Institution: University of Nottingham

Unit of Assessment: UoA1

Title of case study:
Preventing the gastroduodenal hazards of non-steroidal anti-inflammatory drugs and aspirin through widespread adoption of proton pump inhibitors

1. Summary of the impact

Non-steroidal anti-inflammatory drugs (NSAIDs) are valuable analgesics, but cause dyspepsia, ulcers and hospitalisation (UK: 3,500pa, USA: 100,000pa) for complications that can lead to death (UK: 400-1,000pa, USA: 16,500pa). Acid inhibition by proton pump inhibitors (PPIs), the only widely accepted preventative strategy, was proposed and systematically proved by studies from Nottingham. NICE now recommends PPIs for all patients using NSAIDs and PPIs are central to all major international guidelines. PPI co-prescription has increased worldwide (from 27.6% in 2008 to 44.1% in 2012, in the UK); and reduces the risk of hospitalisation for gastrointestinal bleeding by 54% and symptomatic ulcer by 63%, thereby preventing up to 540 deaths per annum in the UK.

2. Underpinning research

Scale of the problem: Non-steroidal anti-inflammatory drugs (NSAIDs) cause two clinically important gastroenterological problems - ulcer complications (largely bleeding) which are relatively rare but dangerous, and dyspepsia which is common, impairs quality of life and restricts NSAID use. NSAIDs have an attributable rate of hospitalisation of approximately 2.7-4.0 per 1,000 patient years in patients aged >60. On the basis of this, prior to widespread adoption of proton pump inhibitor (PPI) co-prescription, NSAIDs were conservatively calculated to cause 3,500-4,000 hospitalisations and 400-1,000 deaths pa in the UK [Pharmacoepidemiol Drug Saf, 2001;10:13-19]. In trials, between 13 and 31% of patients report dyspepsia [Clin Ther 2010;32:667-677; BMJ 2009;339:b2538].

Nottingham's contribution: Much of the most reliable epidemiological data that identified and quantified the GI risks of NSAIDs emanated from the Department of Therapeutics under Professor Michael Langman (1971-1987). Professor Chris Hawkey (Nottingham Digestive Diseases Centre, 1983-present) then developed the translational models described here, becoming a UK leader in this field. Hawkey also developed the therapeutic interventions discussed, before their evaluation in clinical trials.

Translational basis: Our translational facility enabled strategies for mucosal protection and underlying mechanisms to be investigated. Investigations were based on *ex vivo* pharmacology, mucosal injury, spontaneous and induced bleeding and healing of mucosal breaches. Of more than twenty strategies evaluated, use of omeprazole (first of the then novel PPI class of drugs) appeared to be most effective. Omeprazole was potent and reliable in its ability to virtually abolish mucosal injury, measured as acute microbleeding.

Initial trials: This caused us to suggest to Astra that they conduct trials with omeprazole in NSAID users, but these suggestions were not taken up. Our team therefore collaborated with rheumatological and gastroenterological colleagues in Nottingham and Glasgow to do a proof of principle investigator-initiated study with the H2 antagonist famotidine. This study showed that acid inhibition with high, but not standard, doses of famotidine was effective in preventing and healing ulcers and treating the dyspepsia caused by NSAIDs[1].

Definitive omeprazole trials: This work provoked renewed interest by Astra. As co-Chief Investigators, Professors Hawkey and Neville Yeomans (Melbourne, Australia) developed and coordinated a large international programme of three linked studies of primary and secondary prevention, and ulcer healing, which the company funded[2,3]. These studies showed that omeprazole had clear efficacy and tolerability advantages over the H2 antagonist ranitidine and the prostaglandin analogue misoprostol, which were used as comparators. This work authoritatively established the effectiveness of PPIs for ulcer prevention, healing and maintenance, and for symptom control, and this was reflected in the ensuing licensed indications for omeprazole and, later, other PPIs. The nature and quality of the team's academic relationship led Astra to support a

pivotal investigator-initiated trial of little commercial interest which was important in showing *H.pylori* eradication to be insufficient as an alternative strategy[4].

Broadening the evidence: As co-Chief Investigators, Professors Hawkey and Yeomans later reported similar finding with esomeprazole[5], and effectiveness was shown for other PPIs. Because the GI hazards of aspirin were an important unmet need, Hawkey and Yeomans persuaded AstraZeneca to support investigator-initiated studies that established efficacy of PPI prophylaxis here too[6], leading to a successful regulatory claim for a combination preparation.

3. References to the research

1. Taha AS, Hudson N, **Hawkey CJ**, et al. Famotidine for the prevention of gastric and duodenal ulcers caused by non-steroidal anti-inflammatory drugs. N Engl J Med 1996; 334(22):1435-1439. http://dx.doi.org/10.1056/NEJM199605303342204

2. **Hawkey CJ**, Karrasch JA, Szczepanski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. N Engl J Med 1998; 338(11):727-734
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3. Yeomans ND, Tulassay Z, Juhasz L, Racz I, Howard JM, van Rensburg CJ, Swannell AJ, **Hawkey CJ** for the ASTRONAUT Study Group. A comparison of omeprazole and ranitidine for treating and preventing ulcers associated with non-steroidal anti-inflammatory drugs. N Eng J Med 1998; 338(11):719-726.
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4. **Hawkey CJ**, Tulassay Z, Szczepanski L, et al. Randomised controlled trial of *Helicobacter pylori* eradication in patients taking non-steroidal, anti-inflammatory drugs: The HELP NSAIDs Study. Lancet 1998; 352(9133):1016-1021.
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5. **Hawkey CJ**, Talley NJ, Yeomans ND, et al. Improvements with esomeprazole in upper gastrointestinal symptoms in patients taking non-steroidal anti-inflammatory drugs including selective COX-2 inhibitors (NASA1 – SPACE1). Am J Gastroenterol 2005,100(5):1028-1036. http://dx.doi.org/10.1111/j.1572-0241.2005.41465.x

6. Yeomans N, Lanas A, Labenz J, van Zanten SV, van Rensburg C, Racz I, Tchernev K, Karamanolis D, Roda E, **Hawkey C**, Naucler E, Svedberg LE. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. Am J Gastroenterol. 2008,103(10):2465-2473.
http://dx.doi.org/10.1111/j.1572-0241.2008.01995.x

Relevant grants total over £2m, from Astra, Astra Zeneca, Merck Sharpe & Dohme, MRC ROPA, Novartis and University of Dundee/EMEA (via unrestricted grant from Pfizer). All awarded to CJ Hawkey for work between 1993 and 2013 for research on NSAID complications and their prevention, including co-prescription of NSAIDs and PPIs.

4. Details of the impact

Our research has had an impact in six main areas: patient safety, quality of life, healthcare costs, management guidelines, prescribing practice and opportunities for the pharmaceutical industry.

Patient safety:

Before our research, the only way to reduce the risk of a non-steroidal anti-inflammatory drug (NSAID)-associated ulcer complication was to avoid using NSAIDs or to use low doses. Previously recommended measures such as the use of slow release or effervescent preparations or enteric coating were at best ineffective. NSAIDs were regarded as the biggest iatrogenic cause of

hospitalisation and death worldwide. The most conservative estimates (UK) were that 1 in every 250-370 people being treated with NSAIDs would be hospitalised for ulcer complications each year [Pharmacoepidemiol Drug Saf, 2001;10:13-19]. With at least a 10% death rate, this resulted in an estimated societal burden of 3,500-4,000 admissions and 400-1,000 deaths per annum. Estimates from other societies and meta-analyses of clinical trials suggested greater harm, with annual ulcer complication rates of 1 in 67 users, with two estimates of death rates in the USA of 7,000-10,000 [Clin Ther 2010;32:667-677] and 16,500 [Gastroenterol, 1985;96,647-655].

Based on a Health Technology Appraisal (HTA) meta-analysis drawing on our work [HTA 2006, 10(38); Am J Gastroenterol 2006,101:701-710] and studies by others with other proton pump inhibitors (PPIs), the NICE Osteoarthritis Development Group reported in 2009 that use of PPIs in patients aged 55 or over reduced the risk of hospitalisation for gastrointestinal bleeding by 54% and symptomatic ulcer by 63%, and was the most cost effective prophylactic strategy[a,b]. A pro rata reduction in death could prevent between 216 and 540 deaths per annum in the UK, with higher values if estimates from other countries are used. Worldwide, NSAID use is extensive [PLoS Med 2013;10(2):e1001388]. Using even the most conservative estimate above (1 hospitalisation per 370 users per annum), several hundred thousand life-threatening ulcer complications could be prevented annually, worldwide, by use of proton pump inhibitors.

Quality of Life:
As well as preventing ulcer complications, PPIs improve quality of life by reducing dyspepsia and allowing continuation of treatment that would otherwise be stopped. NICE estimate dyspepsia rates between 5.4% and 9.6% per annum in NSAID users and a 57% reduction with PPI co-prescription[a,b]. Another meta analysis reported higher rates (13.5%-31%) with the 66% reduction by PPIs being identified as the most effective available treatment or preventative measure for NSAID dyspepsia [Am J Med; 2006:119(5):448.e27-36]. NICE estimate that the combined effect of reduced mortality and improved quality of life results in a gain of 5-10 QALYs (quality adjusted life years) per thousand people treated[a,b]. [QALYs are a measure of disease burden used to assess the value of a medical intervention. They are based on the number and quality of years of life that would be added by the intervention. One QALY is one year spent in perfect health.]

Healthcare costs:
NICE report that the ability of PPIs to prevent hospitalisation and other adverse events reduces healthcare costs to the extent that their use 'increases the estimated gain in quality adjusted life years at little or no additional cost" with "savings from not having to treat adverse effects'.[a]

Guidelines:
These observations led NICE to recommend that PPIs are considered for use in all patients taking NSAIDs[a]. All other major guidelines produced or updated in the past five years (Osteoarthritis Research Society International [OARSI] 2008[c], Cardiology 2008[d], American Colleges of Gastroenterology 2009[e], and Rheumatology 2012[f], place the PPI co-prescription strategy that we developed at the heart of their guidelines, particularly for patients at increased risk of ulcer complications. An updated Cochrane analysis[g] supports the strategy, as do other national and international recommendations.

Prescribing practice:

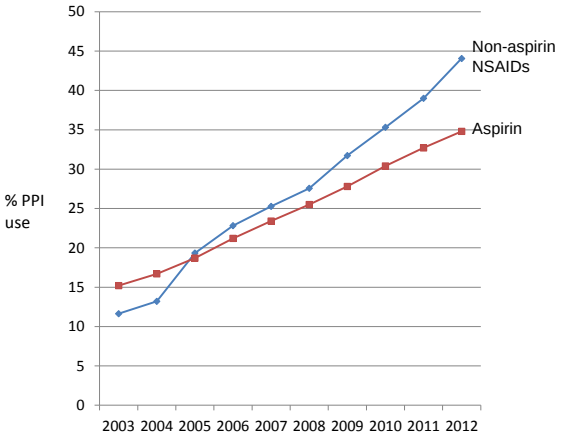

Figure: Rates of UK co-prescription of PPIs in patients using NSAIDs and aspirin by year, based on data routinely collected from general practices with electronic systems that feed into the Clinical Practice Research Database.

To be effective, guidelines must be implemented. Current data show progressive adoption of PPI co-prescription in UK (see figure) and internationally

[Am J Gastroenterol. 2008;103:1097-1103]. Clinical Practice Research Database Statistics[h] show a rise in co-prescription of a PPI in the UK from 27.6% in 2008 to 44.1% in 2012 in patients aged >45 using non-aspirin NSAIDs, resulting in safer symptom relief. During this time, aspirin use has doubled in the UK with a concurrent rise in the proportion of patients receiving PPI protection[h] from 25.5% in 2008 to 34.8% in 2012, allowing patients to access the cardiovascular and anti-cancer benefits of aspirin more safely.

Commercial Opportunities:
Esomeprazole is one of AstraZeneca's 10 leading medicines by sales. Worldwide sales of this drug generated £3.9 billion[i] in revenue for AstraZeneca in 2012, with an increasingly significant contribution from NSAID ulcer prophylaxis. The effectiveness of PPI prescription has also led to development of combination preparations, of which several have so far been approved and launched internationally (Axorid: ketoprofen + omeprazole 2009, Vimovo: naproxen + esomeprazole 2010, and Axanum: Aspirin + esomeprazole:2011)[j].

5. Sources to corroborate the impact

a) Latimer N. Lord J. Grant RL. et al. National Institute for Health and Clinical Excellence Osteoarthritis Guideline Development Group. Cost effectiveness of COX 2 selective inhibitors and traditional NSAIDs alone or in combination with a proton pump inhibitor for people with osteoarthritis. BMJ. 339:b2538, 2009 http://dx.doi.org/10.1136/bmj.b2538

b) National Institute for Health and Clinical Excellence. Osteoarthritis: The care and management of osteoarthritis in adults. http://www.nice.org.uk/nicemedia/pdf/CG59NICEguideline.pdf

c) Zhang W, Moskowitz RW, Nuki G, et al. OARSI Recommendations for the Management of Hip and Knee Osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis & Cartilage 2008; 16: 137-162. http://dx.doi.org/10.1016%2Fj.joca.2007.12.013

d) American College of Cardiology Expert Consensus Document on Reducing the GI risks of Antiplatelet Therapy and NSAID Use 2008: http://cardiocompass.cardiosource.org/cc2/openCont2?objID=108

e) Lanza FL, Chan FKL, Quigley EMM and the Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related Ulcer Complications. Am J Gastroenterol 2009; 104: 728-738. http://dx.doi.org/10.1038%2Fajg.2009.115

f) Hochberg MC, Altman RD, April T, et al, American College of Rheumatology 2012 Recommendations for the use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip and Knee. Arthritis Care & Research 2012; 64(4): 465-474. http://dx.doi.org/10.1002%2Facr.21596

g) Rostom A. Dube C. Wells G. et al. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database of Systematic Reviews http://dx.doi.org/10.1002/14651858.CD002296

h) Scrutiny of CPRD database. Corroborated by Dr Yana Vinogradova (pdf available on request).

i) AstraZeneca 2012 annual report: http://www.astrazeneca-annualreports.com/2012/documents/eng_download_centre/annual_report.pdf

j) Vimovo: http://www.medicines.ie/medicine/14981/SPC/VIMOVO+500+mg+20+mg+modified-release+tablets/#ORIGINAL