Chapter 9

Medical gases

Clinical uses

Air

Clinical indications

- In ventilators and incubators—to provide uncontaminated and controlled airflows.
- Replacement for contaminated atmospheric air.
- Carrier for volatile anaesthetic agents.
- Power source for pneumatic equipment.

Carbon dioxide

Clinical indications

- To rapidly ↑ depth of anaesthesia when volatile anaesthetic agents are administered.
- To facilitate blind intubation in anaesthetic practice.
- To facilitate vasodilatation, lessening the degree of metabolic acidosis during the induction of hypothermia.
- To ↑ cerebral blood flow in arteriosclerotic patients undergoing surgery.
- To stimulate respiration after a period of apnoea.
- To prevent hypocapnia during hyperventilation.
- For clinical and physiological investigations—e.g. insufflation into Fallopian tubes.
- For tissue-freezing techniques.

Entonox (50:50 mixture of nitrous oxide and oxygen (O_2))

Clinical indications

Used exclusively for the relief of pain:

- trauma
- dental work
- wound and burn analgesia
- childbirth analgesia.

Administration of Entonox

The gas is administered using a facemask or mouthpiece; gas flow is controlled by a sensitive demand valve which is activated by the patient's inspired breath. This enables pressurized gas from the cylinder to flow through a pressure regulator into the lungs at a steady rate. Longer and deeper breaths enable greater volumes of gas to be taken into the lungs, if necessary.

The gas is rapidly absorbed on inhalation, providing analgesia within minutes. The patient safely controls the dosage and, under normal conditions, there is no risk of overdose because the patient's level of consciousness governs their ability to maintain the flow of gas.

Helium

Clinical indications

Helium is used with at least 21% O_2:

- to assist O_2 flow into the alveoli of patients with severe respiratory obstruction
- to prevent atelectasis.
- for gas-transfer lung function tests.

Oxygen

Clinical indications

- To provide life support by restoring tissue O_2 levels—e.g. asthma, myocardial infarction (MI), and sickle cell crisis.
- Management of sudden cardiac or respiratory arrest.
- Resuscitation of the critically ill.
- Anaesthesia.

Oxygen delivery systems are listed in Table 9.1.

Typical dosing for O_2 in acute conditions

- Cardiac or respiratory conditions: 100%.
- Hypoxaemia with $PaCO_2$ <5.3kPa: 40–60%.
- Hypoxaemia with $PaCO_2$ >5.3kPa: 24% initially.

Long-term O_2

Used to improve mortality and morbidity in patients with chronic hypoxia caused by chronic obstructive pulmonary disease (COPD), pulmonary malignancy, heart failure, and other lung diseases such as cystic fibrosis and interstitial lung disease. Should be considered if arterial PaO_2 <7.3kPa or 7.3–8kPa if the patient has polycythaemia or evidence of pulmonary hypertension.

Nitrous oxide

Clinical indications

- Nitrous oxide is used as an inhalation anaesthetic in combination with either a volatile or an IV anaesthetic agent.
- Used in combination with 50% O_2 as an analgesic agent.

Table 9.1 Oxygen delivery systems

Type	Flow rate	Inspired O_2 concentration
Low flow (Ventimask-controlled)		24%/28%/31%
Nasal prongs	1–2L	24–28%
High-flow mask	1–15L	24–60%
Non-rebreathing mask		≤90%
Anaesthetic mask or endotracheal tube		100%

Oxygen† Integral value

Cylinder code	CD	HX	ZX	ZH(2)	DF(2)
Cylinder order code	101-CD	101-HX	101-ZX	101-ZH	101-DF
Nominal contents (litres)	460	2300	3040	2400	1360
Nominal cylinder pressure (bar)	230	230	300	300	137
Nominal outlet pressure (bar)	4	4	4	4	4
Valve outlet flow connection	6mm firtree	6mm firtree	6mm firtree	6mm firtree	6mm firtree
Valve outlet pressure connection	Oxygen Schrader (BS 5682)	Oxygen Schrader (BS 5682)	Oxygen Schrader (BS 5682)	Oxygen Schrader (BS 5682)	
Valve operation	handwheel	handwheel	handwheel	handwheel	handwheel
Flow-rate (litres/min)	Firtree: 1-15/Schrader: 40	Firtree: 1-15/Schrader: 40	Firtree: 1-15/Schrader: 40	Firtree: 2-4/Schrader: 40	2-4
Dimensions* L×D (mm)	520×100	930×140	930×143	595×175	690×175
Water capacity (litres)	2.0	10.0	10.0	8.0	9.4
Nominal weight full (kg)	3.5	19.0	14.0	14.0	12.0

Cylinder code	ZA	ZB	ZC(2)	AD(1)	DD(2)
Cylinder order code	101-ZA	101-ZB	101-ZC	139-AD	109-DD
Nominal contents (litres)	300	300	300	460	460
Nominal cylinder pressure (bar)	300	300	300	230	230
Nominal outlet pressure (bar)	4	4	4	4	4
Valve outlet flow connection	6mm firtree	6mm firtree	6mm firtree	6mm firtree	6mm firtree
Valve operation	handwheel	handwheel	handwheel	handwheel	handwheel
Flow-rate (litres/min)	0.1-15	1-15	0.1-5	8	2-4
Dimensions* L×D (mm)	366×85	390×85	390×85	480×100	520×100
Water capacity (litres)	1.0	1.0	1.0	2.0	2.0
Nominal weight full (kg)	1.55	2.7	2.7	4.0	3.5

Oxygen† Standard valve

Cylinder code	AZ	C	D	E	J	AF(2)	F	G
Cylinder order code	298121-AZ	101-C	101-D	101-E	101-J	101-F	101-F	101-G
Nominal contents (litres)	170	170	340	680	6800	1360	1360	3400
Nominal cylinder pressure (bar)	137	137	137	137	137	137	137	137
Valve outlet connection	Pin-index	Pin-index	Pin-index	Pin-index	Pin-index (side spindle)	5/8" BSP (F)	5/8" BSP (F)	5/8" BSP (F)
Valve outlet specification	ISO 407	ISO 407	ISO 407	ISO 407	ISO 407	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)
Valve operation	key	key	key	key	key	key	key	key
Dimensions* L×D (mm)	290×106	430×89	535×102	865×102	1320×229	670×175	930×140	1320×178
Water capacity (litres)	1.2	1.2	2.3	4.7	47.2	9.4	9.4	23.6
Nominal weight full (kg)	2.5	2.5	3.9	6.5	78.0	12.0	17.0	39.0

Keynotes: (1) The indicated cylinders are for specialised applications and availability is restricted. (2) For domiciliary use only. * (inc valve) † White

Fig. 9.1 Medical cylinder data. Information is current and is UK specific. Reproduced with permission from BOC Medical, part of the BOC Group PLC. http://www.bochealthcare.co.uk/en/index.shtml

Nitrous Oxide* Standard valve

Cylinder code	AZ	C	D	E	F	G	J
Cylinder order code	298122-AZ	141-C	141-D	141-E	141-F	141-G	141-J
Nominal contents (litres)	450	450	900	1800	3600	9000	18000
Nominal cylinder pressure (bar)	44	44	44	44	44	44	44
Valve outlet connection	Pin-index	Pin-index	Pin-index	Pin-index	11/16"×20TPI(M)	11/16"×20TPI(M)	11/16"×20TPI(M)
Valve outlet specification	ISO 407	ISO 407	ISO 407	ISO 407	BS 341 No 13	BS 341 No 13	BS 341 No 13
Valve operation	key	key	key	key	handwheel	handwheel	handwheel
Dimensions* L×D (mm)	290×106	430×89	535×102	865×102	930×140	1320×178	1520×229
Water capacity (litres)	1.20	1.20	2.32	4.68	9.43	23.60	47.20
Nominal weight full (kg)	3.0	2.0	5.0	9.0	22.0	52.0	105.0

ENTONOX† (50% O_2/50% N_2O) Integral valve

Cylinder code	EA	ED	HX
Cylinder order code	211-EA	211-ED	211-HX
Nominal contents (litres)	350	700	2200
Nominal cylinder pressure (bar)	21	217	137
Nominal outlet pressure (bar)	4	4	4
Valve outlet pressure connection	Entonox Schrader (BS 5682)	Entonox Schrader (BS 5682)	Entonox Schrader (BS 5682)
Valve operation	handwheel	handwheel	handwheel
Flow-rate (litres/min)	Schrader: 40	Schrader: 40	Schrader: 40
Dimensions* L×D (mm)	366×85	520×100	940×140
Water capacity (litres)	1.00	2.00	10.00
Nominal weight full (kg)	2.4	4.0	19.0

ENTONOX† (50% O_2/50% N_2O) Standard valve

Cylinder order code	D	F	G
Nominal contents (litres)	211-D	211-F	211-G
Nominal cylinder pressure (bar)	500	2000	5000
Nominal outlet pressure (bar)	137	137	137
Valve outlet connection	Pin-index	Pin-index	Pin-index
Valve outlet specification	ISO 407	ISO 407 (side spindle)	ISO 407
Valve operation	key	key	key
Dimensions* L×D (mm)	535×102	930×140	1320×178
Water capacity (litres)	2.32	9.43	23.60
Nominal weight full (kg)	4.0	18.0	34.5

Helium‡ Standard valve

Cylinder code	F
Cylinder order code	163-F
Nominal contents (litres)	1200
Nominal cylinder pressure (bar)	137
Valve outlet connection	5/8" BSP(F)
Valve outlet specification	BS 341 No. 3 (Bullnose)
Valve operation	key
Dimensions* L×D (mm)	930×140
Water capacity (litres)	9.43
Nominal weight full (kg)	17.0

HELIOX21§ (79% He/21% O_2) Integral valve

Cylinder code	HX
Cylinder order code	173-HX
Nominal contents (litres)	1780
Nominal cylinder pressure (bar)	200
Nominal outlet pressure (bar)	4
Valve outlet flow connection	6mm firtree
Valve outlet pressure connection	Heliox Schrader (BS 5682)
Valve operation	handwheel
Flow-rate (litres/min)	Firtree: 1-15/Schrader: 40
Dimensions* L×D (mm)	940×140
Water capacity (litres)	10.0
Nominal weight full (kg)	15.5

Standard valve

Cylinder code	HL
Cylinder order code	173-HL
Nominal contents (litres)	8200
Nominal cylinder pressure (bar)	200
Nominal outlet pressure (bar)	4
Valve outlet connection	Side outlet
Valve outlet specification	ISO 5145 No. 26
Valve operation	handwheel
Dimensions* L×D (mm)	1540×230
Water capacity (litres)	50.0
Nominal weight full (kg)	85.0

* Blue; †Blue and white quarters; ‡Brown; §Brown and white quarters

Fig. 9.1 (*Contd.*)

Carbon Dioxide* Standard valve

Cylinder code	C	E	LF	VF
Cylinder order code	201-C	201-E	201-LF	201-VF
Nominal contents (litres)	450	1800	3600	3600
Nominal cylinder pressure (bar)	50	50	50	50
Valve outlet connection	Pin-index	Pin-index	0.860"×14TPI (M)	0.860"×14TPI (M)
Valve outlet specification	ISO 407	ISO 407	BS 341 No.8	BS 341 No.8
Valve operation	key	key	handwheel	handwheel
Dimensions* L×D (mm)	430×89	865×102	930×140	930×140
Water capacity (litres)	1.20	4.68	9.43	9.43
Nominal weight full (kg)	3.0	8.5	22.0	22.0

Air‡ Standard valve

Cylinder code	AZ	E	F	G	J
Cylinder order code	298123-AZ	191-E	191-F	191-G	191-J
Nominal contents (litres)	160	640	1280	3200	6400
Nominal cylinder pressure (bar)	137	137	137	137	137
Valve outlet connection	Pin-index	Pin-index	5/8" BSP (F)	5/8" BSP (F)	Pin-index
Valve outlet specification	ISO 407	ISO 407	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)	ISO 407 (side spindle)
Valve operation	key	key	key	key	key
Dimensions* L×D (mm)	290×106	865×102	930×140	1320×178	1520×229
Water capacity (litres)	1.2	4.7	9.4	23.6	47.2
Nominal weight full (kg)	2.5	6.5	17.0	39.0	78.0

Carbon Dioxide/Oxygen mixtures§

	(5% CO_2/95% O_2)		(10% CO_2/90% O_2)		(20% CO_2/80% O_2)	
Cylinder code	AV	L	AV	L	AV	L
Cylinder order code	299031-AV-PC	299031-L-PC	299032-AV-PC	299032-L-PC	299954-AV-PC	299033-L-PC
Nominal contents (litres)	1460	7300	1460	7300	1530	7650
Nominal cylinder pressure (bar)	137	137	137	137	137	137
Valve outlet connection	5/8" BSP (F) (Side Outlet)	5/8" BSP (F) (Side Outlet)	5/8" BSP (F) (Side Outlet)	5/8" BSP (F) (Side Outlet)	5/8" BSP (F) (Side Outlet)	5/8" BSP (F) (Side Outlet)
Valve outlet specification	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)
Valve operation	handwheel	handwheel	handwheel	handwheel	handwheel	handwheel
Dimensions* L×D (mm)	680×180	1540×230	680×180	1540×230	680×180	1540×230
Water capacity (litres)	10.0	50.0	10.0	50.0	10.0	50.0
Nominal weight full (kg)	19.0	85.0	19.0	86.0	19.0	87.0

Oxygen/Carbon Dioxide mixture† (95% O_2/5% CO_2)

Cylinder code	F	G	J
Cylinder order code	131-F	131-G	131-J
Nominal contents (litres)	1360	3400	6800
Nominal cylinder pressure (bar)	137	137	137
Valve outlet connection	5/8" BSP (F)	5/8" BSP (F)	5/8" BSP (F)
Valve outlet specification	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)
Valve operation	key	key	key
Dimensions* L×D (mm)	930×140	1320×178	1520×229
Water capacity (litres)	9.43	23.6	47.2
Nominal weight full (kg)	17.0	39.0	78.0

Lung Function mixtures Types 1-4§

Cylinder code	AV	AK
Cylinder order code	Various	Various
Nominal contents (litres)	1500	6000
Nominal cylinder pressure (bar)	150	150
Valve outlet connection	5/8" BSP (F) (LH) (Side Outlet)	5/8" BSP (F) (LH) (Side Outlet)
Valve outlet specification	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)
Valve operation	handwheel	handwheel
Dimensions* L×D (mm)	680×180	1540×230
Water capacity (litres)	10.0	40.0
Nominal weight full (kg)	18.0	59.0

* Grey; †Grey and white quarters; ‡Black and white quarters; §Green

Fig. 9.1 (*Contd.*)

Carbon Dioxide/Air mixture† (5% CO_2/95% Air)

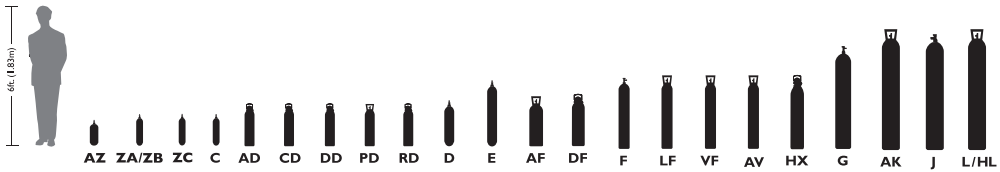
Cylinder code	AV	L
Cylinder order code	299034-AV-PC	299034-L-PC
Nominal contents (litres)	1350	6750
Nominal cylinder pressure (bar)	137	137
Valve outlet connection	5/8" BSP (F) (Side Outlet)	5/8" BSP (F) (Side Outlet)
Valve outlet specification	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)
Valve operation	handwheel	handwheel
Dimensions* L×D (mm)	680×180	1540×230
Water capacity (litres)	10.0	50.0
Nominal weight full (kg)	18.0	82.0

Helium/Oxygen/Nitrogen mixture† (56% N_2/35% O_2/9% He)

Cylinder code	AV	L
Cylinder order code	299035-AV-PC	299035-L-PC
Nominal contents (litres)	1310	6580
Nominal cylinder pressure (bar)	137	137
Valve outlet connection	5/8" BSP (F) (Side Outlet)	5/8" BSP (F) (Side Outlet)
Valve outlet specification	BS 341 No.3 (Bullnose)	BS 341 No.3 (Bullnose)
Valve operation	handwheel	handwheel
Dimensions* L×D (mm)	680×180	1540×230
Water capacity (litres)	10.0	50.0
Nominal weight full (kg)	18.0	81.0

*(inc valve) Green

Cylinder types



Valve types

Pin index types

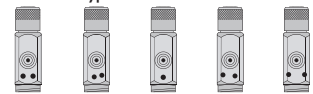


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Fig. 9.1 (*Contd.*)

Cylinder identification coding

Cylinders are made from either from steel or, more recently, aluminium wrapped with Kevlar. Each cylinder is marked with a specific colour for each gas type, according to standards BS1319C and ISO 32, and fitted with outlet valves of various types. The top of the cylinder has a tapered thread into which is permanently fitted a valve. The valve can be opened by a handwheel, thumbwheel, or special key. The gas outlet from this valve is connected to a pressure-reducing regulator, pressure gauge, and other devices, depending on the application.

Four main types of cylinder outlet valves are in use: bullnose, pin index, handwheel, and valve and side spindle pin-index valves. More recently, cylinders have been introduced that carry an integrated valve/regulator. These are also known as 'star valves' or 'combi-valves'.

The most important valve in use is the pin-index valve, which has a system of non-interchangeable valves designed to ensure that the correct gas is filled into the cylinder and that the cylinder can only be connected to the correct equipment.

Medical gas flowmeters

Medical O_2 and air flowmeters normally have differently calibrated flow tubes, but the fitting of the cylinder onto the regulator is the same. The Entonox cylinder is fitted with a demand valve, because administration depends on patient demand.

The cylinder labelling includes details of the following (Fig. 9.1).

- Product name, chemical symbol, and pharmaceutical form.
- Safety phrases.
- Cylinder size code.
- Nominal cylinder contents in litres.
- Maximum cylinder pressure in bars.
- Product shelf-life and expiry date.
- Reference to the medical gas data sheet (which details clinical indications, dosage schedules, and contraindications—ensure that you are aware of location of this information in the pharmacy).
- Storage and handling precautions.

At the pressures used, some gases liquefy within the cylinder and therefore behave differently during storage and delivery.

O_2 and Entonox remain gases, whereas nitrous oxide and carbon dioxide (CO_2) liquefy. The liquids will cool considerably during expansion and this can cause problems, although this drawback is put to good use in cryosurgery where nitrous oxide evaporation and expansion are used as the energy source. Entonox should not be stored below freezing point (0°C) because the mixture (50% nitrous oxide and 50% O_2) can separate.

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Guideline for oxygen use in adult patients

Oxygen has traditionally been used in hospitals in an uncontrolled manner, sometimes with inadequate monitoring. It is a treatment that should be used with discrimination and responsibility, as with any form of treatment.

Clinical indication, policy, and potential errors.

Additional inspired oxygen is used to improve oxygen delivery to the tissues, i.e. it is a treatment for hypoxaemia not breathlessness.

Each hospital should develop guidelines to ensure a requirement for oxygen to be prescribed according to a target saturation range and for those who administer oxygen therapy to monitor the patient and keep within the saturation target range.

Oxygen prescription

Oxygen should be prescribed to achieve a target saturation of 94–98% for the most acutely ill patients or 88–92% for those at risk of hyper-capnic respiratory failure.

Oxygen administration

Oxygen should be administered by staff who are trained in oxygen administration. These staff should use appropriate devices and flow rates in order to achieve the target saturation range.

Monitoring and maintenance of target saturation

Oxygen saturation and delivery system should be recorded on the patient's monitoring chart alongside the oximetry result. Oxygen delivery devices and flow rates should be adjusted to keep the oxygen saturation in the target range.

Oxygen should be signed for on the drug chart on each drug round.

Weaning and discontinuation

Oxygen should be reduced in stable patients with satisfactory oxygen saturation, assuming that corrective action has been undertaken to resolve the cause of hypoxaemia. Oxygen should be crossed off the drug chart once the decision has been taken to stop oxygen therapy.

Errors

- Patients with chronic ventilatory failure are sometimes given inappropriately high concentrations of oxygen, which results in worsening carbon dioxide retention and respiratory acidosis.
- Patients who are otherwise hypoxic, including those with acute ventilatory failure, are given unnecessarily low inspired oxygen concentrations.

Management of respiratory failure

Type 1 respiratory failure (hypoxia with normal $PaCO_2$)

- Occurs in a wide variety of patients with acute or chronic cardiac or respiratory disease.
- Hypoxia can be confirmed by measurements of oxygen saturation but arterial blood gas analysis is required to exclude CO_2 retention.
- The objective of treatment is to achieve normal levels of oxygenation.

Type 2 respiratory failure (hypoxia with elevated $PaCO_2$)

Acute ventilatory failure

- This occurs in most conditions resulting in acute respiratory distress—e.g. asthma, pulmonary oedema, pneumonia, etc.
- Hypoxia can be confirmed by measurements of oxygen saturation. Blood gas analysis is required to confirm acute ventilatory failure with an elevated $PaCO_2$, low pH, and normal bicarbonate (acute respiratory acidosis).
- The objective of treatment is to restore normal oxygenation. High concentrations of inspired oxygen are *not* contraindicated.
- There should be urgent assessment of the need for assisted ventilation.

Chronic ventilatory failure (± acute component)

- This should be suspected in a variety of situations including patients with chronic lung disease (COPD), neuromuscular disease, and skeletal disorders.
- It is confirmed on the basis of blood gas analysis, which shows an elevated $PaCO_2$, normal or reduced pH, and elevated bicarbonate.
- The objective is to achieve safe but not normal levels of oxygen. A PaO_2 of 6–8 or saturations of 80–90% are acceptable.
- Low concentrations of oxygen should be administered using a system working on the Venturi principle, which delivers precise concentrations of 24%, 28%, 31%, etc.
- If, in the chronic situation, nasal cannulae are used, oxygen saturation should be monitored to achieve saturation levels of ~85%.

Further reading

O'Driscoll BR *et al.* (2008). BTS guideline for emergency oxygen use in adult patients. *Thorax* **63** (Suppl vi): vi1–68.

Domiciliary oxygen therapy

Domiciliary oxygen therapy, of which there are three forms, is the administration of oxygen at concentrations greater than that available in room air (which is 21%). It is prescribed for the following reasons.

- To correct hypoxaemia—a deficiency of oxygen in arterial blood, leading to an arterial oxygen tension (PaO_2) ≤7.3kPa (normal values are 11.5–13.5kPa). Complications, if left untreated, include cor pulmonale, secondary polycythaemia, and pulmonary hypertension.
- To prevent hypoxia—a lack of oxygen in the tissues resulting in cell death.

Long-term oxygen therapy

There are several conditions which may lead to long-term oxygen therapy (LTOT) being prescribed to correct the chronic hypoxaemia which can result. Screening patients with the use of pulse oximetry is advisable for those with an underlying condition, with a referral for an LTOT assessment made if oxygen saturations fall below 92%. The LTOT assessment must include arterial blood gas analysis so that oxygen and carbon dioxide levels can be reviewed.

The assessment should take place during a period of clinical stability and therefore requires consideration in terms of timing as the treatment for the underlying condition needs to be reviewed and optimized. If an assessment is undertaken during an exacerbation of a condition, LTOT may be inappropriately indicated and subsequently prescribed.

Conditions that could result in chronic hypoxaemia include:

- COPD (the disease for which LTOT is most commonly prescribed)
- cystic fibrosis
- bronchiectasis
- interstitial lung disease
- pulmonary lung disease
- primary pulmonary hypertension
- pulmonary malignancy
- chronic heart failure.

Studies have shown improved exercise endurance in COPD patients breathing supplemental oxygen, with improved walking distance and ability to perform daily activities. Additional benefits of LTOT in COPD patients include reduction of secondary polycythaemia, improved sleep quality, and reduced sympathetic outflow, with increased sodium and water excretion, leading to improvement in renal function.[1–3]

1 Chapman S *et al.* (eds) (2005). Long-term oxygen therapy. *Oxford Handbook of Respiratory Therapy*, pp.632–5. Oxford: Oxford University Press.
2 National Clinical Guideline Centre (2010). *Chronic Obstructive Pulmonary Disease: Manage of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care*. London: National Clinical Guideline Centre (available online at: http://guidance.nice.org.uk/CG101/ Guidance/pdf/English I(accessed 1 June 2010).
3 Esmond G, Mikelsons C (2009). Oxygen therapy. *Non-invasive Respiratory Support Techniques: Oxygen Therapy, Non-invasive Ventilation and CPAP*, pp.47–88. Chichester: Wiley–Blackwell.

The term LTOT refers to the number of hours per day therapy is used rather than the number of years it is used for, although it is likely to be lifelong treatment once commenced. This form of therapy is based on two landmark trials conducted in the 1980s, in which the main outcome was improved survival in those patients receiving oxygen for at least 15h per day and an increase in 5-year survival and an overall improvement in quality of life.[4,5] For this to be achieved, the following is necessary.

- The daytime oxygen tension should be kept at or above 8kPa (the equivalent to an oxygen saturation (SpO_2) ≥92%.
- The equipment used to deliver LTOT is suitable to administer oxygen therapy for at least 15h per day.

When therapy is indicated, an oxygen concentrator is a more convenient and reliable way to supply LTOT than oxygen cylinders. This runs off the normal household electricity supply and does not require replenishing like an oxygen cylinder does. However, it requires yearly maintenance. This device draws in atmospheric/room air (consisting of approximately 78% nitrogen and 21% oxygen) and separates these gases through the use of zeolite, which captures nitrogen molecules, resulting in a continuous supply of oxygen in the home of up to a flow rate of ~5L/min. A back-up oxygen cylinder should be supplied to patients using an oxygen concentrator in case of emergencies such as mechanical breakdowns or an electricity supply failure.

Nasal cannulae, designed to deliver a typical low flow of oxygen at 1–4L/min, are more frequently used than facemasks to deliver oxygen to the patient because:

- they are less obvious and obtrusive
- communication is not hindered
- the patient is able to eat and drink while using oxygen.

NB: higher flows of oxygen (>4L/min) may cause the nasal passages to become dried out, resulting in inflammation, nosebleeds, and pain, which could affect adherence to treatment.)

Facemasks are seldom used in LTOT as they are often considered to act as a barrier to communication and need to be removed in order for the patient to eat and drink. However, there are circumstances which would warrant provision of a facemask. Such instances include the presence of a nasal defect or high flow rates not being tolerated via nasal cannulae. When a mask is used, the most appropriate is a fixed-concentration mask in the form of a Venturi mask which will deliver a more accurate concentration of oxygen. It is also advisable to provide the patient with nasal cannulae so that oxygen can continue to be delivered during periods of eating and drinking.

4 Nocturnal Oxygen Therapy Trial Group (1980). Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease: a clinical trial. *Annals of Internal Medicine* **93**: 391–8.

5 Medical Research Council (1981). Long term domiciliary oxygen therapy in hypoxemic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* **i**: 681–6.

Ambulatory oxygen therapy

Ambulatory oxygen therapy provides oxygen during exercise and activities of daily living for patients who have chronic hypoxaemia or exercise oxygen desaturation. It enables patients to leave home for a longer period of time to fulfil activities of daily living and improve their quality of life. Several factors need to be taken into account when deciding if a prescription of ambulatory oxygen is indicated. This may involve patients having to undertake a timed walking test or a shuttle walking test during assessment.

Patients suitable for this type of therapy can be divided into two main categories:

- those with PaO_2 ≤7.3 kPa (i.e. those patients already on LTOT) who are also mobile.
- Patients with PaO_2 of 7.3–8.0kPa who desaturate on exercise or show an improvement in exercise capacity or dyspnoea with oxygen.

Different types of equipment can be used to deliver ambulatory oxygen.

- Portable oxygen cylinders, of which there are four types available.
  - DD—a lightweight cylinder containing 460L of oxygen that lasts for 3h 50min at 2L/min.
  - F size—contains 1360L of oxygen and lasts approximately 11.5h at 2L/min.
  - PD—a smaller but heavier cylinder than the DD type which contains 300L of oxygen and lasts for 2.5h at 2L/min.
  - E size—a lightweight portable cylinder containing 600L of oxygen which lasts for 5h at 2L/min.

NB: the duration of use of the chosen cylinder may be increased by adding an oxygen-conserving device into the circuit, which ensures that oxygen is only delivered on inspiration.

- Liquid oxygen.
- Portable concentrator.

Apart from E size portable oxygen cylinders and portable concentrators, ambulatory oxygen equipment is available on the NHS.

Short-burst oxygen therapy

Short-burst oxygen therapy (SBOT) lasts for 10–15min at a time and is frequently given to patients with normal oxygen levels to alleviate breathlessness due to hypoxia after exercise. Some patients are noted to use a burst of oxygen prior to exertion, such as climbing the stairs.

SBOT is an expensive treatment, best provided by using one or more oxygen cylinders (usually F size) placed strategically round the house, with little published evidence to support its use. It is considered for patients with episodes of severe breathlessness due to hypoxia which is not relieved by other means, such as the use of oral morphine or benzodiazepines. This mode of therapy may also be used for palliation—e.g. terminal stages of lung cancer, which causes distressing shortness of breath, where some patients describe a subjective benefit in their breathlessness from using short bursts of oxygen during this time.

The practicalities of domiciliary oxygen therapy

- Patients needing domiciliary oxygen therapy should have stopped smoking before commencing therapy. Studies indicate that the benefit of such therapy, LTOT in particular, is limited in continued smokers, with an increased risk of fire.[1,3]
- The specialist home oxygen assessment services should be contacted when domiciliary oxygen is indicated for a patient. This service assesses, prescribes, reviews, and follows up patients requiring domiciliary oxygen in the UK. (Previously, oxygen was prescribed by a GP following recommendation from a respiratory physician.)
- These services are funded by the primary care trust (PCT), which can give details of who should be contacted if an assessment is needed.
- Once a patient has been assessed for domiciliary oxygen, a home oxygen order form (HOOF) is completed by the specialist oxygen assessment service for the provision of the correct form of domiciliary oxygen.
- The completed HOOF is faxed to the oxygen supplier, who then contacts the patient to arrange a date for installation. (Details of oxygen suppliers can be found on the primary care contracting website www.pcc.nhs.uk)
- Follow-up reviews of patients are carried out by the specialist home oxygen assessment service to ensure compliance and ongoing requirement for domiciliary oxygen.
- Patient education in the use and maintenance of long-term, ambulatory, or short-burst oxygen therapy and maintenance of equipment is important and requires the involvement of specialist respiratory nurses.

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Chapter 10

Patient management issues

Drug use in liver disease

Terminology used in liver disease is summarized in Table 10.1. The liver is the main site of drug metabolism and the principal location for CYP450 metabolism (see 📖 p.21). In most cases, metabolism leads to inactivation of the drug, although some drugs have active metabolites (e.g. morphine) or require metabolism to be activated (e.g. cyclophosphamide). Despite this, it is frequently unnecessary to modify the dose (or choice) of drug in liver disease because the liver has a large reserve of function, even if disease seems severe. However, special consideration of drugs and doses are required in the following situations:

- **Hepatotoxic drugs**—whether the hepatotoxicity is dose-related or idiosyncratic, these drugs are more likely to cause toxicity in patients with liver disease and so should be avoided if possible.
- **Protein binding**—the liver is the main source of synthesis of plasma proteins (e.g. albumin). As liver disease progresses, plasma protein levels fall. Thus, with less protein available for binding, there is more free drug available, which can lead to ↑ effects and toxicity, especially if the therapeutic index is narrow or the drug is normally highly protein bound (e.g. phenytoin). If albumin levels are significantly ↓, serum levels measured for TDM might have to be adjusted to give a corrected level.
- **Anticoagulants/drugs that cause bleeding**—the liver is the main source of synthesis of clotting factors and there is an ↑ risk of bleeding as liver function deteriorates. Anticoagulants should be avoided (and are rarely indicated because of the ↓ in clotting factors) and drugs that ↑ the risk of bleeding (e.g. NSAIDs, selective serotonin re-uptake inhibitors (SSRIs)) should be used with caution. Avoid intramuscular injections because there is a risk of haematoma.
- **Liver failure**—patients with clinical signs of liver failure (e.g. significantly deranged liver enzymes, ascites, or profound jaundice) usually have altered drug handling (Table 10.2). In addition, drugs that could worsen the condition should be avoided:
  - Hepatic encephalopathy could be precipitated by certain drugs. Avoid all sedative drugs (including opioid analgesics), drugs causing hypokalaemia (including loop and thiazide diuretics) and drugs causing constipation.
  - Oedema and ascites could be exacerbated by drugs that cause fluid retention (e.g. NSAIDs and corticosteroids). Drugs with high sodium content (e.g. soluble/effervescent formulations, some antacids and IV antibacterials) should also be avoided.

Table 10.1 Terminology in liver disease

Hepatocellular injury	Damage to the main cells of the liver (hepatocytes)
Hepatitis	Inflammation of the liver, a type of hepatocellular injury. Could be caused by viruses, drugs, or other agents, or could be idiosyncratic.
Cirrhosis	Chronic, irreversible damage to liver cells, usually caused by alcohol or hepatitis C. If the remaining cells cannot maintain normal liver function (compensated disease), ascites, jaundice, and encephalopathy can develop (decompensated disease).
Cholestasis	Reduction in bile production or bile flow through the bile ducts.
Liver failure	Severe hepatic dysfunction where compensatory mechanisms are no longer sufficient to maintain homeostasis. Could be acute and reversible, or irreversible (e.g. endstage cirrhosis).

Drug dosing in liver disease

The effects of liver disease, and consequent impairment of drug handling, are diverse and often unpredictable. Unlike renal disease, drug clearance does not ↓ in a linear fashion as liver function worsens. In addition, whereas in renal disease measuring creatinine clearance gives a good predictor of drug clearance, in liver disease there is no good clinical factor that predicts drug clearance and thus dose adjustment.

Impaired elimination is usually only seen in advanced liver disease. The following markers indicate significant impairment:

- ↓ albumin (↑ or ↓ in acute liver disease)
- ↑ prothrombin time
- ↑↑ liver function tests (LFTs).

The following four main factors affect drug clearance:

Hepatic blood flow

Hepatic blood flow might be altered in liver disease because of cirrhosis (fibrosis inhibits blood flow), hepatic venous outflow obstruction (Budd–Chiari syndrome), or portal vein thrombosis. Even in the absence of liver disease, hepatic blood flow might be ↓ in cardiac failure or if BP is massively ↓ (e.g. in shock).

The clearance of drugs that are highly metabolized by the liver (high-extraction/high-clearance drugs) is directly related to blood flow. When these drugs are administered orally, their first-pass metabolism is significantly ↓ (if hepatic blood flow is ↓) and so bioavailability ↑. Administration by non-enteral routes, especially IV administration, avoids the effect of first-pass metabolism and therefore bioavailability is unaffected. Thus the effect of liver impairment on the clearance of these drugs is fairly predictable, being directly related to hepatic blood flow.

Drugs that are poorly metabolized (low-extraction/low-clearance drugs) are unaffected by changes in hepatic blood flow. Clearance of these drugs is affected by a variety of other factors.

In both situations doses should be titrated according to clinical response and side effects (Table 10.2).

Decreased hepatic cell mass

Extensive liver cell damage can occur in both acute and chronic liver disease. High-extraction drugs are metabolized less efficiently and therefore doses should be ↓ because peak plasma levels are ↑. Low-extraction drugs will have ↓ systemic clearance, leading to delayed elimination. Thus the dose should remain the same but the dose interval should be ↑ (Table 10.2).

Table 10.2 High- and low-extraction drugs

High-extraction drugs

Dose at 10–50% normal for oral administration
Dose at 50% normal for IV administration
↑ dose interval in portal systemic shunting

- Clomethiazole
- Glyceryl trinitrate
- Lidocaine
- Metoprolol
- Morphine
- Pethidine
- Propranolol
- Verapamil

Low-extraction drugs

Dose at 50% normal (all routes)
↑ dose interval

- Ampicillin
- Atenolol
- Chloramphenicol
- Chlordiazepoxide
- Cimetidine
- Diazepam
- Digoxin
- Furosemide
- Lorazepam
- Naproxen
- Prednisolone
- Spironolactone
- Tolbutamide
- Warfarin

Portal systemic shunting

If cirrhosis or portal hypertension is present, a collateral venous circulation, which bypasses the liver, could develop. This means that drugs absorbed by the GI tract might enter the systemic circulation directly. Thus there is minimal first-pass metabolism of high-extraction drugs and peak concentrations are ↑. The half-life of both high- and low-extraction drugs is prolonged, and so the dose interval should be ↑.

Cholestasis

In cholestasis, substances that are normally eliminated by the biliary system accumulate. This includes some drugs that are eliminated by bile salts (e.g. rifampicin and sodium fusidate). Because lipid absorption depends on

bile salt production, it is theoretically possible that there is a ↓ in absorption of lipid-soluble drugs. In cholestasis, bile salts accumulate in the blood. This could ↑ bioavailability of protein-bound drugs because of competition for binding sites.

Analgesia in liver failure

The choice of analgesic drug in liver failure is problematic because both NSAIDs and opioids are contraindicated. The analgesic of choice is paracetamol because hepatotoxicity only occurs in overdose, when glutathione is saturated. In liver failure, glutathione production is maintained. It is advisable to avoid maximum daily doses of paracetamol because this can ↑ prothrombin time.

Further reading/information

Remington H *et al.* (1992). Drug choice in patients with liver disease. *Pharmaceutical Journal*, **248**: 845–8.
Cavell G (1993). Drug handling in liver disease. *Pharmaceutical Journal*, **250**: 352–5.
Summaries of product characteristics.
Leeds Medicines Information Centre.
General guidelines for prescribing in liver disease are given in Table 10.3.

Table 10.3 General guidelines for prescribing in liver disease

- Avoid hepatotoxic drugs (note that many herbal medicines/adulterants are potentially hepatotoxic)
- Use renally cleared drugs preferentially
- Monitor closely for side effects of hepatically cleared drugs
- Avoid drugs that ↑ the risk of bleeding
- Avoid sedating drugs if there is a risk of encephalopathy
- Avoid constipating drugs if there is a risk of encephalopathy
- In moderate or severe liver impairment consider the following options:
  - ↓ dose of highly metabolized drugs
  - ↑ dose interval for all hepatically cleared drugs
- If albumin levels are low, consider ↓ the dose of highly protein-bound drugs
- Drugs that affect electrolyte balance should be used cautiously and monitored carefully
- In preference, use older well-established drugs if there is experience of use in liver impairment
- Start with the lowest possible dose and ↑ cautiously, according to response or side effects

Hepatorenal syndrome (HRS)

HRS is defined as the development of unexplained renal impairment in patients with severe liver disease. The kidneys are morphologically normal and recover if liver function recovers (e.g. following liver transplantation). However, the condition has a poor prognosis, with a mortality of 95% and mean survival of <2wks. A suggested treatment regime is shown in Table 10.4.

HRS seems to be caused by ↓ renal blood flow and perfusion consequent to the circulatory changes associated with severe liver impairment. It is characterized by oliguria, hyponatraemia, and uraemia.

Management

- Maintain renal perfusion.
  - Correct hypovolaemia—human albumin solution 4.5% is preferred (avoid glucose 5% solution because it exacerbates hyponatraemia).
  - Maintain BP—if necessary using pressor agents. Terlipressin has been used to ↑ BP, but this is an unlicensed indication.
- Investigate and correct other causes of renal failure.
  - Stop diuretics and all potentially nephrotoxic drugs.
  - Start empirical broad-spectrum antibacterials, investigate possible septic focus, and perform blood cultures.
  - Avoid paracentesis without colloid cover.
- Institute renal replacement therapy.
  - Because of the poor prognosis, the decision to institute dialysis should not be taken lightly and only instituted if other organs are functioning well.
  - Continuous haemodialysis/filtration is required because intermittent therapy can lead to significant disturbance of haemodynamics and intracranial pressure.
  - Renal replacement therapy is usually necessary until liver function improves.
  - Molecular adsorbent recirculating system (MARS) is a form of dialysis that removes albumin-bound toxins. Early studies have shown improved survival versus haemofiltration.
- Liver transplantation is the only treatment shown to significantly improve survival, but it is usually inappropriate by the time HRS is established.

Table 10.4 Suggested treatment regimen for HRS

Day 1	Terlipressin 0.5mg IV twice daily
	Albumin 1g/kg body weight
Days 2–5	Albumin 20g/daily
	If no fall in serum creatinine after 48h, ↑ terlipressin dose to 1mg four times daily

Drugs in renal impairment

Patients with renal impairment (who frequently include elderly patients) can experience various problems with drug use and dosing. In addition to the obvious problem of ↓ excretion and thus ↑ toxicity, considerations are as follows.

- Pharmacokinetics of some drugs can be altered, including altered distribution and protein binding.
- Sensitivity to some drugs is ↑, although excretion is not impaired.
- Side effects may be tolerated less well by renally impaired patients.
- Some drugs (notably those that rely on urinary excretion for effect) can be ineffective if renal function is impaired.

This section mainly concentrates on the problem of ↓ excretion because this is what most pharmacists come across in their daily work. For additional information, consult the texts in the 📖 'Further reading' section, p.189.

Distribution

Oedema/ascites could ↑ the volume of distribution of highly water-soluble drugs, so an ↑ dose might be required. Conversely, dehydration or muscle wasting can lead to a ↓ volume of distribution, thereby requiring a ↓ dose.

In uraemic patients, plasma protein binding might be ↓, leading to ↑ levels of free drug but a shorter half-life. This might be significant for drugs with a narrow therapeutic index. In some instances, it is necessary to make compensatory adjustments when assessing plasma levels of certain drugs (e.g. phenytoin).

Metabolism

There are only two clinically significant examples of drug metabolism being affected by renal impairment.

- Insulin is metabolized in the kidney and thus ↓ doses might be required.
- Conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (i.e. active vitamin D; calcitriol) takes place in the kidney. This process might be inhibited in renal impairment. Thus patients with renal failure might require supplementation with α-calcidol or calcitriol.

Excretion

This is the most significant effect because ↑ renal impairment leads to ↓ clearance and the potential for drug toxicity. This includes not only the original drug, but also toxic or active metabolites (e.g. morphine).

Assessing renal function

Renal function is assessed by measuring the glomerular filtration rate (GFR). An estimate of the GFR can be gained by measuring or calculating the creatinine clearance rate. Creatinine is a byproduct of muscle metabolism and is excreted by glomerular filtration. Provided that muscle mass is stable, any change in plasma creatinine levels is directly related to GFR. Thus, measuring the rate of creatinine clearance gives an estimate of GFR.

Measuring creatinine clearance requires 24h urine collection (i.e. all of the patient's urine during a 24h period must be collected). The concentration of creatinine in the urine and total volume of urine is measured to establish the creatinine clearance. This process is inconvenient, involving a delay of ≥24h in obtaining results. A reasonable estimate of the rate of creatinine

clearance can be achieved using the Cockroft and Gault equation (Table 10.5). This equation takes into account the fact that muscle mass (and therefore serum creatinine levels) vary according to gender and weight.

Calculating the rate of creatinine clearance in this way gives a better estimate than simply using serum creatinine, but it is not exact and tends to under- or overestimate the rate by up to 20%. Ideal body weight should be used in obese or fluid-overloaded patients. The equation is particularly inaccurate in pregnant women, children, and patients with marked catabolism or rapidly changing renal function. For children a more accurate creatinine clearance can be calculated (Table 10.5).

Remember that elderly patients nearly always have some degree of renal impairment because of the normal ageing process. Despite its limitations, the Cockroft and Gault equation is extremely useful for assessing renal impairment in this setting and is preferable to using serum creatinine alone. For example, a serum creatinine of 120micromol/L might be normal in a fit young man but could represent significant renal impairment in a frail elderly woman.

Table 10.5 Calculating creatinine clearance

Adults

Cockroft and Gault equation:[1]

$$\text{Creatinine clearance}\,(\text{mL/min}) = \frac{F(140 - \text{age}) \times \text{weight}\,(\text{kg})}{\text{serum creatinine}\,(\text{micromil/L})}$$

where F = 1.04 in females and 1.23 in males.

Use IBW in obese or fluid-overloaded patients.

Modification of Diet in Renal Disease[2] (= eGFR)

$$\text{eGFR}\,(\text{mL/min/1.73m}^2) = 32788 \times \text{serum creatinine}\,(\text{micromol/L})^{-1.154} \times \text{age}^{-0.203} \times X \times Y$$

where X = 1.212 (if African American) and Y = 0.742 (if female)

Children[3]

$$\text{Estimated creatinine clearance}\left(\text{mL/min/1.73m}^2\right) = \frac{40 \times \text{height}\,(\text{cm})}{\text{serum creatinine}\,(\text{micromol/L})}$$

Neonates[4]

$$\text{Estimated creatinine clearance}\left(\text{mL/min/1.73m}^2\right) = \frac{30 \times \text{length}\,(\text{cm})}{\text{serum creatinine}\,(\text{micromol/L})}$$

[1] Cockcroft DW, Gault MH (1976). "Prediction of creatinine clearance from serum creatinine". *Nephron*, **16**(1): 31–41.

[2] Levey AS *et al.* (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Annals of Internal Medicine*, **130**: 461–70.

[3] Morris MC *et al.* (1982). Evaluation of a height/plasma creatinine formula in the measurement of glomerular filtration rate. *Archives of Diseases in Children*, **57**: 611–15.

[4] Schwartz GJ *et al.* (1984). A simple estimate of glomerular filtration rate in full term infants during the first year of life. *Journal of Paediatrics*, **104**: 849–54.

Normal creatinine clearance in adults is ~80–120mL/min (for infants and children, see Table 10.6). In the UK, the following ranges of GFR are considered to represent various degrees of renal impairment:

- mild, 50–20mL/min
- moderate, 20–10mL/min
- severe, <10mL/min.

An alternative method of estimating GFR is to use the Modification of Diet in Renal Disease (MDRD) equation, which is often quoted as estimated GFR (eGFR). This equation is more reliable than the Cockroft and Gault equation for patients with unstable renal function or acute renal failure. However, it quotes the GFR for a standard body surface area (i.e. mL/min/1.73m^2) and so it is unsuitable for patients at extremes of body weight or amputees. It is also unsuitable for certain ethnic groups. Some laboratories are now quoting eGFR in addition to serum creatinine when reporting renal function. This is appropriate in terms of giving a better indication than serum creatinine of whether the patient has any degree of renal impairment. However, most drug dosing recommendations are based on GFR not eGFR, and in this respect calculating the creatinine clearance using the Cockroft and Gault equation gives a better estimate.

Dose adjustment in renal failure

The kidney is involved in the elimination of most drugs, either in their active/unchanged form or as their metabolites, although for some drugs this might be only a very small proportion of the dose. Drugs for which the kidney is a major site of elimination usually require dosage adjustment to avoid accumulation and thus toxicity. Remember that some of these drugs might also be nephrotoxic and drug accumulation can make renal impairment worse.

In patients with mild renal impairment it might only be necessary to monitor closely for side effects, with or without further deterioration in kidney function. However, in moderate or severe renal impairment an alternative drug should be used if possible. The ideal drug in renal failure would have the following attributes:

- <25% excreted unchanged in the urine.
- No active/toxic metabolites.
- Levels/activity minimally affected by fluid balance or protein-binding changes.
- Wide therapeutic margin.
- Not nephrotoxic.

Unfortunately, it is frequently not possible to find a suitable drug that fits these criteria, in which case dose adjustment is usually necessary. Two methods of dose reduction are used, either alone or in combination.

- Give a smaller dose at the same dose interval.
- Give the same dose at a longer dose interval.

It is possible to calculate a corrected dose/dose interval, but a more practical option is to use drug-dosing guidelines. The reader is referred to the sources on 📖 p.205.

Renal impairment prolongs the half-life of any drug excreted by the kidney. The time to steady-state concentration is ~5 times the half-life.

Thus, just as in patients with normal renal function, a loading dose might be needed if an immediate effect is required. This is especially true if the dose interval has been ↑. The loading dose in patients with renal impairment is the same as in patients with normal renal function.

Certain drugs should always be checked if there is any suspicion of renal impairment (Table 10.7). In many instances, not only are these drugs primarily excreted by the kidneys, but some are also potentially nephrotoxic, such that accumulation could lead to further renal impairment. In addition, side effects caused by accumulation might be mistaken for disease deterioration, and the pharmacist should be alert to this and advise medical staff accordingly. Wherever possible, avoid using potentially nephrotoxic drugs in patients with renal impairment.

Remember that renal function might improve or further deteriorate according to the patient's condition and, consequently, doses may need to be readjusted accordingly.

Table 10.6 Normal creatinine clearances in infants and children

Age	Creatinine clearance (mL/min/1.73m^2)
<37wks gestation	<25
Neonate	15–35
1–2wks	35–60
2–4 months	60–80
6–12 months	80–110
12 months to adult	85–150

Table 10.7 Checklist of drugs requiring dose adjustment in renal impairment

Commonly used drugs for which dose reduction is always necessary in moderate or severe renal imirment*

- Aciclovir
- Aminoglycosides
- Capecitabine
- Cisplatin
- Imipenem
- Meropenem
- Methotrexate
- Penicillin
- Thiazide diuretics
- Vancomycin

Commonly used drugs for which dose reduction should be considered in moderate or severe renal impairment*

- Allopurinol
- Amoxicillin
- Cephalosporins
- Cyclophosphamide
- Flucloxacillin
- Digoxin
- Ethambutol
- Furosemide
- Lomustine
- Melphalan
- Opioids
- Quinolones
- Sulphonamides (including co-trimoxazole)

* These lists are not comprehensive—check specialist references (📖 p.205) for further information.

Drug dosing in renal replacement therapies

Renal replacement therapies are used in patients with chronic renal failure whose renal function is so poor that the kidneys are barely functioning. They can also be used temporarily in patients with acute renal failure. There are four types of renal replacement therapy in common use.

- Intermittent haemodialysis (HD).
- Continuous ambulatory peritoneal dialysis (CAPD).
- Continuous arteriovenous haemodialysis (CAVD).
- Continuous arteriovenous haemofiltration (CAVH).

Each method works on the principle of removing toxins from the blood by diffusion or osmosis across a semipermeable membrane into a dialysis solution. Therefore the factors that affect drug removal are much the same for HD, CAPD and CAVD. CAVH is a slightly different technique and is influenced by slightly different factors.

Dialysis-related factors

The following factors influence drug removal by dialysis or filtration:

- duration of dialysis
- blood flow rate in dialyser
- type of dialyser membrane
- flow rate and composition of dialysate.

However, these characteristics are difficult to quantify and therefore it is hard to predict exactly what effect they will have on drug removal. In CAPD, frequent exchanges (e.g. every 1–4h) ↑ drug clearance.

Drug-related factors

It is possible to judge whether or not a drug will be significantly cleared by dialysis according to the pharmacokinetic parameters. Factors that favour drug removal are as follows.

- Low molecular weight—removal ↑ as molecular weight falls below 500 Da.
- Low protein binding (<20%).
- Low volume of distribution (<1L/kg).
- High water solubility.
- High degree of renal clearance in normal renal function.

The exception is CAVH, where molecules with a higher molecular weight (up to that of insulin) are preferentially removed, but there is less removal of smaller molecules (e.g. K^+ and urea).

Drug dosing in renal replacement therapies

Accurately quantifying drug clearance during renal replacement therapies is of limited value. The equations tend to assume constant conditions, but in practice both patient and dialysis conditions can vary. For example, the patient's clinical status (e.g. BP or renal function) could change, which has an effect on drug clearance. In CAPD, peritonitis affects peritoneal permeability and thus clearance.

The most practical approach is to use empirical dosing according to theoretical GFR achieved by the dialysis technique used (Table 10.8). This should be backed up by close monitoring for drug response and toxicity, including TDM.

In patients receiving HD, drugs should be given after the dialysis session to avoid the possibility that the drug might be removed before it has time to act. Because CAVH and CAVD are continuous processes, doses do not need to be scheduled around dialysis sessions. The same is true for CAPD, but the dose might need to be titrated up or down if the frequency of exchanges is ↑ or ↓.

Table 10.8 Theoretical GFR in renal replacement therapy

Renal replacement therapy		Typical theoretical GFR achieved (mL/min)
HD	During dialysis Between dialysis periods	150–160 0–10
CAVD		15–20
CAVH		10
CAPD (4 exchanges daily)		5–10

Further reading

Ashley C, Currie A (eds) (2008). *The Renal Drug Handbook* (3rd edn). Abingdon: Radcliffe Medical Press.

Aronoff GR *et al.* (2007). *Drug Prescribing in Renal Failure* (5th edn). Philadelphia, PA: American College of Physicians.

Summaries of Product Characteristics.

South West Medicines Information Centre.

Drugs in pregnancy

A drug is defined as teratogenic if it crosses the placenta, causing congenital malformations. Teratogenic effects usually only occur when the fetus is exposed during a critical period of development. Even then, not all fetuses exposed will be affected—e.g. <50% of fetuses exposed to thalidomide developed congenital abnormalities.

Various textbooks and reference sources (see 📖 p.193) give information on using drugs in pregnancy (Tables 10.9 and 10.10), but these sources do not always take into account all the relevant factors when assessing risk. To fully evaluate the risk/benefit of a drug in pregnancy, the following factors should be taken into account.

Other possible causes

- ≤10% of pregnancies result in an 'abnormal' outcome (including miscarriage and stillbirth), of which only 2–3% are caused by drugs or environmental factors.
- Maternal morbidity or an acute exacerbation/relapse of the disease could present a higher risk to the fetus than the drug.
- The underlying maternal disease might be associated with congenital abnormalities (e.g. epilepsy).
- Smoking and alcohol use during pregnancy can lead to congenital abnormalities, growth retardation, and spontaneous abortion.

Drug characteristics

- Most drugs cross the placenta.
- High molecular weight drugs do not cross the placenta—e.g. heparin and insulin.
- Non-ionized lipophilic drugs (e.g. labetalol) cross the placenta to a greater extent than ionized hydrophilic drugs (e.g. atenolol).
- A drug can cause fetal toxicity without crossing the placenta—e.g. any drug that causes vasoconstriction of the placental vasculature.

Timing

- If the drug is taken during the first 12 days (pre-embryonic phase), there is an 'all or nothing' effect—i.e. if most cells are affected, this leads to spontaneous miscarriage, and if a few cells are affected, this leads to cell repair/replacement and a normal fetus.
- Exposure during the first trimester (especially weeks 3–11) carries the greatest risk of congenital abnormalities.
- During the second or third trimester the main risks are growth defects or functional loss, rather than gross structural abnormalities. However, cerebral cortex and renal glomeruli continue to develop and are still susceptible to damage.
- Shortly before or during labour there is a risk of maternal complications (e.g. NSAIDs and maternal bleeding) or neonate complications (e.g. opioids and sedation).

Table 10.9 Some drugs that should be avoided* in pregnancy[1]

Drugs known to cause congenital malformations

- Anticonvulsants
- Cytotoxics
- Danazol
- Lithium
- Retinoids (systemic)
- Warfarin

Drugs that can affect fetal growth and development

- ACE inhibitors (after 12wks)—fetal or neonatal renal failure
- Barbiturates, benzodiazepines, and opioids (near term)—drug dependence in fetus
- NSAIDs (after 12wks)—premature closure of ductus arteriosus
- Tetracyclines (after 12wks)—abnormalities of teeth and bone
- Warfarin—fetal or neonatal haemorrhage

* Note that if the benefit clearly outweighs the risk (e.g. life-threatening or pregnancy-threatening disease), these drugs can be used in pregnancy.

[1] Welsh Medicines Resources Bulletin (2000) **7**: 1–5.

Table 10.10 Some drugs that have a good safety record in pregnancy

- Analgesics: codeine (caution near term) and paracetamol
- Antacids containing aluminium, calcium, or magnesium
- Antibacterials: penicillins, cephalosporins, erythromycin, clindamycin, and nitrofurantoin (avoid near term)
- Anti emetics: cyclizine and promethazine
- Antifungal agents (topical and vaginal): clotrimazole and nystatin
- Antihistamines: chlorphenamine and hydroxyzine
- Asthma: bronchodilator and steroid inhalers (avoid high doses in the long term), and short-course oral steroids
- Corticosteroids (topical, including nasal and eye drops)
- Insulin
- Laxatives: bulk-forming and lactulose
- Levothyroxine
- Methyldopa
- Ranitidine

Other considerations

- The presence or absence of teratogenic effects in animals does not necessarily translate to the same effects in humans. Think logically—if the agent causes tail shortening in rats, is this relevant in humans? Some studies use higher doses in animals than would be used in humans.
- Drugs associated with abnormalities at high doses/during the first trimester might be lower risk at low doses/during the second or third trimester (e.g. fluconazole).
- If treatment cannot be avoided during pregnancy, in preference use established drugs that have good evidence of safety. (NB: sometimes a lack of reports of teratogenicity for a well-established/frequently used drug may have to be taken as evidence of safety.)
- Some teratogenic effects are dose-related (e.g. neural tube defects with anticonvulsants). Higher doses or combining more than one drug with the same effect will ↑ the risk.
- Consider non-drug treatments (e.g. acupressure wrist bands for morning sickness) or whether treatment can be delayed until after pregnancy.

Maternal considerations

- Maternal drug-handling changes during pregnancy. Take special care with drugs that have a narrow therapeutic index.
- Remind the mother that some over-the-counter, herbal, and vitamin products should be avoided in pregnancy.
- Many women do not comply with drug treatment during pregnancy because of safety concerns, so discuss this with the mother and reassure her.

Handling potentially teratogenic drugs

There is little published evidence on whether occupational exposure to potentially teratogenic drugs can ↑ the risk of congenital abnormalities. In the absence of evidence or specific guidelines, sensible precautions should be taken to reduce the risk of exposure, especially by pregnant ♀ and ♀ planning a pregnancy. A risk assessment should be performed (using COSHH (Control of Substances Hazardous to Health) data as appropriate), and pregnant ♀ should be excluded from any task that poses even a low risk.

Handling blister-packed versions of a teratogenic tablet presents (virtually) no risk and film-coated or sugar-coated versions present a low risk. A high-risk procedure might involve preparation of cytotoxic infusions or handling crushed tablets of a known teratogenic drug. This type of procedure should not be carried out by pregnant ♀. ♀ (and ♂) of child-bearing potential (especially if planning a pregnancy) should take appropriate precautions (e.g. apron, mask, and gloves). Ideally, potentially teratogenic infusions should be prepared by centralized pharmacy reconstitution service, where the use of cytotoxic cabinets further ↓ the risk of exposure.

Further reading

Briggs GG, Freeman RK, Yaffe SJ (eds) (2008). *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk* (8th edn). Philadelphia, PA: Lippincott–Williams and Wilkins.
Folb PL, Dukes MNG (eds) (1990). *Drug Safety in Pregnancy*. Amsterdam: Elsevier.
Lee A, Inch S, Finnigen D (eds) (2000). *Therapeutics in Pregnancy and Lactation*. Abingdon: Radcliffe Medical Press.
Wolfson Unit Regional Drugs and Therapeutics Centre (Newcastle).
Toxbase drug monographs, including pregnancy risk (password required). www.toxbase.org.
www.motherisk.org.

Drugs in breastfeeding

Breastfeeding has many advantages over bottle feeding. Even if the mother is taking a drug that is excreted in breast milk it can be preferable to continue breastfeeding. General principles to ↓ risk to babies are listed in Table 10.11.

The main questions to consider are as follows.

- Is the drug excreted into breast milk in quantities that are clinically significant?
- Do these drug levels pose any threat to the infant's health?

To answer these questions, the following factors must be considered.

Factors that affect drug transfer into breast milk

- **Maternal drug plasma level**—usually the most important determinant of breast milk drug levels. Drugs enter the breast milk primarily by diffusion. For most drugs, the level in the maternal drug compartment is directly proportional to the maternal plasma level. Thus, the higher the maternal dose, the higher is the drug level in the breast milk. Diffusion of drug between plasma and milk is a two-way process and is concentration dependent. At peak maternal plasma levels (T_{max}) drug levels in breast milk are also at their highest. As the level of the drug in the plasma falls, the level of the drug in breast milk also falls as drug diffuses from the milk back into the plasma. Thus drugs that only have a short half-life only appear in breast milk for a correspondingly short time.
  - During the first 4 days after delivery, drugs diffuse more readily into the breast milk because there are gaps between the alveolar cell walls in mammary capillaries. These gaps permit enhanced access for most drugs, in addition to immunoglobulins and maternal proteins. This results in ↑ drug levels in breast milk during the neonatal stage. After the first 4–7 days, these gaps close.
  - Some drugs pass into breast milk by an active process, such that the drug is concentrated in the milk. This occurs with iodides, especially radioactive iodides, making it necessary to interrupt breastfeeding.
- **Lipid solubility of the drug**—Fat-soluble drugs (e.g. benzodiazepines, chlorpromazine, and many other CNS-active drugs) preferentially dissolve in the lipid globules of breast milk. As a general rule, ↑ lipid solubility leads to ↑ penetration into milk. However, lipid solubility is not a good predictor of milk levels overall because fat represents a relatively small proportion of total milk volume.
- **Milk pH levels**—Breast milk has a lower pH than blood. Thus drugs that are weak bases (e.g. isoniazid and atropine-like drugs) are ionized in milk, which makes them more water-soluble and thus less likely to diffuse back into the plasma. This can lead to accumulation of these drugs in breast milk. Conversely, weakly acidic drugs (e.g. penicillins, aspirin, and diuretics) tend not to accumulate in breast milk.

Table 10.11 General principles to ↓ risk to breastfed babies

- Consider whether non-drug therapy is possible
- Can treatment be delayed until the mother is no longer breastfeeding or the infant is older and can tolerate the drug better?
- Use drugs where safety in breastfeeding has been established
- Keep the maternal dose as low as possible
- In preference, use drugs with a local effect (e.g. inhalers, creams, or drugs not absorbed orally, such as nystatin)
- Use drugs with a short half-life and avoid sustained-release preparations
- Avoid polypharmacy—additive side effects and drug interactions potentially ↑ the risk
- Advise the mother to breastfeed when the level of the drug in breast milk will be lowest. This is usually just before the next dose is due

- **Molecular size/molecular weight of the drug**—As a general rule, 'bulky' drugs do not diffuse across capillary walls because the molecules are simply too large to pass through the gaps.
- **Drug protein binding**—highly protein-bound drugs (e.g. phenytoin and warfarin) do not normally pass into breast milk in significant quantities because only free unbound drug diffuses across the capillary walls. Bear in mind that if a new drug is added that displaces the first drug from protein-binding sites, this could (at least temporarily) ↑ milk levels of the first drug.

Infant factors

- **Bioavailabilty**—drugs that are broken down in the gut or are not absorbed orally (e.g. insulin and aminoglycosides) should not cause any adverse effect because the infant's absorption of the drug is negligible, if any. Similarly, infant serum levels of any drug that has high first-pass metabolism are likely to be low. However, these drugs can sometimes have a local effect on the infant's gut, causing GI symptoms such as diarrhoea.
- **Infant status** must be taken into account. If the baby is premature or sick, they might be less able to tolerate even small quantities of the drug. Consider whether drug side effects could exacerbate the infant's underlying disease. For example, opioids in breast milk may be a higher risk for a baby with respiratory problems than for a healthy baby.
- **Metabolism and excretion** of some drugs is altered in infancy, especially in premature infants who might have impaired renal and hepatic function. Thus the drug effects can be greater than expected because the clearance of the drug is ↓. This can be especially marked for drugs with a long half-life.
- **Drugs that are often administered to infants** (e.g. paracetamol) are generally safe if absorbed in breast milk. As a general rule, <1% of the maternal dose reaches the infant. Thus, if the normal infant dose is >1% of the maternal dose, it is usually safe, but side effects can still occur (e.g. antibiotic-induced diarrhoea).

Other factors to consider

- Some mothers and healthcare workers assume that because the infant was exposed to the drug during pregnancy, it will be safe in breast-feeding. However, in pregnancy it is the maternal organs that clear the drug from the infant's circulation, but during breastfeeding the infant is clearing the drug. In addition, some adverse effects, such as respiratory depression, are not relevant during pregnancy but become relevant after delivery.
- Some mothers are resistant to using conventional medicines during breastfeeding because of perceived risks and decide to use alternative therapies. Mothers should be reminded that herbal or homeopathic medicines might be excreted in breast milk and cause adverse effects on the infant.
- Remember also to advise mothers that over-the-counter medicines, alcohol, and other recreational drugs may be excreted in breast milk.
- Some drugs can inhibit or even stop breast milk production. These includes bromocriptine and other dopamine agonists, diuretics, and moderate to heavy alcohol intake. Drugs that ↑ breast milk production (e.g. chlorpromazine, haloperidol, and other dopamine antagonists) may lead to concern from the mother that the baby is not taking the full amount.
- Sometimes breastfeeding might have to be interrupted or stopped completely if there is no alternative to administering a potentially risky drug. For short courses, it might be possible to stop breastfeeding temporarily. Using a breast pump and discarding the expressed milk until such time as it is safe to resume breastfeeding should encourage continued breast milk production. Some mothers might find bottle feeding difficult because of the more complex processes involved, cost, or cultural issues and might need extra support.

Further reading/information

Briggs GG, Freeman RK, Yaffe SJ (eds) (2005). *Drugs in Pregnancy and Lactation* (6th edn). Philadelphia, PA: Lippincott—Williams & Wilkins.

Hale TW (ed) (2004). *Medications and Mother's Milk*. Amarillo, TX: Pharmasoft Medical Publishing.

Lee A, Incha S, Finnigan D (eds) (2005). *Therapeutics in Pregnancy and Lactation*. Abingdon: Radcliffe Medical Press.

Trent and West Midlands Medicines Information Centre.

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Drugs and dietary considerations

Dietary considerations may impact on drug therapy in various ways. In addition to drug–food interactions (see 📖 pp.20–1), food allergies or intolerances and cultural or religious dietary restrictions may have an impact on choice of drug therapy.

Food allergy or intolerance

Food and drink allergy is reported to affect 5% of children and 3–4% of adults in Westernized countries. It is important to distinguish between a true food allergy (i.e. symptoms of hypersensitivity occur after ingestion of the food) or intolerance (e.g. proven gluten intolerance) and a perceived food intolerance and consequent food exclusion on the part of the patient.

The most common food allergens in adults and children are:

- peanuts and other nuts
- wheat
- eggs
- milk
- soy
- fish and shellfish
- colouring agents.

In these instances a true hypersensitivity reaction, ranging from rash to anaphylaxis, could occur as a result of exposure to the allergen even in the extremely small quantities that might be present as excipients to the drug. Nut allergy is often potentially serious, with anaphylaxis being a risk. Some people will be so sensitive to nuts (especially peanuts) that topical exposure can lead to anaphylaxis. Pharmacists need to be aware that topical agents may contain nut oils, notably arachis (i.e. peanut) oil and sesame seed oil (to which there is often cross-sensitivity).

Food and drink intolerance can vary in severity, but exposure to the offending agent in a drug may lead to symptoms in some patients. Typical examples are:

- gluten (wheat, rye, barley, oats)
- lactose.

Pharmacists need to be aware of the possibility of food allergy or intolerance in their patients and should include questioning regarding this when taking a drug history. Listing drugs which may contain food allergens is beyond the scope of this section. If a patient reports significant symptoms as a result of exposure to a food or drink substance, pharmacists should check whether any new drugs contain the offending agent. This information can frequently be found in the summary of product characteristics (SPC), or contact the manufacturer for advice.

Egg allergy is often a cause for concern with vaccinations as some vaccines are derived from egg culture. The UK Department of Health advises that a history of hypersensitivity to eggs contraindicates influenza vaccine, and that a history of anaphylaxis to eggs contraindicates influenza and yellow fever vaccines. All other vaccines, including MMR (but check SPC as brand specific) are considered safe.

Cultural or religious considerations

Some drugs and formulation components (e.g. capsule shells) are derived from animal sources or may contain animal derivatives as excipients. This may affect drug choice for strict vegetarians or vegans and for those who avoid certain animal products for religious reasons. However, ingestion of the animal product may be permitted if it is for medical purposes or because it is not taken orally—e.g. Jewish law permits the use of heparins, even though they are of porcine origin, as they are not taken by mouth. It is important to remember that gelatin capsules are usually derived from animal sources. Lactose is a common excipient, but as it is milk derived it will be avoided by Jews who keep dietary laws strictly which prohibit consumption of milk and meat together.

Where alcohol is avoided for religious or cultural reasons, this may also affect the choice of drug or formulation as some liquid medicines and injections contain alcohol. Some individuals will also have concerns about the use of topical agents which contain alcohol as they could inadvertently ingest it by getting the alcohol-containing product on their hands.

Fasting for religious reasons (e.g. during Ramadan) may mean that patients miss both oral and parenteral medicines. Most religions exempt people who are sick from fasting, but patients who are well and on long-term therapy may wish to observe the fasts. Pharmacists can assist these patients by adjusting timings and frequency of medicines. Diabetics should be advised to be cautious about fasting, as it is difficult to maintain glycaemic control.

Further information

Drugs Derived from Pigs and their Clinical Alternatives: An Introductory Guide for Patients and Carers. www.mcb.org.uk/uploads/PBEnglish.pdf.

Glucose 6-phosphate dehydrogenase (G6PD) deficiency

G6PD is an enzyme that produces reduced glutathione, which protects red blood cells against oxidant stress. Exposure to an oxidant in G6PD-deficient individuals can lead to acute haemolysis of RBCs. G6PD deficiency is an X-linked genetic disorder. Thus ♂ are either normal or deficient, whereas ♀ are normal, deficient, or intermediate.

G6PD deficiency is distributed worldwide, with the highest prevalence in Africa, Southern Europe, the Middle East, Southeast Asia, and Oceania. Thus patients originating from any of these areas should be tested for G6PD deficiency before being administered an at-risk drug.

There are varying degrees of G6PD deficiency, with people of African origin generally having a lower level of deficiency (and therefore being more able to tolerate oxidizing drugs) and those of Oriental and Mediterranean origin generally having a high level of deficiency. Mild deficiency is defined as 10–15% of normal activity. Note that young red cells are not deficient in G6PD. Thus false-normal levels can occur during or immediately after an acute haemolytic attack, when new red cells are being produced.

Although many people remain clinically asymptomatic throughout their lives, they are all at risk of acute haemolytic anaemia in response to one of the following trigger events:

- infection
- acute illness
- fava (broad) beans
- oxidizing drugs.

A haemolytic attack usually starts with malaise, sometimes associated with weakness, lumbar pain, and abdominal pain. This is followed several hours or days later by jaundice and dark urine. In most cases, the attack is self-limiting, although adults (but rarely children) can develop renal failure.

Drug treatment in G6PD deficiency

- Patients in at-risk groups should be tested for G6PD deficiency. The normal range is 1.2–1.72 units/10^{10}RBC (3.2–6.4 units/gHb).
- Patients with severe deficiency should not be prescribed highly oxidizing drugs (Table 10.12), and drugs with a lower risk should be prescribed with caution.
- Patients with a lesser degree of deficiency may be able to tolerate even the drugs listed in the Table 10.12, but exercise caution.
- The risk and severity of haemolytic anaemia is almost always dose-related. Thus, even severely deficient patients can tolerate low doses of these drugs if there is no alternative. For example, for treatment of *Plasmodium vivax* or *plasmodium ovale*, a dose of primaquine 30mg once weekly for 8wks can be used instead of the usual dose of primaquine 15mg once daily for 14–21 days.

Table 10.12 Drugs to be used with caution in G6PD deficiency

Drugs with *definite* risk of haemolytic anaemia in most G6PD-deficient patients (avoid)

- Dapsone and other sulphones
- Methylthioninium chloride (methylene blue)
- Nalidixic acid
- Nitrofurantoin
- Primaquine
- Quinolones
- Sulphonamides

Drugs with *possible* risk of haemolytic anaemia in some G6PD-deficient patients (caution)[*]

- Aminosalicylic acid
- Amodiaquine
- Ascorbic acid
- Aspirin (doses >1g/day)
- Chloramphenicol
- Chloroquine[†]
- Dimercaprol
- Hydroxychloroquine
- Isoniazid
- Levodopa
- Menadione (water-soluble vitamin K derivatives)
- Penicillins
- Probenecid
- Pyrimethamine
- Quinidine
- Quinine[†]
- Streptomycin

[*]Use with caution; low doses probably safe.

[†]Acceptable to treat acute malaria at usual doses.

- Drug manufacturers do not routinely carry out testing to identify the potential risk of their drug to G6PD-deficient patients. Do not assume with new drugs that if there is no warning in the SPC, the drug is safe.

Treatment of a haemolytic attack

- Withdraw drug
- Maintain high urine output
- Blood transfusion, if indicated

Drugs in porphyria

The porphyrias are a group of rare hereditary metabolic disorders in which there are defects in the haem biosynthesis pathway. In the acute porphyrias (alanine (ALA) dehydratase deficiency, acute intermittent and variegate porphyrias, and hereditary coproporphyria) there is overproduction of porphyrin precursors as well as porphyrins which can lead to systemic symptoms including:

- acute (often severe) abdominal pain
- constipation
- nausea and vomiting
- hypertension
- tachycardia and cardiac arrhythmias
- muscle weakness and loss of sensation
- convulsions
- confusion, disorientation, hallucinations, paranoia
- hyponatraemia and hypokalaemia.

Numerous drugs have been linked to precipitating an acute porphyria attack, but these are mostly based on animal or *in vitro* studies. Pharmacists need to be aware of which drugs should be avoided and which are considered safe in porphyria, as an acute attack is serious and potentially life-threatening. The Welsh Medicines Information Centre provides specialist advice on porphyria and publishes a list of drugs considered safe in acute porphyria.[1]

In serious or life-threatening conditions a drug should not be withheld just because it is not on the 'safe' list. If there is no alternative 'safe' drug, treatment should be commenced and urinary porphobilinogen measured regularly. If levels increase or symptoms of an acute attack occur the drugs should be stopped.

Patients with acute porphyrias need to be aware that drugs can precipitate an attack and to inform healthcare professionals that they have porphyria. The British Porphyria Association publishes a series of fact sheets for patients including advice on drugs.[2]

Treatment of an acute attack is symptomatic and supportive, ensuring that the drugs used are those considered safe in porphyria (Table 10.13). Specific treatment is with haem arginate, which replenishes the body's haem stores and so through negative feedback reduces the production of porphyrins and porphyrin precursors.

1 http://www.wmic.wales.nhs.uk/pdfs/porphyria/Porphyria_Safe_List_2010_with_letter_August%202010.pdf.
2 www.porphyria.org.uk.

Table 10.13 Drug treatments in acute porphyria: symptomatic treatment

Condition	Drug category	Drug*
Abdominal pain	Analgesics	Aspirin
		Diamorphine
		Dihydrocodeine
		Ibuprofen
		Morphine
		Paracetamol
		Pethidine
Vomiting	Antiemetics	Chlorpromazine
		Ondansetron
		Prochlorperazine
		Promazine
Hypertension and tachycardia	Antihypertensives	β-blockers, e.g. atenolol, labetalol, propranolol
Neurosis, psychosis, and seizures	Sedatives, tranquillizers, and anticonvulsants	Chlorpromazine
		Clonazepam
		Lorazepam
		Promazine
Constipation	Laxatives	Bulk-forming (ispaghula)
		Lactulose
		Senna

* Drugs are listed alphabetically rather than preferred order of treatment. Management of symptoms should be individualized to meet the needs of the patient.

The non-acute or cutaneous porphyrias are associated with skin photosensitivity but do not show the serious systemic symptoms associated with the acute porphyrias. Thus it is not necessary to avoid exposure to 'unsafe' drugs in these conditions (with the exception of chloroquine and related drugs in antimalarial treatment and prophylaxis doses in patients with porphyria cutanea tarda). Patients should avoid exposure to the sun by sun avoidance and wearing appropriate clothing, as the majority of sun screens do not filter out the long UVA wavelengths and visible light which activate porphyrins.

Further reading

www.cardiff-porphyria.org—diagnostic and clinical advisory service.
www.wmic.wales.nhs.uk/porphyria_info.php.

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