Ibuprofen Safety: A Look Back 50 Years

Poster #36

Giustino Varrassi, MD;[1] Joseph V. Pergolizzi, Jr., MD;[2] Rohit Nalamasu, DO;[3] Jo Ann LeQuang, BA;[2] Robert Colucci, PharmD;[4] Frank Breve, PharmD; [5] Peter Magnusson, MD; [6,7] Dean Mariano, DO;[8] and Paul J. Christo, MD[9]

[1]Paolo Procacci Foundation, Rome, Italy; [2]NEMA Research, Inc., Naples, Florida; [3]University of Nebraska Medical Center Department of Physical Medicine and Rehabilitaiton, Omaha, Nebraska; [4]Colucci & Associates, LLC, Newtown, Connecticut; [5]Department of Pharmacy Practice, Temple University School of Pharmacy, Temple University, Philadelphia, Pennsylvania; [6]Centre for Research and Development, Region Gävlegborg/Uppsala University, Gävle, Sweden; [7]Department of Medicine, Cardiology Research Unit, Karolinska Institutet, Stockholm, Sweden; [8]Mariano Medical, LLC, Pain/Addiction Consultants, West Hartford, Connecticut; [9]Associate Professor, Division of Pain Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

PURPOSE

- Ibuprofen is nearing its golden anniversary (50 years) and remains among the most widely prescribed and frequently taken over-the-counter analgesic in the world. First developed in the United Kingdom by Boots Pure Drug Company, Limited,[1] the drug evolved when scientist Stewart Adams sought to elucidate the anti-inflammatory effects of aspirin which seemed to him to be a clear advantage over acetaminophen.[2] Adams and his colleague John Nicholson developed over 200 compounds and brought four to clinical trials with disappointing results. It was the fifth drug they tried that succeeded and came to market in 1969 in the United Kingdom and in 1974 in the United States.[3] An anecdote told by Adams himself said that he took the first dose of the new drug himself to treat a hangover.[1]

- Despite lengthy clinical experience with ibuprofen, new safety concerns had been raised about its role in infections[4] and its safety for COVID-19 patients.[5] Ibuprofen is unique in the NSAID family in that it appears to block both cyclooxygenase (COX) 1 and COX 2 enzymes. The COX enzymes synthesize prostaglandins which are associated with the inflammatory cascade. Safety concerns related to COX-1 inhibition mainly involved gastrointestinal adverse events; the introduction of selective COX-2 inhibitors or coxibs likewise raised safety concerns, in particular relating to cardiovascular events. Almost all NSAIDS may be associated with elevating blood pressure but the safety profiles of various NSAIDs are unique. Ibuprofen's position of balance "middle of the road" position as being neither strongly selective for COX-1 or COX-2 has afforded it a strong safety and tolerability profile.

- The authors sought to review safety data on ibuprofen at the half-century mark and to consider the advantages and disadvantages of this versatile and popular analgesic.

RESULTS

- Ibuprofen is an analgesic and antipyretic. Its T_{max} is 1.9 ± 1.4 hours in healthy subjects with a half-life of about 2.2 ± 0.4 hours. (1.4 hours).[6] In safety studies, ibuprofen was found in the Paracetamol, Aspirin, and Ibuprofen New Tolerability (PAIN) study to have similar rates of adverse events as acetaminophen (paracetamol) at doses of ≤ 1200 mg/day and significantly fewer adverse events compared to ≤ 3000 mg/day of aspirin.[7,8]

- The PRECISION trials of osteoarthritis and rheumatoid arthritis patients found that in long-term follow-up NSAID toxicity occurred in 5.3% of ibuprofen patients compared to 4.1% of celecoxib and 4.8% of naproxen patients.[9] A meta-analysis (n=2187 patients) found that ibuprofen was associated with a numerical frequency of adverse events similar or lower than placebo patients.[10]

- In the Ibuprofen Paracetamol Study in Osteoarthritis (IPSO), 222 patients were randomized to receive 400 mg ibuprofen three times a day or acetaminophen (paracetamol) 1000 mg three times a day; ibuprofen was the more effective pain reliever with a similar risk of gastrointestinal adverse events as paracetamol over the 14-day study.[11]

- The association of ibuprofen to infections is complex because in some cases, it confers a benefit (cystic fibrosis) but in others, it appears to exacerbate the infection. Ibuprofen was not found to be associated with increased bleeding risk following surgery.[12] Hypersensitivity reactions in various NSAIDs have been reported but are so rare there are insufficient data to compare individual agents.

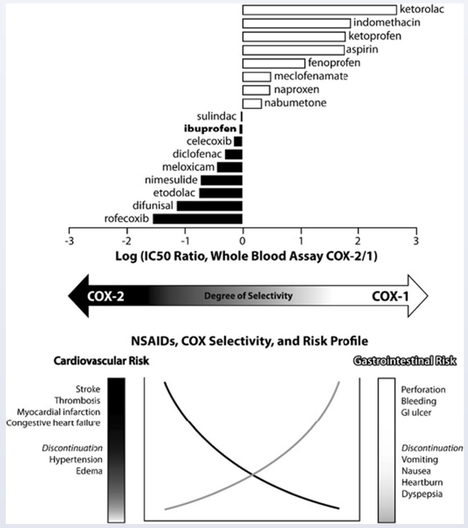

Fig. 1 (above) The class of NSAIDs contains drugs that exhibit pronounced COX-2 selectivity (such as rofecoxib) on the one hand for pronounced COX-1 selectivity on the other hand (such as ketorolac)

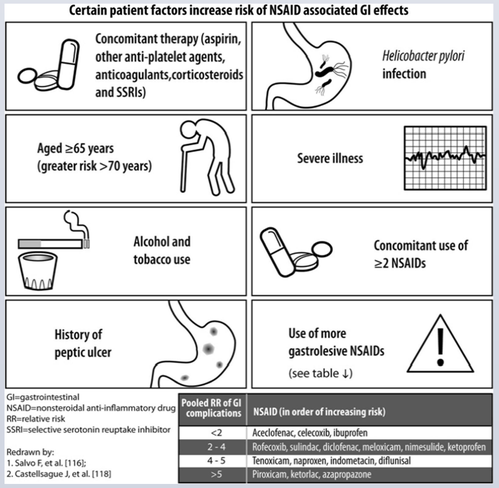

Fig. 2 (above) Known risk factors for GI adverse events associated with NSAIDs, including ibuprofen

CONCLUSIONS

- After 50 years, new evidence continues to emerge regarding the safety profile of ibuprofen. Taken as directed in the therapeutic dose range, ibuprofen is associated with significant anti-inflammatory action, effective analgesia, and a comparatively low risk of GI, CV, renal, hepatic, or infectious side effects. Ibuprofen, with its favorable safety profile, may be considered the safest of all NSAIDs pain relievers. Risks for GI, CV, renal, and hepatic side effects are lower than other NSAIDS. Prescribers must always balance benefit against risk with any medication and NSAIDs should only be taken at the lowest effective dose for the shortest amount of time.. Ibuprofen may not be appropriate for all patients, but its safety profile makes it an attractive first line for many acute and chronic pain conditions., Clinicians should evaluate the evidence and safety when making prescribing choices or recommending OTC products to their patients.

REFERENCES

1. Ferry G. Stewart Adams Obituary. The Guardian. https://www.theguardian.com/science/2019/feb/13/stewart-adams-obituary. Published 2019. Accessed June 4, 2019.
2. Prescott FL. Paracetamol: Past, Present, and Future. *American Journal of Therapeutics, 2000, Vol7(2), pp143-148.* 2000.
3. An interview with Stewart Adams. Cell Press. Trends in Pharmacological Sciences Web site. https://www.cell.com/trends/pharmacological-sciences/pdf/S0165-6147(11)00194-5.pdf. Published 2012. Accessed June 4, 2019.
4. Taylor N. France's ANSM warns about NSAIDs following safety review. Regulatory Affairs Professionals. EU Regulatory Roundup Web site. https://www.raps.org/news-and-articles/news-articles/2019/4/eu-regulatory-roundup-frances-ansm-warns-about-n. Published 2019. Accessed June 4, 2019.
5. World Health Organization. Could #ibuprofen worsen disease for people with #COVID19? Twitter. https://twitter.com/WHO/status/1240409217997189128_Published 2020. Accessed April 1, 2020.
6. Albert KS, Gernaat CM. Pharmacokinetics of Ibuprofen. *The American Journal of Medicine, 13 July 1984, Vol77(1), pp40-46.* 1984.
7. Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs. *Ther Clin Risk Manag.* 2015;11:1061-1075.
8. Moore N, Van Ganse E, Le Parc J, et al. The PAIN study: Paracetamol, aspirin and ibuprofen new tolerability study - A large-scale, randomised clinical trial comparing the tolerability of aspirin, ibuprofen and paracetamol for short-term analgesia. *Clin Drug Investig.* 1999;18(2):89-98.
9. Solomon DH, Husni ME, Libby PA, et al. The Risk of Major NSAID Toxicity with Celecoxib, Ibuprofen, or Naproxen: A Secondary Analysis of the PRECISION Trial. *Am J Med.* 2017;130(12):1415-1422.e1414.
10. Moore A, Crossley A, Ng B, Phillips L, Sancak Ö, Rainsford KD. Use of multicriteria decision analysis for assessing the benefit and risk of over-the-counter analgesics. *J Pharm Pharmacol.* 2017;69(10):1364-1373.
11. Boureau F, Schneid H, Zeghari N, Wall R, Bourgeois P. The IPSO study: ibuprofen, paracetamol study in osteoarthritis. A randomised comparative clinical study comparing the efficacy and safety of ibuprofen and paracetamol analgesic treatment of osteoarthritis of the knee or hip. *Ann Rheum Dis.* 2004;63(9):1028-1034.
12. Kelley BP, Bennett KG, Chung KC, Kozlow JH. Ibuprofen May Not Increase Bleeding Risk in Plastic Surgery: A Systematic Review and Meta-Analysis. *Plast Reconstr Surg.* 2016;137(4):1309-1316.

Disclosures: JVP discloses the following relationships: Consultant/ Speaker and Researcher for US World Meds, BDSI, Salix, Enalare, Scilex, Pfizer, Lilly, Teva, Regeneron, Redhill, Grunenthal, and Neumentum. DM is a Medical Fellow for Eli Lilly & Co. The other authors have nothing to disclose.