



Magnesium

Normal range: 0.75–0.95 mmol/L¹

Local range

Magnesium is the second most abundant cation in the intracellular fluid. It is an essential electrolyte, and is a cofactor in many enzyme systems. The body is very effective at maintaining magnesium concentration, through control of absorption and excretion, which makes it difficult to establish a daily requirement. However, there is a recommended nutrient intake (RNI) for adults, as shown in Table M1.²

Table M1 Recommended nutrient intake of magnesium	
Adult male	12.3 mmol/day (300 mg)
Adult female	10.9 mmol/day (270 mg) (with an extra 2.1 mmol (50 mg) required if breast-feeding)

Hypomagnesaemia

Symptoms

Symptoms include anorexia, nausea, muscle weakness, tetany, tremor, muscle fasciculations (small, local contractions) and, rarely, seizures. Hypomagnesaemia often occurs in association with hypocalcaemia and hypokalaemia, so symptoms are not specific to magnesium alone.²

Causes

Causes include:

- dietary deficiency
- malabsorption syndromes

- excessive loss, most commonly via the gastrointestinal tract, e.g. chronic diarrhoea, but may also be because the kidneys are not reabsorbing it adequately²
- drugs, including: diuretics, alcohol, aminoglycosides, cisplatin, amphotericin, ciclosporin, foscarnet and pentamidine¹

Treatment

In mild deficiency states, oral replenishment may be sufficient; however, the oral route is of limited benefit because high doses will cause diarrhoea, leading to further losses, and there may be poor gastrointestinal absorption. The oral preparation most often used is magnesium glycerophosphate (unlicensed), at a dose of 24 mmol magnesium daily in divided doses. Doses up to 50 mmol magnesium daily have been used depending on the individual patient's requirements. Solid and liquid formulations are available as specials. (A 1 mmol/mL solution is available from Special Products, 49 High Street, Addlestone, Surrey, tel: 01932 820666.)

Magnesium glycerophosphate may be expressed in several ways:

$$1 \text{ g magnesium glycerophosphate} \equiv 125 \text{ mg Mg} \equiv 5.1 \text{ mmol Mg} \equiv 10.3 \text{ Eqmmol/L Mg}^2$$

Magnesium aspartate (unlicensed) has recently been introduced to the health care market as single-use sachets (Magnaspartate, Kopa Healthcare). Each sachet contains the equivalent of 10 mmol magnesium, although the ability of this formulation to deliver magnesium systemically is as yet not validated.³

If the oral route is unsuitable, or hypomagnesaemia is severe, magnesium sulphate may be given intravenously or intramuscularly. The intravenous route is preferred as the intramuscular route can be very painful.

The magnesium deficit in symptomatic hypomagnesaemia is estimated to be 0.5 to 1 mmol/kg. Up to one-half of the intravenous magnesium dose will be excreted in the urine during replacement, therefore 1 to 2 mmol/kg will be required to replenish body stores.

Body stores are replaced slowly, and may take several days. Even if serum magnesium levels return to normal in 24 hours it is important to recognise that body stores will probably not have been replenished in this time.

Patients with moderate to severe renal impairment should have their magnesium level monitored frequently, and may require a lower dose or longer intervals between infusions.

A typical replacement regimen would be:

- day 1: give 0.5 mmol/kg
- days 2–5: give 0.25 mmol/kg, up to a maximum of 160 mmol in 5 days

Magnesium sulphate injection is available as a 10% solution (containing 4 mmol/10 mL), and a 50% solution (containing 2 mmol/mL).

To administer as an infusion, add the required dose to 250–500 mL of sodium chloride 0.9% or glucose 5%. Infuse at a rate of 4 to 8 mmol/hour.⁴



Hypermagnesaemia²

Symptoms

Symptoms include nausea, vomiting, central nervous system and respiratory depression, hyporeflexia, muscle weakness and cardiovascular effects, e.g. peripheral vasodilatation, hypotension, bradycardia and cardiac arrest.

Causes

Causes include:

- excessive parenteral administration of magnesium salts
- patients with impaired renal function who have been taking large doses orally, e.g. as laxatives or antacids

Treatment

In mild cases, restricting magnesium intake is sufficient to return the serum concentration to normal. In severe cases, ventilatory and circulatory support may be required. Calcium gluconate 10% is recommended to reverse the effect on the circulatory and respiratory systems. It is given at a dose of 10 to 20 mL by slow intravenous injection (see *Calcium* for administration details).

Providing renal function is normal, adequate fluids should be given to promote renal clearance of magnesium. This may be increased by adding furosemide to the prescription.

Haemodialysis using a magnesium-free dialysis solution is an effective way of removing magnesium if the patient has renal impairment, or if other methods have proved ineffective.

References

1. Weisinger J R, Bellorin-Font E. Electrolyte quintet: magnesium and phosphorus. *Lancet* 1998; 352: 391–396.
2. Sweetman S, ed. *Martindale: The Complete Drug Reference*, London: Pharmaceutical Press, 2005.
3. Letter: *Launch of Magnaspartate* 2004. KoRa Healthcare, Frans Maas Ho, Swords Business Park, Swords, Dublin.
4. Shulman R, Drayan S, Harries M *et al.*, eds. *Injectable Drug Administration Guide*. London: Blackwell Science, 2002.

Notes:



Medication history-taking

Obtaining an accurate record of medication being taken by a patient on admission to hospital is important because:

- it provides an appropriate starting point for evaluating the efficacy of the patient's existing drug therapy
- drug causes of adverse effects can be identified and allergies properly documented
- concordance problems can be recognised
- changes made to drug therapy during the hospital stay can be accurately communicated to the patient's general practitioner (GP) on discharge

It has been shown that pharmacist-conducted medication histories gather more data concerning a patient's use of prescription and non-prescription medicines than those obtained by any other member of the health care team.^{1,2}

Useful sources of information

There are several useful sources of information concerning a patient's current treatment and many of them are listed below. The source(s) of information used to determine each drug and its dosage should be recorded, either on the in-patient chart or in the notes, particularly as some of these sources of information may no longer be available later in the patient's stay in hospital.

Patient and/or carer

See below for key points on interview technique.

Repeat slip from the GP clinical system

Repeat slips list medication the patient receives regularly without a formal consultation. Most repeat slips include dates when the item was last issued and it is worth looking at these to confirm that the patient has recently received the listed medication. If not:

- the GP may have advised the patient to stop taking the medication but not deleted the drug from the clinical system
- the patient may have decided not to take the medication because of side-effects or lack of efficacy. Such a decision made by the patient may have precipitated admission to hospital and thus needs further investigation
- if all such drugs are prescribed and administered on admission the patient may experience adverse effects, so it is important that the pharmacist can provide guidance to prescribers on these matters

Patient summary from the GP clinical system

Instead of writing lengthy referral letters, many GPs now print a patient summary from their computer systems to accompany the patient into



Medication history-taking

hospital. This includes a brief medical history, recent consultations and a full list of medications recently prescribed. The list of medicines usually includes both repeat medications and also 'acute' medications (normally prescribed following consultation with the doctor). This list will also usually include issue dates which may provide additional information.

Patients' own drugs (PODs)

If these are available they provide a wealth of information about medicines being taken by the patient. As well as providing a list of drugs prescribed for the patient:

- dates on labels may provide useful information concerning current use
- it is important to check that label and container contents match because medicines are commonly decanted. Asking questions about this can highlight compliance problems with certain types of container
- looking at the general condition of the medicines presented often provides an insight into how the patient is managing the medication
- if packed in a monitored-dosage system, this will indicate that the patient will need a similar system on discharge from hospital. Lack of awareness will result in patients being issued with a supply that is useless to them when they go home: not only will the patient be unable to take essential medication, but the supply issued will be wasted

The PODs also provide a useful *aide-mémoire* during any discussions with the patient or carer.

Telephone calls

If the above fails to provide the information needed, then a telephone call to one of the following may help:

- the GP surgery to ask for information from the patient's record
- the community pharmacist who normally dispenses the patient's medication should hold a patient medication record for the patient in question
- if the patient is resident in a care home, the staff should be able to provide information about medicines administered

Issues concerning patient confidentiality and right to privacy may have a bearing on contact with such third parties. If possible, seek the patient's permission beforehand.

Interview technique

Good communication skills and a methodical approach will ensure a detailed medication history is obtained. Some points to be remembered are as follows.

Introduction

- Introduce yourself to the patient, smile and make eye contact



- state the purpose of your visit
- ask if it is a convenient time to talk, e.g. has lunch just arrived?

Interviewing technique

- use open-ended questions, e.g. 'what did the doctor tell you the medication is for?'
- use lay terms, e.g. 'water tablets', and reflect the language and pace of speech used by the patient
- be empathetic: listen and show understanding

Current medication

- ask about all current medications, using the patient's own drugs as an *aide-mémoire* if available. It is worth asking specific questions about those items that patients often consider are 'not really drugs', e.g. the contraceptive pill, eye drops, creams, nutritional supplements, herbal medicines, over-the-counter medicines and also 'borrowed' medicines
- ideally record the start date, indication, dose and frequency of each medication, e.g. 'antibiotic course started by GP'. Also ask patients if they are *actually* taking the medicines as prescribed, to check concordance

Past medication

- has the patient recently stopped taking any medication? If so, why? Possible answers could be adverse drug reaction, or the medication 'did not work'. Dates of issue on medication bottles or the repeat slip may prompt questions concerning specific drugs

Allergies

- is the patient allergic or intolerant to any medication? If so, what happened and when? Responses to such questions are often sketchy but record what you can
- has the patient ever been re-challenged with this medication?

Answers to questions obtained during such interviews should be fully recorded as dictated by local policy, either on forms designed for the purpose or in the patient's notes.

References

1. Titcomb L C. The pharmacist's role in drug history taking. *Br J Pharm Pract* 1989; 11: 186–195.
2. Higham C. Drug history taking – a role for the ward pharmacist. *Pharm J* 1982; 228: 302–305.



Notes:

Mesna

Mesna is used to protect a patient from the urothelial toxic effects of oxazaphosphorines (ifosfamide or cyclophosphamide). The duration of treatment is equal to that of the oxazaphosphorine plus the time taken for the concentration of oxazaphosphorine metabolites to fall to non-toxic levels.

The oral dose of mesna is 40% w/w of the oxazaphosphorine dose, rounded down to the nearest whole tablet. A dose is sometimes prescribed equivalent to half a tablet, i.e. 200 mg, and although the tablet can be halved, it has such a good safety profile, that the normal minimum dose is 400 mg.¹

Mesna regimens vary according to the protocols used in chemotherapy. The following examples are as listed in the Summary of Product Characteristics.

Dose of mesna for intermittent oxazaphosphorine therapy

Oral mesna is given 2 hours before, then 2 and 6 hours after oxazaphosphorine dosing. Alternatively an intravenous dose of mesna (20% w/w of the oxazaphosphorine dose) can be given with the initial injection, followed by two oral doses 2 and 6 hours after the infusion (see Table M2).¹

	-2 hours	0 hours	+2 hours	+6 hours
Cyclophosphamide/ ifosfamide		1 g intravenous injection		
Mesna Regimen 1	400 mg orally		400 mg orally	400 mg orally
Mesna Regimen 2		200 mg intravenous injection	400 mg orally	400 mg orally



Dose of mesna where ifosfamide is used as a 24-hour infusion

An intravenous bolus dose of mesna is given before, then continuously during the oxazaphosphorine infusion, followed by oral mesna at the end of the infusion, then 2 and 6 hours after the infusion (see Table M3).¹

	0 hours	0–24 hours	24 hours	26 hours	30 hours
Ifosfamide		5 g/m ² infusion			
Mesna	1 g/m ² intravenous bolus	5 g/m ² continuous infusion	2 g/m ² orally	2 g/m ² orally	2 g/m ² orally

Dose of mesna where ifosfamide is used as a long-term continuous infusion

An intravenous bolus dose of mesna is given before, then continuously with the ifosfamide infusions, followed by oral mesna, as shown in Table M4.¹

Intravenous administration

Mesna can be given as a bolus injection (over 3 minutes), as a short intravenous infusion (over 15–30 minutes), or as a continuous infusion. For infusions, use a convenient volume of either sodium chloride 0.9% or glucose 5%.²

For continuous infusions dilution of mesna to a concentration of 20 mg/mL is recommended. The solution is stable for 24 hours, and is compatible with ifosfamide.³

References

1. Summary of Product Characteristics. *Uromitexan Tablets*. Thetford, Norfolk: Baxter Healthcare, 1999.
2. Shulman R, Drayan S, Harries M *et al.*, eds. *Injectable Drug Administration Guide*. London: Blackwell Science, 2002.
3. Trissel L A, ed. *Handbook on Injectable Drugs*, 12th edn. Bethesda, MD: American Society of Health-System Pharmacists, 2005.

Notes:





Table M4 Dosing of mesna for ifosfamide as a long-term continuous infusion								
	Day 1		Day 2		Day 3		Day 4	
Ifosfamide	0 hours	0–24 hours	0–24 hours	0–24 hours	0–24 hours	24 hours	26 hours	30 hours
Mesna	0.4 g/m ² intravenous bolus	2 g/m ² infusion	2 g/m ² infusion	2 g/m ² infusion	2 g/m ² infusion	2 g/m ² orally	0.8 g/m ² orally	0.8 g/m ² orally

Methadone

Methadone is the drug of choice for the management of withdrawal syndrome from opioids. It is long-acting (half-life is 15 hours initially, and 25 hours in a regular user), making stability from daily dosing easier to achieve; it is easy to titrate to achieve the correct dose; and it is less likely to be injected than other opioids.

Opioid withdrawal symptoms

Classic opioid withdrawal symptoms are weakness; insomnia; yawning/sneezing; irritability/aggression; sweating; muscle spasms and jerking; diarrhoea; tremors; nausea and vomiting; goose bumps; loss of appetite; dilated pupils; high temperature but feeling cold; lacrimation and rhinorrhoea; abdominal cramps; tachycardia; hypertension and increased bowel sounds.¹

If a patient is admitted to hospital who is on a managed opioid withdrawal regimen, or who is a substance misuser and is likely to exhibit withdrawal symptoms during admission, it is important to seek out and follow any local guidelines for your hospital. The following points should also be borne in mind.

Prior to prescribing methadone

Patients' consent should be obtained to contact their usual prescriber or community pharmacist, to confirm their dose. If this is not possible, and patient has their own supply, it should only be used as a means of identifying the dose if the label has not been tampered with, and if it has been dispensed within the last 7 days.

The patient's community pharmacist and the local drug service will need to be informed as soon as possible to avoid potential diversion of the community supply to another individual.

The telephone number of the local drug service is

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If it is necessary to contact a drug service outside of the locality, the National Drugs Helpline (0800 776600) may be of help. They provide 24-hour free and confidential advice, including information on local services.

Prescribing methadone without an established dose

If patients present who are receiving methadone, or are in opioid withdrawal, and it is not possible to establish their normal dose, they should be prescribed methadone mixture 1 mg/mL, 10 or 20 mg, and observed for 2 to 4 hours to ensure they do not become intoxicated.

The aim is to provide an effective level of physical and psychological comfort, while minimising the likelihood of overdose.



Methadone

Supplementary doses should only be considered where there is evidence of persistent opioid withdrawal. If a daily dose has been greater than 40 mg methadone, the patient should be closely monitored as deaths have occurred with 40 mg commencement doses. The prescriber should consider the cumulative effect of administering methadone because of its long half-life.

If after 4 hours there are still withdrawal symptoms, another dose may be given depending on the severity of the symptoms:

- mild withdrawal symptoms: give no further methadone
- moderate withdrawal symptoms (muscle aches, dilated pupils, nausea, yawning): give 5 to 10 mg methadone
- severe withdrawal symptoms (vomiting, piloerection, tachycardia, elevated blood pressure): give 20 mg methadone

It should be remembered that, whereas methadone overdose can be fatal, withdrawal is not.

Once a whole 24 hours have passed, the total amount of methadone administered during that period should be prescribed thereafter as a single daily dose.

Methadone equivalents

If a patient is not on a withdrawal programme but is a known substance misuser and control of withdrawal symptoms is necessary, then the above advice should be followed. However, it can be useful to be aware of the approximate methadone equivalent doses of other opioids (Table M5): extreme caution should still be exercised if the equivalent dose is in excess of 40 mg methadone.

Drug	Dose	Approximate methadone equivalent dose
Buprenorphine	200 µg sublingual tablet	5 mg
	400 µg sublingual tablet	10 mg
	300 µg ampoule	8 mg
	8 mg sublingual tablet	40 mg
	4 mg sublingual tablet	20 mg
	2 mg sublingual tablet	10 mg
Codeine phosphate	100 mL linctus (300 mg)	20 mg
	15 mg tablet	1 mg
	30 mg tablet	2 mg
	60 mg tablet	4 mg
Dextromoramide (Palfium)	5 mg tablet	5–10 mg
	10 mg tablet	10–20 mg



Diamorphine (heroin)	10 mg tablet 30 mg ampoule	20 mg 60 mg
Diamorphine (street heroin)	Difficult to estimate because of wide variations in purity: 1 g is roughly equivalent to 50–80 mg methadone. The dose should be titrated against the severity of the withdrawal symptoms	
Dihydrocodeine	30 mg tablet	4 mg
Dipipanone (Diconal)	10 mg tablet	4 mg
Gee's linctus 100 mL	16 mg anhydrous morphine	10 mg
J. Collis Brown 100 mL	10 mg extract of opium	10 mg
Morphine	10 mg ampoule	10 mg
Pentazocine (Fortral)	50 mg capsule 25 mg tablet	4 mg 2 mg
Pethidine	50 mg tablet 50 mg ampoule	5 mg 5 mg

If it is necessary to switch between oral and parenteral forms of methadone, there are a variety of views as to the appropriate equivalence. The Department of Health guidelines suggest using the same dose. In cancer care it has been suggested that the oral dose should be halved for parenteral use.² The indications for prescribing in both cases are different, so dose comparisons may be inappropriate: a patient switched between forms for any reason should be monitored for signs of over- or under-dosing, and the dose subsequently adjusted accordingly.

Adjuvant drugs for withdrawal symptoms

As well as methadone it may be appropriate to control the physical symptoms of withdrawal with more conventional therapy, e.g. loperamide for diarrhoea, metoclopramide for nausea and vomiting, paracetamol and non-steroidal anti-inflammatory drugs for headaches and muscular pains.

Stabilisation and reducing regimen

The dose of methadone is initially increased by not more than 10 mg weekly, usually over a period of 6 weeks, to between 60 and 120 mg daily. During this time the patient and carers should watch for signs of toxicity.

Once stable, and provided there is abstinence from heroin, the dose should be reduced. This will be by 5 to 10 mg every week or fortnight, depending on the size of the starting dose and the needs of the patient, until a stable dose is reached. This usually takes 4 to 6 months provided there is still abstinence from heroin.



Methadone

It can subsequently take months or years for the patient to cease the need for methadone. It is during this time that the issues that led to the drug misuse should be addressed. The overall goal is to maximise the patient's health, and this may actually mean continuing with maintenance treatment.

Other licensed withdrawal agents

Buprenorphine^{1,3,4}

Buprenorphine is a partial agonist/antagonist of the mu (μ) and kappa (κ) opioid receptors in the brain. It is used to treat opioid dependence, but because of the nature of its pharmacology it can precipitate withdrawal symptoms in opioid-dependent individuals. This is more likely with patients taking high doses of opioids (typically > 30 mg methadone, or equivalent, daily).

An initiation dose from 0.8 to 4 mg is given as a single dose, at least 4 hours after the last dose of opioid (or 24–48 hours after the last methadone dose), or preferably when the first signs of opioid withdrawal occur. If the patient has been taking methadone, the dose of methadone should have been less than 30 mg daily (unless withdrawal is to be conducted by specialist drug services).

The dose is increased on subsequent days, usually by 2 to 4 mg (although 8 mg steps are sometimes used), according to clinical response, and to a maximum dose of 32 mg daily. It may take 1 to 2 weeks for the patient to feel comfortable with the buprenorphine, and lofexidine may be needed in the first 2 days to help with any withdrawal symptoms.

Lofexidine^{1,5}

During sudden withdrawal of an opioid there is an increase in the amount of noradrenaline (norepinephrine) released, which results in an increased rate of neuronal firing, and this is seen in the patient as the symptoms of the withdrawal syndrome. Lofexidine is a presynaptic adrenergic alpha-2-receptor agonist. Its pharmacological effect is to decrease noradrenaline release and neuronal firing rate, thereby dampening down the withdrawal symptoms.

Lofexidine is used to relieve withdrawal symptoms in patients undergoing opioid detoxification. It is not used to treat opioid dependence. It is useful for patients with only a short history of opioid misuse who have been taking up to a quarter of a gram of street heroin daily, or to complete methadone withdrawal, e.g. when the methadone dose falls to 15 mL/day.

Blood pressure should be measured before and during treatment, and if there is a clinically significant decrease in blood pressure, treatment with lofexidine should be discontinued. It is unsuitable for people with pre-existing low blood pressure or bradycardia.

The starting dose is 200 micrograms (1 tablet) twice daily, increasing in steps of 200–400 micrograms daily as necessary, to a maximum of 2.4 mg daily. The duration of treatment is usually 7 to 10 days. It is with-



drawn over 2 to 4 days, but a longer period may be needed if withdrawal symptoms manifest.

References

1. *Drug Misuse and Dependence – Guidelines on Clinical Management*. Department of Health Scottish Office; Department of Health Welsh Office; Department of Health and Social Services, Northern Ireland. Norwich: Stationery Office, 1999.
2. Säwe J. High-dose morphine and methadone in cancer patients: clinical pharmacokinetic considerations of oral treatment. *Clin Pharmacokinet* 1986; 11: 87–106.
3. Summary of Product Characteristics. Subutex. <http://emc.medicines.org.uk/> (accessed 22 December 2004).
4. Ford C, Morton S, Lintzeris N *et al*. *Guidance for the Use of Buprenorphine for the Treatment of Opioid Dependence in Primary Care*, 2nd edn. London: Royal College of General Practitioners, 2004.
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Notes:

