Analgesia alert

As the proportion of older patients in the population is set to rise so is the consumption of analgesics, whose adverse drug effects may cause problems in cardiovascular and other patients. Leicestershire general practitioner, John Inman, explores important issues raised in this increasingly acknowledged problem area.

Abstract

The mode of action of non-steroidal anti-inflammatory drugs and the role of the cyclo-oxygenase enzymes COX1 and COX2 and their inhibitors is described. These can have potentially serious effects on the cardiovascular and renal system which are discussed.

The alternative, widely-prescribed analgesic, paracetamol, is also discussed, as are two theories 'confounded by indication' and 'protopathic bias' to help explain why paracetamol is sometimes described as being linked to asthma and upper gastro-intestinal damage, both effects not expected from a knowledge of its mode of action.

Key words: pain, elderly, analgesics, heart failure, hypertension, adverse effects.

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'Universal concern over the gastrointestinal side effects of NSAIDs does not seem to extend to the potentially serious problems which may occur in cardiovascular and renal patients'

John Inman

Table 1. Cyclo-oxygenases (COX) and prostaglandins simplified

- Cyclo-oxygenase enzymes metabolise arachidonic acid to prostaglandin
- Cyclo-oxygenases (COX) exist in two isoforms, COX 1 and COX 2
- Prostaglandins, via COX 1, maintain renal blood flow and gastrointestinal integrity
- Prostaglandins, via COX 2, mediate inflammation and pain

Table 2. A simplified comparison of the role of the cyclo-oxygenase enzymes, COX 1 and 2

COX 1	COX 2
Gut protective	
Maintains renal blood flow	Inflammatory mediator
● Damages the cardiovascular system via thromboxane A2	● Protects CV system via prostacyclin (PGI2)

Introduction

Pain is common and analgesics are effective. The principal and most widely available drugs used to treat musculoskeletal pain are paracetamol and those of the non-steroidal anti-inflammatory (NSAID) group. British general practitioners (GPs) write 20 million prescriptions for NSAIDs annually.

The gastrointestinal side effects of NSAIDs are appreciated by both doctors and the public, but this universal concern does not seem to extend to the potentially serious problems which may occur in cardiovascular and renal patients, many of whom are in the largest group of all – older patients.[1]

This short review aims to draw together some current issues in analgesic prescribing, many of which were raised in a presentation by Stewart Hillis, Professor of Cardiovascular and Exercise Medicine at Glasgow University, at a recent conference staged in The Netherlands, entitled 'Analgesia and Public Health'.

Non-steroidal anti-inflammatory drugs and cyclo-oxygenases

NSAIDs exert their effect by inhibiting cyclo-oxygenases (COX), which have analgesic, anti-inflammatory and antipyretic actions. COX enzymes metabolise arachidonic acid to prostaglandins and are expressed principally in two forms, COX 1 and COX 2 (see table 1) .[2]

COX 1 are found in most cells and are involved in the production of homeostatic or 'housekeeping' prostaglandins (PG) which maintain gastrointestinal (GI) mucosal integrity and renal blood flow (see table 2). In platelets, COX 1 also mediates the production of a PG, thromboxane A2, which promotes vasoconstriction, platelet activation and aggregation. Inhibition of COX 1, therefore, is associated with gastrointestinal toxicity and the now established beneficial reduction in thrombogenesis (table 3).

Table 3. A comparison of the actions of cyclo-oxygenase inhibitors in cardiovascular disease

COX 1 inhibitors	COX 2 inhibitors
Benefit cardiovascular system	Prescription may damage cardiovascular system
• by inhibiting thromboxane A2 production	• by reducing prostacyclin
• improves endothelial dysfunction	• no beneficial inhibition of thromboxane A2
• inhibits LDL oxidation	

Key messages

Simple analgesia prescribing guidelines

- Use/recommend paracetamol as first-line agent
- Identify those groups at risk of NSAID side effects:
  - elderly
  - hypertension
  - cardiac failure
  - renal impairment
  - drug interactions (aspirin, diuretics, antihypertensives, anticoagulants, steroids)
  - other co-morbidities (e.g. dyspepsia, asthma)
- Consider adding codeine (in therapeutic dose)
- Consider topical NSAID or capsaicin
- If there is a need to use oral NSAID, then use low dose with short half life
- Monitor blood pressure, renal function and cardiac function

COX 2, in contrast, mediates inflammation and pain (table 2). It is generally expressed at low levels but may be rapidly induced resulting in increased PG and prostacyclin (PGI2) production at sites of inflammation. PGI2 is a vasodilator and inhibitor of platelet function. It is proposed that COX 2 inhibition exhibits a prothrombotic effect by reducing PGI2 – 'inhibiting the inhibitor' of platelet aggregation (table 3). This is one of a number of possible explanations for the excess in cardiovascular thrombotic adverse events in COX 2 patients shown in the VIGOR[3] study which compared naproxen with rofecoxib.

Platelets do not express COX 2, so COX 2 inhibition would not be expected to directly affect platelet function – vasculopathic patients are therefore advised to continue prophylactic aspirin when on COX 2 therapy (undermining the favourable GI risk profile).

NSAIDs alter renal blood flow leading to increased sodium and water retention and may interact with loop diuretics and angiotension-converting enzyme (ACE) inhibitors, thereby aggravating pre-existing heart failure[2] by altering pre- and afterload. At particular risk are the elderly, of whom 10% of those over 75 years have heart failure. Blood pressure increases may be induced by NSAIDs and control may be lost amongst patients on treatment. The VIGOR[3] study showed an increased incidence of cardiac failure in the COX 2 group. In addition, there was a mean blood pressure increase of 4.3 mmHg systolic and 1.7 mmHg diastolic with rofexicob (COX 2 specific) compared with naproxen. Based on established data,[4] a blood pressure increase of 3 mmHg may give rise to a 10–20% rise in cardiac failure, 20% increase in cerebrovascular accidents and a 12% increase in angina.

Paracetamol – 'confounded by indication' and subject to 'protopathic bias'

The obvious alternative choice to NSAIDs for over the counter (OTC) and prescribed analgesia is the safe and well-established paracetamol, although in recent months adverse reports have linked it with asthma and upper GI damage. This is surprising as paracetamol is thought to act predominantly by inhibiting prostaglandin synthesis in the central nervous system rather than peripherally, so how might these observations be explained?

At the meeting in Amsterdam, Dr Lisa Signorello, an epidemiologist from the USA, introduced two powerful new concepts, 'confounding by indication' and 'protopathic bias'. Her presentation considered the wide indications for OTC analgesics and whether these very indications might act as confounding factors in studies. For example, many patients taking paracetamol do so specifically because they are at risk of GI damage from NSAIDs and data have shown that current users of paracetamol are 3.6 times more likely to suffer such GI problems. She explained that any conclusion that paracetamol might be responsible for the adverse effect is most likely due to a patient population bias and is not a drug effect. Similarly, asthma-prone patients take paracetamol to avoid asthma and are shown to suffer apparently coincidental increased asthma. In epidemiological terms this is known as 'confounding by indication'.

Patients in early stage (or preclinical) disease tend to use analgesics for evolving pain symptoms. When their disease process is finally recognised, the spurious association is made once again as

the final diagnosis may be attributed to the analgesic. Of course, heavy analgesic users will tend to have high levels of co-morbidity. This results in 'protopathic bias'.

Conclusion

The message is clear – all those involved in advising or providing analgesia for those with renal, hypertensive and cardiac problems (all of which are common co-morbidities in the elderly) should be mindful of the potential adverse effects of NSAIDs. In these groups, paracetamol, taken properly, remains the proven safe and effective first-line analgesic for OTC use and prescription. Should NSAID use be unavoidable, then the choice must be a drug with a short half-life given in a low dose with careful and ongoing monitoring of blood pressure, renal and cardiac function.

John K Inman
General Practitioner
Syston Health Centre, Syston,
Leicestershire, LE7 2EQ.
(e-mail: jk.inman@gp-C82078.nhs.uk)

References

1. Page J, Henry D. Consumption of NSAIDS and the development of congestive cardiac failure in elderly patients: an underrecognised public health problem. *Arch Intern Med* 2000;**160**:777-84.
2. Targum SL. FDA rofecoxib review. February 2001.
3. Bombardier C, Laine L, Reicin A *et al.* for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;**343**:1520-8.
4. ALLHAT Collaborative Research Group: Major cardiovascular events in hypertensive patients randomised to doxazosin v chlorthalidone: the antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT) *JAMA* 2000;**283**:1967-75.