Prescribing Bulletin

Supporting prescribing excellence - informing colleagues in primary and secondary care

Issue 122 - May 2024

What's in this edition?

In this edition of the Bulletin:

- Safe oral paracetamol prescribing in patients with risk factors for hepatotoxicity
- Don’t let your patients get ‘stuck’ on lidocaine plasters
- MHRA Drug Safety Update – Fluoroquinolones (-oxacins) January 2024
- Codeine linctus – reclassification to prescription only medication

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Safe oral paracetamol prescribing in adult patients with risk factors for hepatotoxicity

Paracetamol is a frequently prescribed non-opioid oral analgesic which can cause liver damage in patients with risk factors for hepatotoxicity (*reference 1)*. In the BNF, there are no specific oral paracetamol dose reduction recommendations for adult patients with risk factors for hepatotoxicity, instead it is recommended that clinical judgement is used *(reference 2)*.

To reduce the risk of acute liver failure secondary to oral paracetamol, guidance from the British Hepatology Pharmacy Group *(reference 3)* recommends oral paracetamol dose reduction in adult patients which have the following risk factors for hepatotoxicity:

- Dry body weight under 50kg
- Elderly/frail
- Renal insufficiency
- Decompensated liver disease
- Chronic malnutrition
- Chronic dehydration
- Cachexia
- Chronic alcohol consumption or regular consumption of alcohol in excess of recommended amounts
- Long-term treatment with liver enzyme-inducing drugs e.g. carbamazepine, phenytoin, primidone, rifampicin, phenobarbital, St John's Wort or other drugs that induce liver enzymes.

Recommended dosing in these patient groups

Dosing guide for adult patients with risk factors for hepatotoxicity with oral paracetamol. Clinical judgement **must** always be used.

	Weight less than or equal to 40kg*	*Weight* 41kg to 49kg*	*Weight* greater than 50kg*
Oral paracetamol dosing	500mg Four times daily	500mg to 1g Three times daily	500mg to 1g Four times daily
Maximum oral daily dose of paracetamol	2g	3g	4g

Prescribing notes
***** *Dry weight should be used*

- If over 50kg (dry weight), 1g four times daily orally is safe for short periods of time (less than or equal to 7 days)
- If needed regularly long-term (greater than 7 days), reduce dose
- Irrespective or weight where the patients eGFR is less than 30 ml/min/1.73m^2, the interval between dosing must be a minimum of 6 hours.

Electronic prescribing systems in primary and secondary care are being updated within NHS Lothian to provide the above guidance at point of prescription; for example, a DNOTE will be added to HEPMA. Additionally, prescribers are asked to review the course length and prescribe for the shortest time

possible. If a course is required for more than 7 days, prescribers are urged to consider reducing the dose to reduce the overall risk of hepatotoxicity.

To summarise, at the point of prescribing oral paracetamol, prescribers are required to:

- obtain an accurate up to date weight to inform dosing
- check cumulative paracetamol dose over previous 24 hours
- consider risk factors for hepatoxicity as listed above and adjust dosing accordingly
- ensure prescription length is appropriate for indication. If prescribing for more than 7 days, consider reducing dose further.

During oral paracetamol treatment, prescribers must:

- regularly review the risks and benefits of the prescription
- monitor liver function, weight and renal function in at risk patients
- check for interactions if commencing new medicines
- ensure that patients prescribed a lower dose are counselled on the reasons for this and provide advice on purchasing general sale list paracetamol.

With thanks to Dr Emma Morrison, Consultant in Acute Medicine, Toxicology and Medicines Management, Royal Infirmary of Edinburgh and National Poisons Information Service who contributed to this article.

Reference 1

Aurobindo Pharma - Milpharm Ltd. SPC Summary of Product Characteristics: Paracetamol Tablets 500mg (POM)

www.medicines.org.uk/emc/product/10817/smpc

Reference 2

BNF Online

bnf.nice.org.uk/drugs/paracetamol/

Reference 3

Position Statement March 2022. Prescribing weight – adjusted oral paracetamol in adults. British Hepatology Pharmacy Group
www.basl.org.uk/uploads/BHPG/Paracetamol%20Position%20Statement_Mar%202022.pdf

Don’t let your patients get ‘stuck’ on lidocaine plasters

Lidocaine plasters are listed as a fifth-line treatment option on the East Region Formulary (ERF) for post herpetic neuralgia (PHN) in adults, the only indication they are licensed for (*reference 1*). The ERF also recognises their use in paediatrics and within the Scottish Palliative Care Guidelines, however they are increasingly being used off-label for the treatment of other neuropathic pain conditions.

Mechanism of action

Lidocaine is a local anaesthetic, and the topical application of plasters has a dual mechanism of action; through the continuous diffusion of drug into the skin and through the mechanical action of the plaster protecting the hypersensitive area. The lidocaine is thought to stabilise neuronal membranes by causing down regulation of sodium channels, thereby resulting in pain reduction and resolving the allodynic component of neuropathic pain.

Evidence

The evidence to support their use is weak and it is worth noting that NICE removed them from their guideline on the treatment of neuropathic pain for this reason. Additionally, the Specialist Pharmacy Service conducted a review of lidocaine plasters and classified them as ‘an item of low clinical effectiveness’ (*reference 2*). Still there are patient groups who find them helpful, and SIGN recommends they be considered for the treatment of patients with PHN if first-line pharmacological therapies have been ineffective (*reference 3)*. The Scottish Palliative Care Guidelines (SPCG) also recommend the use of lidocaine plasters for three indications: localised neuropathic pain that is unresponsive to opioids and

adjuvant analgesics; locally painful bone metastases unresponsive to standard treatments; and the short-term treatment of localised, severe uncontrolled bone or neuropathic pain while adjuvant analgesics are being titrated.

Review of efficacy

The benefit should be seen in the first two weeks of starting treatment. If not, this is a good indicator to discontinue therapy. Plaster-free periods are useful to assess if lidocaine plasters need to be continued. Plaster-free periods should be at least 24 hours long and differ from the usual 12 hour 'off' periods. These breaks should be repeated by the patient on at least a monthly basis. It is important to note that long term lidocaine use can cause desensitisation of the nerve endings meaning the risk of continued use may outweigh the benefits (*reference 4*).

Plaster-free periods – Trial without a plaster for at least 24 hours

- If, after initiation, pain does respond after 7 days try a plaster-free period. If the pain worsens restart but if the pain remains stable then discontinue

- Try a plaster-free period on a monthly basis to assess therapeutic benefit.

- Clinical studies showed that the number of plasters used decreased over time. Gradually, therapy can be withdrawn by reducing the number of plasters used or increasing the duration of the plaster-free interval. (*reference 5*).

Monitoring

If lidocaine plasters are initiated during a hospital admission their use should be reviewed prior to discharge. If they have been effective, it should be made clear on the discharge letter the indication, start date and site of application with advice on assessing efficacy at four weeks after initiation. Patients should also be counselled on plaster-free periods and encouraged to assess their own response and report back to the medical team who can look at optimising their treatment.

Prescribing

Local prescribing systems and ScriptSwitch messaging will highlight cost efficient prescribing options. Lidocaine plasters are currently packaged in sachets of 5 to 10 plasters depending on current suppliers.

KEY POINTS

Lidocaine plasters are licensed for the treatment of PHN. There is low quality evidence to support their use in localised neuropathic pain, however they are included in the ERF and SPCG for limited indications.

Their efficacy should continue to be monitored and plasters should be discontinued if there is no clinical improvement after four weeks. Monthly reviews are required as risks of side effects might outweigh benefits.

The ERF provides information on first-line alternatives for the treatment of neuropathic pain and information on other licensed treatments for pain.

With thanks to Luke Pattison, Rotational Pharmacist, Royal Infirmary of Edinburgh who contributed to this article.

Reference 1

East Region Formulary (2024) Pain with a neuropathic component OR neuropathic pain

www.formulary.nhs.scot/east/central-nervous-system/pain-related-conditions/pain/?m=pain-with-a-neuropathic-component-or-neuropathic-pain

Reference 2

Specialist Pharmacy Service (2017) A review of lidocaine 5% medicated plasters for Post-herpetic Neuralgia

www.england.nhs.uk/wp-content/uploads/2017/11/sps-lidocaine-plasters.pdf

Reference 3

SIGN 136 (2019) Management of chronic pain

www.sign.ac.uk/media/2097/sign136_2019.pdf

Reference 4

Derry, S, Wiffen, P J, R, A M, & Quinlan, J (2014) Topical lidocaine for neuropathic pain in adults. Cochrane Database of Systematic Reviews, 7.

doi.org/10.1002/14651858.CD010958.pub2

Reference 5

Lidocaine Grunenthal 700mg medicated plaster - Summary of Product Characteristics (SmPC

Lidocaine Grunenthal 700 mg medicated plaster - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

MHRA Drug Safety Update – Fluoroquinolones (-oxacins) (January 2024) – New restrictions

The recent MHRA warning on Fluoroquinolone use (2024) advises that fluoroquinolones must now only be prescribed when other commonly recommended antibiotics are inappropriate (*reference 1*).

The Scottish Antimicrobial Prescribing Group (SAPG) has published their position statement supporting the recent MHRA Fluoroquinolone warning and reinforcing the place of antibiotic stewardship in decision making (*reference 2*).

All formulary pathways where fluoroquinolones appear have subsequently been reviewed by the ERF infection working group to reflect this.

General advice is:

1. Use the ERF for indications where fluoroquinolones may be used.
2. Prescribers must be aware of patient groups at highest risk of adverse effects (for example transplant patients, renally impaired, aged >60 years), discuss with patients and proceed with caution if appropriate.
3. Outline the risks to patients and advise on seeking medical advice if side effects present.
4. Provide/signpost patients to the MHRA Fluoroquinolone Patient Information Leaflet (*reference 3*)

5. Avoid co-administration of a corticosteroid with a fluoroquinolone since this can exacerbate fluoroquinolone-induced tendinitis and tendon rupture.

6. Report all adverse events to the MHRA via the Yellow Card Scheme.

KEY POINTS on the risk of tendon damage with fluoroquinolones, corticosteroids and in renal impairment

- The use of corticosteroid in itself can increase the risk of tendinopathy, this risk increases when used with other drugs that can cause tendinopathy.
- The risk of tendon rupture due to oral corticosteroids increases with the dose and tends to occur in those with chronic inflammatory diseases managed with long-term corticosteroids (such as lupus, psoriasis, and rheumatoid arthritis). The duration of use before tendon rupture ranges from four months to several years but may be shorter.
- Inhaled corticosteroids have also been implicated, but a study suggests that they do not affect the risk of Achilles or bicep tendon rupture at any level of exposure (*reference 2*).
- Although no specific information on tendinopathy is currently available for topical corticosteroids, systemic absorption and therefore adverse effects may occur in certain situations (depending on potency, surface or application, skin integrity, duration of exposure etc). A risk can therefore not be totally excluded.
- Most of the information on tendinopathy with corticosteroids seems to relate to systemic or local use (injection), and the European Medicines Agency specifically cautions the use of fluoroquinolones in patients on systemic corticosteroids.
- Fluoroquinolones are mainly cleared by the kidneys, and renal impairment may be associated with an increased risk of tendinopathy as it is a dose-dependent effect.

Reference 1

MHRA Drug Safety Update. Fluoroquinolone antibiotics: must now only be prescribed when other commonly recommended antibiotics are inappropriate. January 2024.

www.gov.uk/drug-safety-update/fluoroquinolone-antibiotics-must-now-only-be-prescribed-when-other-commonly-recommended-antibiotics-are-inappropriate

Reference 2

Scottish Antimicrobial Prescribing Group. Updated MHRA fluoroquinolone advice. March 2024

www.sapg.scot/guidance-qi-tools/antimicrobial-specific-guidance/updated-mhra-fluoroquinolone-advice/#:~:text=SAPG%20supports%20the%20restrictive%20use,view%20of%20the%20MHRA%20advice

Reference 3

MHRA. Fluoroquinolone antibiotics (-oxacins): what you need to know about tendons, muscles, joints, nervous system, and psychological side effects. Patient Information Leaflet. January 2024.

assets.publishing.service.gov.uk/media/65aa9125c69eea0010883840/FQ_Patient_Information_Sheet_-_TO_PUBLISH.pdf

MHRA Drug Safety Update – Nitrofurantoin and renal impairment (February 2015) – Reminder

The antibacterial efficacy of nitrofurantoin in the treatment of UTIs depends on renal secretion in the urinary tract. In renal impairment, reduced secretion may result in reduced efficacy and possible treatment failure, as well as an increased risk of side-effects. The MHRA Drug Safety Update therefore advises that:

1. Consider checking renal function when choosing to treat with nitrofurantoin, especially in the elderly
2. Nitrofurantoin is contraindicated in patients with an eGFR of less than 45 ml/min/1.73m2
3. A short course (3 to 7 days) may be used with caution in certain patients with an eGFR of 30 to 44 ml/min/1.73m2. Only prescribe to such patients to treat lower UTIs with suspected or proven multidrug resistant pathogens when the benefits of nitrofurantoin are considered to outweigh the risks of side effects.
4. Closely monitor for signs of pulmonary, hepatic, neurological (in particular peripheral neuropathy), haematological, and gastrointestinal side effects during treatment (see BNF for more detail and MHRA Drug Safety Update April 2023) (*reference 3*).
5. Nitrofurantoin should not be used to treat sepsis syndrome secondary to UTIs or suspected upper UTIs.

With thanks to Hélène Legay and Carol Philip, Antimicrobial Pharmacists, NHS Lothian who contributed to this article.

Reference 1

MHRA Drug Safety Update. Fluoroquinolone antibiotics: must now only be prescribed when other commonly recommended antibiotics are inappropriate. January 2024.

www.gov.uk/drug-safety-update/fluoroquinolone-antibiotics-must-now-only-be-prescribed-when-other-commonly-recommended-antibiotics-are-inappropriate

Reference 2

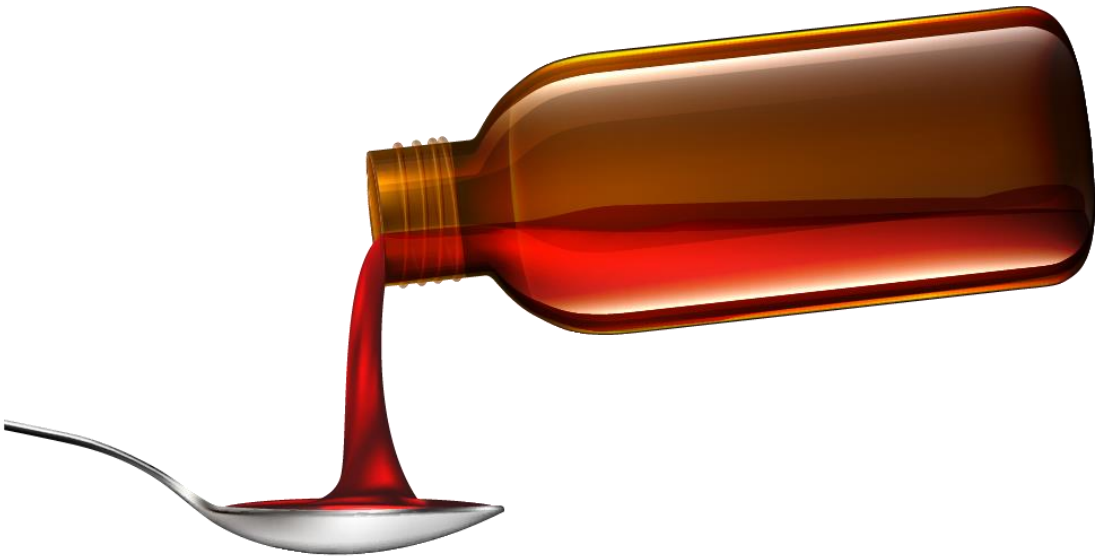
MHRA Drug Safety Update. Nitrofurantoin now contraindicated in most patients with an estimated glomerular filtration rate (eGFR) of less than 45 ml/min/1.73m2. February 2015.

www.gov.uk/drug-safety-update/nitrofurantoin-now-contraindicated-in-most-patients-with-an-estimated-glomerular-filtration-rate-egfr-of-less-than-45-ml-min-1-73m2

Reference 3

MHRA Drug Safety Update. Nitrofurantoin: reminder of the risks of pulmonary and hepatic adverse drug reactions. April 2023. www.gov.uk/drug-safety-update/nitrofurantoin-reminder-of-the-risks-of-pulmonary-and-hepatic-adverse-drug-reactions

Codeine linctus – reclassification to prescription-only medication



Codeine Linctus BP (15mg in 5ml) is licensed for use in a dry cough in adults and children aged 12 years and over without breathing difficulties. It has been used as a cough medicine, or 'antitussive', for many years, despite limited evidence of its effectiveness (*reference 1*). It is only considered to be effective in those with a cough lasting over 8 weeks. In February 2024, the MHRA issued a drug safety update reclassifying codeine linctus cough medicines to a prescription-only medicine (*reference 2*).

How does codeine work?

Codeine acts as a prodrug and is converted into morphine in the liver by the enzyme cytochrome P450 2D6 (CYP2D6). Morphine itself has been demonstrated to have efficacy in randomised controlled trials, but there is very little clinical evidence supporting oral codeine use in chronic cough. It has been found that some people are 'fast metabolisers' of codeine, whereas others are 'slow metabolisers' and therefore it is impossible to predict the degree of opiate effects or side effects. Because of this, both underdosing and overdosing can occur in an unpredictable manner (*reference 1*). It is for this reason that the European Medicines Agency have restricted the use of codeine cough-and-cold medications in children. The BNF also states to avoid in CYP2D6 ultra-rapid metabolisers of any age, who are at risk of opioid toxicity (*reference 3*).

What was the concern?

The MHRA noted safety information which revealed that codeine linctus was being used recreationally for its opioid effects, rather than for its intended use as a cough suppressant (*reference 2*). Unregulated websites may sell codeine linctus illicitly, including in a recreational drink called 'Purple Drank', which

contains varying amounts of codeine linctus and has been popularised among young adults via social media.

Common side effects and risks of codeine:

- Constipation
- Dependence and addiction
- Overdose or co-administration with benzodiazepines, or concomitant use with alcohol, sedatives or other medications can cause sedation, respiratory depression, coma and death

Doses

Codeine 15mg in 5ml solution was a pharmacy medication and has now been reclassified to prescription-only medication. The stronger preparation of 25mg in 5ml oral solution has always been a prescription-only medication and is included on the formulary for specific pain indications where codeine tablets cannot be swallowed (*reference 4*). There is a risk of overdose if the incorrect strength is used.

What alternatives can be offered for cough?

All patients with a cough lasting longer than 4-6 weeks should be reviewed by a clinician, to establish the underlying cause. For acute cough, there is little evidence to support the use of cough suppressants. Patients can be advised:

- To inhale warm moist air for symptomatic relief
- To drink plenty of fluids
- That chesty coughs can last up to two weeks, whilst dry coughs can continue for three weeks
- To quit smoking
- Pharmacy First can prescribe simple linctus (citric acid). The patient should approach community pharmacies for a consultation.
- Alternative non-prescription cough medications for acute cough or an irritated throat are available to purchase. These include honey and lemon mixtures. The patient can also make honey and lemon in warm water at home.

KEY POINTS

Codeine is an opioid and is addictive.

Going forward, codeine linctus will only be available on prescription. This action has been taken to reduce the risk of addiction or overdose.

Take care with doses of codeine linctus – only the 15mg in 5ml dose is licensed for cough.

Report side effects, including dependence, through Yellow Card | Making medicines and medical devices safer (mhra.gov.uk)

Reference 1

Morice A and Kardos P ‘Comprehensive evidence-based review on European antitussives’. *BMJ Open Respiratory Research* 2016: volume 3, article e000137

Comprehensive evidence-based review on European antitussives - PubMed (nih.gov)

Reference 2

MHRA Drug Safety Update Codeine linctus (codeine oral solutions): reclassification to prescription only medicine. February 2024

www.gov.uk/government/news/codeine-linctus-to-be-reclassified-to-a-prescription-only-medicine-because-of-risk-of-abuse-and-addiction

Reference 3

NICE. BNF. Aromatic inhalations, **cough preparations** and systemic nasal decongestants.

https://bnf.nice.org.uk/treatment-summaries/aromatic-inhalations-cough-preparations-and-systemic-nasal-decongestants/#cough-preparations-in-children

Reference 4

Codeine - formulary approved indications. East Region Formulary (2024)

formulary.nhs.scot/east/medicines/C/775354007

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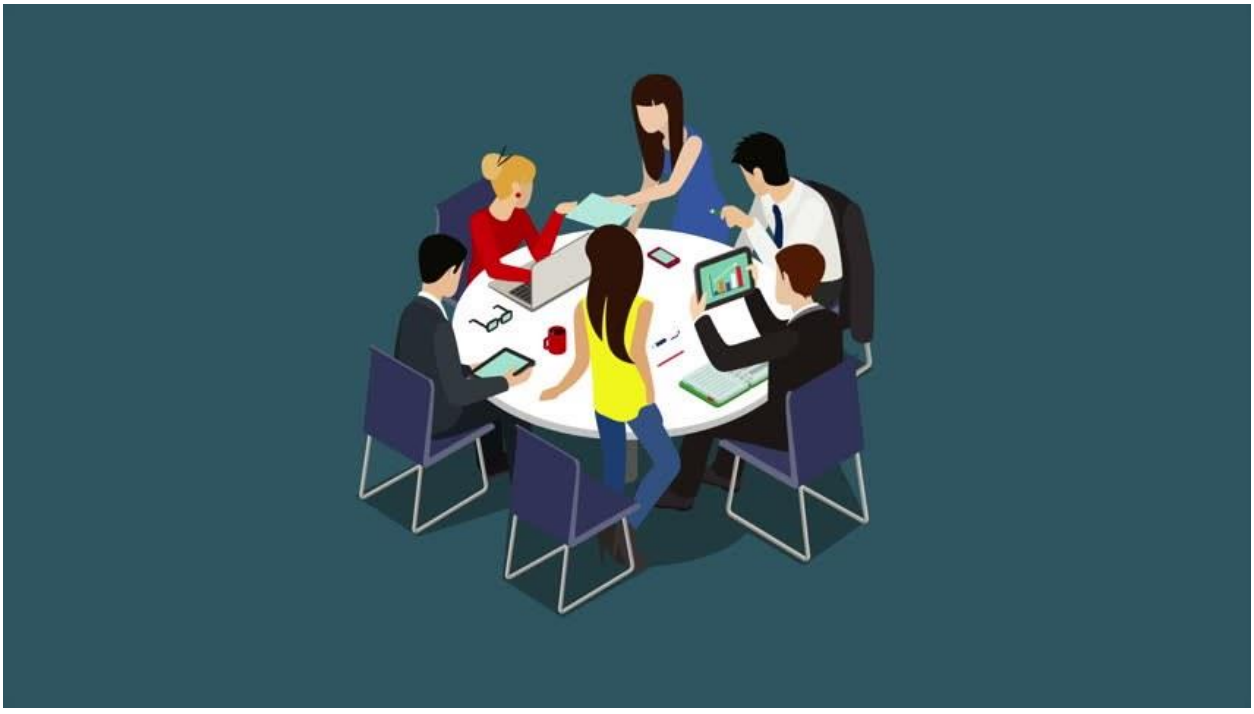

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Access the formulary at *formulary.nhs.scot/east*