Reflections on the Diclofenac Debacle

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• Background
• Implications
• Questions Raised
• Suggested Solutions
EMA recommendation, 28th June 2013:

“Use of diclofenac is contra-indicated in patients with established congestive heart failure (NYHA class II-IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease.”

• PRAC/CMDh decision
Diclofenac

• Potent NSAID
  – Prostaglandin effect on smooth muscle

• Widely used:
  – Postoperative Analgesia
  – Rheumatoid Arthritis

• phenylacetic acid derivative
  – Cox 1/Cox 2 non-specific: increases efficacy but does this give increased cardiac risk?
Increased Cardiac Risk with NSAIDs

• Rofecoxib Withdrawn 2004
• Suggested risk with other NSAIDs
• Studies ongoing from 2006-2013
• Lancet Meta-Analysis: [1]

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

Coxib and traditional NSAID Trialists’ (CNT) Collaboration†
BUT....

DDDs for common NSAIDs:[1]

- M01AB05 diclofenac 0.1 g (=50mg BD)
- M01AE01 ibuprofen 1.2 g (=400mg TDS)
- M01AE02 naproxen 0.5 g (=250mg BD)

Diclofenac routinely 75mg BD (max 150mg daily)
Ibuprofen routinely 200-400mg TDS (max 2.4g daily)

[1] WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway, ATC DDD Index [http://www.whocc.no/atc_ddd_index/]
• Are we now under treating pain?
Populations in Pain

- Rheumatology population - already at increased cardiac risk
- Chronic Pain
- Acute trauma pain
- Postoperative pain
- Palliative Care
- Intravenous Drug Users
- Others
One Size Fits All?
EDITORIAL

Coxibs, Science, and the Public Trust

ORIGINAL INVESTIGATION

National Trends in Cyclooxygenase-2 Inhibitor Use Since Market Release

Nonselective Diffusion of a Selectively Cost-effective Innovation

Carolanne Dai, BSc, MSc; Randall S. Stafford, MD, PhD; G. Caleb Alexander, MD, MS
Pain and blockbusters – a long history?

- Opium
- Cocaine
- Pethidine
- Diamorphine/Heroin
- Benoxaprofen
- Co-Proxamol (Distalgesic®)
- Dihydrocodeine
- Tramadol
- Pregabalin
- Tapentadol
- Patches (opioid/lidocaine)
• Suffered from psoriatic arthropathy
• “left high and dry” by the withdrawal of benoxaprofen in the 1980s
Opiophobia vs Opiophilia (USA)

- 1980s fear of prescribing opioids
- 2005 JCI/APS: the 5\textsuperscript{th} Vital Sign
- 2011 FDA REMS

\textit{Atkinson, Schatman & Fudin} \textit{Journal of Pain Research} \textbf{2014:7} 265–268
Knee jerk reaction?
Who decides on what advice?

- EMA & HPRA (IMB)
- Individual prescribers?
- Individual organisations?
- NICE/ SIGN/ MeReC/ NeLM....

- In Ireland?
  - HSE Medicines Management Programme
  - HIQA
Role of Medicines Regulator

• The European Medicines Agency's (EMA) main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.
Special Article

Regulators Should Better Leverage Effectiveness Standards to Enhance Drug Value

Huseyin Naci, ¹,* and George Caleb Alexander²

¹LSE Health, London School of Economics and Political Science, London, UK; ²Center for Drug Safety and Effectiveness, Johns Hopkins University, Baltimore, Maryland

Regulators show some flexibility in the evidentiary standards of effectiveness that must be demonstrated for

[Further text...]
Regulators & “Regulatory Capture”

• George Stigler 1971: *the process by which regulatory agencies eventually come to be dominated by the very industries they were charged with regulating.*

• “Black Box” concept

• Influence can be unintended
Medicines regulation now part of “Enterprise & Industry” at EU level?

**EUROPEAN COMMISSION**

**PRESS RELEASE**

Brussels, 10 September 2014

The Juncker Commission: A strong and experienced team standing for change

*Changes for DG SANCO:*
- Units SANCO B2 (Health Technology and Cosmetics), SANCO D5 (Medicinal Products – Authorisations, European Medicines Agency) and SANCO D6 (Medical Products – Quality, Safety and Efficacy) move from DG SANCO to DG Enterprise and Industry (ENTR).
How did the IMB handle Diclofenac?

1. Does IMB safety advice take precedence over the product SPC?
2. How soon after the issue of IMB safety advice should we expect that product SPCs would be amended to reflect that advice?
Have the SPCs been amended?

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active gastric or intestinal ulcer, bleeding or perforation
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Last trimester of pregnancy (see section 4.6)
- Hepatic failure
- Chronic Kidney Disease Grade 5 (GFR <15)
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contra-indicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid/aspirin or other NSAID’s.
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.
- Active gastric or intestinal ulcer, bleeding or perforation
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Last trimester of pregnancy (see section 4.6 Pregnancy and lactation).
- Hepatic failure
- Chronic Kidney Disease Grade 5 (GFR <15)
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Voltarol is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs. With...
0.5mls Sodium Bicarbonate 8.4%

- Product discontinued – reduced demand?
- Alternative products had buffering requirement
- Protocol changes needed
But can we not make up our own minds?

- Potential journals: 10,000
- Potential new articles per week: 40,000
- Even if 97% are not relevant: 1,200
- Time to read each article: 15 minutes

- 10h a day, 6 days a week = 240 articles.
- So at the end of the first week you are about 4 weeks behind in your reading.
- At the end of the first month, you are 4 months behind in your reading.
- And at the end of the first year you are almost 5 years behind in your reading.

Credit: Richard Smith, BMJ
• Figure 2. The number of published trials, 1950 to 2007.

http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1000326
An echocardiography expert?

- 25,400 journals in science, technology, and medicine, and their number is increasing by 3.5% a year
- In 2009, they published 1.5 million articles.
- PubMed now cites more than 20 million papers.

Credit: Prof Neal Maskrey. NICE
• Assume a new entrant to the subspecialty can read five papers an hour (one every 10 minutes, followed by a break of 10 minutes) for eight hours a day, five days a week, and 50 weeks a year; this gives a capacity of 10,000 papers in one year.

• Reading all papers referring to echocardiography would take 11 years and 124 days, by which time at least 82,142 more papers would have been added, accounting for another eight years and 78 days.

• Before our recruit could catch up and start to read new manuscripts published the same day, he or she would—if still alive and even remotely interested—have read 408,049 papers and devoted (or served a sentence of) 40 years and 295 days.

• On the positive side, our recruit would finish just in time to retire.

Credit: Prof Neal Maskrey. NICE
Evidence based medicine: a movement in crisis?

Trisha Greenhalgh and colleagues argue that, although evidence based medicine has had many benefits, it has also had some negative unintended consequences. They offer a preliminary agenda for the movement's renaissance, refocusing on providing useable evidence that can be combined with context and professional expertise so that individual patients get optimal treatment.
HIQA?

• The Health Information and Quality Authority is the independent Authority established in May 2007 to drive continuous improvement in Ireland’s health and social care services.

• Reporting directly to the Minister for Health, our (HIQA’s) role is to promote quality and safety in the provision of health and personal social services for the benefit of the health and welfare of the public.
Aims to promote safe, effective and cost-effective prescribing of medicines by:

- Enhancing evidence-based prescribing and optimising patient safety through a reduction in medication-related adverse events
- Facilitating cost-effective prescribing through initiatives targeting high cost medicines, e.g. Preferred Drugs initiative and Prescribing and Cost Guidance
- Focusing on cost effectiveness to ensure value for money in relation to all medicines
- Encouraging generic prescribing
- Ensuring that patients have access to essential medicines
- Supporting prescribers to prescribe safely and appropriately in a wide range of therapeutic areas through drug safety initiatives, e.g. Prescribing Tips and Tools.

http://www.hse.ie/eng/about/Who/clinical/natclinprog/medicinemanagementprogramme/yourmedicines/aboutmmp/
• Networks of experience
  – Informal networks
  – HPAI Chat Forum
  – IMSN
• Or all of the above working together?
Where is the leadership?