Toying With the Wrong NSAID: Diclofenac – the Commonest and the Most Harmful

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THE STUDY: McGettigan P, Henry D. Use of Non-Steroidal Anti-Inflammatory Drugs That Elevate Cardiovascular Risk: An Examination of Sales and Essential Medicines Lists in Low-, Middle-, and High-Income Countries. *PLoS Med* 2013; 10(2):e1001388.

BACKGROUND

The cyclooxygenase (COX) enzyme has 2 main types: COX-1, which is the constitutive isoform involved in gastric cytoprotection and prevention of thrombosis via production of prostacyclin. COX-2 is the inducible form, induced by inflammatory stimuli and cytokines. It is the inhibition of COX-2 which gives NSAIDs their anti-inflammatory properties.

NSAIDs are first line of therapy in various chronic inflammatory diseases and musculoskeletal disorders [1]. Since non-selective COX inhibitors inhibit both the physiological and inducible forms of the enzyme, they cause irritation of the stomach lining and may causes adverse effects such as dyspepsia, abdominal pain and gastro-duodenal ulcers [1]. COX-2 inhibitors do not affect the stomach's function; however, they are known to cause a decrease in the amount of prostacyclins produced via the COX-2 pathway. Since platelet function mediated by the COX-1 pathway remains unaffected, the balance is shifted towards thrombogenesis and increased risk of cardiovascular disease (CVD) and atherosclerosis [1]. Numerous trials and meta-analysis confirm serious adverse effects including gastrointestinal distress and more importantly, the increased risk of CVD [2, 3]. Even though the adverse gastrointestinal outcomes can be curtailed with the use of proton pump inhibitor therapy, there is no evidence that low dose aspirin reduces the risk of NSAID-induced cardiovascular toxicity [4].

WHY WAS THE STUDY CONDUCTED?

It is well known that some NSAIDs have greater adverse effect on the cardiovascular status; diclofenac, rofecoxib and etoricoxib are the most common culprits, as compared to naproxen. The researchers tried to investigate the extent to which this available evidence has translated into guidance and sales in 15 low, middle and high income countries.

HOW WAS THE STUDY CONDUCTED?

Firstly, NSAIDs were ranked according to their cardiovascular risk; Relative Risk (RR) values derived from published meta-analysis of randomized controlled trials and controlled observational studies.

Secondly, the published essential medicines lists (EML) of various countries were obtained and compared with the World Health Organization (WHO) model list of essential medicines. Thus, for the countries with published EMLs, a comparison was made on the information provided about cardiovascular risks of individual NSAIDS and their inclusion in the EML.

Thirdly, the sales on individual NSAIDs were measured in different countries using the intercontinental medical statistics health (IMS health) data. This data was purchased from IMS health for the year 2011 of 13 countries in South Asia, Southeast Asia and Asian Pacific regions. These countries included Pakistan. Whereas sales data was use for the above mentioned regions, NSAID prescriptions dispensed during 2011 were used for Canada and England.

EML inclusions: EMLs published on the WHO website revealed the following NSAIDs to be most commonly recommended: aspirin by 88 countries, ibuprofen by 90 countries, diclofenac by 74 countries, indomethacin by 56 countries and naproxen by 27 countries. Significantly, 51 countries that listed diclofenac did not list naproxen. One of the significant observations is that WHO EML does not contain either diclofenac or naproxen.

Patterns of NSAID use: Undisputedly, diclofenac was the most popular NSAID sold. Diclofenac and etoricoxib together comprised about one-third of the market shares across 15 countries (median 33.2%) and this proportion did not differ between high and low income states.

LEARNING POINTS FROM THE STUDY

It is quite clear from this study that diclofenac is the most widely sold and used NSAID throughout the world in low, middle and high income countries. This is reflected by its market shares across the world. Diclofenac is shown to have a relative risk profile similar to or possibly greater than rofecoxib [5]. Rofecoxib was quite notorious for its cardiovascular toxicity and was withdrawn from the world markets about 8 years ago [6]. However, despite the available information on diclofenac's adverse health profile in 2006, it is still very widely used.

Taking a toll on low and middle income countries: The incidence of CVD is significantly rising in low and middle income countries. According to WHO, 80% of the world's deaths related to CVD occur in low to middle income countries, particularly because they are more exposed to risk factors, have limited access to quality health care and suffer unawareness due to limited prevention programs [7]. Amongst the South Asian countries, greatest frequency of use and sales of diclofenac were documented in Bangladesh and Pakistan. Ibuprofen had the greatest market in Pakistan. However, the use of naproxen was negligible in Pakistan as compared to Bangladesh. Although neither naproxen nor diclofenac is included in WHO's EML, national EMLs contain these drugs. This clearly suggests that WHO should not only provide information about those drugs which are included in the list but also explain the reasons behind non-inclusion of other drugs of similar groups. This step might influence the activity of the physicians and other stakeholders involved in preparing national EML. Diclofenac and NSAIDs with comparable cardiovascular toxicity should be banned immediately, especially in those countries where the legislation is weak regarding over-the-counter medicines.

Naproxen the savior: Naproxen was shown to be the safest NSAID. However, it was included in only 27 of the 74 published EMLs. It only contributed to 9% of the sales throughout the world. Thus, if used regularly in place of high risk NSAIDs, it may reduce thousands of preventable deaths attributed to NSAID-induced CVDs.

Deficiencies in the WHO model list of essential medicines: It provides limited guidance for selection of NSAIDs on EMLs. It includes aspirin and ibuprofen but offers no advice on their safety or cost effectiveness relative to each other or to other NSAIDs. There should be attempts to improve such deficiencies.

LIMITATIONS

The risk profiles of patients taking the NSAIDs were not taken into account since they were not available. However, the large amount of NSAIDs consumed makes it very likely that they are being taken by a substantial number of patients at risk for cardiovascular events. Sales data was relied on for 13 countries and prescription sales for England and Canada. Sales data provides a more comprehensive estimate and includes nonprescription and hospital use in addition to community prescribing. Thus, the coverage in the latter two countries was variable.

The study also did not include India, which is the second most populous country in the world. In India, diclofenac is included in the EML but not naproxen.

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