The decline of NSAID gastropathy in rheumatoid arthritis

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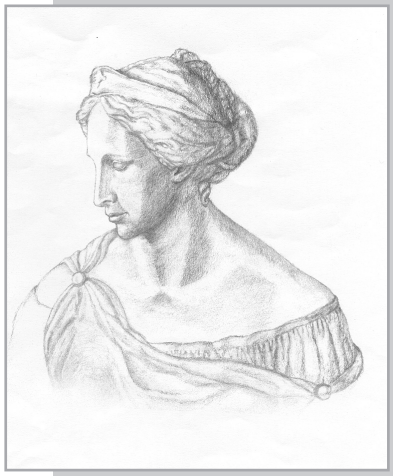
Introduction and aims of the thesis



Non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic and anti-inflammatory properties and are used for the treatment of arthritis and other inflammatory conditions. Worldwide, NSAIDs are among the most frequently prescribed drugs. However, they are associated with gastrointestinal (GI) toxicity, i.e. "NSAID gastropathy" [1]. The spectrum of NSAID gastropathy includes GI complaints (dyspepsia), gastroduodenal ulcers and life-threatening complications of GI ulcers, such as bleedings and perforations. Since these GI ulcers or their complications are not always preceded by dyspepsia, symptoms alone are not sufficient to predict serious GI events.

In view of this substantial morbidity and mortality of NSAID gastropathy, preventive strategies are recommended for all patients at (high) risk for NSAID gastropathy. The most important risk factors for NSAID gastropathy are high age and previous GI ulcers or complications of GI ulcers [2,3]. Other risk factors are high dose of NSAIDs, use of multiple NSAIDs, concomitant use of corticosteroids or anticoagulants, infection with *Helicobacter pylori (H. pylori)* or comorbidity, such as (severe) rheumatoid arthritis (RA) [2,3].

Since the nineties in the past century, NSAID gastropathy has gained much interest. Different strategies for the prevention of NSAID gastropathy have been developed: Firstly, the co-administration of misoprostol. NSAIDs associated gastroduodenal injury is related to the inhibition of prostaglandin synthesis in the gastroduodenal mucosa. Misoprostol is a prostaglandin E1 analogue and it is proven to be effective for the prevention of NSAID-induced damage of the gastroduodenal tract [4,5]. Secondly, the development of selective cyclo-oxygenase (COX)-2 inhibitors (COXIBs). The enzyme COX is responsible for the inhibition of the prostaglandin synthesis. Since the discovery in 1993 of the two iso-enzymes COX-1 and COX-2, it was postulated that blocking COX-1 was responsible for the GI toxicity, whereas inhibiting COX-2 was held responsible for the anti-inflammatory effects. The "traditional" NSAIDs are inhibitors of both enzymes, whereas COX-2 selective inhibitors (COXIBs) inhibit predominantly COX-2 and are as effective as the "traditional" NSAIDs but with lesser GI toxicity [6-8]. Thirdly, the concomitant use of gastroprotective drugs, i.e. proton-pump inhibitors and H2-receptor antagonists. Proton pump inhibitors and high dose H2-receptor antagonists are effective in the prevention of NSAID associated GI ulcers inhibitors [9-11]. Fourthly, the eradication of *H. pylori*. In 1983 the pathogenicity of the bacteria *H. pylori* in active chronic gastritis inhibitors was discovered [12]. After eradication of the bacteria, the gastritis and/or GI ulcer were cured [13].

Data about the relation between *H. pylori* and the use of NSAIDs in the development of GI ulcers are controversial. Some studies have shown a synergistic action between *H. pylori*- and NSAIDs-associated GI ulcers [14,15], whereas other studies have not [16].

In Asian people eradication of *H. pylori* prior to the start of NSAIDs is useful in the prevention of the development of gastroduodenal ulcers [17,18]. It is unknown whether eradication of *H. pylori*

prior to the start of NSAIDs is useful in European people. The effect of *H. pylori* eradication during long-term NSAID treatment has not been fully elucidated [19].

H. pylori is associated, as a pre-carcinogenic risk factor, with the development of intestinal metaplasia and dysplasia through atrophic gastritis. It is indicated that *H. pylori* may contribute to the prevention of the development of gastric malignancy [20].

Rheumatologists should be aware of the high cardiovascular morbidity and mortality in patients with inflammatory rheumatic diseases, such as rheumatoid arthritis (RA) [21,22]. Patients with RA have an increased CV risk, caused by the disease itself through inflammation, by (under-treatment of) "traditional" cardiovascular risk factors, and by the use of COXIBs and NSAIDs. Since the withdrawal of rofecoxib from the market in September 2004, due to an increased risk of myocardial infarctions [23], there is evidence suggesting that both COXIBs and "traditional" NSAIDs increase the risk of CV. It is now apparent that most of the so-called "traditional" NSAIDs are also associated with serious CV events [24,25].

The research line described in this thesis was initiated, ten years ago, initially focussing on the gastrointestinal aspect: we investigated the incidence of NSAID gastropathy in daily practice and its underlying risk factors. One possible option for the prevention of NSAID gastropathy was the eradication of *H. pylori*, another important etiological factor for gastrointestinal ulcer development. Nowadays the comorbidity of the rheumatic patient is shifting more towards cardiovascular (comorbidit) aspects. Hence, rheumatologists should assess the risk of gastrointestinal and cardiovascular comorbidity in the treatment of inflammatory rheumatic diseases, when prescribing NSAIDs and COXIBs to their patients.

The aims of this thesis

Firstly, to evaluate the incidence of clinical manifestations of NSAID gastropathy (dyspepsia, clinically manifest GI ulcers and complications of GI ulcers) in a large cohort of NSAID treated RA patients in 1997, before the introduction of COXIBs. The incidence of GI ulcera and its complications was repeated seven years later, in 2003, after the introduction of COXIBs, while at that time RA was being treated more aggressively.

Secondly, to conduct a large multicentre randomised placebo controlled trial in order to answer questions about the prevalence of *H. pylori* in NSAID users, and about whether eradication of *H. pylori* is useful during long term NSAID use.

Thirdly, to estimate the incidence of cardiovascular events in rheumatoid arthritis and the effect of eradication of *H. pylori* on inflammation and lipid profile.

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