CHRONIC KIDNEY DISEASE

PostScRxipt
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Publication of new UK guidelines for Chronic Kidney Disease (CKD) in 2005 led to a change in the classification of renal impairment. Routine biochemistry profiles now report the estimated glomerular filtration rate to help the classification of renal disease. This has led to some confusion over the implications of this value for drug dosing. In the following article renal specialists, Heather Black (Renal Pharmacist), Dr Jonathan Fox (Consultant Nephrologist) and Dr Alison Thomson (Specialist Pharmacist in Pharmacokinetics), attempt to clarify some of the issues. There is a more detailed version available on our website which discusses the equations for calculating renal function in more detail.

Website
http://www.glasgowformulary.scot.nhs.uk

Introduction

The new CKD guidelines have a five-stage classification ranging from normal renal function to established renal failure. This replaces the categories of mild, moderate and severe renal impairment as used in the BNF. The guidelines emphasise the need for early diagnosis and treatment. Routine reporting of estimated glomerular filtration rate (eGFR) with biochemistry profiles was introduced to help identify patients with kidney disease, particularly those who should be referred for specialist renal advice. Based on the eGFR measurement, the five stages of CKD are:

Stage	eGFR (ml/min/1.73m^2)	Description
1	>90 with another abnormality*	Normal kidney function Other findings point to kidney disease
2	60-89 with another abnormality*	Mildly reduced kidney function Other findings point to kidney disease
3	30-59	Moderately reduced kidney function
4	15-29	Severely reduced kidney function
5	<15	Established renal failure

*Other evidence of chronic kidney damage may be persistent microalbuminuria (in diabetes), persistent proteinuria, persistent haematuria (but no urological cause), polycystic disease or reflux nephropathy. If no other abnormalities are present at stage one and two, kidney function should be regarded as normal.

The GP contract, 'Quality and Outcomes Framework' (QOF), now has a number of indicators relating to identification and management of patients with stage three, four and five CKD (eGFR <60mL/min/1.73m2 for over three months). This is estimated to affect five per cent of the population.

Practices are expected to produce a register of patients aged 18 years and over with CKD. Patients on the CKD register should have had their blood pressure measured in the previous 15 months. Patients on the CKD register with hypertension should be treated with an ACEI or A2RA, unless contra-indicated or not tolerated, aiming for a reading below 140/85mmHg. Some specialist groups suggest targets lower than this used in QOF and that cardiovascular risk assessment should be carried out.

Drug dosing issues

The new classification and the reporting of eGFR can cause confusion when drug dosage regimens are being determined for patients with CKD. eGFR was originally developed as a diagnostic tool to identify kidney disease. It does not take account of an individual patient's size and it was not developed to individualise drug dosage. Most manufacturers recommend dosage alterations for patients with reduced renal function based on estimates of creatinine clearance or the categories of mild, moderate or severe renal impairment. Creatinine clearance estimates are commonly determined using the Cockcroft and Gault equation. Neither eGFR nor estimated creatinine clearance can be used in acute renal failure. See the website article for more details.

A number of drug errors have been reported when eGFR values were incorrectly used to calculate drug doses. These may have major clinical consequences, especially for chemotherapy or drugs with narrow therapeutic ranges such as vancomycin or gentamicin. This issue has been highlighted by the UK Renal Pharmacy Group and raised as an area of risk with the National Patient Safety Agency.

Conclusions

Routine reporting of eGFR provides a quick and easy assessment of kidney function. eGFR values are standardised to a body surface area of 1.73m^2 and should not be used for drug dosing. Alternative approaches are to use creatinine clearance or to correct eGFR for the patient's body surface area. Careful choice and use of drugs is important when prescribing for patients with renal impairment. Further advice on drug dosing in renal impairment can be obtained from the Renal Drug Handbook, **www.renal.org** (eGFR calculator available) or **www.nephron.com** which includes a creatinine clearance calculator.

For all article references, check our website
http://www.glasgowformulary.scot.nhs.uk

Alphabetical list of most recent ADTC decisions

For full details of SMC advice, visit **www.scottishmedicines.org** For NICE advice, visit **www.nice.org.uk** For previous ADTC decisions, visit **www.glasgowformulary.scot.nhs.uk**

Drug	Indication under consideration (There may be other licensed indications)	Glasgow decision	
Anastrozole (Arimidex®)	Adjuvant treatment of early oestrogen-receptor-positive breast cancer.	*Formulary*. Consistent with current guidance.	✓R
Busulfan (Busilvex®)	As part of a combination regimen for conditioning treatment prior to conventional haematopoietic progenitor cell transplantation.	Interim non-*Formulary*. Deferred for consultation with Regional Cancer Advisory Group.	?
Clofarabine (Evoltra®)	Acute lymphoblastic leukaemia in patients under 21 years who have relapsed or are refractory after at least two prior regimens and where there is no other option anticipated to result in a durable response.	Interim non-*Formulary*. Deferred for consultation with Regional Cancer Advisory Group.	?
Daptomycin (Cubicin®)	Complicated skin and soft-tissue infections in adults.	*Formulary*. Acknowledge new formulation. Restricted to use in patients with known or suspected MRSA infection and on the advice of local microbiologists or specialists in infectious disease.	✓R
Deferasirox (Exjade®)	Chronic iron overload associated with the treatment of rare acquired or inherited anaemias requiring recurrent blood transfusions.	*Formulary*. Restricted to specialist use. It is not recommended for patients with myelodysplastic syndromes.	✓R
Dorzolomide/timolol preservative-free unit dose eye drops (Cosopt®)	Elevated intra-ocular pressure in patients with open-angle glaucoma and pseudo-exfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.	*Formulary*. Acknowledge new formulation. Restricted to use in patients for whom a combination of these two agents is appropriate and who have proven sensitivity to the preservative benzalkonium chloride.	✓R
Ertapenem (Invanz®)	Diabetic foot infections of the skin and soft tissue.	*Formulary*. Acknowledge new indications. Restricted to use by specialists managing diabetic foot infection on the advice of a microbiologist. Not for use in concurrent osteomyelitis.	✓R
Exemestane (Aromasin®)	Adjuvant treatment of early oestrogen-receptor-positive breast cancer.	*Formulary*. Consistent with current guidance.	✓R
Insulin, inhaled (Exubera®)	Type 1 and type 2 diabetes.	Non-*Formulary*. The NICE guidance relating to exceptional use is noted.	x
Interferon beta-1b (Betaferon®)	Single demyelinating event with an active inflammatory process, severe enough to warrant treatment with intravenous corticosteroids, where alternative diagnoses are excluded and in patients who are determined to be at high risk of developing clinically definite multiple sclerosis.	Non-*Formulary*.	x
Letrozole	Adjuvant treatment of early oestrogen-receptor-positive breast cancer.	*Formulary*. Consistent with current guidance.	✓R
Omalizumab (Xolair®)	Add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma.	Non-*Formulary*.	x
Pemetrexed (Alimta®)	Second-line monotherapy for locally advanced or metastatic non-small cell lung cancer.	Non-*Formulary* for this indication.	x
Propiverine (Detrunorm XL®)	Urinary incontinence, urgency and frequency in patients who have idiopathic detrusor overactivity (overactive bladder).	Interim non-*Formulary*. Deferred for consideration at *Formulary* section review.	?
Rimonabant (Acomplia®)	As an adjunct to diet and exercise in the treatment of obesity.	Non-*Formulary*. Rimonabant was associated with a reduction in mean weight of about 4-5kg above placebo. Weight was generally regained within one year of stopping treatment.	x
Rituximab (MabThera®)	Severe active rheumatoid arthritis in patients who have had an inadequate response or intolerance to other DMARDs including at least one anti-TNF therapy. Treatment is given with methotrexate.	*Formulary*. Restricted to specialist use in accordance with local protocol.	✓R
Sunitinib (Sutent®)	Advanced and/or metastatic renal cell carcinoma after failure of interferon-alfa or interleukin-2 therapy.	Non-*Formulary*.	x
TachoSil® medicated sponge	Supportive treatment in renal surgery for improvement of haemostasis where standard techniques are insufficient.	Non-*Formulary*. This type of product not currently included in the *Formulary*.	x
Tacrolimus (Prograf®)	Prophylaxis of transplant rejection in heart allograft recipients.	*Formulary*. Acknowledge new indication. Restricted to specialist use in patients where ciclosporin is not suitable.	✓R
Temozolomide (Temodal®)	Newly diagnosed glioblastoma multiforme.	*Formulary*. Acknowledge new indication. Restricted to specialist use in accordance with regional protocol.	✓R
Varenicline (Champix®)	Smoking cessation in adults.	*Formulary*. Restricted to use in patients who have previously attempted to quit smoking more than six months ago using NRT for at least a four-week period. Patients must be linked to one of the recognised smoking cessation support programmes.	✓R

✓= *Formulary* ✓R = *Formulary* (restricted) **x** = *non-Formulary* **?** = awaiting final decision

Buccal midazolam for prolonged seizures

The ADTC has recently added buccal midazolam to the *Formulary* for the treatment of prolonged seizures, following an appeal by teams from Learning Disabilities and Yorkhill. The specialists in the Fraser of Allander Unit at Yorkhill recommend it for prolonged epileptic seizures in children. The unit provides training and written information for all families involved as well as information for prescribers and other health care professionals.

This is an unlicensed, but well recognised, use of midazolam. There are two formulations; Hypnovel® injection can be given by breaking the ampoule and using a filter needle or filter straw (which must be removed before administration) to draw up the required dose into a syringe for buccal administration. The injection is licensed neither for this route of administration, nor for this indication. The other formulation is the unlicensed Epistatus® liquid. This is formulated for buccal use and is more convenient and preferred for this use.

Some patients with refractory epilepsy occasionally require rescue medication for prolonged seizures (lasting five minutes or more) or serial seizures (three or more seizures in an hour). It is vital that prolonged seizures are stopped as soon as possible. There are obvious advantages in managing patients effectively in the community, thus avoiding regular hospital admissions or preventing status epilepticus. Convulsive status epilepticus is the most common neurological medical emergency and is associated with high morbidity and mortality.

Rectal diazepam has many shortcomings when used in the home and community settings. These include difficulties in administration to wheelchair users and unreliable bowel absorption. It is also increasingly socially unacceptable for young people and their carers to be administering medicines rectally, particularly in public places. Parents and carers have found buccal midazolam to be easy to use and a preferable alternative in the community setting.

SIGN guideline 81 indicated that buccal midazolam is as effective as rectal diazepam in the treatment of prolonged seizures. NICE Clinical Guideline 20 notes that an individual who has prolonged or serial seizures in the community should receive urgent care and treatment. Buccal midazolam is one of the recommended treatments. The guideline states it should be used according to an agreed protocol drawn up by the specialist and only following training.

A number of studies have compared the effectiveness and safety of midazolam and diazepam. In general, midazolam

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New drug update

Inhaled insulin (Exubera®▼)

The *Formulary* status of inhaled insulin was reviewed after the recent NICE guidance which supersedes the previous SMC advice. It has not been added to the *Formulary*, as use should be only in exceptional cases. It should be used, with educational support, only for patients who show poor glycaemic control with other treatments and who cannot administer subcutaneously due to a needle phobia (diagnosed by diabetes specialist or mental health professional) or severe problems with injection sites. It should be initiated, and response monitored, by specialist diabetes centres. Treatment should only be continued beyond six months if there is a clinically relevant improvement in HbA1c.

Exubera® is a novel human insulin product utilising the lung for administration and offering an alternative to subcutaneous delivery. It is a rapid-acting dry powder human insulin produced by recombinant DNA technology. It is available in two strengths and is licensed for the treatment of adult patients with type 2 diabetes not adequately controlled with oral antidiabetic drugs and requiring insulin therapy. It is also licensed for the treatment of adult patients with type 1 diabetes in addition to long or intermediate acting subcutaneous insulin for whom the potential benefits of adding inhaled insulin outweigh potential safety concerns.

Of the thirteen trials conducted, six were in type 1 and seven in type 2 diabetes. In summary, the trials demonstrated non-inferiority and a comparable reduction in HbA1c to subcutaneous insulin. There was no significant difference in adverse events with inhaled insulin compared to subcutaneous insulin. One per cent of patients discontinued treatment due to cough. Treatment is contraindicated in smokers, those who have smoked in the last six months, and in patients with asthma or chronic obstructive pulmonary disease.

There are some issues that could lead to confusion. Inhaled insulin is measured in milligrams while subcutaneous insulin is measured in units. The 1mg and 3mg blisters have different bioavailability; therefore three 1mg blisters and one 3mg blister are not interchangeable. There may also be some practical problems. Each blister must be inhaled individually; patients on a high dose may have to perform many inhalations per dose. The size of the device precludes it from being able to be carried in a pocket and some dexterity is required in its use, which could cause problems in the elderly.

Inhaled insulin is more expensive than existing subcutaneous options. As the doses stated on the SPC are lower than those used in some of the trials, there is uncertainty on drug dose and therefore on cost. The Diabetes Managed Clinical Network has agreed to prospectively collect information on any patients who are given this treatment to assess the clinical effectiveness in usual practice.

Buccal midazolam *contd from page 3*

has been shown to be as effective as rectal diazepam and is acceptable to patients and carers. No serious side effects have been seen at the recommended dosage. When given buccally, it can cause a transient stinging or tickling sensation. When used to stop prolonged seizures, the person is usually unconscious and so is not expected to experience side effects. Other effects may include feelings of tiredness, dizziness, light-headedness and sometimes confusion. These effects are short lived and usually milder and last for a shorter time than with rectal diazepam.

Units for reporting concentrations of drugs and poisons

The units used to report concentrations of drugs and poisons is being standardised across the UK. This has been agreed to avoid potential misinterpretation of results when patients or doctors move between areas and to facilitate development of the electronic patient record. Standard units will be introduced across Scotland on 2 April 2007. From this date, concentrations of most drugs and poisons will be reported in mass units (mg/L or µg/L) and the target and toxic ranges will therefore change. A summary of target ranges for common drugs is shown below with conversion factors to allow retrospective comparison of results in molar units with results in mass units.

Details on a wider range of drugs are available on our website. For further information please contact your local biochemistry laboratory or pharmacy department.

Drug	Target range	Conversion factors
Carbamazepine	4.0-12.0mg/L	µmol/L x 0.24 = mg/L
Digoxin	0.5-2.0µg/L	nmol/L x 0.78 = µg/L
Lithium	0.6-1.0mmol/L	
Paracetamol	mg/L	mmol/L x 151 = mg/L *Refer to BNF diagram. Treatment levels - 200mg @ 4h, 100mg @ 8h, 50mg @ 12h (lower if high risk patient).*
Phenobarbital	15-40mg/L	µmol/L x 0.23 = mg/L
Phenytoin	5-20mg/L	µmol/L x 0.25 = mg/L
Salicylate	mg/L	mmol/L x 138 = mg/L *Intoxication >350mg/L, severe toxicity >700mg/L >280mg/L if under 5 years.*
Theophylline	10-20mg/L	µmol/L x 0.18 = mg/L *5.0-10.0mg/L adequate in some circumstances.*
Valproic Acid	50-100mg/L	µmol/L x 0.14 = mg/L *Poor correlation between concentration and effect.*

NHS Greater Glasgow and Clyde

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