Editorial

Nonsteroidal Antiinflammatory Drug Gastropathy: We Started It, Why Don't We Stop It?

The first step toward a cure is to know what the disease is.
— Latin proverb

Three decades ago we took the first step of identifying gastric ulcers associated with nonsteroidal antiinflammatory drug (NSAID) therapy: 28% of our 142 patients with rheumatoid arthritis (RA) taking NSAID were found by random upper gastrointestinal (GI) studies to have gastric ulcers[1]. In contrast to classic peptic ulcers, these were almost always silent, without pain or distress, and were predominantly found in elderly women. Thus, understanding NSAID as key to causation and recognizing the elderly and ulcer-prone host group meant that prevention and cure were at hand, as editorially posited: "We started it, we can stop it."[2]

In the first comprehensive review in the literature[3], we expanded on "NSAID gastropathy," a disease separate from peptic ulcer. Peptic ulcer was classically associated with hyperacidity and was responsive to the H2 receptor antagonist cimetidine, in contrast to NSAID gastropathy, in which no lesions are noted and there is normal or low gastric acidity[4]. This gastropathy was an often-silent gastric lesional iatrogenic disorder ranging from erosions to ulcer-crater disease, including asymptomatic gastric bleeds to perforations, specifically associated with chronic systemic NSAID therapy. The at-risk host population has been characterized as elderly, with a history of gastropathy or ulcer, abuse of alcohol, cigarettes, and concomitant use of aspirin or other NSAID; the illness is especially dangerous when taking corticosteroids or anticoagulants[5].

Osteoarthritis (OA), predominantly seen in elderly with other chronic diseases, is a common chronic musculoskeletal disorder that has claimed considerable therapeutic attention[6]. Subsequent reports, including data from our national rheumatic disease databank (ARAMIS), corroborated these findings and supported cohort data pointing to this alarming iatrogenic public health problem and the most common cause of drug related morbidity and mortality reported to the US Food and Drug Administration (FDA) and regulatory agencies worldwide[7].

Special hearings were then held by the FDA with the Arthritis Advisory Committee, which led to the addition of a "black box" warning. While warnings of dire consequences related to taking NSAID (including selective cyclooxygenase 2 inhibitors, COX-2) were now conflated after the emergence of further cardiorenal and vascular complications (myocardial infarction, stroke, etc.), in a followup report more than a decade later, NSAID gastropathy persisted unabated[8]; moreover, renal dysfunction and even renal failure, clotting events, and possibly other end-organ complications were added to the risks associated with the popular newer selective COX-2 NSAID[9]. And most recently, such complications have led to voluntary withdrawal of the selective COX-2, rofecoxib, and probably more restricted use of all the coxibs[10]. This could herald a switch back to older (and more gastrotoxic) nonselective NSAID.

Additionally, expensive double-drug therapy, so-called "gastroprotective therapy," with misoprostol or proton pump inhibitors, has been introduced and persists to this day as potential defensive measures for combined use with NSAID[11]. About 30% of all NSAID users experience epigastric symptoms and distress that are not necessarily associated with gastric ulcers or mucosal lesional disease, but frequently lead to costly medical visits, medications, studies, and even endoscopy[12]. Instead of expensive NSAID double-drug therapy in such high risk symptomatic patients, one might anticipate change to alternative less toxic non-NSAID medication that could sensibly obviate adverse effects.

Yet ubiquitious use of NSAID persists: *The Wall Street Journal* reports that selective COX-2 prescriptions now approach $3 billion a year in the United States alone, despite warnings of continuing toxicities[13]. Ulcer bleeds continue to be reported by the FDA despite dominant use of selective COX-2 agents, and a major cohort study in an elderly population of 1.3 million in Ontario, Canada, found a 10% increase in the hospitalization rate for GI bleeds compared to a period prior to exploding COX-2 use[14]. This suggests that this widespread popular use was associated with an enormous increase in host risk exposure without the supposed safety of the selective COX-2 NSAID[15]. These observations are consistent with those of Fries, *et al* that as the frequency of NSAID gastropathy diminishes in patients with rheumatoid arthritis (just as disease modifying antirheumatic drugs and biologicals trivialize the role of NSAID), "much of the decline in incidence will have been

countered by increases in (host-risk) exposure"[15]. This, even as low dose aspirin for cardioprotection "increases the relative risk (of bleeds and deaths)"[16].

Combine this development with the April 2004 FDA Advisory to all physicians and health consumers of over-the-counter (OTC) NSAID pointing out the inappropriate self-dosing and unappreciated danger of NSAID and related therapy. The warning followed the Roper Survey report of 1997 and the National Consumer League Survey report of 2002 of over 9000 US health consumers[17,18]. Evidently many consumers did not recognize that OTC NSAID could have serious adverse effects, and they did not know that multiple NSAID or other potent drugs and even alcohol should not be taken together. Although polypharmacy and co-disease ideally required a physician's supervision, the reports suggested that many health consumers preferred to self-medicate NSAID on a continuing, as-needed basis, supposedly to avoid the expense and trouble of having a physician regulate them. Although over 30 million consumers use OTC NSAID daily, over 16,000 people die and over 100,000 are hospitalized from side effects, with 2 to 3 times the risk of gastric bleeds without warning[19,20].

The elderly are still the most common chronic prescription users of systemic NSAID and are most vulnerable to serious NSAID gastropathy complications, with the overwhelming preponderance of reported silent ulcer bleeds and deaths[21]. The pathophysiological basis for this has been classically described by Szabo and Goldberg as the shrunken microvasculature of the gastric submucosal bed in the very elderly that cannot defensively respond to sustained use of NSAID, selective COX-2 or not, without this potentially fatal threat[22]. Therefore, the challenge of changing to alternatives that are not end-organ toxic demands reexamination.

The useful antiinflammatory benefits of NSAID can be achieved without such toxicity by using nonacetylated salicylates, which are totally prostaglandin-sparing. However, these older generic agents are not always readily available due to absence of marketing. That these older, inexpensive agents are less analgesic can be balanced against the marked lack of end-organ toxicity; they are antiinflammatory at safe therapeutic doses that can be serologically monitored[23]. Moreover, since a plethora of non-NSAID analgesics exist, as well as topical therapies for localized problems, the antiinflammatory benefits of a nonacetylated salicylate can be combined with a non-NSAID analgesic, without end-organ toxicity risk, and without the expense or side effects of a gastroprotective agent.

Since NSAID have a limited ceiling for pain relief, opioids are more commonly used for more severe pain[24]. Opioids are not end-organ toxic, but must be used with discretion and require monitoring to avoid abuse. Undertreatment of pain is a recognized issue in medicine. And it is this same, very elderly group that often suffers severe chronic pain with advanced arthritis of weight-bearing joints and spine, and who are often a poor surgical risk for intervention. Opioid controlled-release delivery systems for 24 hour or longer relief can now be used with care and safety; however, their use remains controversial[25]. Yet these agents are not associated with the devastating GI bleeds and renal complications common to chronic systemic NSAID therapy; and they are frequently the most efficacious therapy for more severe pain and suffering.

Finally, intraarticular corticosteroids and now hyaluronan are a choice for localized arthritis problems. Topical NSAID agents, which are already used in most Western countries, may soon be available in the USA. Randomized controlled trials suggest these agents may be as effective as systemic NSAID therapy for localized arthritis with safety and targeted efficacy, as confirmed by metaanalyses[26,27]. Topical NSAID have been used successfully for over 15 years, with only uncommon local skin reactions and *no* confirmed associated systemic toxicities, as shown by recent longterm randomized control data[28].

To therapeutically attack selective common OA problems in those higher risk patients with chronic systemic NSAID may be compared to "carpet bombing," with the expected end-organ risks considered "collateral damage." Alternaively, we can avoid these risks by using non-NSAID analgesics, or when practical, target the arthritis precisely with topical NSAID and/or intraarticular agents.

RECOMMENDATIONS

- Stop NSAID gastropathy and related complications by stopping (or at least minimizing) chronic systemic NSAID therapy (selective COX-2 or not) in the well defined at-risk patient
- Avoid NSAID in combination with anticoagulants, corticosteroids, or aspirin co-therapy
- Consider nonacetylated salicylates for inflammation and non-NSAID analgesics for pain
- Consider carefully 24 hour or other controlled release opioids for chronic nonresponsive severe pain, with appropriate screening and monitoring
- Evaluate intraarticular therapy selectively and consider topical NSAID therapy over chronic systemic NSAID when and where available

From the earliest reports we have identified the cause of NSAID gastropathy as a disease specific to the effects of NSAID therapy itself. The relative failure of "safer" NSAID and expensive double-drug gastroprotective therapies associated with poor longterm compliance to eliminate an iatrogenic disease of public health dimensions begs a definitive cure. In the face of the many alternative therapies reviewed, the cure is simple: Avoid or stop all NSAID in the at-risk population.

In our oath of Hippocrates we pledged not only to relieve

pain and suffering, but also "to do no harm." Now, after identifying the persisting iatrogenic disease NSAID gastropathy and other end-organ toxicities, and determining some specific cures for those at risk, we should fulfill that oath and *stop* NSAID gastropathy, and its attendant risks, once and for all!

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Note added in proof: At the time of publication, not only is Vioxx withdrawn but Bextra has been suspended from further sale by the US Food and Drug Administration and all nonsteroidal antiinflammatory drugs are under safety review, with additional strong warnings on Celebrex.

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