EDITORIAL

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Fifty years of ibuprofen: advancing pain and fever management

Overview

It is now 50 years since the first discovery by Dr (now Professor) Stewart Adams (of the Boots Pure Drug Company, Nottingham, UK) of the pharmacological effects of the non-steroidal anti-inflammatory drug (NSAID), ibuprofen, in a guinea pig model of skin inflammation. It is now over 40 years since this drug was introduced into clinical use at doses of 1800–2400 mg/d for the treatment of arthritic pain and inflammation. Subsequently, the acceptance of its relatively favourable safety profile led to approval by the UK authorities in 1983 and the US FDA in 1984 of low-dose ibuprofen (< 1200 mg/d) for non-prescription over-the-counter (OTC) sale direct to the public.

Historically, the development of ibuprofen by Dr Adams at Boots was based on the need to have a safer form of aspirin (a 'super aspirin'), without the gastro-intestinal (GI) effects of aspirin, and without the serious adverse effects of phenylbutazone and corticosteroids; these being the principal anti-inflammatory agents available at the time. With particular attention to the pharmacokinetics, GI effects and liver toxicity, ibuprofen was selected after an extensive programme of drug screening.

Ibuprofen is now widely used in many countries, often as a first-line treatment for the relief of symptoms of pain, inflammation and fever. The OTC formulations are available in over 80 countries, with the prescription dosage being available in many other countries.

A large number of mega-trials in recent years have focussed on the clinical uses, safety and pharmacological properties of ibuprofen given at prescription level doses (< 2400 mg/d) compared with newer NSAIDs (including cyclo-oxygenase-2 selective inhibitors [coxibs]). In many of these studies, ibuprofen was used as the reference drug in view of its established safety and efficacy profile. These studies have shown that ibuprofen has comparable safety and efficacy with that of newer drugs in long-term usage (6 months or more).

An immense number of investigations have also been performed on the pharmacological and therapeutic activities of ibuprofen. Modern models of assessing acute pain have been employed to show the quantitative effects of ibuprofen in comparison with other NSAIDs and analgesics. In dental pain, following removal of third molars, ibuprofen has been quantified to have a Number Needed to Treat (NNT; an empirical method), which is dose-related and ranges from about 1–3. A few more potent and longer half-life NSAIDs (e.g. etoricoxib) may have smaller values for NNT of about 1–2, but for the majority of NSAIDs, ibuprofen is in the more potent group and is more active than paracetamol. In other pain models (sore throat, migraine and headache), ibuprofen is relatively potent and effective at OTC doses, is comparable with other NSAIDs and possibly more effective than paracetamol.

Spontaneous reports of adverse events and adverse drug reactions (ADRs) in long-term coxib comparator mega-trials, as well as in epidemiological studies, show that the risks of GI, hepato-renal and other rarer ADRs with ibuprofen is relatively low compared with other NSAIDs and coxibs. A limited risk of cardiovascular (CV) events has been reported in some, but not all, studies but the risks are, in general, lower than with some coxibs and diclofenac. The possibility that ibuprofen may interfere with the anti-platelet effects of aspirin, although arguably of low grade or significance, has given rise to caution for its use in patients who are at risk for CV conditions and take aspirin for preventing these conditions.

Ibuprofen has unique pharmacokinetics and features, such as low plasma elimination half-life and lack of systemic accumulation, that account for the relatively low overall toxicity of the drug in humans. Ibuprofen also has a broad spectrum of action on different inflammatory pathways, as well as inhibiting pathways of prostaglandin metabolism. This may not only be of considerable significance for the actions of ibuprofen in relation to controlling multiple pathways of inflammation, but also in relation to its relatively low toxicity.

Use of ibuprofen in paediatric populations has shown that it has relatively few safety concerns, especially in comparison with paracetamol, and is as effective as a treatment of acute pain. In addition, it is probably more effective than paracetamol as an antipyretic. At OTC doses (< 1200 mg/d) in adults, ibuprofen has a comparable safety profile with that of paracetamol.

The anti-inflammatory activity of ibuprofen is linked to its analgesic effects. The analgesic activity at OTC doses or higher is related to reduction in the *ex vivo* production in blood of cyclo-oxygenase

Outline of the historical development of ibuprofen and its current status

(COX)-1 and COX-2 derived prostanoids. Moreover, both enantiomers of ibuprofen have been found to individually contribute to the broad basis of the analgesic action of the drug. S(+)-ibuprofen inhibits both COX-1 and COX-2. The R(−) isomer has little direct effect on both COX activities, except after absorption when about 40–60% is metabolically converted to the actively inhibitory S(+) form. COX-1 inhibition by S(+)-ibuprofen in the stomach is masked by the R(−) enantiomer, which can compete with the S(+) enantiomer at the active site of the COX-1 enzyme. This along with unique physicochemical properties of ibuprofen combined with its short plasma half-life may account for the apparent low incidence of GI ulcers and bleeding, particularly at low OTC doses. The R(−) enantiomer affects the production of leucocyte-derived proteases and leukotrienes and this may contribute to the spectrum of anti-inflammatory activity of ibuprofen.

Patients taking ibuprofen at OTC doses are at a relatively low risk of developing renal and associated CV events, although interactions with diuretics and antihypertensive agents can influence the development of these adverse reactions. Serious adverse reactions are rare and most minor reactions are reversible upon cessation of the drug. OTC ibuprofen does not represent a risk for developing liver injury, in contrast to the irreversible liver damage observed with paracetamol and the occasional liver reactions caused by aspirin.

Thus, over the years, ibuprofen has withstood competition from newer NSAIDs and paracetamol and commands a place in the mainstay of therapy for pain and inflammation. The future for ibuprofen may be in the development of new formulations and novel applications to meet specific needs for patients with complex chronic diseases. For example, combination with lecithin-type phospholipids may reduce the gastric reactions from OTC ibuprofen in the stomach of elderly and other at-risk patients. Combinations of ibuprofen with anti-acid secretory compounds are also being explored at present and might be of benefit in reducing gastric irritation, although this would represent a more expensive alternative with the additional consideration of adverse reactions from the anti-acid secretory agents (e.g. esomeprazole, famotidine).

Exciting observations have been reported over the years that ibuprofen might reduce the development of some cancers, Alzheimer's and Parkinson's diseases, as well as other neurodegenerative disorders. The widespread long-term use of ibuprofen by the public may lead to what could be described as 'collateral benefits' in reducing the incidence of these diseases in addition to the self or prescribed applications for relief of pain and other inflammatory symptoms. It is remarkable that following the simple discovery of the anti-inflammatory effects of ibuprofen half a century ago, remarkable therapeutic benefits have accrued over the years and more will doubtless develop in the future.

Disclosures

The author is a consultant and expert witness on the safety of ibuprofen to Reckitt Benckiser and has also consulted on NSAIDs for other pharmaceutical companies. The author does not hold any shares, stocks or options, or any other financial instruments in any pharmaceutical company.

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