial, so that the concentration is 50 mg/mL. The volume of the dose is 1 mL.

The monographs in Medicine monographs (in alphabetical order) advise how to take into account the displacement value for all drugs in which it is significant.

12.2 Sodium content

Some medicines can have a high sodium content which should be taken into consideration when patients are sodium restricted. Sodium may be included in the medicine because:

- It is part of the drug itself, e.g. benzylpenicillin sodium.
- It is in the excipients, e.g. sodium citrate, which is used to control the pH of a medicine.
- It is part of the diluent – many ready diluted medicines are actually formulated in sodium chloride 0.9%, e.g. ciprofloxacin and metronidazole.

If patients are sodium restricted it may be beneficial to dilute their medicines in glucose if possible. The amount of sodium from medicines is rarely greater than the amount that would be delivered in 500 mL or 1 L sodium chloride 0.9%. The sodium content of medicines, and of sodium chloride solutions, is listed in the monographs in Section B.

12.3 Drop size

The presence of solvents in some medicines may affect the drop size of the infusion. A drop in a standard adult administration set is 0.05 mL but may be reduced to 0.03 mL by the excipients that amiodarone is formulated with. This can result in inaccuracies if relying on drop-counting methods to control the administration rate. Therefore, amiodarone should be given only by devices that control the rate of administration by volume, i.e. a volumetric pump or syringe pump.

12.4 Layering

This phenomenon can occur if there is insufficient mixing of solutions with different densities. An example of this is the addition of potassium chloride to IV infusion bags. If potassium chloride injection is added to glucose 5%, it remains in the bottom of the IV bag because it is denser than the glucose solution. Thus, if the bag is not mixed thoroughly, a high concentration of potassium will remain in the lower part of the bag. Infusion of the solution may result in cardiac arrest due to the high concentration of potassium delivered in a short space of time.

When adding to an infusion bag, care must be taken to ensure that all additives are thoroughly mixed within an infusion fluid.

12.5 Fluid restriction

Medicines that require dilution in large volumes for administration may cause problems in patients who are fluid restricted. Drugs that are irritating to veins, because of high osmolarity or non-physiological pH in their concentrated form, are usually recommended for dilution in large volumes of fluid. This reduces their irritancy. However, fluid overload may also arise when patients are administered numerous intravenous medicines that may require dilution. Therefore, the amount of fluid intake from intravenous medicine administration must be considered when prescribing maintenance fluid requirements. In the monographs, advice has been given to indicate the smallest volume with which a medicine can be given. Much of this information is based on anecdotal experience compiled in the UKCPA document *Critical Care Group Minimum Infusion Volume*, 3rd edition, 2006.

High fluid intake often accompanies the following medicines:

- Co-trimoxazole.
- Sodium fusidate.
- Erythromycin.
- Intravenous nutrition.
- Liposomal amphotericin (AmBisome).
- Aciclovir.

13 Factors influencing medicine stability and compatibility of injectable medicines

An important aspect of parenteral therapy is to ensure that the patient receives the intended dose of each medicine. A proportion of the medicine will be lost between the time of preparation of the injection and entry into the bloodstream, e.g. if the medicine undergoes degradation, precipitates with the diluent or interacts with the delivery system. It is important to understand the reasons for such loss of potency in order to assess the likely clinical implications.

The following section briefly discusses some of these problems.

13.1 Degradation

13.1.1 *In aqueous solution*

On reconstitution, dry powder medicines are relatively unstable in aqueous vehicles and normally degrade by hydrolysis (decomposition of a substance by a chemical reaction with water). This reaction may be accelerated by a change in pH, resulting either from the diluent or from a second medicine. Such degradation may be minimised and prevented by using the recommended diluent, e.g. erythromycin must be reconstituted with water for injections because it will not dissolve in sodium chloride 0.9% or glucose 5%. After it has been dissolved it should be diluted in sodium chloride 0.9% and not glucose 5% because it degrades at an acidic pH. Alternatively sodium bicarbonate may be added to a glucose 5% bag to ensure the pH is in the range at which erythromycin is stable. See the monograph for erythromycin in Section B for further details.

13.1.2 *Photodegradation*

Photodegradation is the breakdown of a substance by light. It occurs to a significant degree in a small number of medicines, e.g. sodium nitroprusside. Degradation is usually the result of ultraviolet (UV) light, which is found in daylight but not artificial fluorescent light, although sodium nitroprusside is rapidly degraded by both fluorescent and UV light.

Photodegradation of some other light-sensitive medicines (e.g. ciprofloxacin or furosemide) is not clinically important provided that direct exposure to strong daylight or sunlight is avoided. Intravenous nutrition should be light protected as some vitamins are light sensitive.

13.2 Precipitation

Precipitated medicines are pharmacologically inactive but hazardous to the patient. Precipitates can block catheters and damage capillaries and may lead to coronary and pulmonary emboli. The injection of medicine precipitates must therefore be avoided.

13.2.1 Causes of precipitation

i pH

The most likely reason for precipitation is the mixing in the infusion container or the infusion line of two medicines with very different pH values, especially if one is acidic and the other alkaline.

ii Medicine–medicine co-precipitation

This occurs most commonly from the mixing of organic anions (ions with a negative charge) and cations (ions with a positive charge), which join together to form ion pairs. Gentamicin and other aminoglycosides are incompatible with heparin, penicillins and cephalosporins because of this. It is essential to avoid these interactions. Medicines that could form an ion pair should never be allowed to mix in an infusion container, syringe or administration line. Flushing between the administration of different medicines helps avoid such interactions (see Section A8 for further details).

iii Temperature

Most medicines are more soluble as the temperature increases. Generally, if a refrigerated injection does not precipitate, warming to 37°C (as occurs when an injection passes slowly through the cannula) will not cause precipitation. One exception to this is calcium phosphate, which is less soluble at 37°C than at room temperature.

Mannitol, at concentrations of 15% or more, crystallises out when exposed to low temperatures. A mannitol solution containing crystals should not be used.

13.3 Binding of medicines to plastics

Administration of IV medicines relies almost entirely on equipment made from plastic. Some medicines bind to certain plastics. The extent of binding is difficult to predict because it depends on: medicine concentration, vehicle, flow rate, available surface area of plastic, type of plastic, temperature, pH and time. The main plastic with which drugs interact is polyvinyl chloride (PVC). Syringes are generally PVC-free, and there is a movement towards the use of PVC-free infusion bags too: Baxter

Viaflo bags do not contain PVC. At the time of writing, most administration sets still contain PVC. If medicines incompatible with PVC need to be given, a PVC-free set should be obtained. These are commonly stocked in haematology areas, where they are most likely to be used. The packaging of administration equipment should state the material from which the device is made.

The table below shows some clinically relevant examples of drug–plastic interactions.

Medicine	Plastic affected	Management advice
Insulin	Any (and glass)	Do not add to infusion bags. Dilute to 1 unit/mL and give via a syringe pump. Monitor blood sugar and adjust infusion rate accordingly
Diazepam	PVC	Administer via a syringe pump and PVC-free administration set
Nimodipine	PVC	Use the polyethylene administration set provided with the drug
Nitrates (GTN, ISDN)	PVC, nylon	Administer via a syringe pump and PVC-free administration set

13.4 Destabilisation of parenteral emulsions

Care is necessary to avoid destabilising emulsions in IV lines, junctions and catheters where injections may mix during administration. Fat emulsions (e.g. Intralipid) are used widely in parenteral nutrition as an energy source. Other medicines that are prepared as a fat emulsion as a result of their poor water solubility include propofol and diazepam (Diazemuls).

Fat emulsions can be destabilised by ions with a high positive charge: calcium and magnesium may destabilise the fat emulsion in intravenous nutrition. Diazemuls may be diluted, but sodium chloride 0.9% rapidly destabilises the emulsion and should not be used.

13.5 Leaching of plasticisers

The presence of oils and surfactants can leach (leak) out toxic plasticisers, especially from PVC materials. This can happen if intravenous nutrition is made in PVC bags. Leaching from administration sets and bags during infusion can also occur. Ciclosporin solution contains polyethoxylated castor oil, which causes phthalate (a plasticiser) to leach from PVC containers and tubing. If the infusion is administered for more than 6 hours, a low sorbing PVC administration set and an infusion bag

should be used to infuse the ciclosporin. Leaching from rubber plungers of plastic syringes may occur and can affect medicine stability, e.g. ergocalciferol.

13.6 Blood and blood products

The Department of Health states that the co-administration of blood or concentrated red blood cells with any other medicine or vehicle is hazardous. Examples of incompatibility with blood include mannitol solutions (irreversible crenation of red cells), dextrans (rouleaux formation and interference with crossmatching), glucose (clumping of red cells) and oxytocin (inactivated).

In extreme circumstances medicines have been mixed with blood in the catheter, e.g. experience seems to show that furosemide can mix safely with blood. In contrast, human serum albumin has been shown to be incompatible with many intravenous infusions. Overall experience remains limited and no studies have been reported.

14 Allergic reactions to injectables

A true allergic reaction resulting in anaphylaxis will occur in a patient who has become sensitised to a medicine, via an immunologically mediated pathway, and so must have had previous exposure to the medicine. Therefore, anaphylaxis will occur on administration of the second rather than the first dose of the medicine. In a patient already sensitised to a specific medication, the risk of an allergic reaction to that medication is greatest when given intravenously and least when given orally. This is thought to be a function of the rate of medicine delivery.

Pseudoallergic or 'anaphylactoid' reactions are medicine reactions that exhibit clinical signs and symptoms of an allergic response but are not immunologically mediated. Unlike true allergic reactions, which require an induction period during which a patient becomes sensitised to an antigen, pseudoallergic reactions can occur on the first exposure to a medicine. The development of pseudoallergic reactions may be dose related and manifest only when large doses of the medicine are administered. Patients frequently exhibit anaphylactoid reactions to intravenous iron.

14.1 Latex allergy

A small number of patients are allergic to natural latex. Natural latex is made from the rubber tree. It is thought that some individuals become sensitive to the proteins present in the latex through repeated exposure. Patients with spina bifida are particularly prone to acquiring natural latex allergy, because they frequently require surgery, during which they may be exposed to latex from surgical equipment. Healthcare workers are also prone to acquiring latex allergy from the same equipment. There is a movement to eliminate the use of natural latex within healthcare precisely because of this problem.

Synthetic latex does not contain these proteins, so it does not pose a risk to those with a natural latex allergy. For most injectable medicines, if they have latex packaging, it is made with synthetic latex. Unfortunately some medicines are packaged with natural-latex-containing materials. The septum of a vial is occasionally manufactured with material containing natural latex. As a needle pierces a septum, small fragments of latex break away and enter the drug fluid. These particles may be subsequently drawn up and injected into a patient. Normally this would have no effect on a patient, but in patients with latex allergy a hypersensitivity reaction may be triggered.

Occasionally manufacturers use materials containing natural latex to make equipment used to administer injectable medicines. For example, the syringe cap or needle sheath of some pre-filled syringes may contain latex. If these come into contact with a latex-sensitive patient, it may cause an allergic reaction.

Medicines may also come into contact with latex on the production line: conveyor belts used to transport vials through a factory may contain natural

latex, so the outer surface of medicines may be contaminated with small latex particles.

The only way to definitively establish whether the packaging of medicine contains natural latex is to contact the manufacturer of the medicine. Local pharmacy medicines information departments can facilitate this.

Pharmaceutical manufacturers recognise the problem with using latex in their packaging, and will usually confirm whether it is in their product. They will not, however, guarantee whether their product has come into contact with natural latex on the production line. However, the latter is generally not thought to pose a serious risk since drug packaging and patients should not come into contact with each other.

For full details regarding the management of latex allergic patients refer to local guidelines.

15 Compatibility of drugs in a syringe driver for subcutaneous use

Continuous subcutaneous infusions are commonly used in palliative care. Analgesics, antiemetics and drugs for reducing respiratory and gastrointestinal secretions may be diluted in a small volume of fluid and administered over 24 hours. This avoids the need for administration of multiple medicines by the oral or intravenous routes and can be a much more comfortable and convenient way of giving medicines to the patient. It also ensures the medicine is delivered to the patient if there are problems with absorption from the intestine, or if the patient is unable to take oral medicines because of vomiting or gastrointestinal disease or if the patient is sedated.

It is often necessary to give more than one medicine by the SC route. However, not all medicines are suitable for administration by this method because of limited aqueous solubility or extremes of pH. The table below and Section B of this *Guide* list those medicines that are commonly given by SC infusion. Specialist texts that give advice about possible compatible combinations of medicines for SC use are available for those who routinely use syringe drivers. However, the following simple precautions will minimise the risk of problems of incompatibility and instability:

- Do not leave medicines running in a syringe pump for more than 24 hours.
- Regularly check the solution for signs of precipitation or colour changes, and respond to the pump alarm if it signals an occlusion.
- Protect the contents of a syringe from direct sunlight.
- Check with your local pharmacy department for specific stability information before using any unusual combinations.

pH is a useful predictor of the compatibility of medicine combinations. If two medicines with differing pH values are mixed, the solubility and chemical stability of combinations may be affected.

The table below shows the maximum stable concentrations of **diamorphine** (a commonly used opioid in the palliative care setting) with various agents, made up with **water for injections** (unless otherwise stated). At concentrations above those shown, there is an increased potential for the mixture to precipitate.

Additive	Maximum stable concentration of additive in syringe pump (mg/mL)	Maximum stable concentration of diamorphine in syringe pump (mg/mL)	See note
Cyclizine	10	50	1
Dexamethasone sodium phosphate	1.6	50	2
Haloperidol	1.5	50	
Hyoscine butylbromide	20	150	
Hyoscine hydrobromide	0.4	150	
Ketamine			3
Levomepromazine (methotrimeprazine)	10	50	4
Metoclopramide	5	150	5
Midazolam	5	43	
Ketorolac	12	400	6
Octreotide	0.075	25	3

Notes

- 1 Cyclizine is likely to precipitate in the presence of sodium chloride 0.9%. In addition, the solubility of cyclizine is reduced by the presence of other medicines in solution. Check for precipitation before administration. Certain higher concentrations of cyclizine may be compatible with lower concentrations of diamorphine. Contact pharmacy for details.
- 2 Check for precipitation before administration. Dexamethasone should be added last to the syringe after dilution of other medicines.
- 3 The maximum compatible concentrations of this combination are not known. No formal stability studies have been published. Sodium chloride 0.9% is the preferred diluent for these combinations.
- 4 Solutions containing levomepromazine have developed a purple discoloration in UV light: such solutions should be discarded.
- 5 Under some conditions metoclopramide may become discoloured: such solutions should be discarded.
- 6 Ketorolac and diamorphine should be mixed in sodium chloride 0.9%. The 'maximum' concentrations stated are the maximum concentrations reported in the literature. The absolute maximum compatible concentrations of ketorolac and diamorphine are not known.

Most health units have a local syringe driver policy which the reader should refer to for further information.

16 Risk assessment of injectables and risk reduction

In March 2007 the National Patient Safety Agency published the patient safety alert *Promoting Safer Use of Injectable Medicines*. This required all healthcare organisations using injectable medicines to complete a series of activities to minimise the risks associated with these products. The NPSA required risk assessment for every injectable practice in each organisation to be completed, according to set criteria relating to the preparation and administration of each injectable. On identification of high-risk activity, organisations were obliged to take steps to minimise the risk.

16.1 Risk assessment

Each injectable practice across UCLH was assessed according to the eight NPSA criteria, described in the table below. The risk assessment was conducted in all clinical areas in order to capture local variations in practice. Many injectables are used in multiple different ways, so were risk assessed multiple times according to local practice. For example, a dopamine infusion in UCLH Cardiology is prepared and administered in a different way to that in UCLH Neonatal Unit. The criteria are outlined in the following table.

All injectable practices were given a final score out of eight, according to the number of criteria that applied to that practice. The NPSA advises that practice that scores 1–2 is low risk, 3–5 is moderate risk and 6 or more is high risk. The NPSA requires risk reduction strategies to be put in place to minimise high-risk practices and mitigate the risk if possible. Our scores have been embedded into the monographs in Section B.

At UCLH it was recognised that the NPSA risk scores are very much weighted towards the preparation of the injectable rather than the clinical risk. For example, a morphine bolus would get a low score because it was relatively easy to prepare, despite being potentially very harmful to the patient. Thus a database of all practice rated as high risk according to the NPSA rating plus any practice known to be high risk for other reasons was created. The additional inclusion criteria included all opiates, anaesthetic agents, benzodiazepines, all drugs with a narrow therapeutic index which require blood monitoring, and all drugs that require acute monitoring to ensure efficacy or monitoring for serious adverse effects, e.g. beta-blockers.

The database comprises approximately 100 high-risk injectable practices across the Trust. These were further stratified according to how widespread they are and how frequently they are performed in order to identify which practices should be prioritised for risk minimisation. Some examples of high-risk and widely used injectables at UCLH are given in the table below.

Number	Risk factor	Applies when
1	Therapeutic risk	There is significant risk of patient harm if the injectable medicine is not used as intended ¹
2	Use of a concentrate	The product must be further diluted (after reconstitution) before it can be injected
3	Complex calculation	A complicated calculation must be performed in order to prepare or administer the product. This includes calculations with more than one step, or conversions between dose units, e.g. percentage to milligrammes per millilitre
4	Complex method	More than five non-touch manipulations are required to prepare the product, or when syringe-to-syringe transfer or a filter is used
5	Reconstitution of powder in a vial	Where a dry power preparation must be reconstituted
6	Use of a part vial or ampoule, or use of more than one vial or ampoule	Part or multiple vials/ampoules are required to fulfil the prescription
7	Use of a pump or syringe driver	An infusion device is required to give the injectable
8	Use of a non-standard giving set/ device required	A low sorption, air inlet or light-protected administration set needs to be used to administer the injectable

¹ As the first item, therapeutic risk, is open to interpretation; it was applied for any drug that could cause serious adverse effect if administered incorrectly, including if there was a risk of extravasation with the drug. The injectable was also given this score if patient harm was likely if the patient did not receive the correct dose of the drug or did not receive the drug at all because of an error in preparation or administration.

Drug	Administration method	Indication
Aciclovir	Intermittent IV infusion	Viral infection
Caspofungin	Intermittent IV infusion	Fungal infection
GTN	Intermittent IV infusion	Hypertension, angina
Heparin	Continuous IV infusion	Anticoagulation
Calcium gluconate	Intermittent IV infusion	Severe calcium deficiency
Morphine	Intermittent/continuous IV infusion via a PCA	Pain
Gentamicin	Intermittent IV infusion	Bacterial infection
Foscarnet	Intermittent IV infusion	Viral infection
Infliximab	Intermittent IV infusion	Immunomodulation
Iron dextran infusion (Venofer)	Intermittent IV infusion	Iron deficiency

16.2 Risk reduction

Since the risk assessment was performed, a series of risk reduction strategies have been put in place, tailored to the drug and the circumstances in which it is used. For example, nurses have traditionally made morphine 50 mg/50 mL syringes for PCA pumps on the ward. The morphine PCA pumps scored highly in the risk assessment because:

- They are complicated to make as they require multiple transfers of drug and fluid.
- They are administered using a pump.
- They are very widely and frequently used across the Trust.
- Morphine is a high-risk drug clinically because of the risk of respiratory and CNS depression if given in excess. Conversely if not enough morphine is given it may result in serious pain.

Gradually the preparation of morphine PCAs by nurses on the ward will be phased out and replaced with a ready-made product. This minimises the risk from errors in preparation, but does not influence the other factors that make it high risk. The UCLH PCA policy has been revised and an education programme for all those involved in the administration and monitoring of PCAs is underway to raise awareness of the potential risks from this intervention.

The NPSA recommends several risk reduction strategies including:

- Guideline production, to support those who prescribe, dispense, prepare and administer high-risk medicines.
- Rationalisation of products, e.g. stocking only one strength of a product to minimise risk in preparation. For example, at UCLH, heparin 1000 unit/mL is now the only product available on wards; all 5000 unit/mL preparations have been removed.
- Purchasing of ready-to-use medicines. Across London this work is being co-ordinated so that products that are not commercially available but are widely used across many hospitals, such as the morphine PCA, are available.

Risk reduction requires a co-ordinated multidisciplinary approach with inventive strategies to engage the healthcare workers who use high-risk medicines. The primary motivation for risk reduction is to improve patient safety, at the heart of healthcare.

17 Useful resources

17.1 Websites

The following websites may be of interest to readers.

www.rcn.org.uk

The Royal College of Nursing has produced *Standards for Infusion Therapy*, an excellent and comprehensive document covering nursing aspects of injectable practice.

www.nmc-uk.org

The Nursing and Midwifery Council publishes a range of standards to which registered practitioners should adhere. Their standards for medicines management are of particular relevance to this *Guide*.

www.ukcpa.org

The UK Clinical Pharmacy Association promotes expert practice in medicines management. Its critical care group publishes the document *Minimum Infusion Volumes for Fluid Restricted Critically Ill Patients*.

www.extravasation.org

A comprehensive website about extravasation, describing risk factors and outlining management advice. It also contains a database of known extravasation incidents and a reporting system.

www.bnf.org and **www.bnfc.org**

The British National Formulary and the British National Formulary for Children.

http://emc.medicines.org.uk

The Electronic Medicines Compendium contains the Summary of Product Characteristics for a large number of UK licensed medicines.

www.medicinescomplete.com (subscription required)

Provides a range of pharmaceutical publications including *Martindale, the Complete Drug Reference* edited by Sweetman and *Handbook on Injectable Drugs* by Trissel (an excellent resource for drug compatibility).

www.npsa.nhs.uk

The National Patient Safety Agency promotes patient safety. The NPSA published *Promoting Safer Use of Injectable Medicines* in 2007.

www.ukmi.nhs.uk (password required)

The UK Medicines Information website has a latex allergy information page, and also features a database that details which injectable medicines contain synthetic or natural latex within their packaging.

17.2 Further reading

Intravenous Therapy in Nursing Practice by Lisa Dougherty and Julie Lamb, 2nd edition, Blackwell Publishing, is an excellent and comprehensive text on intravenous therapy. Advanced practitioners and those involved in teaching relating to intravenous therapy may be particularly interested in this book.

