

Clinic for Rheumatic Diseases and Rehabilitation
Clinical Hospital Center Zagreb ♦ Kišpatićeva 12 ♦ 10000 Zagreb ♦ Croatia

CONCERN ABOUT ONE DRUG OR ENTIRE CLASS OF DRUGS PROBLEM JEDNOG LIJEKA ILI CIJELE SKUPINE LIJEKOVA

Božidar Ćurković

Nonsteroidal antiinflammatory drugs (NSAIDs) are the most widely used class of therapeutic agents for the treatment of a variety of acute and chronic rheumatic conditions to provide analgesia and suppress inflammation. Most treatment is short-term management for the relief of signs and symptoms in osteoarthritis, but NSAIDs are widely used too in the long-term treatment of patients with rheumatoid arthritis. Although NSAIDs are highly effective in the treatment of rheumatic disease it is also clear that they carry a risk of adverse events particularly in the gastrointestinal tract.

Both the therapeutic and side effects of NSAIDs result from their inhibition of prostaglandin synthesis mediated by cyclooxygenase (COX) enzyme. The beneficial actions of NSAIDs can be associated with inhibition of cyclooxygenase-2 (COX-2) whereas their harmful side effects are associated with inhibition of cyclooxygenase-1 (COX-1). The development of more selective inhibitors of COX-2 promised important advances in reduction of GI toxicity. Trials of comparison of selective COX-2 inhibitors vs standard NSAIDs generally showed lower levels of GI side effects such as evidence of endoscopic erosions and ulcerations (1,2). However, the evidence is still missing about reducing risk of complicated GI events (perforation, bleeding, obstruction) (3). "Head to head" studies conducted to compare the coxibs are still insufficient (4,5). Concern about other side effect of COX-2 specific inhibitors, particularly cardiovascular, existed but has not been conclusively resolved (6,7,8). Grazio and Anić review in this issue of *Reumatizam* evidence based data regarding efficacy and side effects of NSAIDs, comment controversies, recommendations and perspectives.

Over the past 4 years, the pharmaceutical industry, researchers, statisticians, and doctors, through numerous publications, have proclaimed significant advancement in the treatment of musculoskeletal disease with the new nonsteroidal antiinflammatory drugs (COX-2

specific inhibitors) which have the same efficacy but significantly fewer gastrointestinal side effects, confirmed by numerous short and long-term studies, but consensus about other side effects, predominantly cardiovascular has not yet been achieved.

With great interest we have followed the controversy tied to the "voluntary" withdrawal of specific COX-2 inhibitor rofecoxib and recently valdecoxib. Also, another story of shared responsibility, involving drug regulatory agencies (FDA, EMEA), pharmaceutical companies on the one side and many respectable scientific journals, as well as, *New England Journal of Medicine*, *British Medical Journal*, *The Lancet* and *JAMA* on the other side, started up. Is the regulatory agency failed to protect the public health? Are scientific medical journals responsive too? Coxibs have been aggressively marketed directly to consumers in the United States and have rapidly dominated the prescription-drug market for NSAIDs. The quality of particular articles in eminent journals is curiously variable in spite of proclaimed set standards and independent reviewers. One gets the impression that results are sometimes related to the statistical recklessness which often "draw" results and present them as more significant than they are.

How huge is problem? Meta-analyses of randomized trials and large randomized trials show no convincing evidence for increased cardiovascular adverse events (9,10,11). How huge is really problem regarding other drugs like corticosteroids, opioids, immunosuppressive and biologic agents? How huge is problem in Croatia?

At the time of rofecoxib withdrawal, there was only two coxibs on the Croatian market (rofecoxib and celecoxib) but neither was reimbursed by insurance. Due to the high cost of these drugs we estimate a low number of users particularly long-term. But, if all NSAIDs (standard and coxibs) share the same cardiovascular risk we have to be seriously worried and we need fast resolution.

Božidar Ćurković, Ph.D., Professor

Clinical Hospital Center Zagreb ♦ Kišpatićeva 12 ♦ 10000 Zagreb ♦ Croatia ♦ e-mail: bcurkov@mef.hr

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