

Newsletter



DECEMBER 2007

Ibuprofen Experts' Forum, Royal Society of Medicine, September 2007

Specialists from many branches of medicine met in London recently to review the latest evidence on the effectiveness and safety of OTC ibuprofen. They reaffirmed current thinking that low-dose ibuprofen is well tolerated and supported by a long track record of therapeutic use.

Ibuprofen: a progressive evolution of use

Professor Kim Rainsford, Professor Emeritus of Biomedical Sciences Biomedical Research Centre at Sheffield Hallam University and Chairman of the conference, noted that the success of ibuprofen is due to its optimal balance of potency and safety. Its clinical use reflected an initial cautious approach: when it was introduced at a low dose; this was increased in response to clinical demand and evidence of tolerability. It was not marketed aggressively and treated as a commodity. This slow and progressive evolution in its use meant that clinicians gradually came to understand its properties more fully¹.

Professor Rainsford pointed out that some guidelines for the management of osteoarthritis have stated that paracetamol is the analgesic of first choice. This recommendation is, however, based on historical use rather than the evidence of clinical trials. Furthermore, osteoarthritis is characterised by flares for which short-term treatment is needed to reducing inflammation and relief of pain². The evidence shows that the analgesic efficacy

of paracetamol is small^{2,3}. Systematic and critical reviews have shown that NSAIDs such as ibuprofen provides superior pain relief compared with paracetamol in patients with osteoarthritis.^{3,4}

Evidence for tolerability

Professor Nicholas Moore, Head of Clinical Pharmacology, CHU de Bordeaux - University Victor Segalen, France, explained that the tolerability and safety of ibuprofen compared with other NSAIDs is well established. A large review of several studies confirmed that, overall, low-dose ibuprofen was associated with no increase in risk.⁵ In one study evaluating the risk of major upper gastrointestinal events (e.g. gastric ulcer) in patients taking NSAIDs, occasional use of ibuprofen was not associated with increased risk; by contrast, occasional use of aspirin was associated with a statistically significant doubling in risk.⁶ The risk associated with regular use of prescribed doses of ibuprofen, he pointed out, is dose-dependent and consistently found to be lower than that of other NSAIDs.⁵

Professor Moore said that the frequency of side effects reported by patients varies according to their illness: for example, patients with chronic disorders such as osteoarthritis report more side effects than those who do not have long-term illness.⁷ This difference, which persists after allowing for differences in medication, may be associated with underlying illness or because people who are unwell are more inclined to report problems with their treatment. Most evidence suggests that low-dose ibuprofen and paracetamol are

equally well tolerated, though one study found that, in patients taking several prescribed medicines, ibuprofen may cause fewer side effects.⁸

NSAIDs and cardiovascular risk

Concerns about the possible risks of heart attack and stroke associated with some prescribed NSAIDs were addressed by **Dr Henry Purcell**, Senior Fellow in Cardiology, Royal Brompton at the Royal Brompton Hospital, London. He said it is now clear that the selective COX-2 NSAIDs increase the risk of atherothrombosis (by 42 per cent), mainly because the risk of myocardial infarction (by 86 per cent).⁹ As a result, this class of NSAID is contraindicated in patients with ischaemic heart disease.¹⁰ There have been signals in comparative studies with COX-2 selective agents that older, non-selective NSAIDs may be associated with a slight increase in the risk of myocardial infarction.^{11,12} For ibuprofen in particular, analysis of prescriptions captured in the UK General Practice Research Database showed that, compared with no treatment at all, the long-term use of high doses was associated with a 1.2 -1.4-fold increase in the risk of hospital admission for heart failure (with a previous diagnosis of heart failure being the biggest risk factor)¹³ or heart attack.¹⁴

There has also been concern that ibuprofen may interfere with the cardioprotective effects of low-dose aspirin. The evidence that this is clinically significant is conflicting¹⁵⁻¹⁸ and medical advice should be sought before taking these drugs together.

Taken together, these data have prompted the European regulatory authorities to recommend a cautious approach to prescribing NSAIDs, advising that any prescribing decision should be based on the overall safety profile of NSAIDs (particularly the gastrointestinal safety profile), and the individual risk factors for the patient; all NSAIDs should be used at the lowest dose for the minimum necessary period.¹⁰

NSAIDs and gastric side effects

NSAIDs reduce prostaglandin synthesis by inhibiting the enzyme COX. This occurs in two forms, COX-1 and COX-2. COX-1 is believed to have a 'housekeeping' role in preserving the stomach lining; inhibiting it causes the gastric side effects characteristic of all NSAIDs. COX-2 is thought to promote inflammation and selectively inhibiting it should control the symptoms of arthritis with a lower risk of gastric side effects.

This is the 'COX dogma' and it is incorrect and misleading, said **Professor Ingvar Bjarnason**, Professor of Digestive Diseases, King's College Hospital and Guy's, King's and St Thomas' Medical School, London. The gastric side effect of NSAIDs are caused by a more complex combination of a topical effect on the stomach and inhibition of both forms of COX.

The rate of gastrointestinal symptoms associated with low-dose ibuprofen (1200 mg/day) is similar to that reported with paracetamol and placebo, but less than with aspirin,⁷ Professor Bjarnason continued. This is distinct from regular use of prescribed doses. One study in which approximately 2,000 patients taking NSAIDs were compared with 11,500 controls showed that, on average, regular use of a prescribed NSAID increases the risk of serious gastrointestinal side effects by a factor of three. There is, however, a hierarchy of risk among the NSAIDs, with high-dose ibuprofen ranking among the lowest.¹⁹ A second study comparing the risk of any serious upper gastrointestinal side effect in approximately 52,000 patients taking NSAIDs and 74,000 controls, has confirmed that prescribed ibuprofen was one of the NSAIDs associated with least risk.²⁰

Using NSAIDs in children with asthma

One in six children - regardless of age, sex, ethnicity, socioeconomic background and geographical location - have asthma symptoms at some time in their lives. All NSAIDs have the potential to worsen asthma, either acutely or gradually, and

they should be prescribed with caution in children with asthma. However, **Dr Dipak Kanabar**, Consultant Paediatrician, Evelina Children's Hospital, London, said his clinical experience showed that children with asthma had been treated with NSAIDs without experiencing any exacerbation of symptoms. It is therefore possible that NSAIDs, and ibuprofen in particular, may be safe to use in selected patients.

Asthma is one symptom associated with aspirin sensitivity, which affects about 10 per cent of adults and 5 per cent of children after the age of 10. There is almost complete cross-sensitivity between aspirin and NSAIDs in aspirin-sensitive individuals but it has been claimed that paracetamol is a safe alternative. However, there is also cross-sensitivity between paracetamol and aspirin in aspirin-sensitive individuals, though the asthma precipitated by paracetamol appears to be milder than that associated with aspirin.²¹ One systematic review found that the overall prevalence of paracetamol sensitivity among aspirin-sensitive people was 7 per cent but prevalence was higher in patients with more severe aspirin sensitivity.²²

But is there any harm in recommending paracetamol in preference to alternative analgesics? There is some evidence that frequent maternal use of paracetamol during pregnancy may increase the risk of wheezing in children. In one study, the risk of wheezing at age 30 - 42 months was approximately doubled in infants born to mothers who used paracetamol on most days or daily during weeks 20 - 32 of pregnancy, compared with infants whose mothers did not use paracetamol.²³ By contrast, aspirin use during this period was not associated with increased risk. The mechanism by which paracetamol may cause these effects is uncertain; one possibility is that high paracetamol use may reduce glutathione levels in the lung and increase oxidative stress, resulting in damage to the bronchiolar epithelium.²⁴

Several studies have compared ibuprofen and paracetamol in children with fever.

Two found no difference in the occurrence of asthma symptoms in children not known to have asthma^{25,26} but a third, in 1,879 febrile children with asthma, found that the risk of an outpatient visit due to asthma was 44 percent lower for ibuprofen than for paracetamol; the corresponding risk for hospital admission for asthma was 37 percent lower.²⁷

Dr Kanabar concluded that NSAIDs are often withheld from children due to fear of exacerbating asthma for what is, in some cases, a theoretical risk. He suggested that doctors could consider prescribing ibuprofen for some children with asthma provided sufficient safeguards are in place.

Ibuprofen and beyond: implications for clinical practice and research

Professor Rainsford concluded the day's proceedings by reviewing what may lie on the horizon for ibuprofen.

There is growing evidence that ibuprofen could have a role in the treatment of inflammatory lung diseases such as cystic fibrosis, especially in combination with the antibiotic azithromycin. Epidemiological studies have consistently demonstrated that a relatively low dose of ibuprofen is associated with a reduced risk of breast cancer, prostate cancer and colorectal cancer. There are also experimental and epidemiological data to suggest that ibuprofen use is associated with delayed onset of dementia, though clinical studies have reported inconsistent findings.

Ibuprofen has been shown to have a wide range of effects on cellular and intercellular events, including inhibition of several key pro-inflammatory processes, early response gene inflammatory regulators and apoptosis (programmed cell death). In experimental models, ibuprofen has been shown to inhibit oxidative damage. The therapeutic potential of these properties is still undetermined. There are also opportunities for developing novel formulations and technologies for site-specific delivery of ibuprofen.

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**Further information from:
Secretariat**

**International Ibuprofen Foundation
PO Box 2566, Marlborough, SN8 4YY, UK
Tel/Fax: +44(0)1672 810836**

**Email: ibuprofen@healthcom.eu.com
Website:
www.ibuprofen-foundation.com**