

Newsletter



No uncertain way - the man who led the way to ibuprofen

The man whose leadership gave us ibuprofen has been honoured with the opening of a new research facility in his name. The Stewart Adams Building is the latest phase of Nottingham's BioCity (www.biocity.co.uk), a project to nurture bioscience businesses that is based in the original buildings where Dr Adams led the research team that developed ibuprofen. We took this opportunity to find out more about the discovery of ibuprofen.

Ask Stewart Adams how it feels to be the man who led the development of one of the most popular medicines in the world and he says, "I don't reflect on it much, to be honest, but I'm always delighted when people say: 'Thanks for ibuprofen, it really works.' That makes it worthwhile."

This modest son of a railwayman grew up in the Midlands and left grammar school at sixteen to work in a Boots pharmacy. Dr Adams says it was a 'fantastic experience' but he learned that retail pharmacy wasn't for him. Nevertheless, the bug had bitten and he left to read pharmacy at University College, Nottingham, before returning to Boots on the industrial side. This was the 1940s, and he hoped to get involved in research on a new antibiotic, penicillin. But the job was routine and he moved on to the company's research department, where he developed an assay for heparin that remained the pharmacopoeial standard for many years. Convinced that research was easier than it turned out to be, he did a PhD at Leeds before again returning to Boots.

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He recalls that the company's research was badly organised, by current standards. His laboratory was the front room and kitchen of a Victorian house but, in these inauspicious surroundings, he made the key decision that was to set him on the path to discover ibuprofen.

"When I took over, there was one person and one technician doing a spot of work on corticosteroids. I realised it had no future - the Americans were in it in a big way and even then we knew there were problems with toxicity," he says. "I decided to look at what we called 'non-hormonal anti-rheumatic drugs.'" In 1956, he prepared a report for Boots proposing what turned out to be a 15-year research programme. He developed a laboratory model for screening for anti-inflammatory activity and decided to look at aspirin analogues - surprisingly, never previously tested for anti-inflammatory activity. Joined by chemist John Nicholson, their strategy was to strive for the right balance of efficacy and low toxicity. Many aspirin analogues were synthesised but none were superior to aspirin. This failure did provide some chemical leads and, after many more disappointments, led to the discovery and development of the propionics. Ibuprofen emerged as the preferred candidate and, almost unbelievably, its first clinical trial demonstrated efficacy in patients with rheumatoid arthritis at doses of only 100 - 200 mg three times daily.

Dr Adams' self-effacing account of the ibuprofen story belies his years of perseverance and his unwavering search for safety. The greatest accolade came in the mid-80s, when both the UK and US regulatory authorities ("Both very safety conscious.") approved ibuprofen for OTC use. "That established its safety in no uncertain way," he says. He is also pleased that ibuprofen has now been approved for closure of patent ductus arteriosus and with its popularity as a medicine for children.

When did he realise that ibuprofen was special? "Well, it took a long time," Dr Adams admits. "We were always very concerned about safety and reluctant to push the dose too far, but when we began to increase the dose it proved to be much more effective but still well tolerated. It still has the advantage of tolerability over other NSAIDs at doses up to 1600 mg/day."

In recognition of its achievement in developing ibuprofen, Boots was awarded the Queen's Award for Technological Development for that year and, in 1987, Dr Stewart Adams was awarded the OBE (Order of the British Empire). More about the story of ibuprofen is available on the IIF website at www.ibuprofen-foundation.com/what-ibuprofen/story.htm.

Ibuprofen - Happy 45th!

The original patent for ibuprofen was granted on January 12th, 1962. It seems astonishing that there is anything left to learn about ibuprofen after 45 years but research is constantly revealing new surprises. Over the last couple of years, we have covered three main themes in the IIF newsletter: ibuprofen's safety; the link between ibuprofen use and reducing cancer risk; and its use in children.

Safety

The discovery that COX-2 selective NSAIDs are associated with an increased risk of serious cardiac events raised

concerns about older, non-selective NSAIDs such as ibuprofen when prescribed as long-term treatment at high doses. In 2005, the European Medicines Agency (EMA) conducted a comprehensive review and concluded that any risk associated with such use was small. It therefore recommended no changes to clinical practice (www.emea.eu.int/pdfs/human/press/pr/24732305en.pdf), adding that OTC ibuprofen has an excellent safety record and is unlikely to be associated with any measurable increase in the risk of cardiovascular events (www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dID=1428&noSaveAs=0&Renderition=WEB).

During 2006, studies had shown that short-term use of ibuprofen has negligible effects on blood pressure (*J Hypertens* 2006;24:1457-69) and that ibuprofen was not associated with an increased risk of myocardial infarction or sudden cardiac death (*eular2006SCIE abstract*). The EMA repeated its analysis in 2006 to take account of new evidence and concluded that, while a small increased risk could not be excluded with long-term, high-dose use of prescribed NSAIDs, the balance of benefit and risk remained positive (www.emea.eu.int/pdfs/general/direct/pr/41313606.pdf).

Research from the US drew attention to a lack of understanding about OTC analgesics among the public (*J Rheumatol* 2005;32:2218-24). The majority of people questioned said they never read dose instructions and half were unconcerned about possible side effects. An earlier survey had revealed that over a third of respondents said they used a prescribed and an OTC NSAID at the same time. These findings illustrate the value of seeking the advice of a health professional when taking OTC medicines.

Risk of cancer

Epidemiological studies are consistently showing that regular use of NSAIDs - of

which ibuprofen is often the most widely used - is associated with a reduced long-term risk of certain cancers. In 2006, two case-control studies found that using ibuprofen for 5 years was associated with a 28 percent reduction in the risk of ovarian cancer (*Epidemiology* 2006;17:104-7) and a 72 percent lower risk of breast cancer (*BMC Cancer* 2006;6:27; doi:10.1186/1471-2407-6-27) compared with people who did not use NSAIDs.

These and other observational studies do not prove that regularly taking ibuprofen causes a reduction in cancer risk. However, the findings of various studies are generally positive and there is a plausible mechanism for this effect - inhibition of the enzyme cyclo-oxygenase. This year, however, researchers from Germany suggested that ibuprofen may also promote programmed tumour cell death (apoptosis) and inhibit replication by a non-COX mechanism (*Eur J Pharmacol* 2006;540:24-33). It remains unclear whether this means ibuprofen may have specific anti-tumour activity in addition to its effect of COX inhibition that is shared with other NSAIDs.

Using ibuprofen in children

In 2006, ibuprofen injection was approved within the European Union for the treatment of patent ductus arteriosus (PDA) in premature infants. A systematic review of trials comparing ibuprofen with indomethacin (*Semin Perinatol* 2006;30:114-20), formerly the standard treatment, concluded that their roles may differ. While they are equally effective overall, indomethacin was associated with a higher risk of adverse effects (abnormal renal function, reduced mesenteric and cerebral blood flow) whereas ibuprofen was not shown to reduce the risk of intraventricular haemorrhage. The authors suggested that indomethacin may be preferred on the first day of life and thereafter ibuprofen may be the drug of choice due to its superior safety profile.

The Scottish Medicines Consortium (www.scottishmedicines.org), which advises NHS boards in Scotland on the cost effectiveness of new medicines, has now approved the use of ibuprofen injection for closure of haemodynamically significant PDA.

Ibuprofen has also been shown to be as effective as zolmitriptan in relieving migraine headache in children (*Neurology* 2006;67:497-9). Although management guidelines have long recommended ibuprofen for migraine, this was among the first trials to prove that it is as effective - and better tolerated - as the more expensive, migraine-specific treatment.

Looking to the future

2012 will be the 50th anniversary of ibuprofen's patent and 2008 will see the 25th anniversary of its first introduction as an OTC medicine - a remarkable achievement. During these years, the uses of ibuprofen have widened and evidence of its safety has been confirmed, but we still have a lot to learn about what ibuprofen can do (and how it does it).

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