Preventing NSAID-Induced Gastrointestinal Toxicity
Economic Considerations, Methodological Problems and Results

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The iatrogenic effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the upper gastrointestinal (GI) tract are well documented in the medical literature. Investigators have reported lesions such as minor erosions of the gastroduodenal mucosa, ulcers and rare complications (e.g. bleeding and perforation) that can lead to death. Because NSAIDs are widely and increasingly used, these adverse effects constitute a major public health issue. In addition, their occurrence also stimulates debate about the economics of NSAID therapy and the cost-benefit ratios of effective prevention strategies.

Three drugs have proven to be effective in the prevention of upper GI lesions in patients with rheumatoid arthritis or osteoarthritis. Misoprostol, a prostaglandin analogue, has shown efficacy in preventing both gastric and duodenal ulcers when co-prescribed with various NSAIDs.\[1,2\] Moreover, a fixed combination of misoprostol and diclofenac has been shown to be effective in these indications,\[3-5\] and is associated with a lower incidence of upper GI lesions compared with diclofenac alone. Ranitidine has been shown to reduce the incidence of duodenal ulcers when prescribed concomitantly with NSAIDs.\[6\] Finally, omeprazole has been shown to protect the duodenal mucosa from short term, naproxen-induced damage in healthy volunteers, but has no protective effect on the stomach.\[7\]

Pharmacoeconomic studies of the prevention of NSAID-induced gastric and duodenal toxicity have therefore been performed, to assess the economic implications of drug prophylaxis. Thus far, the published material has focused solely on the use of misoprostol, as reviewed by Barradell and co-workers.\[8\] These authors also discussed the costs of NSAID-induced toxicity. However, a discussion of these costs is beyond the scope of this article, the purpose of which is to review the economics of preventing NSAID-induced GI toxicity. We will, however, discuss the findings of studies published since the review by Barradell et al.\[8\] There are 3 main areas of debate.

First, there is contention regarding the target of prophylaxis of NSAID-induced gastropathy. Should the aim be to prevent GI symptoms, which are frequent in NSAID therapy, minor GI lesions, ulcers, or severe life-threatening complications such as haemorrhage and/or perforated ulcers? This debate is related to different clinical theories regarding the natural history of NSAID-induced upper GI lesions.

Secondly, and not unrelated to the first point, the quantitative and qualitative importance of NSAID-induced GI lesions is disputed. There is considerable variation in the literature on the incidence of these lesions, and although such variations can be dealt with in pharmacoeconomic studies through sensitivity analysis, their existence nevertheless raises questions about the robustness of study results.

Finally, existing pharmacoeconomic studies of preventive strategies in NSAID-induced GI toxicity have used a variety of methodologies. This di-
versity reflects the debate on what should be considered as a relevant outcome to assess the economic value of a preventive treatment. It also reveals problems linked to the availability of relevant data on resource utilisation for the treatment of NSAID–induced upper GI damage in different countries.

1. Primary versus Secondary Prevention

Although there is evidence that various types of upper GI damage can present with various degrees of severity, there is still an open debate as to whether the aim of prophylaxis should be to prevent only severe, life-threatening complications that lead to hospitalisation and intensive care, or all upper GI damage irrespective of severity. Considering the large number of people taking NSAIDs, this discussion has a major impact on the economics of prevention. For example, using 1980 morbidity data, around 10.5 million people in France are potential users of NSAIDs, on an episodic or long term basis.\[9,10]\n
For the purposes of this review, primary prevention is defined as the prevention of all upper GI damage irrespective of severity. Secondary prevention is defined as prevention of severe life-threatening complications only, for patients who either have a previous history of upper GI damage, or are identified as being ‘at risk’ of such damage. Thus, the terms ‘primary’ and ‘secondary’ as they are used here do not refer to their conventional definitions (i.e. preventive treatment given before and after the occurrence of the first adverse GI event, respectively).

Primary prevention is medically justified if mild (as opposed to life-threatening) upper GI damage is frequent, causes painful symptoms that reduce compliance with NSAID therapy, or necessitates the use of lower and less effective dosages or specific GI therapy. It is also justified if there is a potential risk that mild GI damage left untreated may lead to more severe complications. This implies that the natural evolution of some mild upper GI lesions is increased severity, the end-point of which is perforation of an ulcer, haemorrhage or both.

Moreover, there are risks inherent in not treating mild upper GI damage in patients taking NSAIDs because the analgesic effect of these drugs might mask the symptoms of GI toxicity. Finally, there is evidence that although patients receiving NSAIDs often complain of upper GI symptoms, the occurrence of such symptoms is not proven to correlate with actual GI damage.

Indeed, because physicians are aware of the potential GI toxicity of NSAIDs, they either adopt prudent prescription habits or co-prescribe anti-ulcer drugs to treat or prevent GI damage. For example, a survey among 356 French physicians, general practitioners and rheumatologists showed that 32% of respondents would occasionally prescribe either antacids or histamine H2-antagonists together with NSAIDs for patients with GI symptoms suggestive of NSAID–induced damage, or patients with associated risk factors (e.g. past history of ulceration).\[111]\n
If this point of view is correct, then the potential benefits of effective prevention lie in a reduction in severe events, increased efficacy of NSAID therapy (through increased tolerability) and a lower incidence of mild upper GI damage, including endoscopically proven ulcers that require treatment. The fact that a previous history of ulcer disease is an important risk factor for complications may also be seen as indirect evidence of a link between initial mild damage, including ulceration, and unpredictable severe complications.\[12]\n
If it is assumed that there is no relationship between mild upper GI damage and the development of severe complications, then only secondary prevention may be medically and economically justified. Somerville and Hawkey\[13]\ adopted a very prudent standpoint, suggesting that significant bleeding and gastric ulceration may develop by mechanisms different to those that lead to minor bleeds or lesions. In addition, they suggested that patients at risk may be those who lack normal mechanisms of adaptation to the ingestion of NSAIDs.