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Editorial

Trend of Unbridled Use of Self Prescribed NSAIDs for Toothache - FDA Warnings and Safety Concerns to Optimize Patient Care

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used over the counter (OTC) drugs across the world, constituting 5% of all the prescribed medicines. It is estimated that more than 35 million people use NSAIDs daily worldwide. Commonly used NSAIDs for toothache are diclofenac, aceclofenac, ketorolac, nimesulide, naproxen, celecoxib, eteriocoxib, ibuprofen, meloxicam and acetaminophen. Non-selective NSAIDs inhibit both COX-1 and COX-2 enzymes. Inhibition of COX-1 augments the risk of GI bleeding whereas COX-2 selective NSAIDs maintain analgesia efficacy while minimizing the GI effects associated with COX-1 inhibition. In July 2015, the FDA updated the label warnings on nonaspirin. NSAIDs as a result of findings presented at the joint meeting of Arthritis Advisory Committee (AAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) in February 2014 which revealed the data that shows NSAIDs have a higher toxicity than previously suspected in 2005. The common adverse events observed included GI bleeding, peptic ulceration, hemorrhagic CVA (Cerebrovascular accidents), and renal impairment. A prospective, cross sectional multi-centered study in India, which included 8 medical colleges across the country, reported NSAID related GI complications in 30.08% of cases. In Pakistan, a study, analyzing 820 patients who had undergone upper GI endoscopy revealed that NSAID related peptic ulcer occurred in 14.7% of patients, where duodenal ulcer was more predominant (65.3%) than gastric ulcer (42.3%). Advent of modern imaging techniques including capsule endoscopy and double balloon endoscopy detected evidence of a myriad of lesions including erosions, petechiae, varix, reddened folds, loss of villi, and ulcers in chronic NSAID users. Selective COX-2 inhibitors (Coxib) have a greater edge over non-selective COX inhibitors for their GI protective property. Despite the potential GI benefit, COX-2 selective NSAIDs are presumed to have an increased risk of cardiovascular events. In a trial including 8076 patients with a history of osteoarthritis or rheumatoid arthritis treated with naproxen and rofecoxib where the report showed a five fold increase in MI events in patients treated with rofecoxib. After the voluntary withdrawal of valdecoxib and rofecoxib due to their CV safety issues, the only FDA approved COX-2 inhibitor available is Celecoxib with a boxed warning. In 2015, after evaluation of observational studies and a combined analysis of clinical trials of several previous years, FDA strengthened the warnings regarding CV events with nonaspirin NSAID use including the increased risk of thrombolysis like stroke and myocardial infarction. In some studies CV events were estimated to be 10% to > 50% depending on OTC NSAIDs use and the incidents of heart attack stroke or heart failure were reported to be increased with long term or high dose use of NSAIDs in cardiac patients. Naproxen, a nonselective NSAID is thought to have a better CV safety profile because of its potent COX-1 inhibition and long half-life but ineffective in acute throbbing pain like acute pulpitis. In addition to CV and GI complications, NSAIDs also carry a significant risk of kidney damage which includes multiple nephrological complications like acute kidney injury (AKI) and chronic kidney disease (CKD) encompassing electrolyte imbalance, glomerulonephritis, renal

papillary necrosis, fluid retention induced hypertension, renal tubular acidosis, hyponatremia and hyperkalemia etc. NSAIDs come next to aminoglycoside as most notorious drug to cause nephrotoxicity; 15-25% cases of AKI (Interstitial nephritis) have been found associated with NSAID usage in patients older than 65 years and another report has been documented that OTC use of NSAID may lead to acute renal failure in a pediatric population. There is a strict restriction of prescribing NSAIDs in CKD patients, who are often on medications like ACEs, ARBs and diuretics which in fact interact with NSAIDs which may worsen the situation. Additionally, through the inhibition of COX 1 and COX-2, NSAIDs affect kidney function by decreasing renal perfusion, which leads to changes in renal flow which in turn enhances the blood pressure and edema in patients taking anti-hypertensives. NSAIDs are reported to blunt the action of Furosemide and potassium sparing action of spironolactone, interfere with the action of warfarin, sulfonylureas, phenytoin and methotrexate by displacement from the plasma binding site. Some NSAIDs are also reported to have a certain amount of hepatotoxicity for what they have been withdrawn from the market (Bromfenac and Lumiracoxib). Although the two most extensively used NSAIDs, sulindac and diclofenac are most linked to hepatotoxicity. Aspirin exacerbated respiratory distress (AERD) is a respiratory complication associated with aspirin and COX-1 inhibiting NSAIDs which causes bronchospasms and precipitate asthma attacks in patients with respiratory diseases. Delay in wound healing is also reported with the consistent use of NSAIDs as they have antiproliferative effect on blood vessels and tissues. Ketorolac, the very common NSAID that used for toothache is absolutely contraindicated in renal failure, hepatic failure and severe heart failure and chronic peptic ulcer disease. FDA issued ketorolac black box warning breastfeeding as studies in women breastfeeding have demonstrated harmful infant effects. So, the patient should stop breastfeeding while using this medication. Diclofenac, another popular medication in dentistry is now contraindicated in ischemic heart disease (IHD), peripheral vascular disease and cerebrovascular disease as it may have a higher risk of heart CV thrombotic events including stroke, myocardial infarction. According to FDA boxed warning diclofenac and aceclofenac are strictly contraindicated in the setting of coronary artery bypass graft (CABG) surgery, GI bleeding and perforation. Nimesulide is one the most notorious NSAID for its hepatotoxicity which can lead to occurrence of Nimesulide induced acute hepatitis. FDA blacklisted the drug and it was banned also in 2000 in various countries like Spain, Switzerland and US etc., whereas in India it was banned in 2011 which was too late to be banned and still available in India for adult use for pain episodes like toothache despite of its hepatotoxicity and possible drug interactions. In the coming years, FDA will request that manufacturers update the existing cardiovascular risk information in Drug Facts labels for OTC non-aspirin NSAIDs. According to FDA, consumers and health care professionals should remain alert for the development of heart and stroke related symptoms throughout the time a consumer takes NSAIDs. The golden sentence advocated by FDA's Dr Karen Mahoney regarding NSAIDs is "Take the lowest effective dose for the shortest amount of time possible". So, keeping in mind of the fatal consequences patient education and pharmacist's thorough evaluation of patients (both prescription and OTC) medical history, drug history are necessary to avoid potential risk of interactions and organ damage and the patients should be encouraged to take NSAIDs at the lowest possible doses for the shortest duration to avoid health hazards.

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