Derbyshire Medicines Management UPDATE

www.derbyshiremedicinesmanagement.nhs.uk

Reviewing Non-Steroidal Anti-Inflammatory Drug (NSAID) Prescribing

An update on current issues

Date Updated: August 2017

NSAIDs and coxibs are commonly prescribed drugs in primary care with around 2.5 million items prescribed annually across Derbyshire; of which an estimated 45% is for people with the long term condition of osteoarthritis, predominantly prevalent in older age. NSAIDs and coxibs may be effective therapies but they are also highly toxic:

- While gastro intestinal toxicity is well documented the MHRA have issued further advice around the cautious use of piroxicam, ketoprofen and ketorolac.
- There is evidence on the cardiovascular toxicity of coxibs and NSAIDs (in particular long term diclofenac) and the need to review high risk patients to safer alternatives.
- Following a Europe-wide review of cardiovascular safety in patients taking diclofenac has prompted the MHRA to issue further advice including new contraindications. Diclofenac is no longer available "over the counter"
- Treatment with NSAIDs should be continued for the shortest time and at the lowest dose necessary to control symptoms. A Danish study suggests that the increased relative risk could be largely independent of the duration with harms within the first few weeks of treatment http://www.npc.nhs.uk/merec/resp/cond/resources/merec_monthly_42.pdf

Cardiovascular Complications

Coxibs, as a class, are associated with an excess risk of thrombotic events compared with no treatment (about three per 1000 users treated for one year)

- This risk increases with dose and persists throughout treatment, especially within the first 8-30 days of use with high doses
- All coxibs are contraindicated for patients with established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease

Traditional NSAIDs may also be associated with an increased risk of thrombotic events.

The PRECISION study demonstrated that celecoxib 200mg/day is non inferior to naproxen 750mg/day or ibuprofen 1.8g/day as regards CV risk. Additionally, Bally et al (BMJ 2017) confirm using higher doses than this (or diclofenac >100mg/day) increases acute MI risk, especially in the first 8 - 30 days of use.

- Long-term diclofenac150mg/day appears to be associated with a similar excess risk to that of coxibs, whereas low dose Ibuprofen (1200mg/day) and naproxen 750mg/day appear to be associated with a lower risk. Ibuprofen at doses ≥ 2400mg daily have been shown to have similar CV risk as to other NSAIDs (EMA May 2015)
- There is inadequate evidence to suggest that there is a loss in the cardio protective effect of aspirin when given with ibuprofen

Beware of prescribing NSAIDs in patients with heart failure and renal problems

Standard naproxen (film coated) is considerably cheaper than Naproxen EC

Gastro Intestinal Complications

All NSAIDs carry a risk of GI side-effects

- Risk increases with age, presence of co-morbidities and dose of NSAID
- Ibuprofen (1200mg daily or less) has a lower GI risk than other NSAIDs.
- EC products are not safer

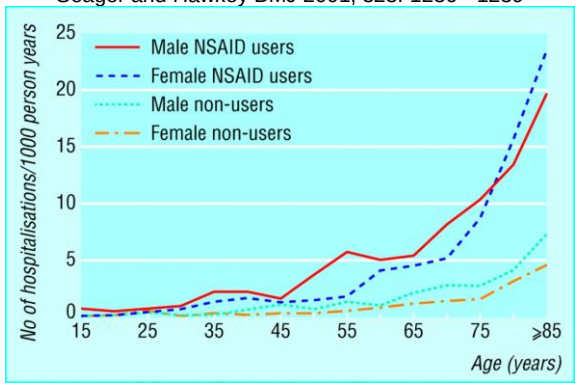
Coxibs have a slightly lower GI risk than traditional NSAIDS but:

- Dyspepsia can still occur and may be as common as with traditional NSAIDs
- Severe and sometimes fatal GI reactions can occur
- Not all coxibs may be equal
- Benefits diminished when co-administered with aspirin

Using a PPI (e.g. lansoprazole 15mg) significantly reduces the risk of serious GI adverse effects and dyspepsia with any NSAID

- No good evidence that adding a PPI to a coxib is more beneficial than adding a PPI to a traditional NSAID
- PPI + NSAID is more beneficial than coxib alone

Hospitalisations due to complications associated with NSAIDs
Seager and Hawkey BMJ 2001; 323: 1236 - 1239



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People at high CV risk

- Those with established CVD
- Those taking CV medication, especially anti-platelets
- Older men
- Smokers
- People with diabetes
- Renal problems

People at high GI risk

Age ≥65 years

- History of GI bleeding, ulcer or perforation
- Those taking medicines that increase risk of upper-GI AEs (e.g. warfarin, **aspirin**, SSRIs and corticosteroids)
- Serious co morbidity, e.g. **CV disease**, renal or hepatic impairment, **diabetes**, or hypertension
- Prolonged duration or maximum doses of NSAID
- Excessive alcohol use
- Heavy **smoking**

Some risk factors increase both CV and GI risk – people with these need particular attention

Key points

All of this particularly applies to those aged over 65

Don't use NSAIDs unless you have to:

- The only way to prevent NSAID side effects is not to use them
- Regular, full dose paracetamol +/- codeine (prn) is an effective choice
- Employ non-drug interventions routinely and over the counter rubefacients
- Consider 1 – 2 week course of topical NSAID (e.g. Ibuprofen gel 5%, 10%)

If you have to use them, use them wisely:

- The balance of benefits and risks needs to be carefully assessed; think about CV, GI and renal issues routinely
- Evidence suggests Coxibs (dose dependant) and diclofenac confer a higher CV risk than paracetamol or other NSAIDs
- The MHRA June 2013 have advised that clinicians should review the use of systemic formulations of diclofenac in patients with established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and congestive heart failure, as well as in those patients with significant risk factors for cardiovascular events.
- Use a *safer* drug (ibuprofen or naproxen) in the lowest effective dose for the shortest period PRN where possible (safest doses are <1200mg/d for ibuprofen or <750mg/d naproxen)
- NSAID users should be a high priority for medication review: Are NSAIDs effective/needed? Drug holidays? Don't issue repeat prescriptions without review

Consider gastro-protection in those at high risk

NSAIDs contribute to hospital admissions

How ard RL, et al. Br J Clin Pharmacol. 2006; 63: 136-147

Preventable drug-related admissions

Antiplatelets (including aspirin)	16.00%
Diuretics	15.9%
NSAIDs	11.0%
Anticoagulants	8.3%

Estimated annual NSAID adverse drug reactions per 100,000 patients where 3,800 over '65s take NSAIDs

Bandolier 2000; Number 79: 6-8

Upper GI Bleed	18
Acute renal failure	10
Congestive heart failure	22

- Long term diclofenac 150mg daily and coxibs may cause an excess thrombotic risk of about 3 cases per 1000 users treated for one year **on average**
- To set the 3 in 1000 in context:
  We treat people at 20% 10 year CVD risk with statins.
  20% over 10 years is 20 people out of 100 having an event in 10 years. That's the same (assuming a linear rate of events) as 20 people out of 1000 in one year. Since the relevant risk reduction in events with statins is 25% that means we use statins to reduce the rate of events by 5 in 1000 people per year. Some NSAIDs increase the rate of events by 3 in 1000.

So at a population level is important, even if the risks to an individual are not that great.

- Prescribing of **coxibs** may be responsible for approximately **240** additional or premature CV events per year in England alone
- Approximately 2000 additional or premature CV events per year could be caused by **diclofenac** prescribing

Some options to consider:

- Review the appropriateness of non-steroidal anti-inflammatory drug (NSAID) prescribing widely and on a routine basis, especially in people who are at higher risk of both gastrointestinal and cardiovascular morbidity and mortality (for example, older people).
- Aspirin and NSAIDs (is NSAID necessary? Is the best choice made?
- Review MR preparations (expensive) and switch: a good alternative is standard Naproxen (not EC) which has a long half-life