PostScRxipt
from the
GGNHSB Area Drug & Therapeutics Committee
Issue 30 November 2005

PRESCRIBING FOR CHILDREN

Prescribing for children is an area fraught with problems. Many practitioners have had difficulty in accessing specialist knowledge to help with the choice of drugs and doses which are often being used outwith the product licence. Here, James Wallace and Jenny MacDonald from Yorkhill's Pharmacy department provide an update on the BNF for Children, a major new development.

Children are not just small adults; they differ markedly in their handling of, and response to, drugs. Children include neonates, infants and school age children up to adolescents of 18 years. Safe, effective prescribing requires an understanding of the wide variability and constant changes in drug handling and response that occur from birth to adulthood. Extra care must be taken when choosing drugs, formulations, doses, routes and methods of administration and associated risks must be recognised and managed.

There are about 75 million children in the European Union, representing 20% of the population. 67% of children in European hospitals and 11% of UK children treated by their GP receive unlicensed or off-label medicines (not licensed for use in the age, route, dose or indication required). This does not reflect inappropriate prescribing but shows the lack of suitably licensed medicines for children.

In order to obtain a licence to market a medicine, the manufacturer has to provide clinical trial evidence of the efficacy and safety of the medicine and the stability of the formulation. There are many ethical, logistical and financial reasons why clinical trials are difficult to carry out in children and this has meant that manufacturers have not licensed medicines for children.

Legislation is currently passing through the European Parliament to provide a framework for licensing of medicines in children. Manufacturers of new medicines will be required to carry out clinical trials in children where appropriate and to publish all results, whether positive or negative, in the SPC. It is expected that an extended period of market exclusivity will be granted to encourage this. Financial support will be put in place to encourage extension of licensing of existing medicines. This bodes well for the future, but prescribers currently do not have access to the range of licensed medicines needed for the treatment of children.

To support this significant knowledge gap, practical information on the use of medicines in children of all ages was published in *Medicines for Children*. The information was based on published evidence and UK consensus of best practice and was gathered by a collaboration of UK paediatricians and paediatric pharmacists. The value of this publication and the need for further information led to the preparation of the *BNF for Children* (BNFC; **http://bnfc.org**). The first edition will be distributed by the Scottish Executive from November. Athens password holders can access it now from Medicines Complete (**http://www.medicinescomplete.com/mc/**).

The BNFC provides a great deal of advice which goes beyond the product licences. Many products for children need to be specially manufactured or imported. Careful consideration has been given to establishing the clinical need for unlicensed interventions with respect to both evidence and experience of safety and efficacy.

The information has been compiled from
- emerging evidence,
- best practice guidelines,
- local paediatric formularies,
- clinical experts,
- manufacturers' literature.

All prescribers now have access to a source of the most up-to-date and authoritative information on the use of medicines in children. This should provide them with the confidence that they are providing safe and effective drug treatment.

In this issue . . .

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

What's the fuss about generic prescribing?

The concept of generic prescribing is now widely accepted by prescribers and patients. Almost 80% of primary care prescriptions in Glasgow are issued generically and generic prescribing is measured by the Scottish Executive through the Performance Assessment Framework. Yet recently, concerns have been raised over the suitability of two generic products. The ADTC has reviewed the relevant information and supports generic prescribing of lamotrigine and alendronic acid. The reasons are detailed below.

Strict criteria are set by the Medicines and Healthcare products Regulatory Agency (MHRA) which must be met before a license is granted for the manufacture of a generic product. The vast majority of medicines are suitable for generic prescribing, exceptions include products with a narrow therapeutic index and these are indicated in the *Glasgow Formulary.*

Lamotrigine
Concern has been expressed that switching a patient stabilised on Lamictal® to generic lamotrigine could lead to changes in plasma levels and possibly affect seizure

contd on page 4

Incremental alphabetical list of published SMC advice on which Glasgow decisions have recently been taken.
For further information and a full list of SMC advice, visit **www.scottishmedicines.org**

Drug	Reason for consideration	Indication/pharmacology	SMC decision	Glasgow decision
Anagrelide (Xagrid®)	New medicine (Resubmission)	Reduction of elevated platelet counts in at-risk essential thrombocythaemia patients intolerant to current therapy or whose platelet counts are not reduced to an acceptable level by current therapy.	Accepted for use within NHS Scotland.	*Formulary.*
Atorvastatin (Lipitor®)	New indication	Adjunct to diet for the reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides in children aged 10 years and older with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other non-pharmacological measure is inadequate.	Accepted for restricted use within NHS Scotland. Restricted to initiation by paediatricians or physicians specialising in the management of lipid disorders.	*Formulary*. Acknowledge new indication. SMC restrictions apply.
Bemiparin, (Zibor®)	New medicine	Prevention of thromboembolic disease in patients undergoing general surgery Prevention of thromboembolic disease in patients undergoing orthopaedic surgery. Prevention of clotting in the extra-corporeal circuit during haemodialysis. Treatment of venous thromboembolism.	Not recommended for use within NHS Scotland. Not recommended for use within NHS Scotland. Not recommended for use within NHS Scotland. Not recommended for use within NHS Scotland.	Non-*Formulary*. Non-*Formulary*. Non-*Formulary*. Non-*Formulary*.
Carbomer (Liquivisc®)	New medicine	Symptomatic treatment of dry eye syndrome where a carbomer product is the treatment of choice.	Accepted for use within NHS Scotland.	Non-*Formulary* following consultation with ophthalmologists.
Cetuximab (Erbitux®)	New medicine (independent review panel assessment)	In combination with irinotecan for the treatment of patients with epidermal growth factor receptor expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.	Not recommended for use within NHS Scotland.	Non-*Formulary*.
Docetaxel (Taxotere®)	New medicine	In combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node-positive breast cancer.	Accepted for use for use within NHS Scotland.	*Formulary*. Acknowledge new indication.
Fosamprenavir (Telzir®)	New medicine	Treatment of HIV-1 infected adults in combination with other antiretroviral products.	Accepted for use for use within NHS Scotland.	Non-*Formulary* following consultation with Brownlee Centre HIV Special Interest Group.
Glyceryl Trinitrate (Rectogesic®)	New medicine	Relief of pain associated with chronic anal fissure.	Not recommended for use within NHS Scotland.	Non-*Formulary*.
Infliximab (Remicade®)	New indication (Resubmission)	Treatment of ankylosing spondylitis in patients who have severe axial symptoms, elevated serological markers of inflammatory activity and who have responded inadequately to conventional therapy.	Accepted for restricted use within NHS Scotland.	*Formulary*. Acknowledge new indication. Restricted to use in accordance with British Society of Rheumatology guidelines 2004. Subject to PMG approval.
Pregabalin (Lyrica®)	New indication (Resubmission)	Treatment of peripheral neuropathic pain in adults.	Not recommended for use within NHS Scotland.	Non-*Formulary* for this indication.
Triptorelin (Decapeptyl SR®)	New indication	Treatment of endometriosis in patients for whom the use of triptorelin is appropriate and who would benefit from reduced frequency of administration compared with injection every 4 weeks.	Accepted for use for use within NHS Scotland.	Non-*Formulary*.
Omeprazole intravenous infusion (Losec®)	*Formulary* review	Prophylaxis of acid aspiration and treatment of benign gastric ulcer, duodenal ulcer and gastro-oesophageal reflux.		*Formulary*.

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

Eplerenone (Inspra®)
Eplerenone has been added to the *Glasgow Formulary.* It is restricted to initiation in patients with left ventricular systolic dysfunction (LVSD) accompanied by evidence of heart failure (HF) manifesting within 3-14 days of myocardial infarction (MI). The SMC accepted it for this use in addition to standard therapy including beta blockers. It has also been added to the *Formulary* for patients who have intolerable sex hormone mediated adverse effects with spironolactone.

Eplerenone is a selective aldosterone receptor antagonist. Aldosterone promotes sodium and water retention which may worsen cardiac function and increase blood pressure. The EPHESUS trial (n = 6,632) showed that adding eplerenone to standard therapy including beta-blockers reduced all cause mortality and cardiovascular (CV) morbidity and mortality among patients with LVSD and HF post-MI. The number needed to treat over one year is 50 to save one life and 33 to prevent one CV death or one hospitalisation for a CV event.

Eplerenone is the second aldosterone antagonist marketed in the UK. Spironolactone reduces mortality and morbidity in patients with chronic HF. It is considerably cheaper than eplerenone (£2.10 vs £42.72 per month), however the two agents are not directly comparable as major trials were conducted in different patient populations with different end-points. There are no clinical effectiveness data including comparisons of outcomes with spironolactone and eplerenone. A 12-week randomised study published in abstract showed a significant reduction in brain natriuretic peptide (a surrogate marker for heart failure) with eplerenone 50-100mg daily and spironolactone 25mg daily, but not eplerenone 25mg daily, compared to placebo ($p < 0.05$).

Eplerenone should be initiated at 25mg daily and titrated to 50mg daily where possible. Potassium should be monitored at the start of therapy, within the first week, after one month or dose adjustment, and periodically thereafter. No adjustment of the starting dose is recommended for elderly patients (the risk of hyperkalaemia is increased due to age-related decline in renal function) or patients with mild to moderate hepatic impairment.

Eplerenone has a significant potential for drug interactions. Concomitant use with potassium-sparing diuretics or strong CYP3A4 inhibitors, eg clarithromycin, itraconazole or ketoconazole is contraindicated. The most common adverse effects are GI disorders, abnormal renal function, dizziness and hyperkalaemia. It has been postulated that eplerenone has a potential for fewer side-effects than spironolactone, but this has not yet been confirmed by long-term, head to head trials.

Summary
• Eplerenone has been added to the *Glasgow Formulary.* It may be initiated in patients with LVSD plus evidence of HF manifesting within 3-14 days of MI.
• Spironolactone has been shown to reduce morbidity and mortality in chronic heart failure; eplerenone and spironolactone have different licensed indications.
• Eplerenone has significant potential for drug interactions.

Atomoxetine *on page 4*

Formulary news *contd from page 3*

Atomoxetine (Strattera®)
Atomoxetine has been added to the *Glasgow Formulary* for restricted use in the treatment of attention deficit hyperactivity disorder (ADHD) following the recent SMC decision. Use is restricted to patients who do not respond to stimulants or in whom stimulants are contraindicated or not tolerated.[1] Initiation is restricted to physicians with appropriate knowledge and expertise in treating ADHD. Since costs are higher than other treatments, it is not recommended first line.

ADHD is a behavioural disorder thought to involve several neurotransmitters including adrenaline, noradrenaline and dopamine. Atomoxetine is a selective noradrenaline reuptake inhibitor but its exact mode of action is unknown. It is licensed for the treatment of ADHD in adolescents and children over 6 years of age. It is not subject to the Misuse of Drugs Regulations.

Atomoxetine has been shown in clinical trials to have statistically significant benefits compared to placebo.[2] In most trials the primary outcome was the ADHD rating scale. This involves 18 questions rated by an investigator following interviews with the parent or teacher and sometimes the child.

A study comparing immediate release methylphenidate to atomoxetine found no difference in hyperactivity and clinical global impression.[2] A randomised double-blind trial of atomoxetine and methylphenidate MR showed 45% of patients who did not respond to methylphenidate MR did respond when switched to atomoxetine.[2] There are currently no published studies comparing atomoxetine with dexamphetamine. Atomoxetine may be beneficial in patients suffering from co-morbidities such as tics and Tourette's syndrome which are contraindications for use of stimulants.

The most common adverse effects are gastro-intestinal including vomiting, loss of appetite and weight loss. Atomoxetine has been linked with rare but serious liver damage and an increased risk of suicidal thoughts and behaviour.[3] Treatment should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Patients should be carefully monitored for signs of depression, suicidal thoughts or behaviour and referred for alternative treatment if necessary.

NICE issued their Final Appraisal Determination for the treatment of ADHD in children and adolescents in May 2005; the full published guidance is awaited. The suggested place for atomoxetine is broadly in line with the SMC determination.[2]

Summary

• Atomoxetine has been added to the *Glasgow Formulary*. It should be restricted to patients who have failed to respond to stimulants or in whom stimulants are contra-indicated or not tolerated.
• Patients who have not responded to methylphenidate may respond to atomoxetine.
• There are links with rare but serious liver damage and increased suicidal thoughts and behaviour.
• Atomoxetine is significantly more expensive than methylphenidate. Annual costs range from £655 - £1,310 compared to £33 - £765.[4]

Generic prescribing *contd from page 1*

control. Some anti-epileptic medicines have a narrow therapeutic index or non-linear pharmacokinetics which makes them unsuitable for generic prescribing due to differences between formulations. Lamotrigine has a fairly wide therapeutic index and linear pharmacokinetics; this means that minor differences in absorption between formulations are unlikely to have any clinical consequences.

MHRA data have shown that generic lamotrigine is bioequivalent to Lamictal® and the Department of Health issued a statement supporting its use:

"The MHRA will ensure that bioequivalence is established between the brand Lamictal® and potential generic alternatives. Some commentators have suggested that there should be no switching of products used in the treatment of epilepsy. But in this instance, there is no compelling evidence to suggest that switching from the originating brand to a generic alternative will have an adverse clinical outcome. However, it is open to prescribers to modify their usual generic prescribing practice if, in their clinical judgement, the circumstances of individual patients warrant such action."

The ADTC supports generic prescribing of lamotrigine when appropriate for an individual patient. This should be at the discretion of the prescriber with the patient involved in the decision.

Alendronic acid
This bisphosphonate has a relatively low oral bioavailability which is significantly reduced by factors such as food and gastric pH. There were concerns that the generic was not equivalent to the brand, but recent studies from Germany have demonstrated bioequivalence between two test and reference formulations using both *in vitro* (dissolution) and *in vivo* (bioavailability) tests.

The ADTC recommends that alendronic acid should be prescribed generically as there is no compelling evidence to support preferential prescribing of the brand.

PostScRipt
GGNHSB
Area Drug & Therapeutics Committee
Chair: Professor M J Brodie

Publications Sub-group
Chair: Mrs A Thompson
Dr K Beard, Dr D Gaffney, Ms K Greschner, Dr K R Paterson, Dr A Power, Mr I Speirits, Mr C Tuhan, Ms J Watt

Published by the Publications Sub-group to reflect the views of the Area Drug & Therapeutics Committee but not necessarily those of Greater Glasgow NHS Board.

PostScript
Editor: Mrs A Thompson
Medicines Management Adviser, Greater Glasgow Primary Care NHS Trust, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow G12 0XH tel: 0141 211 0327 fax: 0141 211 3826

Web editor: Dr A Power

Design, layout and production control:
Strathcashel Publications Project Management (01505 850 344)
Printed by: Core Image, East Kilbride