Non-steroidal anti-inflammatory drugs do not have anti-inflammatory effects

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23 June 2021

These drugs are analgesics, but doctors falsely believe that they also have an anti-inflammatory effect. They very often use them in combination with paracetamol because of this belief, even when randomised trials have failed to find an additional effect of the combination compared to using paracetamol alone.

I have explained in two of my books why the belief is false. The following excerpt is from chapter 2, "Confessions from an insider," in Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted health care. London: Radcliffe Publishing; 2013.

In 1977, I was offered a job at Astra-Syntex, a new joint-venture company between Astra and the California-based Syntex. My task was to establish a medical department and to be responsible for clinical trials and registration applications for new drugs and indications. I was very happy to leave marketing but also had concerns about the research the industry did and wanted to leave. I chose the most arduous way out and started to study medicine in 1978 while I continued to work for the company. I qualified 6 years later and left the company to work at different hospitals in Copenhagen.

Astra-Syntex's survival hinged on just one drug, naproxen (Naprosyn), a nonsteroidal anti-inflammatory drug (NSAID) used for arthritis. I performed several trials with the drug and discovered along the way that I wasn't immune to company influence. There were many NSAIDs on the market, but somehow you get so used to the idea that *your* drug *might* be better than the others that you end thinking it *is* better, just as if it had been your child. One of the reasons why marketing of medicines is so effective is that the salespeople believe they are selling a very good drug.

A clear indication of my naïvety was that I asked the European headquarters in London why we didn't perform a trial comparing naproxen with a simple analgesic such as paracetamol, for example in sports injuries. The medical director kindly explained that they were not interested in such a trial but never said why, although I asked on more than one occasion. The reason was of course that such a trial might show that a much cheaper analgesic was equally effective, and on top of that we already knew that paracetamol was much safer than naproxen. In order to lure people into preferring naproxen for paracetamol, it was therefore necessary to give the doctors the impression – without having any data to support it – that naproxen was more effective.

The trick was done using theoretical arguments. This is a very powerful marketing tool, although the arguments rarely hold water. In textbooks of pharmacology, naproxen is described as having anti-inflammatory properties and the hyped argument goes somewhat like this: When you have a sports injury, there is tissue injury and inflammation with oedema, and it is important to dampen the inflammation to speed up the recovery.

It is very easy to lure doctors into doing wrong things by making them listen to the songs of the sirens while paying many of them, both for singing and for listening (*see* Chapter 8). As I shall explain in detail later, NSAIDs are dangerous drugs and many thousands of people are killed every year because of bleeding stomach ulcers and heart attacks, to mention just the two worst harms. But marketing is all that is needed. A couple of years ago, Danish TV focused on the liberal use of NSAIDs in professional football clubs for all sorts of pain. The prescription status of the drugs wasn't a hindrance, as the sports doctors provided large supplies of the drugs, letting the footballers take as many as they wanted without even asking. There was a scandal, but as is usual with scandals, it quickly died out and I suppose it is now business as usual.

Around 1980, I was approached by a rheumatologist who looked after the Danish national football team. He wanted to find out whether naproxen was better than aspirin for sports injuries. Aspirin is also an NSAID – the oldest one in existence and very cheap – but it is often used in low doses where it is assumed to have no

anti-inflammatory effects, only an analgesic effect. We did the trial, using low-dose aspirin despite the concerns of my superiors in London, and just as they had predicted, there were no significant differences between the two drugs. However, the results were analysed by our statistics department in Sweden, which went on a 'fishing expedition' that eventually found something that could lessen the company's pains that naproxen wasn't any better than aspirin. The abstract of the published paper says:[13]

'Fresh injuries were over-represented in the acetylsalicylic acid group ($p<0.01$), and when all patients were analyzed together [i.e. from both treatment arms], a significantly better treatment result was obtained the shorter the interval between injury and start of treatment. This might have influenced the results from this study.'

Oh boy. I have contributed to this as an author. In principle, there is nothing wrong with reservations in an abstract, but imagine if naproxen had been significantly better than aspirin and there had been more fresh injuries in the naproxen group. Would this reservation about the good news for the company then have made it into the abstract? Hardly, and I doubt there would have been anything about this in the main text of the article either.

We first submitted our paper to *British Journal of Sports Medicine*. The editor was keenly aware of the commercial priorities in the industry; he said he was surprised that we posted our study from Syntex, as our work contradicted the claims the company had made about naproxen being more effective than paracetamol and aspirin. We were startled that an editor so frankly sided with a company's commercial interests and his next remark made us laugh. He noted that 18 patients received aspirin during the first 3 days of injury compared to only 2 on naproxen. He then suggested that a more fair comparison could be made if we were to treat another group of patients, at least 16 in number, with naproxen during the first 3 days following the injury. If we were willing to do this, he would reconsider our paper seriously. My goodness! How did he imagine we could include another 16 patients on only one of the drugs in a randomised double-blind trial? It cannot be done. We effectively buried the trial – although it wasn't our intention – by publishing it in a fairly unknown journal that stopped coming out 5 years later.[13]

I always wondered how it was possible to say that NSAIDs have anti-inflammatory effects, or whether it was only a marketing ploy. If a drug has an analgesic effect, it will lead to faster mobilisation, which would be expected to decrease the oedema. How could one then postulate that there was also a separate anti-inflammatory effect? NSAIDs had some effect in rats that had been treated in such a way that their paws were swollen and tender, but what did that prove? I often raised this issue with rheumatologists, but I never received a satisfactory answer.

However, one day I was contacted by a group of orthopaedic surgeons who wanted to study the effect of naproxen in ankle distortions. I grabbed the opportunity to study also the effect on the oedema, which we measured by immersing the foot in water and comparing its volume with that of the other foot. It was a highly interesting study. We randomised 173 patients twice: to crutches or no crutches (mobilisation), and to naproxen or placebo. This so-called factorial design is much underused despite its elegance, which is that it can provide answers to two questions without needing more patients than if only one question was asked. The results surprised us.[14] The patients recovered faster when they were mobilised, which also decreased the oedema, whereas naproxen had no effect on the oedema. Our marketing-oriented bosses in Sweden interfered again with our research, and there were no numerical data on either of these outcomes in our published paper. However, I have kept the more comprehensive internal study report and the effect of mobilisation was dramatic. At the first follow-up visit after 2–4 days, 30 of 68 patients had recovered, compared to only 10 of 63 patients in the group using crutches, and the difference in volume between the two feet was only 28 mL when the patients were mobilised, compared to 71 mL when crutches were used.

It was a beautiful study that had implications for practice. Years later, after a serious ankle distortion, I stumbled along in great pain during a trip to London to attend the *British Medical Journal*'s (*BMJ*) advisory board meeting and I moved with immense difficulty. One of the other members of the board asked me why I didn't use crutches and I replied that I had shown in a trial that patients recover faster if they don't. Our trial inspired him to do a systematic review of bed rest for all diseases and he identified 39 trials (5777 patients) with 15 different conditions.[15] He found that it is harmful to immobilise people in a bed; not a single outcome improved significantly whereas several outcomes worsened.

We submitted our trial to *Acta Orthopaedica*, a humble Nordic journal, but its editors didn't understand how important it was and rejected it. We had also tried the *BMJ* and my co-authors now just wanted to get

the trial out. I couldn't convince them that it was too important to publish in Danish, but that's what happened after we had translated the paper. Years later, I was approached by a researcher working on a systematic review of treatment of soft tissue injuries, and he told me that our study was not only the largest but also the best, so he asked me to translate our Danish paper into English!

In 1990, I defended my doctoral thesis, *Bias in Double-Blind Trials*,[16] which consisted of six papers. I had analysed 244 reports of trials in depth that had compared one NSAID with another. It was the first time a whole therapeutic area had been so thoroughly investigated and I uncovered an overwhelming amount of bias favouring the sponsoring company's drug over the control drug. The trial reports were generally so unreliable that they should be seen not as scientific publications but as advertisements for the drugs.

I had also assembled trials that compared an NSAID with placebo, which I used to study whether there is any anti-inflammatory effect with NSAIDs. In some trials, the researchers had used jeweller rings to measure if the drugs had an effect on swollen finger joints in patients with rheumatoid arthritis. They hadn't.[17] I therefore believe the idea of an anti-inflammatory effect of NSAIDs is a hoax, like so many other myths about drugs that the drug companies have invented and marketed.

13 Andersen LA, Gøtzsche PC. Naproxen and aspirin in acute musculoskeletal disorders: a double-blind, parallel study in sportsmen. Pharmatherapeutica. 1984; 3: 535–41.
14 Jørgensen FR, Gøtzsche PC, Hein P, et al. [Naproxen (Naprosyn) and mobilization in the treatment of acute ankle sprains]. Ugeskr Læger. 1986; 148: 1266–8.
15 Allen C, Glasziou P, Del Mar C. Bed rest: a potentially harmful treatment needing more careful evaluation. Lancet. 1999; 354: 1229–33.
16 Gøtzsche PC. Bias in double-blind trials. Dan Med Bull. 1990; 37: 329–36.17 Gøtzsche PC. Sensitivity of effect variables in rheumatoid arthritis: a meta-analysis of 130 placebo controlled NSAID trials. J Clin Epidemiol. 1990; 43: 1313–18.

In chapter 9, "Physical pain," in my book, Gøtzsche PC. Survival in an overmedicated world: look up the evidence yourself. Copenhagen: People's Press; 2019, I write this about NSAIDs:

NSAIDs

I would not dream of taking aspirin for pain, because this drug belongs to the drug class that is misleadingly called non-steroidal, anti-inflammatory drugs (NSAIDs). These drugs are harmful, and aspirin might cause bleeding among other things.

Many people take NSAIDs, some of which can be bought over-the-counter without prescription, e.g. ibuprofen. People believe they are harmless, which is a dangerous misconception. NSAIDs are among the worst killers we have, and they kill in many different ways, including bleeding stomach ulcers and heart attacks.[1] These drugs are so toxic that they should be avoided. A rheumatologist recently told me that if a patient with rheumatoid arthritis was in treatment with an NSAID, it was because the patient was not treated sufficiently with disease-modifying drugs (which are not harmless either, but since the disease destroys the joints, the harms can be a necessary cost in order to reap the benefits - not the case for NSAIDs).

The fraud in research and marketing of NSAIDs is formidable.[1] The biggest lie is probably the one that has given rise to the name of these drugs: anti-inflammatory. The story behind this is when newly synthesized cortisone was first given to patients with rheumatoid arthritis in 1948, the effect was so striking that some people believed a cure had been discovered.[2] The initial enthusiasm evaporated quickly, however, when the drug's serious harms came to light.

The name - non-steroidal, anti-inflammatory drugs - suggests that NSAIDs have dramatic effects similar to steroids like cortisone because they are anti-inflammatory like steroids. It is rare to name drugs after what they are not (non-steroidal), but that was a carefully planned marketing trick, and it worked so well, that one in eight Danes now get NSAIDs every year.[1]

However, I have shown in my research that these drugs are not anti-inflammatory.[1] They merely reduce pain and fever like paracetamol but are far more dangerous and expensive. They delay wound healing and it is therefore particularly bad practice to use them for sports injuries, also because pain is an important signal

that has helped us survive throughout evolution. When something hurts after an injury, it is a warning about letting that body part rest until it heals. If the signal is blunted with pain killers, it could make matters worse and cause acute problems to become chronic.

Not all pain goes away quickly, and if you do not know what caused it, you should try to find out. The hope is to find a cause and a treatment that works. Not a pain killer but a treatment that can remove the cause.

1 Gøtzsche PC. Deadly medicines and organised crime: How big pharma has corrupted health care. London: Radcliffe Publishing; 2013.
2 Hench PS, Kendall EC, Slocumb CH, et al. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Staff Meet Mayo Clin 1949;24:181–97.