PostScript

NHS Greater Glasgow and Clyde

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This edition contains articles on:

Yellow Cards and adverse drug reactions

The Yellow Card Scheme was set up in 1964 after thalidomide highlighted the need for routine monitoring of medicines safety. More than 400,000 reports of suspected adverse drug reactions (ADRs) have been submitted to the Medicines and Healthcare products Regulatory Agency since then. The scheme has highlighted a number of toxicity issues, eg potential toxicity of antipsychotic drugs, cardiotoxicity of clozapine, hepatotoxicity with cyproterone, oesophageal ADRs of alendronate, cardiomyopathy with tacrolimus, and convulsions with quinolones.

How common are ADRs?

The frequency of ADRs depends, in part, on how hard you search for them and how you define them. Estimates suggest:

- Approximately 6.5% of hospital admissions are in some way due to an ADR.
- Between 5 and 15% of patients in hospital suffer an ADR.
- Up to 0.4% of ADRs in hospitalised patients may be fatal.
- In the USA it has been estimated that ADRs are between the 4th and 6th leading cause of death.

What ADRs should be reported?

All that is required is a reasonable suspicion that a health effect has been caused by a medicine in normal therapeutic use. It is important to remember that proof of association, for example, by a rechallenge, is NOT necessary.

In the case of serious reactions it is still important to report well recognised ADRs since this information is used to allow relative toxicity of drugs that are in the same class to be compared and to develop policies, eg on withdrawal of licences or over the counter marketing.

When a medicine is first licensed for use, the numbers of patients that have been exposed is generally relatively small, as compared to the number that will eventually receive it. Relatively uncommon reactions may therefore not have been detected. All reactions to any black triangle medicines (▼) should be reported.

What ADRs were reported in NHSGGC?

1,008 Yellow Card reports were submitted from Scotland between April 2010 and March 2011. Of these reports 215 (21%) were received from NHSGGC.

- Black triangle reports accounted for around 30% of the NHSGGC reports
- Around three-quarters of NHSGGC reports were for serious reactions; this was one of the highest rates in Scotland.
- The overall rate of reporting was marginally below the Scottish average at 18 reports per 100,000 population per year.
- 26% of NHSGGC reports came from hospital doctors, 20% from GPs, 13% from pharmacists, 10% from nurses and 9% from patients.

The drugs most commonly reported in NHSGGC in 2010-2011 were varenicline, flucloxacillin, HPV vaccines, etanercept, diphtheria-containing vaccines, aripiprazole, etonogestrel, ciprofloxacin, ropinirole and tramadol.

We would encourage all clinicians to report serious ADRs and all ADRs to black triangle drugs through the electronic system at *http://www.yccscotland.scot.nhs.uk*.

2012 *Therapeutics Handbook*

The 2012 *Therapeutics Handbook* is currently being printed. Paper copies will be distributed to appropriate staff on each hospital site and it will be available as a PDF on our website in August. If you have downloaded a copy of the 2011 edition to your computer or phone, please ensure you replace it when the new version is available. The next edition of *PostScript Acute* will highlight the main changes.

For all ADTC decisions see http://www.ggcprescribing.org.uk/blog/category/news/

Updated NHSGGC diabetes guidelines

The newly updated guidelines for management of diabetes are available in the Clinical Guideline Electronic Resource Directory (see page 4). Since the 2009 edition, there have been several new agents added to the therapeutic armoury and NICE and SIGN have also issued new guidance on various aspects of diabetes care.

Structured education programmes are now recommended for patients with both type 1 and type 2 diabetes. All patients newly diagnosed with type 2 diabetes should undergo initial education using the DESMOND (Diabetes Education and Self Management for Ongoing and Newly Diagnosed) programme. Patients with type 1 diabetes who can carbohydrate count and are motivated to monitor their diabetes carefully are offered a variety of programmes such as DAFNE (Dose Adjustment for Normal Eating), BUDDIE (better understanding of diabetes, diet and insulin education) and DICE (Diabetes, Insulin and Carbohydrate Education).

HbA_{1c} > 53mmol/mol (7.0%) is the threshold for initiating oral hypoglycaemic therapy and for moving to second line therapy.

The HbA_{1c} thresholds for initiation and intensifying type 2 diabetes treatment have been altered to take into account recent research which suggests over-aggressive treatment might increase cardiovascular morbidity and mortality in this patient group. HbA_{1c} > 53mmol/mol (7.0%) is the threshold for initiating oral hypoglycaemic therapy and for moving to second line therapy. The threshold for intensifying to third line treatment remains > 59mmol/mol (7.5%).

Metformin remains the first line treatment of choice and should be used in all patients unless contraindicated or poorly tolerated. Second line treatment should usually be a sulfonylurea, with gliclazide the preferred choice. Gliptins are recommended as second line treatment only if major reservations are present with metformin, sulfonylureas or pioglitazone. This change in emphasis reflects the growing cost of gliptin prescribing given a modest reduction of HbA_{1c} (9 - 10mmol/mol; 0.9%). Effects are greatest with higher initial HbA_{1c} levels. Used as third line treatment, gliptins may delay the use of insulin therapy for a short period.

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The use of pioglitazone or gliptins should be reviewed at six months and treatment withdrawn if HbA_{1c} has not fallen by more than 4.4mmol/mol (0.5%). Additional warning about the small risk of bladder cancer with pioglitazone is now included.

Since the previous guidelines, the GLP-1 analogues liraglutide and once weekly exenatide have been introduced. GLP-1 analogues should only be considered in patients with a BMI > 30kg/m^2. Exenatide is the less expensive option. Liraglutide should not be used at its highest dose of 1.8mg, since this dose is not considered to be cost effective. In accordance with NICE recommendations, if the treatment targets of HbA_{1c} reduction of at least 11mmol/l (1%) **and** loss of 3% of the initial body weight are not met by 6 months, treatment should be withdrawn. The optimum duration for these agents has not been determined so all patients started on GLP-1 analogues must be carefully monitored and audited.

The updated guidelines now clearly state that all patients with type 2 diabetes who require insulin therapy should be started on human insulins. There is no evidence for additional benefit from analogue insulins in patients with type 2 diabetes. Human Insulatard® should be used as background insulin while insulin detemir and insulin glargine should be reserved for patients who have problems with nocturnal hypoglycaemia. Where patients are already on analogue insulins but have no specific indication, consider a change to Human Insulatard®. These and future guidelines take account of cost effective prescribing for patients with diabetes.

Insulin is a high risk drug commonly associated with medication errors and there is a drive to improve prescribing and reduce risk. The e-learning module, *The safe use of insulin*, is freely accessible to all health care staff at http://www.diabetes.nhs.uk.

www.ggcprescribing.org.uk

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ADTC decisions summary

See the website for full details of indications and restrictions.

Some additions to the Adult *Total Formulary*:

- Alteplase (Actilyse®): fibrinolytic treatment of acute ischaemic stroke up to 4.5 hours post-stroke (extended from 3 hours). Restricted.
- Bee / Wasp venom immunotherapy (Pharmalgen®) for treatment of IgE-mediated bee and wasp venom allergy in people with severe systemic reaction. Restricted.
- Exenatide (Byetta®): adjunctive therapy to basal insulin +/- metformin and/or pioglitazone in adults with type 2 diabetes who have not achieved adequate glycaemic control. Restricted.
- Icatibant acetate (Firazyr®) for the symptomatic treatment of acute attacks of hereditary angioedema in adults (with C1-esterase-inhibitor deficiency). Restricted to specialist use on the advice of Immunology.
- Pregabalin oral solution (Lyrica®). Restricted.
- Rivaroxaban (Xarelto®): treatment of DVT, prevention of recurrent DVT and PE where the intended duration of treatment is three to six months. For longer duration, treatment should be low molecular weight heparin followed by warfarin.
- Tobramycin (TOBI Podhaler®): suppression of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis. Restricted to specialist initiation; second-line after colistin.

The following medicines were among those not added to the Adult *Formulary*

- Belatacept (Nulojix®) for prophylaxis of graft rejection in adults receiving a renal transplant.
- Bevacizumab (Avastin®) for use in combination with capecitabine as first-line treatment of patients with metastatic breast cancer.

Non-*Formulary* (*Adult Formulary*) pending protocol / consultation

- Collagenase clostridium histolyticum (Xiapex®) for the treatment of Dupuytren's contracture.
- Dexmedetomidine (Dexdor®): sedation in ICU.
- Dexamethasone (Ozurdex®) for macular oedema following either branch retinal vein occlusion or central retinal vein occlusion.
- Everolimus (Afinitor®) for unresectable or metastatic, well or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.

Some additions to the *Paediatric Formulary*:

- Abatacept (Orencia®) with methotrexate for moderate to severe active polyarticular juvenile idiopathic arthritis.
- Adalimumab (Humira®) with methotrexate for active polyarticular juvenile idiopathic arthritis.
- Etanercept (Enbrel®) for active polyarticular juvenile idiopathic arthritis in children.
- Tocilizumab (RoActemra®) for active systemic juvenile idiopathic arthritis.
- All four of the above medicines are restricted to specialist use within paediatric rheumatology.
- Insulin detemir (Levemir®) for diabetes mellitus in adolescents and children aged 2 years and above. Restricted to patients unable to achieve good glycaemic control with established insulins.

Non-*Formulary* (*Paediatric Formulary*) pending protocol / consultation

- Etanercept (Enbrel®) for chronic severe plaque psoriasis.
- Somatropin (Saizen®) for growth failure and disturbance.

New *NHSGGC Paediatric Formulary*

This was endorsed by ADTC at the last meeting and is available as a PDF on the GGC Prescribing website. It is primarily aimed at prescribers working in paediatric services, but will also provide GPs with a useful information resource. It includes licensed medicines, several unlicensed medicines, unlicensed preparations and unlicensed uses of licensed medicines, all of which are clearly annotated. The *Formulary* will be updated after each meeting of the NHSGGC Paediatric Drug and Therapeutics Committee. To avoid confusion with prescribers, the main *GGC Formulary* has been renamed the *GGC Adult Formulary* and entries that are purely for use in children will be removed in due course.

Other NHSGGC *Formularies*

In addition to the *Adult* and *Paediatric Medicine Formularies*, other formularies have been developed within NHSGGC applicable to other areas of healthcare. These can all be found on our website under "other formularies" and include:

- The *Urinary Catheter Formulary* lists products and order codes for products which should be used in NHSGGC. It gives some general prescribing advice including information on suitable durations for use.
- The *Primary Care Wound Management Formulary* offers guidance on dressings for specific wounds.
- The *Community Pharmacy Minor Ailment Scheme Formulary* offers guidance on what to supply to eligible patients for treatment of minor ailments and conditions in NHSGGC community pharmacies.

Safety update: PPIs

The MHRA issued advice in the April edition of *Drug Safety Update* about long term use of PPIs and risk of fractures and hypomagnesaemia (http://www.mhra.gov.uk/home/groups/dsu/documents/publication/con149785.pdf).

Fractures

Observational studies suggest there may be a modest increase in the risk of hip, wrist, or spine fracture, especially if PPIs are used in high doses and over long durations (over a year). The increased risk (10-40% above baseline) was observed mainly in elderly patients, and it is possible that other risk factors are contributing. The primary studies varied in the extent to which they adjusted for other potential risk factors and use of calcium and / or vitamin D. Patients at risk of osteoporosis should be treated according to current clinical guidelines to ensure they have an adequate intake of vitamin D and calcium.

Hypomagnesaemia

Severe hypomagnesaemia has been reported infrequently in patients on PPIs, although the exact incidence is unknown. A review of case reports suggests that PPIs may cause hypomagnesaemia. Some cases occurred after three months' of PPI therapy, but most occurred after one year of treatment. Symptoms such as fatigue, tetany, delirium, convulsions, dizziness, and ventricular arrhythmia, can occur; but they may begin insidiously and be overlooked. In most case reports, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

NHSGGC Biochemistry advice is that magnesium levels should be checked:

- For routine, symptom-free patients; after a minimum of three months' treatment with a PPI, and then annually.
- For patients taking digoxin or a diuretic; measure magnesium before starting a PPI then every six months.
- Consider measuring magnesium levels if the patient has symptoms consistent with hypomagnesaemia, or the patient is found to have hypokalaemia or hypocalcaemia.

As part of the drive to review ongoing PPI prescribing, there are several prescribing indicators in primary care related to attempting to decrease dose or use of PPIs, including:

- Reducing the overall prescribing of PPIs by a reduction in defined daily doses (DDDs) dispensed per 1000 weighted patients per day.
- Reducing the dose of PPIs for individual patients by a reduction in use of high strength oral PPIs.

Tacrolimus: prescribe by brand

Advice has been issued by the MHRA (http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON152758) that oral tacrolimus should be prescribed and dispensed by brand name only to minimise the risk of medication errors. Reports suggest that switching between products has been associated with toxicity and graft rejection.

When prescriptions have previously been written generically, the brand on which the patient has been stabilised should be established to ensure they are supplied with the same product. There are currently 13 different brands available.

If a prescriber intends to switch between brands, this should be accompanied by careful medical supervision and therapeutic monitoring. Patients should be advised to take careful note of their usual brand and check with their doctor or pharmacist if they receive a different brand or have any other questions about the prescription, eg about the dose.

See *PostScript 69* for the ADTC generic prescribing policy.

Webwatch: Clinical Guideline Resource Directory

The Clinical Guideline Electronic Resource Directory (http://www.staffnet.ggc.scot.nhs.uk/Info%20Centre/PoliciesProcedures/GGCClinicalGuidelines/Pages/CGDirectory.aspx) was developed to support the implementation of the Clinical Guideline Framework, providing a central location for staff to access clinical guidelines developed and approved for use. The system operates an automatic prompt function which alerts authors of the need to instigate the review process ensuring documents should be up to date.

To enable easier retrieval of the clinical guidelines stored within the directory, clinical guidelines can be filtered by classification (based on a combination of BNF categories and proposals from clinical staff) or by area of applicability. This will allow users to locate clinical guidelines applicable in their working area. The directory also has a search function.

The site is currently being populated with the guidelines. If you cannot find what you are looking for, please check the Clinical Guidelines under Clinical Info. This site will remain active until the migration to the new repository is complete.
http://www.staffnet.ggc.scot.nhs.uk/Clinical%20Info/Clinical%20Guidelines/Pages/default.aspx