Suggestions For Drug Monitoring in Adults in Primary Care

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A Collaboration between London & South East Medicines Service, South West Medicine Information Service and Croydon Clinical Commissioning Group

The monitoring parameters cited are derived from a range of guideline sources, other reference sources and expert opinion and must therefore be considered suggestions only. Adherence to them will not ensure a successful outcome in every case. The ultimate judgement regarding a particular clinical result must be made by the doctor in light of the clinical data presented by the patient and the diagnostic and treatment options available. For any enquiries contact David Erskine david.erskine@gstt.nhs.uk and Alison Alvey Alison.Alvey@uhbw.nhs.uk

New - SPS is changing the way we will present drug monitoring material in the future. We believe that there is a better way to display this high quality material to better meet users' needs. We are creating an interactive on-line tool for therapeutic drug monitoring content which we are planning to release by the end of January 2021. If you are involved with drug monitoring as part of your role and you would like to share your experience please get in touch (silvia.ceci@nhs.net).

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ACE inhibitors and angiotensin II receptor antagonists

Tests prior to starting treatment

- U&Es (incl sodium, potassium urea and creatinine)[1,3]
- Renal function/ eGFR[2,4,7]
- BP[1,2,3,6,9]

Consult specialist for support with treatment initiation in patients with hyponatraemia (< 130mmol/L), hypovolaemia, severe or unstable heart failure, known renovascular disease, hypotensive (SBP < 90mmHg) or taking multiple or high-dose diuretics or high-dose vasodilators. [6]

Seek further advice in patients with hypertension or eGFR < 30ml/min/1.73m^2 [6]

In patients with CKD, ACEI/ARB therapy should not normally be started if the pre-treatment serum potassium is >5.0mmol/L. [7.]

Monitoring until patient is stabilised

In General
There are minor differences between the monitoring recommendations for each indication – the most comprehensive monitoring is recommended for patients with heart failure and it may be appropriate to adopt that locally as the standard monitoring requirements for all patients starting ACEIs or ARBS.

Heart Failure
Measure BP, serum sodium, potassium and assess renal function 1-2 weeks after initiation and after each dose increment. [1, 9] Earlier monitoring (after 5-7 days) may be required for people with:

- existing CKD stage 3 or higher.
- aged 60 years or over.
- with relevant comorbidities such as diabetes mellitus or peripheral arterial disease.
- taking a combination of an ACE-inhibitor plus a diuretic or an aldosterone antagonist

Once at target dose or maximum tolerated dose monitor these parameters monthly for 3 months and at any time the patient becomes acutely unwell.[1]

Hypertension
NICE do not provide specific advice on monitoring ACEI/ ARB therapy in hypertension except in when using further diuretic therapy for resistant hypertension at step 4, where they suggest monitor blood sodium and potassium and renal function within 1 month.[8]

CKS recommend that renal function and serum electrolytes are checked 1–2 weeks after starting treatment and 1–2 weeks after each dose increase. BP should be measured 4 weeks after each dose titration.[6] For people who are at higher risk of hyperkalaemia or deteriorating renal function (for example those with peripheral vascular disease, diabetes mellitus, or pre-existing renal impairment or older people), consider checking renal function and serum electrolytes within 1 week of each dose titration[6]

CKD
Measure serum potassium concentrations, creatinine, BP and e-GFR within 1 to 2 weeks of treatment initiation and within 1 to 2 weeks of each dose increase. [7]

Post-MI
Measure renal function (serum creatinine), electrolytes and BP 1-2 weeks after initiation and after each dose increment [3] More frequent monitoring may be needed in patients at increased risk of deterioration of renal function.

Ongoing Monitoring

A local decision is needed on whether to implement a common monitoring policy irrespective of indication. Again implementing the approach recommended for heart failure may be the most appropriate to optimise patient safety.

Heart Failure
Measure sodium, potassium and renal function every 6 months and at any time the patient becomes unwell.[1]

CKS recommend more frequent monitoring (for example every 3 months) when there are concerns regarding the person's clinical condition, concomitant drugs, or comorbidities[9].

Hypertension
NICE do not provide advice on monitoring ACEI/ ARB therapy in hypertension except in when using further diuretic therapy for resistant hypertension at step 4, where they suggest monitor blood sodium and potassium and renal function within 1 month and repeat as required thereafter. [8]
CKS advise checking electrolytes and renal function annually in stable hypertensive patients that do not have diabetes unless there is a perceived need for more frequent monitoring.[6]

Chronic Kidney Disease (CKD)
Neither NICE nor CKS provide specific advice on monitoring ACEI/ ARB therapy in stable patients.

Post-MI
Measure renal function (serum creatinine), electrolytes and BP at least annually. [3] More frequent monitoring may be needed in patients who are at increased risk of deterioration in renal function. Patients with chronic heart failure should be monitored in line with 'Chronic heart failure' described above.[3, 11]

Action required if abnormal results

Potassium
Stop ACEI/ARB therapy and other drugs known to promote hyperkalaemia and seek urgent clinical advice if serum potassium rises above 6.0mmol/L .[1, 2, 6,9]
A rise to 5.5-6.0mmol/L should also prompt stopping ACEI/ARB and seeking specialist advice. A rise to < 5.5mol/L is acceptable but if the rise persists a review of concurrent medication is warranted. In hypertension CKS advise that that a rise to between 5.0 and 5.9mmol/L should prompt a review of other potassium sparing treatments and if level persists reduce dose of ACEI/ARB and review in 5-7 days.

Sodium
If Na <132mmol/L specialist advice should be obtained [9]

Renal Function
Increases in creatinine of >100% (or a level > 310micromol/L or an eGFR < 20ml/min/1.73m2) should lead to stopping ACEI/ARB and referral to a specialist. [9]

An increase in creatinine of >50% but </= 100% (or level > 256micromol/L or eGFR approx. between 20 and 25ml/min/1.73m^2) should prompt dose reduction/ withdrawal of diuretic (if applicable) and/or stopping ACE/ARB and consideration of specialist referral.[9]

Increases in creatinine of 30-50% (or level > 200micromol/L or eGFR < 30ml min/1.73m2) should prompt a review of volume status, temporary dose reduction or withdrawal of diuretic (if applicable) or ACEI/ARB. If the serum creatinine level increases by more than 20% or the eGFR falls more than 15%, re-measure renal function within 2 weeks. An increase of the serum creatinine level of less than 30% does not require further action

Additional notes

There is an ongoing debate on the safety of advising all patients to temporarily stop these medicines during sick days (ie on days when they are experiencing diarrhoea or vomiting (unless minor) or fever, sweats and shaking to prevent dehydration and thus acute kidney injury. There is a useful statement from the Think Kidneys Board outlining the pros and cons of this approach [10]
CKS advise that patients should be counselled to stop their ACEI/ARB if they have D&V for 1-2 days until they recover [9].If the symptoms persist beyond 2 days the patient should consult their GP to have their renal function checked.

References

1. NICE Clinical Guideline – Chronic heart failure in adults CG 108 (2018)
2. NICE Clinical Guideline - Chronic Kidney Disease: early identification and management of chronic kidney disease in adults in primary and secondary care. CG 182 (2014)
3. NICE Clinical Guideline – Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease CG 172 (2013)
4. BNF – accessed via Medicines Complete December 2019
5. Best Practice in primary care pathology: review J Clin Pathol 2007;60:225-234
6. CKS Guideline on hypertension (not diabetic) (2019)
7. CKS Guideline on chronic kidney disease (2019)
8. NICE Clinical Guideline on hypertension in adults (NG 136) (2019)
9. CKS Guideline on heart failure- chronic (2019)
10. Think Kidneys Board. "Sick day" guidance in patients at risk of Acute Kidney Injury: an Interim Position Statement from the Think Kidneys Board (2020) (link)
11. CKS Guideline on MI – secondary prevention. (2019)

Acetylcholinesterase inhibitors – donepezil, galantamine, rivastigmine

Tests prior to starting treatment

Renal function (if galantamine or rivastigmine)[1]
Liver function[1]
Potassium (if galantamine)[2]

Monitoring until patient is stabilised

None

Ongoing Monitoring

Monitor body weight (rivastigmine only)[1.] However both rivastigmine and galantamine can decrease appetite[2] so perhaps this advice should be applied to patients receiving either treatment.

Action required if abnormal results

See product information for initiation of these agents in patients with impaired liver function (all three drugs) or renal function (galantamine or rivastigmine only).

Galantamine is contraindicated in people with severe renal impairment (creatinine clearance less than 9mL/min or chronic kidney disease stage 5 [estimated glomerular filtration rate < 5mL/minute/1.73m^2]) or severe hepatic impairment (Child–Pugh score greater than 9)[2]

Additional notes

Specialist initiation only but may be continued and monitored by the GP under a shared care protocol.[1,2]

Monitor patient for side effects, most commonly presenting as cholinergic effects. The specialist should be contacted in the event of intolerance or adverse events to the medication. The specialist should also be contacted if there is sudden deterioration in cognitive function[2].

Patients prescribed galantamine should be warned of the signs of serious skin reactions and advised to stop taking galantamine immediately and seek medical advice should such symptoms occur[1]

References

1. BNF – accessed via Medicines Complete December 2019
2. Clinical Knowledge Summary. Dementia. Last revised July 2019

Alfacalcidol

Tests prior to starting treatment

Renal function (urea and electrolytes and creatinine clearance), plasma calcium (ideally corrected for protein binding), and alkaline phosphatase, parathyroid hormone (PTH), serum phosphorus and vitamin D levels (25-hydroxy vitamin D level). (1)

Monitoring until patient is stabilised

Plasma calcium levels and phosphate levels should initially be checked once or twice weekly and whenever nausea and vomiting occurs (4,5); when the dose is stabilised, measurements may be taken every two to four weeks. (5)

Ongoing Monitoring

Local agreement may be needed on who is responsible for monitoring and ensuring that any abnormal results are followed up appropriately

Renal function (urea and electrolytes and creatinine clearance), plasma calcium (ideally corrected for protein binding), and alkaline phosphatase, parathyroid hormone, serum phosphorus and vitamin D levels (25-hydroxy vitamin D level).

When used for secondary hypoparathyroidism [8]

1. CKD stage 3a-3b:
    a. Serum calcium and phosphate: Every 6 to 12 months;
    b. Parathyroid hormone: Frequency based on baseline level and progression of CKD;
2. CKD stage 4:
    a. Serum calcium and phosphate: Every 3 to 6 months;
    b. PTH: Every 6 to 12 months; alkaline phosphatase every 12 months or more frequently in the presence of elevated PTH
3. CKD stage 5 and 5D:
    a. Serum calcium and phosphate: Every 1 to 3 months;
    b. PTH: Every 3 to 6 months;
    c. Alkaline phosphatase every 12 months or more frequently in the presence of elevated PTH

Additionally, during maintenance therapy, periodic 24-hour urinary calcium and phosphate

When used in chronic hypoparathyroidism
Once patient is well controlled, monitoring may be required on a yearly or twice-yearly basis.

Serum calcium, phosphate, and magnesium; renal function; renal imaging (every 5 years in asymptomatic patients with a history of renal lithiasis or calcinosis or more

frequently as indicated); CNS imaging (basal ganglia and other sites of calcification), and/or bone mineral density as clinically indicated

Additional notes

- Concurrent use of thiazide diuretics or calcium containing preparations may enhance the risk of hypercalcaemia - calcium levels should be monitored more frequently.
- Concomitant oral administration of bile acid sequestrants such as colestyramine may impair the intestinal absorption of oral One-Alpha formulations. One-Alpha should be administered at least 1 hour before, or 4 to 6 hours after the intake of the bile acid sequestrant in order to minimise the potential risk of interaction.

References

1. One-Alpha Capsules SPC; Date of revision of SPC = November 2017
2. One-Alpha Drops SPC; Date of revision of SPC = September 2020
3. Clinical Knowledge Summaries (accessed 17 September 2020)
4. BNF (accessed via NICE on 17 September 2020)
5. NPSA Prevention of harm with alfacalcidol preparations | Signal https://www.sps.nhs.uk/wp-content/uploads/2018/03/Prevention-of-harm-with-alfacalcidol-preparations-Sept-2011-1.pdf
6. Patient.co.uk https://patient.info/medicine/alfacalcidol-capsules-and-drops-one-alpha (accessed 17 September 2020)
7. GP Notebook https://gpnotebook.com/simplepage.cfm?ID=x20060602082922478210
8. UpToDate (accessed 21 September 2020)

Amiodarone

Tests prior to starting treatment

Treatment should be initiated and monitored under hospital or specialist supervision[1,8]

TFTs (FT4, FT3 and TSH) [1,4,5,9]
A UK guideline on TFTs also recommends measuring thyroid peroxidase antibodies (TPOAb) to assess risk for thyroid dysfunction,[3]

LFTs (particularly transaminases)[1,4,5,9]
U&Es [4,5,9]
ECG and potassium level [1,2,4,5,9]
Chest X-ray[1,2,4,5]

Monitoring until patient is stabilised

In warfarinised patients, more frequent monitoring of INR both during and after amiodarone treatment is recommended[1]; initially weekly for first 7 weeks[5]

Ongoing monitoring

TFTs every 6 months[1-5,9] and for some months after discontinuation[1] (UK guideline on TFTs suggests up to 12 months after cessation[3])

Serum TSH should also be measured when thyroid dysfunction is suspected.[1]

LFTs every 6 months[1,4,5,9]
U&Es every 6 months[4,5,9] (AWMSG restrict to patients taking concomitant diuretics in view of risk of hypokalaemia)
Chest X-ray every 12 months[4,5]
ECG every 12 months[4,5]

Unless blurred or decreased vision occurs, ophthalmological examination is recommended annually[1], although the DTB states that these are usually only necessary for patients with visual symptoms[6]

Action required if abnormal results

Thyroid function

If TFTs are borderline repeat test in 6 weeks[7]

Hypothyroidism

Amiodarone may cause isolated biochemical changes (increase free-T4, slight decrease/normal free-T3) in clinically euthyroid patients, but there is no reason in such cases to discontinue amiodarone if there is no clinical or further biological (TSH) evidence of thyroid disease.[1]

AWMSG advise if TSH > 4.5 mU/L and free T4 elevated and duration is less than 3 months – observe and repeat in 3 months. If TSH >10 mU/Land free T4 normal and persisting for over 6 months. Consider treating with levothyroxine or repeat again in 3 months. [9] If TSH > 4.5 mU/L and free T4 is low consider treating with levothyroxine if amiodarone is considered essential.

Hyperthyroidism
Amiodarone-associated hyperthyroidism should be diagnosed only if high circulating free T4 is associated with high or high/normal free T3 and undetectable TSH[3]; such a diagnosis should prompt withdrawal of amiodarone[1] and specialist referral.[3] Clinical recovery usually occurs within a few months of drug withdrawal, although severe cases, sometimes resulting in fatalities, have been reported. Clinical recovery precedes normalisation of TFTs.[1]

AWMSG advise that if TSH < 0.1 mU/L, and T3 and T4 normal or minimally increased, repeat test in 2-4 weeks. [9] If TSH < 0.1 mU/L and T4 elevated, T3 elevated or 50% greater than baseline you should discuss urgently with a specialist who may advise amiodarone withdrawal. Arrange for TSH-receptor antibodies and TPO antibodies.

Liver function
Treatment should be discontinued if severe liver function abnormalities or clinical signs of liver disease develop[2]

Eye problems
If blurred or decreased vision occurs, complete ophthalmologic examination including fundoscopy should be promptly performed. [1]
Appearance of optic neuropathy and/or optic neuritis requires amiodarone withdrawal due to the potential progression to blindness[1] and expert opinion sought[2]

Lung problems
If pulmonary toxicity is suspected, chest X ray should be repeated and lung function tested, including where possible, measurement of transfer factor. [1] Specialist referral advised.[6]
Pneumonitis should always be suspected if new or progressive shortness of breath or cough develops in a patient taking amiodorone[2]

Additional notes

Most patients on amiodarone develop corneal microdeposits (reversible on withdrawal of treatment) which rarely interfere with vision but drivers may be dazzled by headlights at night.[2] Patients should be encouraged to visit an optician annually.[9]

Fresh neurological symptoms should always raise the issue of peripheral neuropathy[2]
Patients should be advised to shield skin from light during treatment and for several months after discontinuing amiodarone and to use a wide-spectrum sunscreen to protect against both long UV and visible light[2]
Because of long half-life of amiodarone, clinical problems may occur up to a year after stopping the drug[3] (hyperthyroidism may occur up to several months after discontinuation[1]).

Measurement of free T3 is required for interpreting results when free T4 or TSH values are outside reference limits, and it is important that information about drugs taken is available to laboratory so that correct thyroid tests can be selected and erroneous interpretation avoided.[4]

TPOAb are present in serum of patients with wide range of immunologically mediated thyroid disorders and may also be found in a small proportion of apparently healthy individuals; their appearance usually precedes development of thyroid disorders[3]

References

1. Summary of Product Characteristics for Cordarone 100mg Tablets. SPC (date of revision Jul 2018)
2. BNF – accessed via Medicines Complete Dec 2019
3. Association for Clinical Biochemistry (ACB), the British Thyroid Association (BTA) and the British Thyroid Foundation (BTF). UK Guidelines for the Use of Thyroid Function Tests July 2006. http://www.british-thyroid-association.org/info-for patients/Docs/TFT_guideline_final_version_July_2006.pdf
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5. Smellie WSA, Forth J, Sundar S, et al. Best practice in primary care pathology: review 4. J Clin Pathol. 2006 September; 59(9): 893–902. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1860479/
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7. Newman CM, Price A, Davies DW, et al. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. Heart 1998;79:121–127. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1728611/pdf/v079p00121.pdf
8. NHS England. Items which should not routinely be prescribed in primary care: guidance for CCGs. Published June 2019.
9. AWMSG. Prescribing of amiodarone for atrial fibrillation and atrial flutter in Wales. (Aug 2010 reviewed and updated Sept 2016)
10. CKS Guideline on atrial fibrillation. Last updated May 2019

Antipsychotic agents

Tests prior to starting treatment

FPG [2,4,5,,6] (NICE state either FPG or HbA1c in bipolar disorder is acceptable[3], SLAM state that although fasting plasma glucose is preferable, random plasma glucose is acceptable[1])
HbA1c[2,3, 5] (NICE state either FPG or HbA1c in bipolar disorder is acceptable[3])
BP [1,2,3,5,6]
Pulse[2,3,5]
FBC,[1,4,5]
LFTs [1,4,5]
U&Es [1,4,5]
Blood lipid profile [1,2,3,4,5,6] (SLAM state that although fasting sample is preferable a non-fasting sample is acceptable[1])
CPK [1]
Smoking history[5],[6]

Weight (include waist circumference) [1,2,3,4,5,6]
BMI [1,3,4,,6]
NICE also advise an assessment of nutritional status, diet and level of physical activity[2]

The BNF states that blood pressure monitoring is advised before starting therapy. Patients with schizophrenia should have physical health monitoring (including cardiovascular disease risk assessment) at least once per year[4]

Prolactin [1,2,3,4,5] –CKS recommend not required for aripiprazole, clozapine, quetiapine, or olanzapine (less than 20mg daily)[5] and SIGN recommends only if clinically indicated.[6] NICE suggest when used in schizophrenia but not in bipolar disorder[2,3]

ECG [1,2,3 4] - NICE/SIGN recommends if clinically indicated or recommended in SPC for that product.[2,3,6] CKS states ECG is mandatory if the person is taking haloperidol, pimozide or sertindole, not required for antipsychotics with no effects, or low-to-moderate effect on the QT interval and where there are no other risk factors for arrhythmia[5.]

Monitoring until patient is stabilised

BP: in schizophrenia NICE recommend monitoring at 12 weeks in schizophrenia.[2] and after each dose change in bipolar disorder[3]
Other guidelines recommend frequent checks during dose titration phase [1,4,5] or at 1 month (if clinically indicated) and 3 months.[6]

Pulse: NICE recommend monitoring at 12 weeks in schizophrenia.[2] and after each dose change in bipolar disorder[3]
FPG: NICE recommend monitoring at 12 weeks[2,3]. Other guidelines recommend checking at 4–6 months, or after 1 month then every 4-6 months[5] or at 1 month (if

clinically indicated) and 3 months [3, 6] (and more often if elevated) [3]. SLAM state that although fasting plasma glucose is preferable, random plasma glucose is acceptable[1]

HBA1c: NICE recommend monitoring after 12 weeks.[2,3]

Weight: In schizophrenia and bipolar disorder NICE recommend weekly for first 6 weeks and then at 12 weeks and 1 year plotted on a chart.[2,3] Other guidelines recommend every 3 months for 1st year [1.4,5,] or at 1 month (if clinically indicated) and 3 months[6]

Lipids: In schizophrenia and bipolar disorder NICE recommend assessment at 12 weeks[2,3]. Other guidelines recommend every 3 months for first year [1,3,4,5], or at 1 month (if clinically indicated) and 3 months[6] (or more often if weight gain is rapid) [3].

ECG: After each dose change [1,5] or if clinically indicated[6]

Prolactin: At 6 months [1,4,5] and if clinically indicated[4],[6]

Smoking history at 3 months[6]

Ongoing monitoring

Every 12 months: FBC, U&Es, LFTs, weight, lipids, prolactin, BP, FPG. [1,3, 5,6.] NICE recommend measurement of weight, waist circumference, BP, pulse, and HbA1c and fasting blood glucose every 12 months in patients being treated for schizophrenia[2] and bipolar disorder[3.] SLAM state that although fasting plasma glucose is preferable, random plasma glucose is acceptable[1]

The BNF states that patients with schizophrenia should have physical health monitoring (including cardiovascular disease risk assessment) at least once per year[4]

Other guideline producers recommend FPG measurements every 4-6 months. [1,4] With increased clinical monitoring of signs and symptoms of hyperglycaemia and worsening of glucose control in patients with diabetes or at risk of developing diabetes mellitus.[2]

CPK if neuroleptic malignant syndrome (NMS) suspected[1]

ECG: after each dose change [1,5] or if clinically indicated[6]- CKS states ECG is mandatory if the person is taking haloperidol, pimozide or sertindole, not required for antipsychotics with no effects, or low-to-moderate effect on the QT interval and where there are no other risk factors for arrhythmia[5.]

Smoking history[6]

Local guidance needed on availability of drug level monitoring and accessing advice on interpretation

The MHRA now advise that clozapine levels should be monitored in the following circumstances [7]

- Patient stops or starts smoking or switches to an e-cigarette
- Concomitant medicines which may interact with clozapine are started or stopped
- Patient has pneumonia or another serious infection
- Poor clozapine metabolism is suspected
- Clozapine toxicity is suspected

They also advise that levels of the following antipsychotics are available (although access to testing may vary locally) and can be helpful in patient management – amisulpiride, aripiprazole, olanzapine, quetiapine, risperidone and sulpiride

Action required if abnormal results

If blood lipids outside range, offer lifestyle advice or consider changing antipsychotic and/or initiating statin therapy. [1]

If weight outside range, offer lifestyle advice. Consider changing antipsychotic and/or dietary/pharmacological intervention. [1]

If hyperprolactinaemia confirmed and symptomatic, switch drugs. [1]
If NMS suspected, stop therapy[1]

If LFTs indicate hepatitis (transaminases x3 normal) or functional damage (PT or albumin change), stop therapy[1]

Additional notes

In schizophrenia and bipolar disorder, NICE advise that the secondary care team should maintain responsibility for monitoring service users' physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer.[2,3]
NICE recommend a regular and systematic assessment of overall physical health and adherence whilst on treatment.[2,3]

Patients with schizophrenia should have physical health monitoring (including cardiovascular disease assessment) at least once per year. [4,6]

When one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase.[4]

Dose adjustment may be necessary if smoking started or stopped during treatment. [4]

Patients should be monitored for 2 years after withdrawal for signs and symptoms of relapse. [4]

References

1. The South London and Maudsley NHS Trust, Oxleas NHS Trust 2018 Prescribing Guidelines 13th edition
2. NICE Guideline: Psychosis and schizophrenia in adults: treatment and management. Issued March2014
3. NICE Guideline on the management of bipolar disorder in adults, children and adolescents in primary and secondary care. Issued Sept 2014, last updated February 2020
4. BNF – accessed via Medicines Complete June 2020
5. Clinical Knowledge Summaries: Schizophrenia. Last revised January 2020
6. SIGN 131: Management of schizophrenia. March 2013
7. MHRA: Clozapine and other antipsychotics: monitoring blood concentrations for toxicity. Issued August 2020. Available: https://www.gov.uk/drug-safety-update/clozapine-and-other-antipsychotics-monitoring-blood-concentrations-for-toxicity#reviews-of-monitoring-advice-for-toxicity

Apixaban

Tests prior to starting treatment

Body weight[1,2]
Renal function (U&Es, calculated CrCl)[1-5] see additional notes section
Baseline clotting screen[3,4]
Full blood count[3,4]
LFTs[1-4]
BP[6]

Monitoring until patient is stabilised

No routine anticoagulation monitoring is needed.[1-4]
First follow-up appointment should be after 1 month[4], then ideally assess patient every 3 months (or more frequently if required) to[3,4]:

- Assess compliance and reinforce advice regarding regular dosing schedule
- Enquire about adverse effects such as bleeding and assess bleeding risk using HAS-BLED score
- Assess for the presence of thromboembolic events
- Enquire about other medicines, including OTC medicines

Ongoing monitoring

No routine anticoagulation monitoring is needed.[1-4]
Clinical monitoring of compliance, adverse effects e.g. signs of bleeding, thromboembolism and concurrent medicines as detailed above.
U&Es, CrCl, LFTs, FBC at least once a year.[3,4]
U&Es, CrCl, LFTs, FBC 6-monthly if the patient is older than 75years or fragile.[4]
If CrCl ≤60mL/min, retest U&Es, Cr, LFTs, FBC every *x*-months (where *x*=CrCl/10*)* [e.g. if CrCl 30mL/min every 3 months, if CrCl 20mL/min every 2 months].[4]

More frequent blood monitoring is advised when a change in renal or hepatic function is suspected, or where intercurrent illness, or concomitant medicinal products may impact on renal or hepatic function.[3,4]

Action required if abnormal results

If CrCl < 15mL/min or undergoing dialysis, apixaban should be avoided.[2] Assess for bleeding and seek advice regarding alternative anticoagulant therapy.[1,2]
If CrCl is 15–29 mL/min, the following recommendations apply:

- For prevention of recurrent DVT or PE, and treatment of DVT or PE, use apixaban with caution.[1,2]
- For prophylaxis of stroke and systemic embolism in a person with NVAF, reduce the dose to 2.5 mg twice daily.[2]

If serum creatinine is 133 micromol/litre or greater and the person is 80 years of age or older or weighs 60 kg or less reduce the dose to 2.5mg twice daily.[1,2]

If severe hepatic impairment or hepatic disease associated with coagulopathy and clinically relevant bleeding, manufacturer advises avoid apixaban.[2]

If mild or moderate hepatic impairment (Child Pugh A or B), apixaban should be used with caution.[2]

If liver enzymes are elevated (ALT/AST >2 x upper limit of normal or total bilirubin ≥1.5 x upper limit of normal) apixaban should be used with caution (these patients were excluded from clinical trials).[2]

Stop if severe bleeding occurs.[1, 2]

A low haemoglobin may suggest that occult bleeding is occurring and may require further investigations.[3]

Additional notes

The Cockcroft-Gault method for calculating CrCl is recommended when assessing patients' renal function.[4,5] Information on using the Cockcroft-Gault method in extremes of body weight is available in a Q&A: https://www.sps.nhs.uk/articles/which-estimate-of-renal-function-should-be-used-when-dosing-patients-with-renal-impairment/.

Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. It should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. It should be restarted after the procedure/surgery as soon as possible provided the clinical situation allows and adequate haemostasis has been established[2]. Further guidance may be found in the UKCPA Handbook of Perioperative Medicine.[7]

If the patient's HASBLED score is more than 3, then the patient is at a high risk of bleeding and apixaban should be used cautiously, with regular reviews.[6]

References

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Azathioprine

Tests prior to starting treatment

BSR recommend that all patients starting DMARDs should have baseline measurement of height, weight and BP[1]

FBC
Renal profile (creatinine/calculated GFR)[1]
Serum albumin[1]
ALT and/or AST[1]
TPMT assay[1,2,5]
LFT[3]

Local decision needed on whether TPMT activity result should be available before treatment is started (see additional notes for further discussion)

BSG recommends testing NUDT15 genotype, if available.[3] BSG guidance notes that genetic variation in NUDT15 has been described in association with myelosuppression.

Local decision needed on how this advice should be implemented

There is a strong rationale for screening for hepatitis B and C in patients at increased risk of infection [1,6] and the BSG recommends this for all patients with IBD commencing immunomodulators [3].

BSG also advises baseline screening for HIV in all patients[3]; BAD advises establishing HIV status in those with risk factors [4].

Screening for lung disease should be undertaken at clinical discretion on a case-by-case basis.[1]

BSG recommends checking VZV immunity if no history of chicken pox, shingles or varicella vaccination, with vaccination if low[3].
BSG recommends checking that cervical screening is up to date[3]

Monitoring until patient is stabilised

In General

BNF recommends weekly FBC monitoring for 4 weeks (more frequently if higher doses or if severe renal impairment) [2]

In Rheumatology

FBC, creatinine/calculated GFR, ALT and/or AST, albumin every two weeks until dose stable for at least 6 weeks then monthly thereafter for 3 months. More frequent monitoring may be required in high-risk patients.[1]

Following a change in dose repeat FBC ALT and/or AST, creatinine/calculated GFR and albumin every 2 weeks until dose stable for 6 weeks and then revert to previous schedule[1]

In Dermatology
FBC and LFTs weekly until stable on maintenance dose. Otherwise same as for rheumatology[4]

In Gastroenteroly
BSG recommends early intensive monitoring for haematological and biochemical toxicity, with tests for FBC, renal and liver biochemistry at 2, 4, 8 and 12 weeks of therapy, with ongoing 12-weekly blood monitoring. Bloods should be repeated 2 weeks after all dose increases[3].
GI specialists from Guys and St Thomas NHS Foundation Trust recommend that the methylmercaptopurine to thioguanine ratio (MeMP:TGN) is measured at Week 4 and 16 (and at Week 4 after each dose change). They also recommend that CRP be checked with each blood test, as a measure of disease activity [11].

Local decision needed on use of MeMP:TGN ratio and use of CRP as a measure of disease response

Ongoing monitoring

In General
BNF recommends a minimum of 3-monthly FBC monitoring and notes that blood tests and monitoring for signs of myelosuppression are essential in long-term treatment[2,]

Local decision needed on whether to follow disease specific guidance as listed or follow BNF advice above

In Rheumatology
Once the maintenance dose has been achieved and stable for 3 months consider monitoring FBC, creatinine/calculated GFR, albumin, ALT and/or AST at least every 12 weeks.
More frequent monitoring is appropriate in patients at higher risk of toxicity.

In Dermatology
No specific guidance offered[4]

In Gastroenterology
BSG recommend monitoring FBC, U&E and LFT at least every 12 weeks[3]

GI specialists from Guys & St Thomas NHS Foundation Trust recommend that the methylmercaptopurine to thioguanine ratio (MeMP:TGN) is measured annually. BSG guidance notes that it is unclear whether routine measurement of metabolites in all patients on azathioprine is beneficial, owing to wide variation in levels[3].

Local decision needed on use of this test as part of routine monitoring. It is unclear if this test is routinely available or used

Action required if abnormal results

Withhold treatment until discussion with consultant specialist if[1]:

- WCC < 3.5 x 109/L,
- Neutrophils< 1.6 x 109/L (BSG guidelines recommend withholding treatment if <2x109/L)
- Unexplained eosinophilia > 0.5x 10 9/L
- Platelets < 140x 109/l,
- AST and/or ALT increase to >100units/L
- Unexplained fall in serum albumin <30g/L
- MCV > 105f/L
- Creatinine increase > 30% above baseline over 12 months and/or calculated GFR < 60ml/min/1.73m2

If patient develops renal impairment (eGFR < 50ml/min) check dosing with specialist

Additional notes

Pneumococcal vaccine and annual flu vaccine should be given[1, 3, 4] (prior to starting treatment if possible)[3], with a single pneumococcal booster at 5 years[3]. Although live vaccinations should not be given during and until at least three months after stopping immunosuppressive therapy [3, 10], the Green Book advises that long-term low-dose corticosteroid therapy and low-dose non-biological DMARDs (azathioprine in doses ≤ 3.0mg/kg/day) are not considered sufficiently immunosuppressive and these patients may receive live vaccines [10]. Live vaccinations should however only be undertaken for those on low-level immunosuppression after careful consideration of risks and benefits [3].

Patients should be advised to seek urgent medical attention if they develop signs or symptoms of azathioprine hypersensitivity, bone marrow suppression or liver impairment; specifically high fever/severe flu-like illness, unexplained bleeding or bruising, or new onset jaundice[2,4].

If neutrophils <1 x 10^9/L, patients should be warned to present for antibiotics ±GCSF if febrile [3]

Thiopurines may increase the risk of non-melanoma skin cancer [9]. Sunscreens and protective clothing should be encouraged to reduce sunlight exposure[4] and people should be monitored for skin cancer [9].

During a serious infection, azathioprine should be temporarily discontinued until the patient has recovered from the infection[1]

TPMT assay: The BNF advise that patients with absent TPMT activity should not receive thiopurine drugs; those with reduced TPMT activity may be treated under specialist supervision. BAD advises that TMPT activity be checked in all patients prior to receiving azathioprine. Those with intermediate (heterozygous) range activity should receive a lower maintenance dose and those with absent activity should in general not be prescribed azathioprine. TMPT genotyping is only required for patients with indeterminate phenotype (i.e. borderline values) or those who have had a recent blood transfusion. [4]
BSR note that in situations where TPMT testing is not available it would be reasonable to increase laboratory monitoring to weekly in the initiation phase of treatment.

BSG advises that TPMT activity be checked in all patients and that the target dose be started once the result is available. Normal TPMT: 2mg/kg; low: 1mg/kg; very low: avoid.

References

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Carbamazepine

Tests prior to starting treatment

- Urea and Electrolytes (U&Es) including renal function
- Full blood count (FBC)
- Liver Function Tests (LFTs)
- Weight and height (BMI)
- Electrocardiogram (ECG) if indicated for patients with prior cardiovascular disease history [3, 6]

The MHRA recommend that patients of Han Chinese, Hong Kong Chinese or Thai origin should be screened for HLA-B*1502 before prescription of carbamazepine due to the risk of severe drug-induced cutaneous reactions.[5,7] Patients with this allele should not start carbamazepine treatment unless the benefits clearly outweigh the risk of Steven-Johnson Syndrome (SJS) and there are no other therapeutic options available. Screening for the newly discovered HLA-A*3101 allele in European and Japanese populations is not currently recommended but patients who are positive for this allele should have benefits and risks of treatment evaluated before initiation.[7]

Monitoring until patient is stabilised

Drug levels

SLAM advise that in bipolar disorder, plasma levels should be measured 2 weeks after initiation and 2 weeks after each dose change.[3,4] Trough levels to determine plasma carbamazepine concentrations should be taken pre-first dose on the day the level is measured.[3] This should be supervised by an epilepsy specialist.[2] Target plasma concentrations in epilepsy range from 4 to 12 mg/L. [1, 3, 5]

Routine plasma levels are **not** recommended in clinically stable patients but may be warranted if there is suspected toxicity, poor adherence, lack of efficacy or a change in clinical state (e.g. pregnancy). [1,2, 3]

Other monitoring

FBC, U&Es and LFTs should be monitored at 6 months post-initiation of treatment. BMI should be measured if the patient gains weight rapidly.[3] Previous NICE guidance indicated that Thyroid Function Tests (TFTs) should be conducted at 6 months if the patient had rapid-cycling bipolar disorder (yearly otherwise) but this has been removed from updated guidance. It would, however, be prudent to consider monitoring such parameters if indicated.

Ongoing monitoring

Drug levels

Routine monitoring of serum carbamazepine concentrations is not recommended[1,2,3] However, as previously discussed, levels would be useful if there were:

1) A change in clinical condition (loss of condition control, patient becomes pregnant)
2) Poor adherence
3) Suspected toxicity
4) Use in children or adolescents

Plasma levels exceeding 12mg/L are thought to be associated with a higher adverse effect burden and toxicity.[3] Appearance of a rash accompanied with fever or malaise (possible DRESS) should be reported by patients immediately and may prompt an urgent plasma concentration measurement.[1,2,3]

Other monitoring
It is recommended that U&Es be repeated every 6 months during treatment but more frequently if clinically indicated. LFTs should also be reviewed periodically if indicated, particularly in patients with a history of liver disease or the elderly. [1, 3]

Annual review of physical health is recommended in patients with bipolar disorder taking carbamazepine. The following should be assessed:

- Thyroid Function Tests
- Lipid Profile
- An ECG (if indicated by history or clinical picture). This should be repeated after each dose increase if abnormalities are then detected.
- Plasma glucose levels (including HbA1c)
- Blood Pressure

Falls assessments should also be conducted regularly for patients on long-term treatment owed to the common side effects of carbamazepine (including dizziness and ataxia).[1]

Local NICE implementation plan needs to be agreed

NICE suggest that FBC, U&Es, liver enzymes, Vitamin D levels, and other tests of bone metabolism (e.g. serum calcium or alkaline phosphatase) should be monitored every 2-5 years for adults with epilepsy taking **enzyme-inducing drugs**[4]

Action required

Treatment should be discontinued if leucopenia develops that is severe, progressive or accompanied by clinical manifestations (e.g. fever or sore throat), or if any evidence of significant bone marrow suppression occurs.[1,5]

Withdraw treatment immediately in cases of aggravated liver dysfunction or acute liver disease.[1,5]

Patients/carers should be told how to recognise signs of blood, liver, or skin disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising or bleeding develop.[5]
Abnormal FBC may warrant serum iron measurement.[1]

Additional notes

Some LFTs (e.g. gamma glutamyl transferase or alkaline phosphatase) may be found to be abnormal in patients on carbamazepine due to enzyme induction. These enhancements of metabolic capacity are not an indication for withdrawal of treatment.[1]

Hyponatraemia, particularly in patients taking diuretics, should not deter treatment if the patient is asymptomatic (and sodium is more than 120mmol/L). [2]

SLAM advise that a dose of at least 600mg/day and a plasma level of at least 7mg/L in affective illness is required for efficacy, though many studies do not consistently support this view. Studies have demonstrated efficacy as a mood stabiliser at doses ranging 800-1200mg daily, but these are higher than standard UK doses.[3]

Carbamazepine is a potent inducer of hepatic cytochrome enzymes and is metabolised by CYP3A4. Interactions occur with many medications including anticoagulants, diuretics, anti-retrovirals, antibiotics (e.g. erythromycin), ciclosporin, hormonal contraceptive pills. H2-antagonist and antifungals. Patient medication should be reviewed regularly for such interaction. Refer to the BNF interactions page for more detail.

References

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Carbimazole

Tests prior to starting treatment

TFTs (FT3 and TSH): All patients with hyperthyroidism should be referred to a specialist at diagnosis to establish the diagnosis and optimal management plan [1,2]
LFTs [3,6]
FBC including white cell count and differential [3,6]

Monitoring until patient is stabilised

Measure TSH, FT4 and FT3 every 6 weeks until TSH is within the reference range[3]

Do not monitor FBC and LFTs unless there is a clinical suspicion of agranulocytosis or liver dysfunction[3]

Ongoing monitoring

Once TSH is within the reference range, monitor TSH (with cascading to check FT4 and FT3) every 3 months until treatment is stopped[3]

Do not monitor FBC and liver function unless there is a clinical suspicion of agranulocytosis or liver dysfunction[3]

Patients experiencing myalgia should have their creatine phosphokinase levels monitored [5]

Action required if abnormal results

If the patient develops any signs and symptoms of hepatic disorder, stop carbimazole and perform LFTs immediately[5]. If abnormal liver function is discovered, treatment should be stopped.[5]

If the patient develops any signs/ symptoms of agranulocytosis or neutropenia, perform WBC count immediately, particularly where there is any clinical evidence of infection[5, 6]. Stop carbimazole promptly if there is clinical or laboratory evidence of neutropenia[4, 5] and consider specialist referral for further management options[3]

If acute pancreatitis occurs, carbimazole should be stopped immediately and permanently[4]

Refer to specialist endocrinologist if FT4 level falls below reference range or TSH is raised[6]

Additional notes

Warn patient or carers to stop carbimazole immediately and seek urgent medical advice if they develop possible symptoms of agranulocytosis or neutropenia, such as sore throat, mouth ulcers, bruising or bleeding, fever, malaise, or non-specific illness [4, 5, 6]

Regular full blood count checks should be carried out in patients who may be confused or have a poor memory.[5]

For adults who have stopped carbimazole, consider measuring TSH (with cascading) within 8 weeks of stopping, then every 3 months for a year, then once a year[3]

References

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2. UK Guidelines for thyroid function tests by Assoc. Clinical Biochemistry, British Thyroid Assoc and British Thyroid Foundation (Jul 2006)
3. NICE guideline [NG145] Thyroid disease: assessment and management. Published 20 November 2019 https://www.nice.org.uk/guidance/ng145
4. BNF. Accessed via Medicines Complete June 2020
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Ciclosporin (Neoral)

Tests prior to starting treatment

In General
Blood pressure (BP) (BNF recommends two measurements before starting treatment) [2]
Renal function (BNF recommends two measurements before starting treatment) [2]
Liver function[2]
Serum potassium[2]
Serum magnesium[2]
Blood lipids[2]

In Rheumatology
BSR recommend that all patients starting DMARDs should have baseline measurement of the following:
Height and weight[1]
Full blood count[1]
Renal function (calculated GFR or serum creatinine)[1]
Liver function (Serum albumin and ALT and/or AST)[1]
Glucose level[1]

Other Considerations:
Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection [1,6]

Baseline HIV status should also be established in those with risk factors [1],[6].

Vaccinations against pneumococcus and influenza are recommended[1]

Monitoring until patient is stabilised

In General
BNF recommends monitoring[2]:Liver function (frequency unspecified)
Serum potassium, especially in renal dysfunction (frequency unspecified)
Serum magnesium (frequency unspecified)
Measure blood lipids (after the first month of treatment)
Serum creatinine

- In dermatological indications: every 2 weeks for first 3 months then every month
- In rheumatology indications: every 2 weeks for first three months then every month for a further 3 months then every 4-8 weeks depending on the stability of the disease, concomitant medication and concomitant diseases

BP (frequency unspecified)

In Rheumatology
FBC
Renal function (Calculated GFR or serum creatinine)[1]

Liver function (Serum albumin[1]and ALT and/or AST)[1]
These parameters should be measured every 2 weeks until on stable dose for 6 weeks then monthly for three months. More frequent monitoring may be required in high-risk patients.[1]

Following a change in dose repeat the above tests every 2 weeks until dose stable for 6 weeks and then revert to previous schedule[1]

BP and glucose should be checked at each monitoring visit

In Dermatology
Measure serum creatinine and BP every 2 weeks for the first 2 months then monthly thereafter.
Additional investigations consisting of fasting lipids, liver function tests, potassium and urate levels can be monitored at less frequent intervals, depending on the results.

In Transplantation
No specific guidance identified

Ongoing Monitoring

Local decision needed on whether to follow general monitoring guidance or indication specific guidance as outlined below. Local consensus may be needed on frequency of monitoring

In General
BNF recommends monitoring:
Liver function(especially if concomitant NSAIDs - frequency unspecified)
Serum potassium, especially in renal dysfunction (frequency unspecified)
Serum magnesium (frequency unspecified)
Serum creatinine- (monthly)
BP (frequency unspecified)

In Rheumatology
FBC
Renal function (Calculated GFR or serum creatinine)[1]
Liver function (Serum albumin[1]and ALT and/or AST)

All measured every month – in patients who have been stable for 12 months consider a reduced frequency on an individual patient basis.

BP and glucose should be checked at each monitoring visit

In Dermatology
Monitor serum creatinine and BP at 2-3 monthly intervals if these parameters appear to be stable after 4 months
Additional investigations consisting of fasting lipids, liver function tests, potassium and urate levels can be monitored at less frequent intervals, depending on the results.

In Transplantation
No specific guidance identified

Action required if abnormal results

Withhold treatment until discussion with consultant specialist if[1]:

- WCC < 3.5 x 10^9/L,
- Neutrophils< 1.6 x 10^9/L
- Unexplained eosinophilia > 0.5x 10^9/L
- Platelets < 140 x 10^9/l,
- AST and/or ALT-increase to >100units/L
- Unexplained fall in serum albumin <30g/L
- MCV > 105 fL (Check B12, folate, TSH levels – if abnormal treat, if normal discuss with specialist team)
- Creatinine increase > 30% above baseline over 12 months and/or calculated GFR<60ml/min/1.73m^2 (Repeat in 1 week, if still more than 30% from baseline, withhold and discuss with specialist team)

BNF advises that ciclosporin should be discontinued in patients that develop hypertension that cannot be controlled with antihypertensives[2]. CKS defines high BP as more than 140/90mmHg [3]

CKS advises that if urinary protein 2+ or more, a mid-stream urine sample should be taken. If there is evidence of infection, this should be treated appropriately. If the mid-stream urine sample is sterile and urinary protein 2+ or more persists on two consecutive measurements, withhold until discussion with specialist team.

CKS advise that consideration should be given to withholding ciclosporin and referring to the specialist team if the patient shows any following signs/symptoms:

- Skin/mucosal reaction — for example rash, pruritus, mouth or throat ulceration.
- Sore throat.
- Fever.
- Unexplained bruising or bleeding.
- Nausea, vomiting, diarrhoea or weight loss.
- Diffuse alopecia.
- Breathlessness, infection or cough.
- Peripheral neuropathy.

Additional notes

Oral capsule formulations may contain significant amounts of ethanol.[5]
Avoid excessive exposure to UV light, including sunlight[2]
Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching. If it is necessary to switch a patient to a different brand, the patient should be monitored closely for changes in blood-ciclosporin concentration, serum creatinine,

BP (and transplant function where applicable)[2]. Switching should be made with caution and under specialist supervision.

References:

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Corticosteroids (long term oral therapy)

Tests prior to starting treatment

Blood pressure[1,2]
Body weight[1,2]
BMI[1,2]
Height (children and adolescents) [1,2]
Optometrist examination for glaucoma and cataract [1]
HbA1c [1]or fasting glucose level[2]
Triglycerides[1,2]
Potassium [1]

Assess for risk factors or pre-existing conditions that may potentially be exacerbated by steroid therapy, such as diabetes, dyslipidaemia, CVD, GI disorders, affective disorders, or osteoporosis. [2]

Patients taking oral glucocorticoids should be considered for fracture-risk assessment.[3]

Monitoring until patient is stabilised

HbA1c, triglycerides and potassium — check 1 month after start of therapy[1]
Check for new onset of diabetes 1 month after start of therapy[1]

Ongoing monitoring

Blood pressure — monitor at every appointment[1]
Triglycerides every 6–12 months[1]
Potassium every 6–12 months[1]
HbA_1C every 3 months - monitor people with confirmed diabetes more closely[1]
Body weight — monitor regularly[1]
Record height of children and adolescents regularly (approximately every 6 months) and plot on a growth chart.[1]
Perform a falls risk assessment, where appropriate, and advise those at increased risk of fractures.[1]

Monitor for signs of adrenal suppression.[1]
Eye exam every 6- 12 months; but earlier for those with symptoms of cataracts; early referral for intraocular pressure assessment if: personal/family history open angle glaucoma, diabetes, high myopia, connective tissue disease (particularly rheumatoid arthritis).[1-2]

Assess BMD at baseline and after 1 year of GC therapy in adults who are expected to be on prednisone ≥5 mg/day (or equivalent) for over 3 months. If BMD is stable at the 1-year follow-up and fracture risk is low, then subsequent BMD assessments can be

performed every 2–3 years. However, if bone density has decreased at the initial 1-year follow-up, both BMD and fracture risk should be assessed annually.[2]

Local decision needed on approach to screening for fragility fracture risk

Action required if abnormal results

Offer weight management advice if necessary.[1]
Treat elevated BP if necessary[1]
In patients with existing diabetes, oral antidiabetic drugs may need to be increased, or insulin therapy started[1]
Refer children and adolescents to a paediatrician if growth suppression is suspected.[1]
If adrenal suppression is suspected, biochemical testing of the HPA axis should be considered after steroid treatment has been reduced to a physiological dose. [2]
Consider referral if fracture risk is high and/or BMD is decreasing[2]

Bisphosphoonate should be considered to prevent vertebral fracture in men and women on prednisolone doses of 7.5 mg daily or greater (or an equivalent dose of glucocorticoids) for three months or more.[3]

Additional notes

Document person's history of chickenpox. Advise all those without a history of chickenpox who are taking systemic corticosteroids to avoid close contact with people who have chickenpox or shingles, and to seek urgent medical advice if they are exposed. Symptoms of and/or exposure to serious infections should also be assessed as corticosteroids are contraindicated in patients with untreated systemic infections.[2]

Ensure that patients have been issued with a blue corticosteroid treatment card and that the treatment information is up to date.

Ensure that patients taking prednisolone 5 mg/day or equivalent for 4 weeks or longer across all routes of administration (oral, topical, inhaled or intranasal) should be issued with an NHS Steroid Emergency Card.[4]

References

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Dabigatran

Tests prior to starting treatment

Body weight[1,2]

Renal function, U&Es, (Calculated CrCl) [1-5,] see additional notes section
Baseline clotting screen[3,4]
Full blood count[3,4]
LFTs[1-4]

BP[6,4]

Monitoring until patient is stabilised

No routine anticoagulation monitoring is needed[1,2]

First follow-up appointment should be after 1 month[4], then ideally assess patient every 3 months (or more frequently if required) to:[3,4]

- Assess compliance and reinforce advice regarding regular dosing schedule.
- Enquire about adverse effects such as bleeding and assess bleeding risk using the HAS_BLED score.
- Assess for the presence of thromboembolic events
- Enquire about other medicines, including OTC medicines

Ongoing monitoring

No routine anticoagulation monitoring is needed[1-4]
Clinical monitoring of compliance, adverse effects e.g. signs of bleeding, thromboembolism and concurrent medicines as detailed above.
U&Es, CrCl, LFTs, FBC at least once a year[3,4]
U&Es, CrCl, LFTs, FBC 6-monthly if the patients if CrCl 30–60 mL/min, patient is older than 75years or fragile[3,4].
If CrCl ≤60mL/min, retest U&Es, Cr, LFTs, FBC every *x*-months (where *x*=CrCl/10*)* [e.g. if CrCl 30mL/min every 3 months, if CrCl 20mL/min every 2 months][4]

More frequent blood monitoring is advised when a change in renal or hepatic function is suspected or where intercurrent illness, or concomitant medicinal products may impact on renal or hepatic function[3,4].

Action required if abnormal results

If CrCl< 30mL/min, use of dabigatran is not recommended[1,2].

Consult product literature for dose recommendations in patients who are elderly, have renal impairment or on concomitant treatment with verapamil[1,2].

If renal function has declined, review treatment, as dabigatran may need to be stopped

or a lower dose may be required [3.]

Dabigatran is contraindicated in hepatic impairment or hepatic disease expected to have any impact on survival[2,3].

If liver enzymes are elevated (>2 x upper limit of normal) dabigatran should be used with caution (these patients were excluded from clinical trials).[2]

Stop if severe bleeding occurs[1,2].

A low haemoglobin may suggest that occult bleeding is occurring and may require further investigations[3].

Additional notes

The Cockcroft-Gault method for calculating CrCl is recommended when assessing patients' renal function[4,5]. Information on using Cockroft-Gault method in extremes of body weight is available in a Q&A: https://www.sps.nhs.uk/articles/which-estimate-of-renal-function-should-be-used-when-dosing-patients-with-renal-impairment/

Dabigatran should be discontinued prior to surgical interventions or invasive procedures. Consult the manufacturers' literature for specific information regarding stopping dabigatran in terms of bleeding risk and renal function[2]. It should be restarted after the procedure/surgery as soon as possible provided the clinical situation allows and adequate haemostasis has been established[2]. Further guidance may be found in the UKCPA Handbook of Perioperative Medicine.[7]

If the patient's HASBLED score is more than [3], then the patient is at a high risk of bleeding and rivaroxaban should be used cautiously, with regular reviews[6].

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Digoxin

Tests prior to starting treatment

- Renal function[1,2,3]
- U&Es[1,-] paying particular attention to potassium,(diuretics can cause hypokalaemia), calcium levels and magnesium levels [especially if on a long-term PPI or other drugs that may cause hypomagnesaemia]) [1,2,3,5,6,8]
- Thyroid function tests- Initiation of digoxin in patients with thyroid disease requires care. [1,2,5,6]

Monitoring until patient is stabilised

Routine digoxin measurement is **not** recommended in clinically and biochemically stable patients [1], but may be warranted if poor adherence is suspected [4,7] or if there are changes in

- clinical state[1,2,4]
- concomitant use of drugs that may impact on toxicity e.g. amiodarone[1,2,4,5,7]
- recognition of situations predisposing to toxicity e.g. notable renal insufficiency.[1,2,4,6,9]

Samples for digoxin measurement should be taken at least 6 hours after the last dose ideally 8-12 hours. [2, 4,5 7 ,9]

Both the initial and maintenance doses of digoxin should be reduced when thyroid function is subnormal. In hyperthyroidism there is relative digoxin resistance and the dose may need to be increased. During the course of treatment of thyrotoxicosis, dosage should be reduced as the thyrotoxicosis comes under control. [2,5,6]

Electrolytes (potassium and calcium levels) should be checked regularly. Magnesium levels should be checked periodically in patients taking long-term PPIs or other medicines that pre-dispose to hypomagnesaemia or if there are concerns about low calcium levels [2,7.5,8]

Ongoing monitoring

Routine monitoring of serum digoxin concentrations is not recommended.[1, 4, 7]

A digoxin level may be useful to confirm a clinical impression of toxicity or non-adherence.[1,4.] The presence of toxic symptoms such as nausea, vomiting, visual disturbance (yellow-green discoloration), or severe dysrhythmias may prompt an urgent measurement.[1,2,4,7]

Digoxin toxicity is more commonly associated with serum digoxin concentrations greater than 2 nanogram/ml.[2,7]

In addition, check blood chemistry (electrolytes, urea, and creatinine) at least annually (more frequently in elderly people and people with renal impairment). These tests will often be done routinely, as renal function is likely to be monitored owing to the use of nephrotoxic drugs (such as diuretics and drugs affecting the renin-angiotensin system). [7]

Action required

Digoxin toxicity can occur even when the serum digoxin concentration is within the therapeutic range (between 0.7 nanograms/mL and 2.0 nanograms/mL); always interpret results in the clinical context. [2,4,7]

If toxicity occurs, digoxin should be withdrawn; serious manifestations require urgent specialist management. Digoxin-specific antibody fragments are available for reversal of life-threatening overdosage.[2],[5]

Appropriate electrolyte monitoring should be carried out in patients predisposed to electrolyte imbalances e.g. patients on loop diuretics, renal dysfunction and elderly patients.[3]
Hypokalaemia, hypomagnesaemia and hypercalcaemia predispose the patient to digoxin related problems.[2,5,7,9.] Hypocalcaemia may indicate that magnesium levels are also low.[1]

Both hypokalaemia and hypomagnesaemia should be corrected either orally or intravenously as appropriate. [2]

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Dronedarone

Tests prior to starting treatment

LFTs[1,3]
Serum creatinine[1,3]
ECG[1,3]
U&Es (potassium and magnesium)[4]

Monitoring until patient is stabilised

LFTs after 7 days[1,3]
Serum creatinine after 7 days[1,3] If an increase is observed, measure after another 7 days.[4]

Ongoing monitoring

LFTs every month for 6 months then at months 9 and 12 and periodically thereafter[1] Specialists at Guys and St Thomas' NHS Foundation Trust recommend annual monitoring throughout therapy[5].

Renal function should be monitored periodically.[1] Specialists at Guys and St Thomas' NHS Foundation Trust recommend annual monitoring throughout therapy.[5]

Needs local agreement on whether annual monitoring of LFTs and renal function is reasonable after 12 months

ECG should be repeated at least every 6 months[1, 3]

Patients should be carefully evaluated for symptoms of heart failure during treatment [1]

Action required if abnormal results

Any potassium or magnesium deficiency should be corrected before initiation and during dronedarone therapy [4]

Discontinue treatment if 2 consecutive alanine aminotransferase concentrations, taken 48-72 hours apart, exceed 3 times the upper limit of normal.[3, 4]

Dronedarone should not be initiated in patients if eGFR is less than 30 mL/minute/1.73 m^2.[3]

Dronedarone is contraindicated in patients with severe hepatic impairment [4]

A slight increase in serum creatinine (average 10 µmol/l) has been observed early on in treatment; in most cases reaching a plateau after 7 days. If an increase is observed

creatinine should be measured after another 7 days [4]. Further increases should prompt consideration of further investigation and treatment discontinuation [1, 4]. Specialists from Guys and St Thomas' NHS Foundation Trust recommend that treatment be stopped if the GFR falls below 30mL/min (using the Cockroft-Gault equation); the patient should then be referred back to the initiating clinician[5].

If AF recurs during treatment consider cessation of dronedarone and if permanent AF develops the drug should be discontinued.[1]

Within the SPC it is advised that if QTc Bazett interval is ≥500 milliseconds, dronedarone should be stopped.[4]

Patients or their carers should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, itching, dark urine, or jaundice develop.[3, 4]

Patients or their carers should be told how to recognise signs of heart failure and advised to seek prompt medical attention if symptoms such as weight gain, dependent oedema, or dyspnoea develop or worsen.[3] If left ventricular systolic dysfunction or heart failure develops, treatment with dronedarone should be discontinued [4].

Onset of dyspnoea or non-productive cough may be related to pulmonary toxicity. If this is suspected, relevant lung examinations should be considered and treatment discontinued if confirmed [1].

References

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Edoxaban

Tests prior to starting treatment

Body weight[1,2]
Renal function (U&Es, calculated CrCl)[1-5] see additional notes section
Baseline Clotting Screen[3,4]
Full blood count[2-4]
LFTs[1-4]
BP[2]

Monitoring until patient is stabilised

No routine anticoagulant monitoring is needed.[1-4]
First follow-up appointment should be after 1 month[4], then ideally assess every 3 months (or more frequently if required) to.[3,4]

- Assess compliance and reinforce advice regarding regular dosing schedule
- Enquire about adverse effects such as bleeding and assess bleeding risk using HAS-BLED score
- Assess for the presence of thromboembolic events
- Enquire about other medicines, including OTC medicines

Ongoing monitoring

No routine anticoagulation monitoring is needed.[1-4]
Clinical monitoring of compliance, adverse effects e.g. signs of bleeding, thromboembolism and concurrent medicines as detailed above.
U&Es, CrCl, LFTs, FBC at least once a year.[3,4]
U&Es, CrCl, LFTs, FBC 6-monthly if the patient is older than 75years or fragile.[3,4]
If CrCl ≤60mL/min, retest U&Es, Cr, LFTs, FBC every *x*-months (where *x*=CrCl/10*)* [e.g. if CrCl 30mL/min every 3 months, if CrCl 20mL/min every 2 months].[4]

More frequent blood monitoring is advised when a change in renal or hepatic function is suspected, or where intercurrent illness, or concomitant medicinal products may impact on renal or hepatic function.[2-4]

Action required if abnormal results

If CrCl < 15mL/min or undergoing dialysis edoxaban should be avoided[1,2]. Assess for bleeding and seek advice regarding alternative anticoagulant therapy.
If moderate to severe renal impairment (CrCl 15-50mL/min) manufacturer advises reduce dose to 30mg once daily. [1,2]
If CrCl>95mL/min re-evaluate treatment choice and consider alternative (see additional notes section below).[4]

If severe hepatic impairment or hepatic disease associated with coagulopathy and clinically relevant bleeding, manufacturer advises avoid edoxaban.[1,2]
If liver enzymes are elevated (ALT/AST > 2 x upper limit of normal) or total bilirubin ≥ 1.5 x upper limit of normal, edoxaban should be used with caution (these patients were excluded from clinical trials).[1,2]
If mild to moderate hepatic impairment, use with caution.[1,2]
Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site[2].
Stop if severe bleeding occurs.[1,2]
Reduce dose in low body weight ≤60kg to 30mg once daily.[1,2]

Additional notes

The Cockcroft-Gault method for calculating CrCl is recommended when assessing patients' renal function.[2,4,5] Information on using the Cockcroft-Gault method in extremes of body weight is available in a Q&A: https://www.sps.nhs.uk/articles/which-estimate-of-renal-function-should-be-used-when-dosing-patients-with-renal-impairment/.

A trend towards decreasing efficacy with increasing CrCl was observed compared to well-managed warfarin.[2] Therefore edoxaban should only be used in patients with high creatinine clearance after a careful evaluation of the individual thrombo-embolic and bleeding risk.[2,4] In the US, edoxaban is not licensed in patients with NVAF who have CrCl>95mL/min, due to reduced efficacy.[7]

If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, edoxaban should be stopped as soon as possible and preferably at least 24 hours before the procedure[2]. Further guidance may be found in the UKCPA Handbook of Perioperative Medicine.[8]

If the patient's HAS-BLED score is 3 or more anticoagulation should be used with caution and more regular reviews.[6]

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Eplerenone

Tests prior to starting treatment

Renal function[1-6]
Serum electrolytes[1-6]

Monitoring until patient is stabilised

Renal function and serum electrolytes 1 week after initiation and after every dose increase, monthly for first 3 months, then every 3 months for a year.[2-6]

In the treatment of early post myocardial infarction patients with heart failure the monitoring of renal function and serum electrolytes is advised after 48 hours as well as at the above time intervals.[2]

Blood pressure before and after each dose increase of eplerenone.[3]

Ongoing monitoring

Monitor renal function and serum electrolytes every 4 to 6 months and at any time the person becomes acutely unwell.[2,3,4,5]

Consider impact of introducing other potassium sparing medicines.[6]

Action required if abnormal results

The manufacturer states that eplerenone should not be started in patients with:

- Severe renal impairment (eGFR < 30 mL/minute per 1.73 m^2)
- Severe liver impairment (Child-Pugh Class C)
- Baseline serum potassium level >5.0 mmol/L [1,6]

NICE states that for people with chronic kidney disease:

- If eGFR is > 30ml/min/1.73m^2 and ≤ 45 ml/min/1.73 m^2 consider lower doses and/or slower titration of dose of eplerenone
- If eGFR < 30ml/min/1.73m^2, the specialist heart failure multi-disciplinary team should consider liaising with a renal physician prior to initiating treatment.
- Monitor response to titration closely taking into account the increased risk of hyperkalaemia. [3]

NICE guidance [2]

- If serum potassium rises to between 5.5 and 5.9 mmol/L, halve the eplerenone dose and monitor closely
- If serum potassium rises to ≥ 6.0 mmol/L, stop eplerenone and seek specialist advice.

Additional notes

Advise patients to avoid NSAIDs not prescribed by a physician ('over the counter') and salt substitutes containing potassium [2,4,5].
If diarrhoea/vomiting occurs or there is an infection with fever leading to intense sweating, patients should be advised to withhold eplerenone and contact their physician [2,4,5].

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Furosemide

Tests prior to starting treatment

Renal function (urea and electrolytes and creatinine clearance), blood pressure, urine and blood glucose, and lipid profile[1]

Monitoring until patient is stabilised

Recheck renal function (urea and electrolytes and creatinine clearance) and blood pressure 1–2 weeks after starting treatment or after each dose increase[2]. However, in high risk patients, recheck 5-7 days after the start of treatment or dose adjustment.

High risk patients may be those with:

- Existing chronic kidney disease stage 3 or higher.
- Aged 60 years or over.
- With relevant comorbidities such as diabetes mellitus or peripheral arterial disease.
- Taking a combination of a diuretic plus an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-II receptor antagonist (AIIRA), or an aldosterone antagonist.

Combining loop diuretics with thiazides[3]:

- When combining loop diuretics (e.g. furosemide) with thiazide diuretics check renal function and electrolytes within five days of starting and then every 5-14 days, depending on an individuals' stability.
- Monitor weight and hydration status and, where diuresis is extensive, consider earlier testing of renal function.
- Once stable, six-monthly checks may suffice unless there is any change in therapy, intercurrent illness or worsening renal impairment.

Combining loop diuretics with spironolactone or eplerenone[3]:

- Check renal function and electrolytes at 1, 4, 8 and 12 weeks. Thereafter at 6, 9 and 12 months and then on a six-monthly basis.
- If hyperkalaemia occurs (between 5.5 mmol/L and 5.9 mmol/L) or serum creatinine rises to ≥220micromol/L on spironolactone, halve the dose to 25 mg on alternate days and recheck U&Es frequently.
- A potassium level ≥6.0 mmol/L or a creatinine level >310 micromol/L, should prompt the immediate stopping of spironolactone and the seeking of specialist advice.

Eplerenone should be monitored in the same way as spironolactone.

Ongoing Monitoring

Once treatment is stable, measure renal function and serum electrolytes at least once every 6 months, or sooner in high-risk patients[2].

Action required if abnormal results[1,2]

- If the serum creatinine level increases by more than 20% or the eGFR falls more than 15%, re-measure renal function within 2 weeks.
- An increase in creatinine of 30–50% (or to greater than 200 micromol/L) or an eGFR rate less than 30 mL/min/1.73 m^2 should prompt clinical review of volume status and dose reduction or withdrawal of diuretics (if the person is hypovolaemic). Re-measure renal function within 1 week.
- If there is an increase in creatinine of more than 50% or to greater than 256 micromol/L (eGFR approximately 20–25 mL/min/1.73 m2), assess volume status, check blood pressure, review other renal function tests including electrolytes and proteinuria, and review other medication for nephrotoxic agents. If the person is hypovolaemic, stop the diuretic; otherwise, manage accordingly.
- Review serum potassium level and consider whether patient is at high risk of cardiac arrhythmias with even mild hypokalaemia. People at higher risk include the elderly, those taking drugs that prolong QT interval (such as amiodarone), those with paroxysmal arrhythmias, unstable angina, or chronic liver disease.
- If potassium level decreases to <3mmol/L (or 4mmol/L in high-risk people), review dose or consider stopping the diuretic
- If potassium decreases to <2.5mmol/L (or 3.5mmol/L in high-risk people), seek specialist advice urgently.

Additional notes

- Advise patients if they develop diarrhoea and vomiting while taking a diuretic, they should maintain their fluid intake and stop the diuretic for 1–2 days until they recover. Stopping treatment for a short time is thought to avoid dehydration, hypotension and acute kidney injury, and should not cause a sudden deterioration in heart failure. If symptoms persist beyond 2 days renal function should be checked[2].

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Hydroxycarbamide

Tests prior to starting treatment

FBC, U&Es (incl renal function), uric acid, LFTs, [1,2,3,6] .
Reticulocyte count, HbF% and lactate dehydrogenase (LDH) recommended when used in Sickle Cell disease[5]
Actual and ideal body weight (for PCV)

Consider NICE recommendations regarding screening for hepatitis B and C in patients at increased risk of infection [4]

Monitoring until patient is stabilised

In Sickle Cell
Weekly FBC for first four weeks then every two weeks for next 8 weeks if stable[5]. BNF recommends monitoring FBC every 2 weeks for first 2 months[7].

In psoriasis
Weekly FBC until an effective dose is established[2]

In polycythaemia vera
No national guidance was identified which addressed monitoring. In BMJ Best Practice it is stated that dose is titrated according to haemocrit (<45%) and sometimes also to normalise WBC and platelet count. Blood counts are monitored every 1 to 2 weeks until stable. [7]

Ongoing Monitoring

A local policy is needed which reflects the guidance outlined below as it differs significantly according to indication

In sickle cell disease
Monthly FBC if blood counts stable and 3 monthly U+Es, LFTs, Urate, LDH and HBF%[5.] However BNF recommends FBC every 2 months unless on maximum dose in which case FBC should continue to be monitored every 2 weeks[6]

In psoriasis
FBC every 1-3 months[2]
Serum creatinine, uric acid and LFTs should also be monitored[1]

In polycythaemia vera
No national guidance was identified which addressed monitoring. However in BMJ Best Practice it is stated that blood counts should be monitored every 2 to 3 months. [7]

Action required if abnormal results

If neutrophils < 1.5 $x10^9$/L, platelets < 80 $x10^9$/L, reticulocytes< 100 $x10^9$/L or Hb drops by >3g/dL from baseline stop hydroxycarbamide until blood counts have recovered[5]

If creatinine clearance < 60ml/min review initiate treatment at half dose in sickle cell disease.[5]

Additional notes

It is important to maintain a high fluid intake during treatment [1]

Patients receiving long-term therapy with hydroxycarbamide should be advised to protect skin from sun exposure[6]

Patients should be advised to avoid live vaccinations[1,2,3]

Patients receiving long-term therapy for malignant disease should be monitored for secondary malignancies[6].

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Hydroxychloroquine

Tests prior to starting treatment

Height[1]
Weight[1]
BP[1]
FBC [1]
Calculated GFR[1]
ALT and/or AST[1]
Serum Albumin[1]

Baseline ophthalmological examination

The Royal College of Ophthalmologists (RCOphth) Jan 2020 guideline recommends that all patients planning to take hydroxychloroquine long term (>5 years) should have a baseline eye examination in a hospital eye department ideally within 6 months, and definitely within 1 year, of starting therapy [including fundus photography and spectral domain optical coherence tomography (SD-OCT)].[2,3] Details of the specific eye tests are in the guideline.[2]

Monitoring until patient is stabilised

None identified.[1,4,5]

Ongoing monitoring

No routine laboratory monitoring but weight and renal function should be checked periodically to ensure dosing remains appropriate.[1,4,5]

The RCOphth recommends that all individuals who have taken hydroxychloroquine for greater than 5 years should receive annual monitoring for retinopathy.[2]

All individuals taking hydroxychloroquine who have additional risk factors for retinal toxicity may be screening annually from the baseline visit or annual screening commenced before 5 years of treatment completed. This is to be decided by a Consultant Ophthalmologist following the baseline visit.[2]

Additional risk factors: Concomitant tamoxifen use, impaired renal function (eGFR < 60ml/min/1.73m^2), dose of hydroxychloroquine greater than 5mg/kg/day.[2]

Patients should be advised to see their optometrist in the first instance if they experience eye symptoms, in the same way as they would if not taking hydroxychloroquine. [2]

All patients on long term therapy should undergo periodic examination of skeletal muscle function and tendon reflexes. If weakness occurs the drug should be withdrawn. [4,5]

Action required if abnormal results

The results of retinal monitoring by the ophthalmologist should by communicated back to the prescribing physician, patient and GP as: normal, possible or definite hydroxychloroquine retinopathy. It is the responsibility of the prescriber to refer patients for monitoring and to act on the results of monitoring.[2] Details for management of patients with possible or definite retinopathy are given in the RCOphth guideline.[2]. Patients with definite toxicity should be advised not to drive until reviewed by an ophthalmologist and should also inform the DVLA.[2,4]

Adjust dose and/or increase screening frequency if impaired renal or liver function[1,2,5,6]

Additional notes

The risk of retinal toxicity can be reduced by ensuring the daily dose of hydroxychloroquine is < 5mg/kg of absolute body weight.[2]
(Previously a dose of hydroxychloroquine of less than 6.5mg/kg/day was considered safe dosing[2], calculated from ideal body weight and not actual body weight.[4,5]) Weight should be checked regularly to ensure the milligram/kg dose is still appropriate.

Concurrent tamoxifen use increases the risk of toxicity; patients need careful dosing and screening.[2]

References

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Leflunomide

Tests prior to starting treatment

Treatment will be initiated and supervised by rheumatology specialists.

Height, weight and BP [1]
FBC (BNF recommends including differential white cell count and platelet count) [1,2]
Renal function (creatinine/calculated GFR) [1]
Serum albumin[1]
ALT and/or AST[1] (BNF states LFTs) [2]

Screening for occult viral infections in patients at increased risk of infection (hepatitis B, hepatitis C, HIV). [1,]

Screening for lung disease should be undertaken at clinical discretion on a case-by-case basis.[1]

Monitoring until patient is stabilised

FBC, creatinine/calculated GFR, ALT and/or AST and albumin **every two weeks** until on stable dose stable for 6 weeks. [1]

Once on stable dose, **monthly** FBC, creatinine/calculated GFR, ALT and/or AST and albumin for 3 months.[1] *
More frequent monitoring is appropriate in patients at higher risk of toxicity. [1]

BP and weight should be checked at each monitoring visit.[1]

Dose increases should be monitored by FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until dose stable for 6 weeks then revert back to previous schedule.[1]

If leflunomide is used in combination with methotrexate then monthly monitoring should be extended longer term (patients who have been stable for 12 months can be considered for reduced frequency of monitoring on an individual basis). [1]

[Alternatively, BNF recommends FBC (including differential WBC and platelets) and LFTs every two weeks for first 6 months.[2]]

Ongoing monitoring

Local decision needed on whether to follow BSR/BHPR Guidance or the guidance outlined in the BNF

Once the maintenance dose has been achieved and stable for 3 months monitor **at least every 12 weeks**: [1]

- FBC

- creatine/calculated GFR
- albumin
- ALT and/or AST

More frequent monitoring is appropriate in patients at higher risk of toxicity. [1]

BP and weight should be checked at each monitoring visit.[1]

[Alternatively, BNF recommends FBC (including differential WBC and platelets) and LFTs every 8 weeks.[2]]

Action required if abnormal results

Withhold treatment until discussion with consultant specialist if[1]:

- WCC < 3.5 x 10^9/L,
- Neutrophils< 1.6 x 10^9/L
- Unexplained eosinophilia > 0.5x 10^9/L
- Platelets < 140 x 10^9/l,
- ALT and/or AST increase to >100 Units/L
- Unexplained fall in serum albumin <30g/L
- MCV > 105fL
- Creatinine increase > 30% above baseline over 12 months and/or calculated GFR < 60ml/min/1.73m^2

Withhold until discussion with rheumatologist if [3]:

- Rash or itch,
- Hair loss,
- Severe sore throat/oral ulceration or abnormal bruising/bleeding (check FBC immediately)
- Hypertension despite standard anti-hypertensives,
- Breathlessness or dry cough
- Unexplained weight loss >10%
- GI upset (nausea, vomiting or diarrhoea)
- Peripheral neuropathy

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Lithium

Tests prior to starting treatment

Renal function and U&Es (DTB recommends particular attention to Na and creatinine, NICE recommend particular attention to calcium)[1,3,4,7]
TFTs[1,3,4,7]
Cardiac function (ECG recommended for patients with risk factors for, or existing CVD) [1,3,7]
FBC [7]
Baseline measurement of weight (and height) or BMI [1, 3,7]

Baseline lithium level before switching to another brand/ preparation[3, 5]

Additionally, as part an annual review of physical health, NICE recommend that patients with bipolar disorder have baseline CV status assessment including pulse and BP, lipid profile, fasting blood glucose levels, liver function and HbA1c[7]

Monitoring until patient is stabilised

Plasma levels
Check levels one week after starting and one week after every dose change, i.e. levels should be monitored weekly until desired level is reached and patient is stable.[1,2,3,7]

NICE advice is to maintain level between 0.6 and 0.8mmol/L a level of between 0.8 and 1.0mmol/L may be appropriate for a trial period of at least 6 months in patients who have relapsed previously or who have sub-threshold symptoms with functional impairment[7].

BNF states that a target serum-lithium concentration of 0.8–1.0 mmol/litre is recommended for acute episodes of mania, and for patients who have previously relapsed or have sub-syndromal symptoms but levels at the lower end of the range 0.4-1.0mmol/L may be acceptable in maintenance therapy and in elderly patients

SLAM suggest that 0.4mmol/L may be effective in unipolar depression, 0.6-1.0 mmol/L in bipolar illness, with slightly higher levels in difficult-to-treat mania[1]

Ongoing Monitoring

Plasma levels

Local decision needed on frequency of monitoring lithium levels after patient has been stable for 12 months

NICE and BNF recommend monitoring levels every 3 months. The BNF states that drug level monitoring should be continued at 3 monthly intervals but NICE state that after 12 months monitoring can be decreased to every 6 months unless patients are elderly, taking drugs that

interact with lithium, have impaired renal function, have impaired thyroid function, raised calcium levels, poor symptom control, poor adherence, or their most recent lithium level was >/= to 0.8mmol/L.[7]

NICE also recommend that levels should be monitored more frequently if urea levels and creatinine levels become elevated, or eGFR falls over 2 or more tests

SLAM recommend levels should be monitored every 6 months unless patient is being prescribed interacting medicines, is elderly, has established renal impairment or other relevant physical illness when more frequent monitoring is advised[1].

Camcolit SPC states that after stabilisation levels should be taken weekly for one month then at monthly intervals thereafter.[5]

BNF recommends additional measurements be made if a patient develops significant intercurrent disease or if there is a significant change in their sodium or fluid intake[2]. Camcolit SPC also recommends additional monitoring when there are signs of manic or depressive relapse, or lithium toxicity[5].

Additional monitoring is also required during pregnancy. Lithium levels tend to decrease in pregnancy but can also sometimes increase again, particularly in late pregnancy. Measure plasma levels once a month until 36 weeks of pregnancy and then weekly until delivery. Women taking lithium should deliver in hospital and be monitored by the obstetric team.[8]

Other monitoring

Thyroid monitoring
NICE and BNF recommend TFTs every 6 months[2, 7] (more often if there is evidence of impaired thyroid function, raised calcium or an increase in mood symptoms that might be related to impaired thyroid function)

Other monitoring
NICE recommend that patients are monitored for signs of neurotoxicity (including paraesthesia, ataxia, tremor and cognitive impairment) which can occur at therapeutic levels[7]

NICE and DTB recommend annual calcium checks[4,7].

Additionally NICE recommend that all patients with bipolar disorder should have annual physical health reviews at least annually which includes[7]

- weight or BMI, diet, nutritional status and level of physical activity
- cardiovascular status, including pulse and blood pressure
- metabolic status, including fasting blood glucose, glycosylated haemoglobin (HbA_{1c}) and blood lipid profile

Liver function **Action required if abnormal results**

Plasma levels
NICE/BNF/SPC states serum lithium levels should be maintained between 0.6 and 1.0 mmol/l

Toxic effects reliably occur at levels >1.5mmol/L[1,3]. If signs of toxicity are present, stop treatment, check plasma levels, and take steps to reverse the toxicity. A concentration of >2mmol/L can be associated with serious toxicity and requires urgent treatment[2].

More frequent testing should be undertaken if there is evidence of clinical deterioration, abnormal results, a change in sodium intake, or symptoms suggesting abnormal renal or thyroid function (e.g. unexplained fatigue) or other risk factors (e.g. patient starting interacting medication)[7]

If urea and creatinine levels become elevated, initiate closer monitoring of dose and blood levels and assess the rate of renal function deterioration[7].

The NPSA alert supporting information states that the management of subclinical hypothyroidism (SCH) remains controversial [9], but the following approach has been suggested. Arrange referral or discuss with an endocrinologist, the urgency depending on clinical judgement, if the suspected cause of SCH is lithium treatment. Consider offering levothyroxine (LT4) monotherapy if the thyroid-stimulating hormone (TSH) level is greater than 10mU/L and free thyroxine (FT4) level is within the reference range on 2 separate occasions 3 months apart[6].

Additional notes

Stopping lithium:
The Camcolit SPC states that if lithium is to be discontinued for reasons other than toxicity the dose should be reduced gradually over a suitable period of time, eg 2 weeks, to prevent the risk of relapse.[3]

NICE recommend that when stopping lithium the dose should be reduced gradually over at least 4 weeks, and preferably up to 3 months, even if the person has started taking another antimanic drug. During dose reduction and for 3 months after lithium treatment is stopped, monitor the person closely for early signs of mania and depression[7]. SLAM recommend that incremental reductions in plasma levels of >0.2mmol/L should be avoided[1]
A lithium treatment pack should be given to all patients on initiation of therapy and they should receive appropriate ongoing verbal and written information. The pack consists of a patient information booklet, lithium alert card, and a treatment record book.[2] The record book should be used to track blood levels.[2, 5, 9].Prescribers and pharmacists should check blood levels are monitored regularly and that it is safe to issue a repeat prescription and/or dispense the prescribed item[9]. Systems to identify and deal with medicines that might adversely interact with lithium therapy should be in place[5,9].

Samples should be taken 12 hours after the dose [2,3,7] (range 11 – 13 hours post dose)[5]
In patients prescribed a single daily dose of a prolonged-release preparation ideally blood samples for plasma lithium level should still be taken 12 hours post-dose. In practice an interval of 10-14 hours is acceptable as long as the interval is the same at each measurement and the delay after the dose noted[4]

NICE recommend that patients should be advised that erratic compliance or rapid discontinuation may increase the risk of manic relapse. Monitor older adults carefully for symptoms of lithium toxicity because they may develop high serum levels of lithium at doses in the normal range, and lithium toxicity is possible at moderate serum levels.[7]

Patients should be advised to:

- avoid dietary changes which reduce or increase sodium intake[2]
- seek medical attention if they develop diarrhoea and/or vomiting[7]
- report the signs and symptoms of lithium toxicity, hypothyroidism, renal dysfunction and benign intracranial hypertension.[2]
- ensure they maintain their fluid intake, particularly after sweating (for example, after exercise, in hot climates or if they have a fever), if they are immobile for long periods or if they develop a chest infection or pneumonia[7]
- Patients taking lithium should be warned not to take OTC NSAIDs[7]

SLAM state that there is no clinically significant difference in the pharmacokinetics of Priadel and Camcolit. However preparations should not be assumed to be bioequivalent and should be prescribed by brand.[1] When switching from one brand or preparation to another a baseline plasma level must be taken 12 hours after the last dose. Switches should only be undertaken if services are in place to permit more frequent monitoring[5].

SLAM also note that lithium citrate liquid is available in two strengths (equivalent to 200mg and 400mg lithium carbonate in 5ml) and that care is needed when prescribing and dispensing to ensure that patient receives the intended dose.

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Mercaptopurine

Tests prior to starting treatment

FBC [3]
LFTs[2, 3]
U&Es [3]
TPMT assay[2, 5, 7]

BSG recommends testing for NUDT15 genotype, if available [3]

BSG recommends screening for HBV, HCV and HIV, with referral if positive. Consider HBV vaccination if naïve [3]. Some also recommend screening for EBV prior to treatment with thiopurines, and considering antivirals in an acute infection [7]

BSG recommends checking VZV immunity (if no history of infection), and vaccinating if low [3]

Monitoring until patient is stabilised

BNF recommends monitoring LFTs (frequency unspecified) [2]

BSG recommends early intensive monitoring for haematological and biochemical toxicity in all patients receiving treatment with thiopurines, with FBC, U&E and LFTs checked after 2, 4, 8 and 12 weeks, and then at least every 3 months[3]. Bloods should be repeated 2 weeks after all dose increases [3]

NICE states that patients should be monitored for neutropenia, even if TPMT activity is normal [5]

GI specialists from Guys and St Thomas NHS Foundation Trust recommend that the methylmercaptopurine to thioguanine ratio (MeMP:TGN) is measured at Week 4 and 16 (and at Week 4 after each dose change).They also recommend that CRP be checked with each blood test, as a measure of disease activity.[4]

Ongoing monitoring

BNF recommends monitoring LFTs (frequency unspecified) [2]

BSG recommends monitoring FBC, U&E and LFTs at least every 3 months [3]

Local decision needed on whether the advice below is feasible and can be implemented locally

GI specialists from Guys & St Thomas NHS Foundation Trust recommend that the methylmercaptopurine to thioguanine ratio (MeMP:TGN) is measured annually. 4 They also recommend that CRP be checked with each blood test, as a measure of disease activity.[4], BSG guidance notes it is unclear whether routine measurement of metabolites in all patients is beneficial, owing to wide variation in levels.[3]

Action required if abnormal results

For people on any DMARD, CKS advise that consideration be made to stopping treatment and referring urgently to a specialist if: [1]

- WCC < 3.5 x 10^9/L
- Neutrophils< 1.6 x 10^9/L (BSG recommend withholding treatment if <2 x 10^9/L)[3]
- Platelets < 140 x 10^9/L
- ALT and/or AST increase to >100 U/L
- Unexplained reduction in albumin to <30g/L

If neutrophils are <1 x 10^9/L, patients should be warned to present for antibiotics ± GCSF if febrile [3]

If creatinine has increased >30% over 12 months and/or calculated GFR<60mL/min, repeat in one week. If it is still >30% from baseline, withhold and discuss with the specialist team[1].

If patient develops renal impairment (eGFR < 50ml/min) check dosing with specialist

If MCV > 105fL: check B12, serum folate and TSH – treat if abnormal, and discuss with specialist team if normal[1]

Thiopurines should be immediately stopped if pancreatitis develops, and re-challenge is not recommended[7].

Additional notes

BSG recommends that IBD patients receiving immunomodulators should receive pneumococcal vaccine and annual influenza vaccination (prior to starting treatment if possible), with a single pneumococcal booster at 5 years[3].

BSG guidance states that live vaccinations should not be given during and until at least three months after stopping immunosuppressive therapy; however singles vaccination may be administered to those on low-level immunosuppression (mercaptopurine ≤1.5mg/kg/day)[3]. The Green Book advises that long-term stable low-dose corticosteroid therapy, either alone or in combination with low-dose non-biological oral immune modulating drugs (including 6-mercaptopurine in doses ≤ 1.5mg/kg/day) are **not** considered sufficiently immunosuppressive and these patients **can** receive live vaccines [6]. BSG cautions however that live vaccinations should only be undertaken for those on low-level immunosuppression after careful consideration of risks and benefits[3]

Patients should be warned to report immediately any signs or symptoms of bone marrow suppression (e.g. inexplicable bruising or bleeding) [2] or liver impairment (e.g. new onset jaundice) [8]

CKS advise that consideration be given to stopping treatment with urgent specialist referral if a person taking any DMARD develops skin/mucosal reaction (e.g. rash, pruritus, or throat ulceration), sore throat, fever, unexplained bruising or bleeding, nausea, vomiting diarrhoea or weight loss, diffuse alopecia, breathlessness, infection or cough, or peripheral neuropathy[1].

Thiopurines may increase the risk of non-melanoma skin cancer[1], and people should be monitored for skin cancer and given appropriate sun protection advice[1].

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Mesalazine

Tests prior to starting treatment

Renal function should be assessed prior to starting treatment. [1,2]
U&Es.[2]
LFTs [2]
FBC[2]
Urine dipstick[2]

Monitoring until patient is stabilised

- Renal function
- U&Es
- LFTs
- FBC
- Urine dipstick

These tests should be monitored 14 days after starting treatment and then a further 2 or 3 tests at intervals of 4 weeks. If results are normal, then tests can be reduced to every 3 months,[2] .

Ongoing monitoring

There is no national standard for long term monitoring. It is left to the discretion of the physician and should take into account the person's risk factors.[2]

- Renal function should be monitored every 6 months for the first 4 years then annually, or more frequently if there are risk factors for renal impairment. [4]

- U&Es
- LFTs
- FBC
- Urine dipstick

Monitored every 6 months or annually based on the person's risk factors.

Action required if abnormal results

Mesalazine should be discontinued if renal function deteriorates.[2-4]
AST, ALT > twice upper limit of reference range, withhold treatment until discussed with the specialist team.[5]

Additional notes

Haematological investigations should be performed if the patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat. Treatment should be stopped if there is suspicion or evidence of blood dyscrasia.[2]

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Methotrexate

Tests prior to starting treatment

BSR recommend that all patients starting DMARDs should have baseline measurement of height, weight and BP[1]

FBC [1, 2,8]
Renal profile (creatinine/calculated GFR)[1,8]
Serum albumin[1]
ALT and/or AST[1] (BNF, BSG and BAD state LFTs [2,3,8])
Serum PIIINP in those with psoriasis [2]

Screening for HIV, HBV and HCV is recommended [2, 8]; BSR recommends consideration of antiviral treatment prior to initiation of immunosuppressive DMARDs in patients with chronic viral hepatitis.[1]

VZV screening is recommended, if there is any doubt as to the patient's VZV status (no history of chicken pox, shingles or varicella vaccination) [2,8]. Where serology is negative, the patient should be considered for VZV vaccination [2]

If there is any suspicion of latent TB, BAD advises screening for latent or active TB infection and treatment if positive, prior to commencing therapy [2]

BSG states it is unclear whether screening for EBV status should be done routinely[8]

BSG recommends a baseline chest x-ray for all patients commencing methotrexate.[8] BSR recommends screening for lung disease should be undertaken at clinical discretion on a case-by-case basis[1] and BAD recommends a chest x-ray and physical examination (and possible lung function tests – discuss with respiratory physicians) if the patient has a disease that affects the lungs (e.g. sarcoid)[2]

The BNF notes that treatment should not be started or should be discontinued if any abnormality of liver function or liver biopsy is present or develops during therapy.[3]

A reduction in methotrexate dose should be considered in those with suboptimal renal function[2], and it should be avoided in severe renal impairment [3]

Monitoring until patient is stabilised

In General

BNF recommends FBC, renal and liver function tests every 1-2 weeks until therapy is stabilised [3]

Rheumatology

FBC, creatinine/calculated GFR, ALT and/or AST, albumin every two weeks until dose stable for at least 6 weeks then monthly thereafter for 3 months. More frequent monitoring may be required in high-risk patients.[1]

If methotrexate is combined with leflunomide, BSR recommend continuing with monthly monitoring until stable for 12 months, then consider reduced frequency monitoring on an individual basis. [1]

Following a change in dose repeat FBC, ALT and/or AST, creatinine/calculated GFR and albumin every 2 weeks until dose stable for 6 weeks and then revert to previous schedule.[1]

Dermatology
BAD recommends FBC, U&Es and LFTs every 1-2 weeks for the first month and until a steady dosing regimen is achieved – FBC should be performed before dosing in week 2[2].

Gastroenterology
BSG recommends FBC, renal and liver biochemistry at 2, 4, 8 and 12 weeks of therapy, and then at least every 3 months, with monitoring for side-effects. Bloods should be repeated 2 weeks after all dose increases.[8]

Ongoing monitoring

A local policy outlining whether endorsing these general monitoring recommendations is more realistic than supporting differing recommendations for each indication is needed

In General
CSM and BNF recommend FBC, U&Es, renal function and LFTs every 2-3 months once therapy is stabilised [3,4] BNF notes that local protocols for frequency of monitoring may vary.[3]

Rheumatology
Once the maintenance dose has been achieved and the patient has had monthly monitoring for 3 months, consider monitoring FBC, creatinine/calculated GFR, albumin, ALT and/or AST at least every 12 weeks.[1,] More frequent monitoring is appropriate in patients at higher risk of toxicity[1].

Additionally the NPSA suggest that CRP, ESR or PV may be monitored every 3 months and creatinine every 3-6 months [7].

Dermatology
Once the patient is on a stable dose, measurement of FBC, LFTs and U&Es can be performed every 2-3 months. Patients with risk factors (e.g. renal insufficiency or advanced age) may need closer monitoring, both at the onset of treatment and after dosage increases[2].

The practicalities of implementing this at a local level would need to be clarified

When used in patients with psoriasis, serial elevation of serum procollagen III levels may be an indication of hepatic fibrosis, and BAD recommend measuring levels at least every 3 months, where available, and that specialist advice be sought if abnormal[2]. NICE recommends that PIIINP levels be used alongside standard LFTs to monitor for abnormalities during treatment, taking into account pre-existing risk factors (e.g. obesity, diabetes and alcohol use), baseline results and trends over time[10]

Gastroenterology
After the first 12 weeks of therapy, BSG recommend monitoring FBC, U&E and LFTs at least every 12 weeks, on an ongoing basis, with monitoring for side-effects[8]

Action required if abnormal results

Guidance from BSR, BAD and BSG vary slightly – local decision needed

BSR recommend that the specialist team be contacted urgently and treatment interruption considered if any of the following develop: [1]

- WCC < 3.5 x 10^9/L,
- Neutrophils< 1.6 x 10^9/L
- Unexplained eosinophilia > 0.5x 10 ^{9}/L
- Platelets < 140 x 10^9/l,
- AST and/or ALT increase to >100units/ml (BSG recommends that methotrexate be stopped if transaminases >2xULN[8]; BAD recommend repeating LFTs in 2-4 weeks if AST and ALT increase by <2xULN and dose reduction/withholding treatment if AST and ALT <2-3xULN)[2]
- Unexplained fall in serum albumin <30g/L
- MCV > 105f/L (check B12, folate, thyroid-stimulating hormone levels – if abnormal treat, if normal discuss with specialist team)[5]
- Creatinine increase > 30% above baseline over 12 months and/or calculated
- GFR<60ml/min/1.73m^2 (repeat in 1 week, if still more than 30% from baseline, withhold and discuss with specialist team)[5]

As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g. gradual decreases in white blood cells or albumin, or increasing liver enzymes)[1]. A downward trend of FBC and neutrophil count or an upward trend in liver transaminases could be a sign of toxicity, even if the absolute levels are normal[2].

Additional notes

Pneumococcal vaccine and annual flu vaccine should be given[1, 8] (prior to starting treatment if possible)[8], with a single pneumococcal booster at 5 years[8]. Although live vaccinations should not be given during and until at least three months after stopping immunosuppressive therapy, the Green Book advises that long-term low-dose corticosteroid therapy and low-dose non-biological DMARDs (including methotrexate <25mg per week) are not considered sufficiently immunosuppressive and these patients can receive live vaccines, after careful consideration of risks and benefits[13].

BNF advises withdrawal of treatment if stomatitis or diarrhoea develops, as this may be the first sign of gastro-intestinal toxicity[3]

During a serious infection, methotrexate should be temporarily discontinued until the patient has recovered from the infection[1].

Patients and their carers should be warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort and dark urine), and respiratory effects (e.g. shortness of breath).[3] [12] BAD recommend that treatment be withheld and FBC checked immediately if a patient presents with a severe sore throat or abnormal bruising. Refer to specialist for advice if a patient presents with new or increasing dyspnoea or dry cough, as treatment may need to be withheld and repeat chest x-ray and pulmonary function tests may be required[2].

Patients should be advised to report all symptoms and signs suggestive of infection, especially sore throat [3]

Patients should be carefully advised of the dose and frequency and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid). They should also be counselled on use of the methotrexate treatment booklet and the need to avoid self-medication with over-the-counter aspirin or ibuprofen[3]

All patients should be co-prescribed folic acid supplementation at a minimal dose of 5mg once weekly [1]

The NPSA advise that patients should be instructed to only take their methotrexate once a week on the same day each week and should be issued with a patient-held record card [3,9]

References

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Minocycline

Tests prior to starting treatment

FBC, renal and hepatic assessment if there is a history suggesting they may be abnormal.1

Monitoring until patient is stabilised

None.[2]

Ongoing monitoring

Local decision needed on whether to monitor on an ongoing basis

If treatment continued for longer than 6 months:

- Monitor every 3 months for hepatotoxicity, pigmentation and for systemic lupus erythematosus (SLE).[3,4] Periodic laboratory evaluations of organ system function, including haematopoietic, renal and hepatic should be conducted .[4]
- Watch for hypersensitivity syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, pericarditis, fever and lymphadenopathy; or for lupus-like or serum sickness-like syndromes 4.

BSR state that no routine laboratory monitoring is required [2].

Action required if abnormal results

Discontinue if the patient develops hepatotoxicity, unusual pigmentation, SLE or lupus-like syndrome, photosensitivity, raised intracranial pressure, hypersensitivity syndrome, serum sickness-like syndrome or if pre-existing SLE gets worse. Minocycline should also be discontinued if there are signs or symptoms of overgrowth of resistant organisms, e.g. enteritis, glossitis, stomatitis, vaginitis, pruritus ani or Staphylococcal enteritis.[4]

Additional notes

Minocycline is not recommended for use in acne as it is associated with an increased risk of drug- induced lupus, skin pigmentation and hepatitis.[5]

References

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Mycophenolate

Tests prior to starting treatment

Height[1]
Weight[1]
BP[1]
FBC[1]
Renal profile (calculated GFR)[1]
LFT's (ALT and/or AST), albumin)[1]

An annual influenza vaccine should be given, and a pneumococcal vaccine should be given preferably before starting mycophenolate. Pneumococcal vaccine should be repeated at 10-yearly intervals if given before starting the DMARD, or at 5-yearly intervals if given after starting the DMARD.[1,2]

Mycophenolate treatment should only be initiated in women of childbearing potential when there is a negative pregnancy test result to rule out unintended use in pregnancy. Two pregnancy tests 8–10 days apart are recommended.[3]

Monitoring until patient is stabilised

FBC, creatinine/calculated GFR, ALT and/or AST, albumin every two weeks until dose stable for at least 6 weeks then monthly thereafter for 3 months. More frequent monitoring may be required in high-risk patients.[1, 2]

Following a change in dose repeat FBC, ALT and/or AST, creatinine/calculated GFR and albumin every 2 weeks until dose stable for 6 weeks and then revert to previous schedule[1, 2]

BNF recommends FBC every week for 4 weeks then twice a month for 2 months then every month in the first year[4]

In females of child-bearing potential, exclude pregnancy whilst on treatment.[3]
People who are taking mycophenolate are more prone to infection, especially in the first 6 months of treatment.[2]

Ongoing monitoring

Once the maintenance dose has been achieved and stable for 3 months consider monitoring FBC, creatinine/calculated GFR, albumin, ALT and/or AST at least every 12 weeks.[1]

Action required if abnormal results

Contact rheumatology team urgently and consider interruption in treatment if:[1,2]

- WCC < 3.5 x 10^9/L,
- Neutrophils< 1.6 x 10^9/L
- Unexplained eosinophilia > 0.5x 10 ^{9}/L
- Platelets < 140 x 10^9/l,
- AST and/or ALT increase to >100units/ml
- Unexplained fall in serum albumin <30g/L
- MCV > 105f/L. Check B12, folate, thyroid-stimulating hormone levels – if abnormal treat, if normal discuss with specialist team.
- Creatinine increase > 30% above baseline over 12 months and/or calculated GFR <
- 60ml/min/1.73m^2. Repeat in 1 week, if still more than 30% from baseline, withhold and discuss with specialist team.
- BP >140/90mmHg. Manage in accordance with hypertension guidelines
- Urinary protein 2+ or more — check mid-stream urine sample. If evidence of infection, treat appropriately. If sterile and 2+ proteinuria or more persists on two consecutive measurements, withhold until discussed with specialist team.
- Monitor for trends in results (e.g. gradual decreases in white blood cells or albumin or increasing liver enzymes

Consider stopping treatment and referring urgently to rheumatology if patient develops:[2]

- Skin/mucosal reaction eg rash, pruritus, mouth or throat ulceration
- Sore throat
- Fever
- Unexplained bruising or bleeding
- Nausea, vomiting, diarrhoea or weight loss
- Diffuse alopecia
- Breathlessness, infection or cough
- Peripheral neuropathy

Additional notes

Advice for prescribing mycophenolate to male patients:[4]

- Available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate medicines, however mycophenolate mofetil and mycophenolic acid are genotoxic and a risk cannot be fully excluded.
- It is therefore recommended that male patients or their female partner use reliable contraception during treatment and for at least 90 days after stopping mycophenolate medicines
- Discuss with male patients planning to have children the implications of both immunosuppression and the effect of prescribed medications on the pregnancy

Reminder for prescribing mycophenolate to female patients:[4]

- Mycophenolate medicines remain contraindicated in women of childbearing potential who are not using reliable contraception and in pregnant women unless there are no suitable alternatives to prevent transplant rejection
- Female patients of childbearing potential must use at least one reliable form of contraception before and during treatment and for 6 weeks after stopping mycophenolate medicines; 2 forms of contraception are preferred
- Report suspected adverse drug reactions associated with mycophenolate medicines, including adverse pregnancy outcomes, to us on a Yellow Card

During a serious infection, mycophenolate should be temporarily discontinued until the patient has recovered.[1]

Advise patient to avoid contact with people that have shingles or chickenpox. If they come in to contact with these people, they must seek urgent medical advice.[2]

Patients should be advised to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow failure.[5]

Live vaccines (for example, yellow fever and rubella) are contraindicated for people who are on DMARDs. Always seek specialist advice if a live vaccine is being considered.[2]

Mycophenolate mofetil 1g is approximately equivalent to mycophenolic acid 720mg. Avoid unnecessary switching because of pharmacokinetic differences.[6]

References

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Nitrofurantoin (long-term)

Tests prior to starting treatment

Contraindications for the use of nitrofurantoin include: [1]

I. deficiency of glucose-6-phosphate dehydrogenase or acute porphyria[1]
II. acute porphyria[1]

eGFR <45 mL/minute/1.73 m2 (as there is a risk of peripheral neuropathy and treatment may be ineffective due to inadequate urine concentrations) [1, 2] (However, may be used with caution as short-course treatment of uncomplicated UTI in individual cases with an eGFR between 30-44 ml/min to treat resistant pathogens, when benefits may outweigh the risks) [1,3,4]

Consider checking renal function, especially in the elderly [3]

Liver function [4]

Monitoring until patient is stabilised

Renal function (no national recommendations available)

Liver function [4]

Monitor closely for pulmonary symptoms, especially in the elderly [4]

Ongoing monitoring

Local decision needed on frequency of monitoring renal and liver function

Renal function (no national recommendations available)

Liver function [4]

Monitor closely for pulmonary symptoms, especially in the elderly [4]

Action required if abnormal results

Treatment should be discontinued if the person develops unexplained pulmonary[4], hepatotoxic, haematological, or neurologic syndromes. [1]

Additional notes

Advise patients to report any signs/symptoms suggestive of pulmonary toxicity (e.g. cough; chest pain; dyspnoea), hepatotoxicity, peripheral neuropathy (sensory as well as motor involvement) or haemolysis. [1]

Note that the onset of hepatotoxicity can be insidious and symptoms can be non-specific (e.g. nausea, rash, headache, flu-like symptoms). Cholestatic jaundice is generally associated with short-term therapy (usually up to two weeks) whereas chronic active hepatitis, occasionally leading to hepatic necrosis, is generally associated with long-term therapy (usually after six months). [1]

The severity of chronic pulmonary reactions and their degree of resolution appear to be related to the duration of therapy after the first clinical signs appear. It is therefore important to recognise symptoms as early as possible. Note that minor symptoms such as fever, chills, cough and dyspnoea may be significant. Pulmonary function may be impaired permanently, even after cessation of therapy. [1]

People taking nitrofurantoin are susceptible to false positive urinary glucose (if tested for reducing substances) [1,4]

Urine may be coloured yellow or brown after taking nitrofurantoin. [1,4]

References

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NSAIDs (including COX IIs)

Tests prior to starting treatment

BP: Elderly and people taking COX-2 inhibitors.[1,2]

No national guidance available but also maybe consider assessment of renal and hepatic function particularly in the elderly or if clinical concern.

Monitoring until patient is stabilised

BP: Two weeks after treatment for etoricoxib[1,2,3] or 1–4 weeks after starting long-term treatment, or increasing dose in patients with hypertension.[1,3]

Renal function: Monitor 1–2 weeks after starting or increasing dose of NSAID in renal impariment.[1]

Liver function: In hepatic impairment.

Haemoglobin levels: Monitor 1-4 weeks after start of treatment in people at high risk of gastrointestinal adverse effects[1]

Consider monitoring BP, renal function, and features of heart failure 1–2 weeks after starting or increasing dose of NSAID, and then regularly thereafter, in:

- Elderly
- Ischaemic heart disease.
- Risk factors for cardiovascular disease.
- Cerebrovascular disease.
- Peripheral vascular disease.
- Heart failure.[1]

Ongoing monitoring

BP: Periodically during treatment in elderly and people taking COX-2 inhibitors.[1]

Renal function: In renal impairment, monitor regularly or at least annually. Also consider monitoring in with additional drugs that can affect renal function (eg, ACE inhibitors, angiotensin-II receptor antagonists, or diuretics).[1]

Liver function: In liver impairment and on long-term NSAID therapy.[1]

Action required if abnormal results

Review risks vs benefits in light of any changes in patient's baseline parameters.

Additional notes

Review appropriateness of NSAID prescribing widely and on a routine basis, especially in people who are at higher risk of gastrointestinal, renal and cardiovascular morbidity and mortality and those taking drugs which may interact with an NSAID. Consider risks and response to treatment, and use clinical judgement to decide what must be monitored and how frequently. Enquire about, and manage, adverse effects.[1]

NSAIDs in the elderly
The use of NSAIDs in elderly patients is potentially inappropriate (STOPP criteria) if prescribed:

- with a vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitor in combination (risk of major gastrointestinal bleeding);
- with concurrent antiplatelet agent(s) without proton pump inhibitor (PPI) prophylaxis (increased risk of peptic ulcer disease);
- in a history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2-receptor antagonist (risk of peptic ulcer relapse)—not including COX-2 selective NSAIDs;
- with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease);
- in patients with an eGFR less than 50 mL/minute/1.73 m2 (risk of deterioration in renal function);
- in severe hypertension or severe heart failure (risk of exacerbation);
- for long-term (longer than 3 months) symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics are preferable and usually as effective for pain relief);
- for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout);
- a COX-2 selective NSAID in concurrent cardiovascular disease (increased risk of myocardial infarction and stroke).[2]

NSAIDs should always be used at the lowest effective dose and for the shortest possible duration.[1]

NSAIDs and asthma
Any degree of worsening of asthma may be related to the ingestion of NSAIDs, either prescribed or (in the case of ibuprofen and others) purchased over the counter.[2]

NSAIDs and cardiovascular events
All NSAID use (including COX-2 selective inhibitors) can, to varying degrees, be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) independent of baseline cardiovascular risk factors or duration of NSAID use; however, the greatest risk may be in those receiving high doses long term.[2]

The lowest effective dose of NSAID should be prescribed for the shortest period of time to control symptoms and the need for long-term treatment should be reviewed periodically.[2]

NSAIDs and gastro-intestinal events
Gastroprotection is indicated in patients:

- At increased risk of gastrointestinal adverse effects (eg with long-term treatment) or elderly.
- Experiencing dyspepsia from standard NSAIDs.[1,2]

The combination of a NSAID and low-dose aspirin can increase the risk of gastro-intestinal side-effects; this combination should be used only if absolutely necessary and the patient should be monitored closely.[2]

NSAIDs and alcohol
Alcohol increases the risk of gastro-intestinal haemorrhage associated with NSAIDs. Specialist sources recommend that concurrent use need not be avoided with moderate alcohol intake, but greater caution is warranted in those who drink more than the recommended daily limits.[2]

Some cases of acute kidney injury have been attributed to use of NSAIDs and acute excessive alcohol consumption.[2]

NSAIDs and Sick Day Rules
Stop NSAID when unwell with vomiting or diarrhoea (unless minor), or fever, sweats and shaking (unless minor).[1]
Restart when well (after 24–48 hours of normal eating and drinking).[1]

References

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D-Penicillamine

Tests prior to starting treatment

FBC including platelets
urinalysis for proteinuria,
U&Es and creatinine[1, 2, 34]
LFTs: ALT and/or AST and albumin

Monitoring until patient is stabilised

Urinalysis for protein/ blood and FBC every 2 weeks until on a stable dose for 3 months, monitor monthly thereafter [1,3] CKS recommends every 2 weeks until dose is stable for 6 weeks. [3]

BNF and SPC recommend urinalysis for protein/ blood and FBC (including platelets) every 1 or 2 weeks for first 2 months and in the week after any dose increase[2,4]

LFTs: ALT and/or AST and albumin every 2 weeks until on stable dose for 6 weeks, monitor monthly thereafter. Patients stable for 12 months can be considered for reduced monitoring (every 3 months) on an individual basis[3].

Creatinine/ calculated GFR every 2 weeks until on stable dose for 6 weeks, monitor monthly thereafter.[4]

Dose increases: monitor all parameters (FBC, U&E, LFTs and urinalysis) every 2 weeks until dose is stable for 6 weeks, then revert to previous schedule[3].

Local decision needed on monitoring guidance in non-RA indications and whether reduced monitoring in stable patients is appropriate

Ongoing monitoring

Urinalysis for protein/blood and FBC every 4 weeks [2,3 ,4.]

CKS also recommend monthly monitoring of creatinine/ calculated GFR, LFTs (ALT and/or AST and albumin). [4]

Once patients have been stable for 12 months CKS advise that consideration on an individual patient level can be given to reduce all above monitoring to 3 monthly. [4]

Fortnightly monitoring of renal function is recommend in the SPC for renally impaired patients treated with penicillamine for rheumatoid arthritis[4].
The BNF and SPC state that longer intervals may be adequate when used in in cystinuria and Wilson's disease[2,4]

Action required if abnormal results

Withhold treatment until discussion with rheumatologist if WBC<3.5, neutrophils<1.6, platelets<150l [1,3]

BNF recommends consideration of withdrawal if WCC < 2.5 or platelets < 120 or there are 3 successive falls in count. Restart at reduced dose when counts return to within reference range but permanent withdrawal necessary if recurrence of leucopenia or thrombocytopenia[2,4]

If proteinuria is 2+ or more, check MSSU: If evidence of infection
treat appropriately. If sterile and 2+ proteinuria or more persists (on two consecutive measurements), withhold until discussed with specialist team.[1,3]

If abnormal bruising or sore throat- withhold until FBC available[1,3]

Additional notes

Ask patient about presence of rash or oral ulceration at each visit. If rash severe or oral ulceration present (late rashes are more serious than early ones), withhold until discussed with specialist. [1,3]

Patients should be told to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexpected bleeding and bruising, purpura, mouth ulcers, or rashes.[2]

Patients who are hypersensitive to penicillin may react rarely to penicillamine.[2]
Longer intervals for blood counts and urine tests may be adequate in cystinuria. [2, 4]
Alteration of taste may settle spontaneously. [1,4]
Especially careful monitoring is necessary in the elderly since increased toxicity has been observed in this patient population regardless of renal function.[4]

References

1. BSR/BHPR Guideline for disease modifying anti-rheumatic drug therapy (DMARD) in consultation with the British Association of Dermatologists (2008). Accessed June 2020 (Penicillamine was not addressed in the BSR 2017 update – therefore the recommendations cited here are taken from the 2008 version.
2. British National Formulary. Last updated June 2020. Accessed online via medicines complete. [Accessed on: 19/06/20]
3. CKS – DMARDs: Penicillamine. Last revised July 2018
4. SPC for D-penicillamine (Distamine™ tablets). Last revised Jan 2014

Phenytoin

Tests prior to starting treatment

The value of routine monitoring of FBC is questioned. However, NICE recommends that patients receiving an enzyme inducing medicine should have FBC, LFTs, U&Es and Vitamin D levels (and other test of bone metabolism such as calcium or ALP) assessed every 2-5 years so baseline values may be useful[2,3,4].

The manufacturers and NICE recommend that phenytoin should be avoided unless essential, in patients of Han Chinese or Thai origin who possess the HLAB* 1502 allele. This is thought to be because these patients are at an increased risk of Stevens- Johnson syndrome [1,3].

The BNF recommends to consider vitamin D supplementation (phenytoin can cause vitamin d deficiency), in patients who are immobilised for long periods or who have inadequate sun exposure or dietary intake of calcium [3]. **Monitoring until patient is stabilised**

SPC suggests frequent FBC monitoring throughout treatment but BNF and SIGN state that evidence of practical value is uncertain[1, 3,4]

Drug level monitoring in patients with epilepsy should NOT be routinely performed unless to assess adherence, in the case of unexplained loss of seizure control, suspected toxicity, after adjustment of phenytoin dose, to manage a pharmacokinetic interaction or following onset of specific clinical conditions (e.g. pregnancy, organ failure, status epilepticus) [2, 4,5]

Where drug level monitoring is felt to be necessary, dosage should be adjusted according to serum levels where assay facilities exist. [1,3]

Ongoing monitoring

Local system needed to ensure implementation on NICE advice on monitoring recommendations

The manufacturers suggest frequent FBC monitoring throughout treatment however the BNF states that the practical value of this is uncertain[1,3,4]

NICE suggest that regular drug level blood test monitoring is not recommended as routine however they do suggest FBC, U&Es, liver enzymes, Vitamin D levels and other tests of bone metabolism every 2-5 years for adults taking enzyme-inducing drugs[2,3,5]

The SPC states to monitor serum folate at least 6 monthly and supplement where necessary but again this is not supported by NICE, SIGN or BNF[1,2,3,4]

Action required if abnormal results

Leucopenia, which is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative)[3]

Asymptomatic minor abnormalities in test results are not necessarily an indication for changes in medication[2]

Symptoms of phenytoin toxicity include nystagmus, diplopia, slurred speech, ataxia, confusion, and hyperglycaemia. [1, 3]

Leucopenia that is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of a suitable alternative). [1, 3]

Additional notes

Patients/carers should be told how to recognise signs of blood or skin disorders[1, 3]. They should also be advised to seek immediate medical attention if symptoms such as fever, rash, mouth ulcers, bruising, or bleeding develop. [1, 3]

Generally, the therapeutic phenytoin serum level is 10-20µg/ml (or 40–80 micromol/ litre) although there are some cases which may be controlled with lower serum levels such as some cases of tonic clonic seizures as well as cases where protein binding is reduced e.g. elderly[1,3]

Doctors and pharmacists should ensure that MHRA advice is followed and that patients are maintained on a specific manufacturer's preparation of phenytoin[3]. Please note that reparations containing phenytoin sodium are not bioequivalent to those containing phenytoin base [1,3,5].

Phenytoin is thought to affect bone mineral metabolism indirectly by increasing the metabolism of Vitamin D3. This may lead to Vitamin D deficiency, hypocalcemia, and hypophosphatemia in chronically treated epileptic patients. [1,2,3]

Phenytoin is highly protein bound [1, 3]. When protein binding is reduced e.g.hypoalbuminemia there will be an increase in unbound phenytoin levels. Under these circumstances therapeutic control may be achieved with total phenytoin levels below the normal range [1, 3] Patients with hepatic impairment may therefore be more susceptible to toxicity [1,3.]

Phenytoin may cause a slight decrease in serum levels of total and free thyroxine, but levels of circulating TSH are not affected, therefore the latter can be used for diagnosis of hypothyroidism in a patient on phenytoin. [1, 3]

Phenytoin is metabolized by hepatic cytochrome (CYP) P450 enzymes CYP2C9 and CYP2C19 and is particularly susceptible to inhibitory drug interactions [1,3]

Phenytoin is a potent inducer of hepatic drug-metabolizing enzymes and may reduce the levels of drugs metabolized by these enzymes e.g. some oral contraceptives hence women of childbearing potential should be counselled regarding the use of other effective contraceptive methods, see latest FSRH Guidance for advice. [1,3,6]

Medical advice regarding the potential risks to a foetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment [1,3]. This is especially important for women planning pregnancy and women who are pregnant [1,3]. Antiepileptic treatment should be reviewed regularly and especially when a woman is planning to become pregnant. In pregnant women being treated for epilepsy, sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as

this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. [1,3]

References

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7. last accessed 11/06/20

Pioglitazone

Tests prior to starting treatment

HbA1c and LFTs.[1, 2]
Weight [1, 3]
FBC[3, 5]
Urine test for macroscopic haematuria[1, 2, 3]**Monitoring until patient is stabilised**

LFTs should be monitored periodically based on clinical judgement[1, 2, 3,]

Monitor HbA1c at 3–6-monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy.[4]

Ongoing monitoring

In the absence of clear national guidance a local guideline may be needed e.g. monitor LFTs at least annually or more frequently if there are concerns about liver impairment.

LFTs should be monitored periodically based on clinical judgement and must be checked if patient develops signs suggesting liver dysfunction.[1, 2, 3,]

Patients should be observed for signs and symptoms of heart failure, weight gain or oedema; particularly those with reduced cardiac reserve. Risk is increased when pioglitazone is used in combination with insulin[1, 3, 4, and 5]

Assess HbA1c regularly (6 monthly) [4]and discontinue if patients do not respond adequately after 3-6 months.[2, 3, 4]

Action required if abnormal results

Check liver enzymes if patient develops symptoms suggesting hepatic dysfunction, which may include unexplained nausea, vomiting, abdominal pain, fatigue, anorexia and/or dark urine, liver enzymes should be checked. [1, 3]

Do not initiate therapy if ALT > 2.5 X upper limit of normal or if there is any other evidence of liver disease [1, 3,]

Investigate any macroscopic haematuria before starting pioglitazone therapy[1]

If ALT levels > 3 X ULN during therapy, liver enzyme levels should be reassessed as soon as possible. If ALT levels remain > 3 x ULN, pioglitazone should be discontinued.[1, 2, 3]

Pioglitazone should be discontinued if there is any deterioration in cardiac status[5] or if jaundice is observed.[1, 3]

Additional notes

Advise patients to seek immediate medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue, anorexia and dark urine develop[3]

Advise patients to promptly seek medical attention if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.[1]

Thiazolidinediones, including pioglitazone have been associated with decreased visual acuity due to worsening or new onset macular oedema. If patients report disturbances in visual acuity ophthalmological referral should be considered [1,]

To mitigate against the bladder cancer risks, the MHRA advises that the safety and efficacy of pioglitazone should be reviewed after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated [3,4,5,6].

The risk of anaemia is increased if haemoglobin is low before starting treatment [3]

References

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Propylthiouracil

Tests prior to starting treatment

Specialist initiation and monitoring only[1, 2]
FBC[1,3]TFTs (TSH and FT4)[1]
LFTs[1,2 3]
renal function (eGFR)[1,2]

Monitoring until patient is stabilised

Monitor TSH, FT4 and FT3 every 6 weeks until TSH within reference range [1,3]

Monitor for signs and symptoms of liver injury (but not LFTs), especially during the first 6 months after initiation of therapy[8].

Ongoing Monitoring

Monitor TSH (with cascading to check FT4 and FT3) every 3 months until propylthiouracil is stopped [1,3]

Do not monitor FBC and LFTs, unless there is a clinical suspicion of agranulocytosis or liver damage.[3] Hepatic disorders including hepatitis, hepatic failure, encephalopathy, hepatic necrosis (usually develop within 6 months of starting propylthiouracil).[1,2]

Bleeding and prothrombin time should be monitored, especially prior to surgery, as propylthiouracil may cause hypothrombinaemia and bleeding.[2]

Stopping propylthiouracil:

For adults consider measuring TSH (with cascading), within 8 weeks of stopping the drug, then, every 3 months for a year, then, once a year.[1,3]

For children and young people, consider measuring TSH, FT4 and FT3 within 8 weeks of stopping, then TSH, FT4 and FT3 every 3 months for the first year, then TSH (with cascading) every 6 months for the second year, then TSH (with cascading) once a year.[3]

Action required if abnormal results

Hepatic impairment — a dose reduction may be required. If significant hepatic enzyme abnormalities develop during treatment, propylthiouracil should be discontinued immediately[1,2]

Renal impairment — Use three-quarters of normal dose if eGFR 10–50 mL/min/1.73m^2; and half normal dose if eGFR < 10mL/min/1.73m^2.[1]

Neutropenia - discontinue propylthiouracil immediately if there is clinical or laboratory evidence[1,2]

Additional notes

Because of the risk of agranulocytosis patients should be advised to immediately report the following symptoms: sore throat, fever, mouth ulcers, bruising, malaise, non-specific illness or other symptoms of infection.[2]

Patients should be advised of the symptoms of hepatic dysfunction (anorexia, pruritus, right upper quadrant pain, etc) and told to report them immediately.[2]

References

1. Clinical Knowledge Summaries: Hyperthyroidism. Revised February 2020. Available at: https://cks.nice.org.uk/hyperthyroidism
2. Summary of Product Characteristics: Propylthiouracil 50mg tablets (Wockhardt). Revised March 2020
3. NICE NG145: Thyroid disease: assessment and management. Published November 2019. Available at: https://www.nice.org.uk/guidance/ng145

Rivaroxaban

Tests prior to starting treatment

Body weight[1]
Renal function, U&Es, (Calculated CrCl) [1-5,] see additional notes section
Baseline clotting screen[3,4]
Full blood count[3,4]
LFTs[1-4]

BP[6,4] **(**needed in conjunction with renal function and liver function if want to calculate HAS-BLED score)

Monitoring until patient is stabilised

No routine anticoagulation monitoring is needed[1-4]
First follow-up appointment should be after 1 month[4], then ideally assess patient every 3 months (or more frequently if required) to:[3,4]

- Assess compliance and reinforce advice regarding regular dosing schedule
- Enquire about adverse effects such as bleeding
- Assess for the presence of thromboembolic events
- Enquire about other medicines, including OTC medicines

Ongoing Monitoring

No routine anticoagulation monitoring is needed[1-4]
Clinical monitoring of compliance, adverse effects e.g. signs of bleeding, thromboembolism and concurrent medicines as detailed above.
U&Es, CrCl, LFTs, FBC at least once a year[3,4].
U&Es, CrCl, LFTs, FBC 6-monthly if the patient is older than 75years or fragile[4].
If CrCl ≤60mL/min, retest U&Es, Cr, LFTs, FBC every *x*-months (where *x*=CrCl/10*)* [e.g. if CrCl 30mL/min every 3 months, if CrCl 20mL/min every 2 months][4].

More frequent blood monitoring is advised when a change in renal or hepatic function is suspected or where intercurrent illness, or concomitant medicinal products may impact on renal or hepatic function[3,4].

Action required if abnormal results

If CrCl< 15mL/min, use of rivaroxaban is not recommended[1,2]. Rivaroxaban should also be avoided in patients undergoing dialysis.[2]

If CrCl is 15–49 mL/min, the following recommendations apply:

- For prevention of recurrent DVT or PE and treatment of DVT or PE, patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the dose

should be reduced to15 mg once daily if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE[1,2].

- For prophylaxis of stroke and systemic embolism in a person with NVAF, reduce the dose to 15mg once daily[2]

If renal function has declined, review treatment, as rivaroxaban may need to be stopped or a lower dose may be required.[3]

Rivaroxaban is contraindicated in severe hepatic impairment or hepatic disease associated with coagulopathy and clinically relevant bleeding[2,3].

Stop if severe bleeding occurs[1,2]

A low haemoglobin may suggest that occult bleeding is occurring and may require further investigations[3]

Additional notes

The Cockcroft-Gault method for calculating CrCl is recommended when assessing patients' renal function[4,5]. Information on using Cockroft-Gault method in extremes of body weight is available in a Q&A: https://www.sps.nhs.uk/articles/which-estimate-of-renal-function-should-be-used-when-dosing-patients-with-renal-impairment/

Rivaroxaban should be discontinued at least 24 hours prior to surgical interventions or invasive procedures. It should be restarted after the procedure/surgery as soon as possible provided the clinical situation allows and adequate haemostasis has been established[2]. Further guidance may be found in the UKCPA Handbook of Perioperative Medicine[7].
If the patient's HASBLED score is more than 3, then the patient is at a high risk of bleeding and rivaroxaban should be used cautiously, with regular reviews[6].

References

1. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press. Accessed via: http://www.medicinescomplete.com on 17/08/2020
2. Summary of Product Characteristics for Xarelto 20mg film-coated tablets.
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Sirolimus

Tests prior to starting treatment

Renal function (serum creatinine), liver function, lipid levels, U&Es (particularly potassium), FBC, fasting blood glucose, and BP [1,2,6]

Consider NICE recommendations regarding screening for HIV and hepatitis B and C in patients at increased risk of infection [3]

Monitoring until patient is stabilised

Blood levels [Note: different references use different units: ng/ml and mcg/L are equivalent]
When used with ciclosporin (for the initial 2-3 months post-transplantation), the trough whole blood sirolimus concentration (chromatographic assay) should be 4-12mcg/L (local treatment protocols may differ).[1,2,6] The first sample should be taken about 4 days or more after the initial loading dose[1], and then weekly for the first month and every 2 weeks for the second month.[4]

Therapeutic drug monitoring is also necessary after changes in the dose of sirolimus or ciclosporin, or of their relative timing. [4,5]

Sirolimus whole blood concentration should be monitored 1–2 weeks after changing between oral solution and tablets, or after switching between different tablet strengths (the 0.5mg Rapamune tablets are not fully bioequivalent to the 1mg, 2mg and 5mg tablets).[1,2]

When concomitant ciclosporin is discontinued, the sirolimus dose should be adjusted to maintain the trough whole blood sirolimus concentration (chromatographic assay) at 12-20 mcg/L (local treatment protocols may differ) [1,2]

Renal function: renal function (including urine proteins) should be monitored, especially when given with ciclosporin.[1,2]

Monitoring of the following parameters should also be undertaken on a routine basis: BP, fasting blood glucose levels, electrolytes (particularly potassium), liver function tests, haematology parameters.[1,2]

Ongoing Monitoring

Renal function
Renal function (including urine proteins) should be monitored, especially when given with ciclosporin.[1,2]
The UK Renal Association recommends that renal transplant recipients have their renal function (serum creatinine and urine protein excretion) recorded at each clinic visit.[6]
They recommend that for the first three months after transplant patients are seen a few times weekly but if uncomplicated from 3 months onwards patients should be seen in clinic every 2-4 weeks, from 6 months onwards every 4-6 weeks and from 12 months onwards every 3-6 months.

Blood pressure
The UK Renal Association recommends that renal transplant recipients have their blood pressure recorded at each clinic visit.[6] (clinic frequency described above)

Lipid levels
Lipid levels should be monitored including serum cholesterol and triglycerides. [1,2]; The UK Renal Association recommends that a fasting lipid level is done on an annual basis in all renal transplant recipients.[6]

Diabetes
Dipstick urinalysis and blood sugar level should be measured at each renal transplant clinic visit to check for the development of new onset diabetes after transplantation.[6] Clinic frequency is described above.

Vaccination
The UK Renal Association recommends that patients should have hepatitis B surface antibody (HBsAb) levels rechecked annually and be revaccinated if antibodytitres fall below 10 mIU/mL. Patients should not receive live attenuated vaccines but should receive annual flu vaccine (unless contraindicated) and a pneumococcal vaccine and a booster every five years.[6]

Action required if abnormal results

In severe hepatic impairment, decrease dose by 50% and monitor whole blood-sirolimus trough concentration every 5–7 days after any dose adjustment or loading dose, until 3 consecutive measurements have shown stable blood-sirolimus concentration.[1,2]

Appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated serum creatinine levels.[1]

Hypertension – a blood pressure of > 140/90 mmHg in clinic (130/80 mmHg if PCR >50 or ACR> 35) should be followed up and treated according to local protocol.[6]

If hyperlipidaemia is detected, subsequent interventions such as diet, exercise, and lipid-lowering agents should be initiated.[1] Treatment targets should be the same as in the general population.[5] In patients with severe refractory hyperlipidaemia, the risk/benefit of continued sirolimus therapy should be re-evaluated.[1]

New onset diabetes after transplant should be managed according to local unit protocol.[6]

Additional notes

Patients should be informed that sirolimus can cause diabetes and should be advised to see their clinician if they develop signs of high blood sugar like confusion, feeling sleepy, more thirst, more hungry, passing urine more often, flushing, fast breathing, or breath that smells like fruit.[8]

Exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.[1] The UK Renal Association recommends use of total

sunblock (SPF≥50) and advises at least twice yearly skin examinations for 5 years post-transplant and then annual skin examinations by a trained healthcare professional.[6]

References

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7. UpToDate Sirolimus: Patient drug information accessed August 2020.

Spironolactone (adjunct in moderate to severe heart failure)

Tests prior to starting treatment

Renal function[3,4]
Serum electrolytes[3,4]

Monitoring until patient is stabilised

Renal function and serum electrolytes 1 week after initiation and after every dose increase, monthly for first 3 months, then every 3 months for a year.[1-5]

Blood pressure before and after each dose increase of spironolactone [2].

Ongoing monitoring

Renal function and serum electrolytes at least every 6 months and at any time the person becomes acutely unwell.[1,2,4,5] .

Action required if abnormal results

The manufacturer states that in patients with severe heart failure spironolactone should not be started in patients with serum potassium ≥5.0 mEq/L[1,4] and serum creatinine ≥2.5 mg/dL (serum creatinine >220 micromol/[1]

The manufacturer advises that in patients with severe heart failure discontinue or interrupt treatment for serum potassium >5 mEq/L or for serum creatinine >4 mg/dL.[1]

SIGN guidance[4]

- If serum potassium rises above 5.5 mmol/L or creatinine rises to >220 micromol/L reduce the dose to 25mg on alternate days and monitor blood chemistry closely.
- If potassium rises to ≥ 6 mmol/L or creatinine to 310 micromol/L, stop spironolactone immediately and seek specialist advice.

ESC guidance[3]

- If potassium rises above 5.5 mmol/L or creatinine rises to 221 micromol/L or eGFR < 30ml/min/1.73m^2, halve dose and monitor blood chemistry closely.
- If potassium rises to >6 mmol/L or creatinine to >310 micromol or eGFR <20mL/min/1.73m^2 stop spironolactone immediately and seek specialist advice.

Additional notes

Advise patients to avoid NSAIDs not prescribed by a physician (‘over the counter’) and salt substitutes that contain potassium.[2,3] If diarrhoea/vomiting occurs or there is infection with fever leading to intense sweating, patients should be advised to hold spironolactone and contact their physician [3,4]

References

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Statins

Tests prior to starting treatment

At least one baseline sample of full lipid profile to measure total cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides. [1, 2,3]. This does NOT need to be a fasting sample[1,3]
Transaminase level (ALT or AST) [1,3]
Renal function and eGFR [1, 2,3]
Thyroid-stimulating hormone (TSH) [1,2,3]
HbA_{1c}[1,3] or fasting blood glucose in people at high risk of diabetes mellitus.[2,3]
BP [1,3]
BMI or other measure of obesity[1,3]Creatine kinase (CK) level in following situations: renal impairment, hypothyroidism, personal or familial history of hereditary muscular disorders, previous history of unexplained muscle pain (whether associated or not with previous lipid-regulating drugs), a history of liver disease or where substantial quantities of alcohol are consumed, in elderly (aged over 70 years), interactions with other medicines where plasma levels may be increased.[3]
CK should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult.
Consider specialist advice in those patients with an extremely elevated baseline CK level, eg because of a physical occupation or rigorous exercise.[2]

Monitoring until patient is stabilised

If patient on a high intensity statin (ie atorvastatin ≥ 20mg daily, rosuvastatin ≥ 10mg daily, or simvastatin 80mg daily) measure total cholesterol, HDL cholesterol and non-HDL cholesterol at 3 months.[1,3]

Measure transaminase levels (ALT or AST) at 3 months[1,3]Ask patient if they are experiencing muscle symptoms (pain, tenderness, weakness) and if so measure CK level[1,3]

HbA_{1c} for fasting blood glucose should be repeated at 3 months if considered to be at risk of diabetes mellitus.[2,3]

Ongoing monitoring

Local guidance on strength of this recommendation may be needed to support practice.

Consider performing a non-fasting blood test for non-HDL cholesterol to help inform discussions at each annual medication review.[1]

Measure transaminase levels (ALT or AST) at 12 months but not again unless clinically indicated.[1]

Ask patient if they are experiencing muscle symptoms (pain, tenderness, weakness) and if so measure CK level[1,3] However if they have previously tolerated statin therapy for more than 3 months explore other possible causes for symptoms and raised CK.[1]

Action required if abnormal results

Statin therapy should not be started/ discontinued if ALT or AST >3x upper limit of normal (ULN) [1, 2,3]. Rosuvastatin is contraindicated if ALT or AST > 3 x ULN.
If CK levels are > 5 x ULN, statin therapy should not be started/ discontinued and re-measured after 7 days. If levels are still 5 x the ULN do not start/ re-start. If levels are raised but < 5 x ULN, start statin treatment at a lower dose.[1,2,4]

If eGFR is less than 30ml/min/1.73m^2 check appropriateness of dosing of statin with a renal specialist.[1]

Rosuvastatin is contra-indicated if creatinine clearance <30ml/min. The 40mg dose is contraindicated if creatinine clearance <60ml/min[4]

Hypothyroidism should be managed adequately before starting treatment with a statin.[2]
Rosuvastatin 40mg is contraindicated in hypothyroidism.[4]

The British Thyroid Assoc. advise that in patients with subclinical hypothyroidism and TSH > 10mU/L there is an increasing evidence of progression to overt hypothyroidism and deterioration in hyperlipidaemia particularly in patients with elevated thyroid peroxidase antibodies (TPOab). There is evidence of improvement in lipid profile and symptoms when patients with modestly raised TSH were rendered euthyroid with thyroxine[5]

Additional notes

Patients should be advised to report unexplained muscle pain.[1],[2,]

References

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Sulfasalazine

Tests prior to starting treatment

Height, weight and BP [1]
Renal function (creatinine/calculated GFR) [1,2,3]
FBC (BNF recommends including differential white cell count and platelet count) [1,2,3]
Serum albumin[1]
ALT and/or AST (BNF states LFTs) [1,2,3]

Screening for occult viral infections in patients at increased risk of infection (hepatitis B, hepatitis C, HIV).[1]

Screening for lung disease should be undertaken at clinical discretion on a case-by-case basis.[1]

Monitoring until patient is stabilised

FBC, creatinine/calculated GFR, ALT and/or AST and albumin **every two weeks** until on stable dose for 6 weeks. [1]

Once on stable dose, **monthly** FBC, creatinine/calculated GFR, ALT and/or AST and albumin for 3 months.[1,3]
More frequent monitoring is appropriate in patients at higher risk of toxicity. [1]

Dose increases should be monitored by FBC, creatinine/calculated GFR, ALT and/or AST and albumin every 2 weeks until dose stable for 6 weeks then revert back to previous schedule.[1]

[Alternatively, BNF recommends FBC (including differential WBC and platelets) and LFTs monthly for first 3 months. They also note that although the manufacturer recommends renal function tests in rheumatic diseases, evidence of practical value is unsatisfactory – they recommend that renal function is assessed at 3 months.[2]]

Ongoing monitoring

Once the maintenance dose has been achieved and stable for 3 months monitor **at least every 12 weeks**: [1]

- FBC
- creatine/calculated GFR
- albumin
- ALT and/or AST

More frequent monitoring is appropriate in patients at higher risk of toxicity.[1]

The BNF suggests that renal function should be monitored annually.[2]

Action required if abnormal results

Withhold treatment until discussion with consultant specialist if [1]:

WCC < 3.5 x 10^9/L,
Neutrophils< 1.6 x 10^9/L
Unexplained eosinophilia > 0.5 x 10^9/L
Platelets < 140 x 10^9/l,
ALT and/or AST increase to >100Units/L
Unexplained fall in serum albumin <30g/L
MCV > 105fL
Creatinine increase > 30% above baseline over 12 months and/or calculated GFR < 60ml/min

Withhold until discussion with rheumatologist if [4]:

- Rash or itch,
- Hair loss,
- Severe sore throat/oral ulceration or abnormal bruising/bleeding
- (check FBC immediately)
- Breathlessness or dry cough
- GI upset (nausea, vomiting or diarrhoea) or weight loss
- Peripheral neuropathy

Additional notes

Advise patients to report any unexplained bleeding, bruising, rash, sore throat, fever, or malaise. Perform a full blood count and stop treatment immediately if a blood dyscrasia or toxicity is suspected.[2,3]
Advise contact lens wearers that some soft contact lenses may get stained with treatment.[2]

References

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5. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults (2019) – Gut 2019;0:1-106

Tacrolimus

Tests prior to starting treatment

ECG (for hypertrophic changes), BP, fasting blood glucose, U&Es (particularly potassium), liver and renal function tests, FBC, blood clotting values, plasma protein.[1,2]

Consider NICE recommendations regarding screening for HIV, hepatitis B and C in patients at increased risk of infection. [3]

Monitoring until patient is stabilised

Renal, Liver and Heart Transplant

Blood levels
Whole blood trough levels (drawn approximately 12 hours post-dose, just prior to the next dose) should be monitored twice weekly during the early post-transplant period.[1,4]. Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20ng/ml.[1]

In clinical practice, whole blood trough levels have generally been in the range 5-20ng/ml in liver transplant recipients and 10-20ng/ml in kidney and heart transplant patients in the early post-transplant period. During maintenance therapy, blood concentrations have generally been in the range of 5-15ng/ml in liver, kidney and heart transplant recipients.[1]

ECG
Patients should be monitored by ECG pre- and post-transplant (e.g. initially at three months and then at 9-12 months) for hypertrophic changes.[1]

Monitoring of the following parameters should also be undertaken on a routine basis: BP, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology and neurological (including visual) parameters, coagulation values, and plasma protein.[1,2]

Other conditions
No specific guidance was identified relating to the monitoring of patients receiving systemic tacrolimus for other conditions.

Ongoing Monitoring

Blood levels
Whole blood trough levels should be monitored periodically during maintenance therapy. [1,2]
Levels should be checked when any medication with possible interactions is prescribed, the dose or formulation is changed, or when there is unexplained graft dysfunction.[1,4]

Renal function
Weekly but if uncomplicated from 3 months onwards patients should be seen in clinic every

2-4 weeks, from 6 months onwards every 4-6 weeks and from 12 months onwards every 3-6 months.[4]

Blood pressure
The UK Renal Association recommends that renal transplant recipients have their blood pressure recorded at each clinic visit.[4] (clinic frequency described above) The UK liver transplantation guidelines recommend aiming for a systolic BP of <140mmgHg and a diastolic BP of <85mmHg. [7]

Lipid levels
The UK Renal Association recommends that a fasting lipid level is done on an annual basis in all renal transplant recipients.[4]

Diabetes
Dipstick urinalysis and blood sugar level should be measured at each renal transplant clinic visit to check for the development of new onset diabetes after transplantation.[4] Clinic frequency is described above.

Vaccination
The UK Renal Association recommends that patients should have hepatitis B surface antibody (HBsAb) levels rechecked annually and be revaccinated if antibody
titres fall below 10 mIU/mL. Patients should not receive live attenuated vaccines
but should receive annual flu vaccine (unless contraindicated) and a pneumococcal vaccine and a booster every five years.

Action required if abnormal results

If hypertrophic cardiac changes occur, consider dose reduction or discontinuation.[1,2]

The UK liver transplantation guidelines recommend aggressive management of dyslipidaemia in post-liver transplant patients. Dietary interventions have little effect on dyslipidaemia.[7]

New-onset diabetes after transplant should be managed according to local unit protocol.[4, 7]

Lower doses and close monitoring of blood concentrations may be required in patients with severe hepatic impairment (Child-Pugh score of 10 or higher) because of reduced clearance and prolonged half-life[6]

Additional notes

Patients should be informed that tacrolimus can cause diabetes and should be advised to see their clinician if they develop signs of high blood sugar like confusion, feeling sleepy, more thirst, more hungry, passing urine more often, flushing, fast breathing, or breath that smells like fruit. [6]

Excessive exposure to UV and sunlight should be avoided.[2] The UK Renal Association recommend covering the skin and use of total sunblock (SPF≥50) and advise at least twice

yearly skin examinations for 5 years post-transplant and then annual skin examinations by a trained healthcare professional.[4]

Oral tacrolimus medicines should be prescribed and dispensed by brand name only.[2,5] Any switching between brands requires careful supervision and therapeutic monitoring by an appropriate specialist.[2]

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Theophylline/aminophylline

Tests prior to starting treatment

U&Es (paying particular attention to potassium)[2,3,5]
LFTs[2,3,5]
Enquire about smoking status for patient, and advise patient to seek advice from doctor if status is likely to change[1]

Monitoring until patient is stabilised

It is advisable to recheck the plasma level at least 5 days after starting treatment for the first time and at least 3 days after dose adjustment.[4]
Levels should usually be taken 4-6 hours after MR dose.[4]

Ongoing monitoring

It is advisable to recheck plasma levels every 6-12 months. Check more regularly in older people and in those with heart failure or hepatic impairment. [5]

Also check plasma theophylline levels if-

- If the person experiences side effects that may suggest toxicity (nausea, vomiting, tremor or palpitations) [5]
- If an enzyme-inhibiting drug (such as erythromycin, clarithromycin, allopurinol, or cimetidine) is prescribed (raises plasma levels) or if an enzyme-inducing drug (such as carbamazepine, rifampicin, or St John's Wort) is prescribed (lowers plasma levels)[5]
- If the person starts or stops smoking — a dose adjustment may be needed because tobacco can lower the plasma levels of theophylline.

Check potassium levels: periodically in at risk patients[2,3,5]
This includes: those taking theophylline alongside beta-$_2$ agonists, corticosteroids, or diuretics, and all people with severe asthma.
Rationale: Plasma potassium concentrations may be reduced by beta-$_2$ agonists, corticosteroids, and diuretics. This effect may be potentiated by theophylline, and further exacerbated by hypoxia.

Monitor alcohol consumption as high levels of consumption can reduce plasma concentration of theophylline.[2,3,4]

Action required if abnormal results

A lower dose may be required in older people, in those with heart failure and in those with hepatic impairment[2,3]

Additional notes

In most individuals a plasma theophylline of between 10-20mg/ litre is required for satisfactory bronchodilation, although a lower plasma theophylline concentration of 5-15mg/litre (or less) may be effective. Adverse effects can occur within the range 10-20mg/ litre and both the frequency and severity increase at concentrations above 20mg/ litre[4]
Note: Aminophylline is monitored therapeutically in terms of plasma-theophylline concentrations.

The BTS/SIGN guidance advises checking levels during pregnancy as protein binding decreases, the free level of drug will increase and so a lower therapeutic range is probably appropriate. They particularly recommend checking levels in pregnant women with acute severe asthma and in those that are critically dependent on therapeutic theophylline levels.[6]
The rate of absorption from modified-release preparations can vary between brands. Patients should therefore be maintained on the same brand.

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Thyroxine (levothyroxine)

Tests prior to starting treatment

TFTs.[1,2] (UK guidance recommends TSH and FT4 as the most important markers[2])
ECG[1,3,4]

Consensus guidance recommends that patients with hypothyroidism only need referral in the following circumstances: age <16 years, pregnant or post-partum, evidence of pituitary disease, , or if there are particular management problems – for example, ischaemic heart disease or treatment with amiodarone or lithium.[5]

Monitoring until patient is stabilised

NICE recommends that TSH levels should be checked every 3 months after initiation of thyroxine therapy, with the dose adjusted according to symptoms and results. If the person has ongoing symptoms, consider also checking FT4.[1,8]
UK guidance recommends that repeat TSH monitoring should not occur within 6 weeks of a dosage change as this is the minimum period required to achieve stable concentrations. [1,2,]

Ongoing monitoring

Once TSH levels and dosage of levothyroxine are stable (stable TSH levels are defined as 2 similar measurements within the reference range 3 months apart), check TSH annually. [1,2, 8]
NICE support annual monitoring of TSH as a means of monitoring adherence and ensuring the dose of levothyroxine is still correct[8]

Action required if abnormal results

The dose of levothyroxine should be individualized on the basis of clinical and biochemical (thyroid function tests) response with the aim of restoring physical and psychological well-being whilst maintaining normal lab range TSH levels and avoiding overtreatment.

Doses of levothyroxine should be adjusted in increments of 25–50 micrograms every 3–4 weeks according to response. For patients aged over 50 years, patients with cardiac disease or patients with severe hypothyroidism, doses should be adjusted in increments of 25 micrograms every 4 weeks according to response.[4, 5,]

Additional notes

Pre-treatment ECG is considered valuable as changes induced by hypothyroidism may be confused with evidence of ischaemia.[1,3]

A change in requirement for thyroid hormone can occur with ageing and in pregnancy. [2]

The MHRA have acknowledged that patients with thyroid cancer, heart disease and pregnancy may be more sensitive to levels of thyroid hormone and require careful dosage titration. However no further recommendations have been made on the monitoring of these patients.[6]

Caution is recommended when prescribing thyroxine to patients with adrenal insufficiency, long-standing hypothyroidism, age >50 years, and/or cardiovascular disorders. [1,3]

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Valproate and sodium valproate

Tests prior to starting treatment

Valproate should only be initiated in adults and children by, or on the recommendation of, a specialist [4, 6].

In February 2020 the MHRA strengthened warnings that valproate must not be used in women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), unless alternative treatments are not suitable. Women and girls of childbearing potential must be fully informed about the risks of taking valproate during pregnancy, and only take valproate if they have a pregnancy prevention programme (PPP) in place, in line with the MHRA safety advice on valproate[4, 8].

Risk management materials for sodium valproate (Epilim) and valproate semisodium (Depakote) are also available on the eMC website (access via the relevant SPC)

LFTs, FBC (including platelet count, bleeding time and coagulation tests) and BMI/weight[1,2,5,6].

Make sure there is no undue potential for bleeding[5]
If used for bipolar disorder NICE additionally recommend assessment of [6]:

- diet, nutritional status and level of physical activity.
- cardiovascular status, including pulse and blood pressure
- metabolic status, including fasting blood glucose, glycosylated haemoglobin (HbA1c) and blood lipid profile

Monitoring until patient is stabilised

LFTs periodically within first 6 months of treatment especially in patients most at risk [5].

Periodically may need to be clarified locally or on a patient-by-patient basis

Ongoing monitoring

FBC (including platelet count), bleeding time and coagulation tests are recommended before surgery[4,5], and in cases of spontaneous bruising or bleeding[1].

LFTs, FBC and BMI after 6 months [2,5,6] and then annually[6].

Regular blood level test monitoring is not recommended as routine, and should be done only if clinically indicated (eg evidence of ineffectiveness, poor adherence, toxicity or clotting studies before surgery)[4,6].

A structured routine review of all people with epilepsy in primary care is recommended at least annually to assess: seizure control and adverse effects of treatment[7].

As part of annual physical monitoring for patients with bipolar disorder NICE additionally recommend: CV status (incl pulse and BP), metabolic status (incl fasting blood glucose, HbA_{1c}, and blood lipid profile[6].

Action required if abnormal results

Raised liver enzymes are usually transient but patients should be assessed clinically and FBC (including platelets) and liver function (including prothrombin time and coagulation tests) monitored until return to normal. Discontinue if abnormally prolonged prothrombin time, abnormal liver function or blood dyscrasias [1, 5,6].

Patients experiencing nausea, vomiting or acute abdominal pain should have a prompt medical evaluation (including measurement of serum amylase). In case of pancreatitis, valproate should be discontinued[1,5].

Additional notes

Patients/carers should be told how to recognise signs of blood or liver disorders and advised to seek immediate medical attention if symptoms develop. Similarly they should be told how to recognise the signs of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea and vomiting develop[1, 5,6].

Valproate is classified as a category 2 drug (i.e. clinical judgement is required when switching between branded original and generic products for epilepsy only)[3].

Following an extensive review of the risk of valproate in 2018, a ban was issued on the use of valproate for the following[8:]

- Migraine or bipolar disorder during pregnancy
- Treatment of epilepsy during pregnancy unless no other effective treatment is available. In this instance, the patient should receive access to counselling about the possible risks should be provided and a Risk Acknowledgement Form signed by both specialist and patient.

Risk of abnormal pregnancy outcomes: a patient booklet guide and card should be provided to all female patients[5, 8].
If valproate is taken during pregnancy, up to 4 in 10 babies are at risk of developmental disorders, and approximately 1 in 10 are at risk of birth defects[8].

If a woman using valproate discovers she is pregnant, she must be immediately referred to a specialist to consider alternative treatment options. Folate supplementation should be started before pregnancy as appropriate. Specialist prenatal monitoring should be instigated to detect possible occurrence of neural tube defects or other malformations when valproate has been used [1,3 5,6,8].

Risk management materials for sodium valproate (Epilim) and valproate semisodium (Depakote) are available on the eMC website (access via the relevant SPC)

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Warfarin

Tests prior to starting treatment

FBC (incl platelets)[1]
Coagulation screen[1]
Renal function[1]
Liver function[1]
Thyroid status[4].
BP[5] (Needed in conjunction with renal function and liver function if want to calculate HAS-BLED score

(local practice may vary to also include FBC, U+E's and blood group and antibodies (aka Group and Save).

Monitoring until patient is stabilised

For rapid anticoagulation, SIGN guidelines recommend daily INR for a minimum of 4 days until desired INR is achieved by adjusting dose according to result and age[1]. Between days 5-14 the INR should be tested every 2-3 days until stable. They note that more careful dosing and monitoring may be required in elderly patients or where there is co-administration with drugs known to increase or decrease INR.

More generally CKS recommend that if rapid anticoagulation is required, warfarin should be initiated at a dose of 5 mg or 10 mg once a day for 2 days and re-measure the person's international normalized ratio (INR) on day three[5]. However, for people with atrial fibrillation there is no need to achieve anticoagulation rapidly; a slow-loading regimen is safe and achieves therapeutic anticoagulation in the majority of people within 3–4 weeks[1, 3, 4].

Generally, CKS[5] recommend that the INR should be measured:

- **Daily, or on alternate days**, until it is within the therapeutic range (usually between 2.0 and 3.0, ideally 2.5) on two consecutive occasions.
- Note: although the INR may be measured each day after starting warfarin, a meaningful INR can only be obtained 3–4 days after starting treatment.
- **Then, twice weekly** for 1–2 weeks, followed by weekly measurements until at least two INR measurements are within the therapeutic range.
- **Thereafter,** depending on the stability of the INR, at longer intervals (for example, up to every 12 weeks, if agreed locally). Once a stable warfarin dose that controls the INR has been established, changes in dose are seldom required.

Ongoing monitoring

12 weekly monitoring of INR is considered acceptable in patients stabilised on warfarin[2,5]

- More frequent routine monitoring (e.g. every 1-2 weeks) of the INR is recommended if the person has an increased risk of overcoagulation: people with severe hypertension, liver disease (including alcoholic liver disease) or renal failure.

- Is at increased risk of bleeding: people on high intensity anticoagulation (INR more than 4.0); age 65 years or over; highly variable INRs; history of gastrointestinal bleeding; uncontrolled hypertension; cerebrovascular disease; serious heart disease; risk of falling; thrombocytopenia, anaemia, or coagulation disorders; malignancy; trauma, renal insufficiency; morbidity changes (such as intercurrent illness, or exacerbations of chronic conditions); or has changed their medication (for example, when starting or stopping prescribed or over-the-counter medicines).
- May find adherence difficult.[4,5]

Reassess anticoagulation for a person with poor anticoagulation control, indicated by any of the following[8]:

- 2 INR values higher than 5, or 1 INR value higher than 8 within the past 6 months.
- 2 INR values less than 1.5 within the past 6 months.
- Time in therapeutic range (TTR) is less than 65%.

All patients on warfarin who are prescribed a drug that may interact with warfarin should have an INR test performed after 3–5 days[3,5].

Those who have had a change in warfarin dose as a result of an interacting drug will need to resume usual maintenance dose following cessation of that drug. [2]

Action required if abnormal results

People with hypothyroidism or hyperthyroidism should be closely monitored on starting warfarin therapy[4, 5]. Similarly if the person or another family member is known to have polymorphisms of CYP2CP or VKORC1, extra care is warranted[5].
If the patient's HASBLED score is more than 3, then the patient is at a high risk of bleeding and warfarin should be used cautiously, with regular reviews.[5]

Establish reason for abnormal INR reading (e.g. missed doses/ inadvertent change in dose, interacting drug, change alcohol intake, significant change in diet, intercurrent illnesses)

Low reading: refer to local anticoagulation guidelines for use of booster doses and how to increase maintenance dose if needed.

High reading: risk of bleeding increases greatly once INR > 5
Refer to local anticoagulant guidelines for advice on number of days to stop therapy and adjustment of maintenance dose if needed further action may also be needed depending on whether there is minor or major bleeding. [2]

For INR > 8, oral anticoagulants should be stopped. Vitamin K (either orally or intravenously depending on presence of bleeding) should be given; repeated dose of vitamin K if INR still too high after 24 hours. Restart warfarin when INR <5.0 [3,8]

Patient characteristics such as older age, uncontrolled hypertension, diabetes, renal or liver failure, previous gastrointestinal or cerebral bleed and use of anti-platelet medication are associated with a higher risk of bleeding.[8]

Additional notes

Refer to BNF for potential drug interaction when prescribing any new drug to patient taking warfarin.

Prescribers should ensure that they are compliant with NPSA recommendations on actions that can make anticoagulant therapy safer.[4]

Ensure patient is given an anticoagulant treatment booklet; this is often referred to as the 'Yellow book'. It includes advice for people taking anticoagulants (e.g. adverse effects), an alert card, and a section for recording the international normalized ration (INR) results.[5]

Patients should be advised to always carry their anticoagulant alert card with them at all times, and they should always take their anticoagulant treatment booklet when they go to the warfarin clinic to have their INR checked.[5]

The MHRA has issued a warning that warfarin may be associated with calciphylaxis. Patients should be advised to consult their doctor if they develop a painful skin rash.[7]

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