Adverse heart effects of rofecoxib may have been identified years earlier

November 23 2009

Clinical trial data indicated an association between the anti-inflammatory medication rofecoxib and cardiovascular risk as early as December 2000, before the product was taken off the market in September 2004, according to a report in the November 23 issue of *Archives of Internal Medicine*.

Rofecoxib was introduced to the market in May 1999 and quickly became a commercial success, with sales reaching $2 billion annually, according to background information in the article. The manufacturer marketed the product (with the brand name Vioxx) as a safer alternative to traditional nonsteroidal anti-inflammatory drugs. However, concerns about its cardiovascular adverse effects reportedly existed during the drug development process. In September 2004, the manufacturer voluntarily withdrew the product from the market after one large trial was terminated early due to an increased risk of cardiovascular events.

In November 2004, the manufacturer's chief executive testified before a U.S. Senate committee that until the halted trial, combined data from all randomized controlled clinical trials showed no difference in the risk of confirmed heart events between patients taking rofecoxib and those taking placebo. To assess whether and when analysis of published and unpublished clinical trial data could have revealed the cardiovascular risks of rofecoxib, Joseph S. Ross, M.D., M.H.S., of Mount Sinai School of Medicine, New York, and colleagues conducted a pooled analysis of all such trials conducted by the manufacturer before September 2004.

The researchers identified 30 randomized, placebo-controlled trials that enrolled a combined 20,152 individuals, lasted from four weeks to four years and assigned a range of 17 to 2,586 participants to take doses of rofecoxib ranging from 12.5 milligrams to 50 milligrams. The authors pooled the data from these studies and analyzed the cumulative results.

"As of December 2000, 21 of these trials had been completed (70 percent) and the risk of a cardiovascular thromboembolic [heart- or blood clot-related] adverse event or death was greater among subjects assigned to the rofecoxib group, raising concerns from a safety standpoint," the authors write. "Subsequently collected data through June 2001 showed that rofecoxib was associated with a 35-percent increased risk of a cardiovascular thromboembolic adverse event or death." The association strengthened as additional data became available—as of April 2002 the pooled analysis showed a 39-percent increased risk, and as of September 2004, a 43-percent increased risk.

The analyses provide a roadmap for how drug safety can be assessed after a product has been introduced into the market, the authors note. New legislation requiring the public disclosure of trial results in the ClinicalTrials.gov database will make available substantial data that has not previously been used to understand drug safety or efficacy. Independent investigators will now be able to conduct comprehensive meta-analyses that can complement and corroborate surveillance done by the U.S. Food and Drug Administration.

"Physicians and the public deserve to be in a position to make informed choices about risks and benefits, and the disclosure and dissemination of information about potential risk immediately after its recognition is absolutely essential. Our study provides insight into what should have been known about the risks of rofecoxib," the authors conclude. "If we are to detect harms early and protect the public's health, while ensuring the availability of new, clinically effective therapeutics, a system must

be established that makes full use of all existing evidence."

More information: Arch Intern Med. 2009;169[21]:1976-1985.

Source: JAMA and Archives Journals (news : web)