Gastric acid suppressing drugs and NSAIDs

NEWS

- General practitioners advised to avoid diclofenac to reduce *Clostridium difficile* disease
- Food and Drug Administration, USA & proton pump inhibitor (PPI) seek 'immediate care' if they develop diarrhea
- Combining PPI and aspirin increases cardiovascular death (CVD) event risk
- NSAIDs 'associated with increased CVD risk'
- Chronic NSAID use doubles cardiovascular deaths in the elderly
- Use of NSAIDs increase atrial fibrillation risk
- NSAIDs in early pregnancy double the risk of miscarriage[1]

(RE)VIEWS

PPI, NSAID and C. *difficile* disease

Based on several case reports implicating diclofenac, a population-based case-control study undertaken in UK, found that among all the NSAIDs, diclofenac usage has been associated with a modest increase in the risk of *C. difficile* associated disease (CDAD). It has been suggested that NSAIDs other than diclofenac may be preferred in patients at risk,[2] which includes acid peptic disorders, GI surgery, diabetes mellitus, hepato renal failure, etc . Whether diclofenac is more effective than other NSAIDs in breaching the GI protective barrier or is a more effective inhibitor of neutrophilic activation or hitherto unknown mechanism is involved in the said association is yet to be established.

In 23 out of 28 observational studies, it has been shown that there is a higher risk of CDAD, associated with PPI exposure.In a recent FDA warning – 'A diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve, which may be a sign of CDAD calling for prompt medical attention'. It has also advised usage of lowest dose and shortest duration of PPI therapy appropriate to the condition. FDA is also reviewing the risk of CDAD to H_2-receptor blockers.[3] It has been suggested that PPIs (and possibly H_2-receptor blockers), could allow the overgrowth of *C. difficile* by altering the gastric pH.

In a retrospective case-control study, it was found that PPI use was associated with recurrent CDAD, though it has called for prospective studies to clarify whether avoidance of PPIs will reduce the incidence of such diarrhea.[4] An earlier study showed elevated risk of developing CDAD in hospitalized patients with acid-suppressive therapy, especially when PPIs were used.[5] Individually, long-term use of PPI or NSAID have been shown to be associated with increased risk of CDAD.[6]

However, there seem to be paucity of data with regard to concurrent usage of PPI and NSAID and the incidence of CDAD. This will be of extreme practical importance, since these two classes of drugs are often co-prescribed for most of the inflammatory pain disorders in day to day practice.

PPI-NSAID combination seems not to stop with association of *C. difficile* (read further for more)…

PPI, NSAID and CVD

In a recent study, the risk of the combined end point of cardiovascular death, myocardial infarction (MI), or stroke associated with the use of PPIs was analyzed. In aspirin treated patients with first time MI, PPI usage was associated with an increased risk of adverse cardiovascular events.[7]

In a systematic review of community-based, controlled observational studies, it has been concluded that naproxen and low-dose ibuprofen are least likely to increase cardiovascular risk, while diclofenac as well as the COX-2 selective inhibitor etoricoxib elevate the risk. The authors have a negative view on the continued clinical use of indomethacin, stating it as a rather toxic drug.[8] Chronic self-reported use of NSAIDs was associated with an increased risk of adverse events (all-cause death, nonfatal MI, or nonfatal stroke) during long-term follow-up.[9]

It will be interesting to note whether naproxen will be the first line drug for inflammatory pain disorders in the light of the above fears.

Atrial flutter/fibrillation – as an additional cardiovascular risk with NSAIDs

Use of non-aspirin NSAIDs (nonselective as well as COX2 selective agents) was associated with an increased risk of atrial fibrillation or flutter. The risk seems to be high for new users, elderly, chronic kidney disease and rheumatoid arthritis patients (lowest for non-selective NSAIDs and highest for COX2 inhibitors). The authors have suggested adding atrial fibrillation or flutter to the list of cardiovascular risks when prescribing NSAIDs.[10]

NSAIDs and abortion

In a study to quantify the association between spontaneous abortion and usage of NSAIDs, it was found that irrespective of the type or dosage, non-aspirin NSAIDs increased the risk of spontaneous abortion. The risk was high for diclofenac > naproxen > celecoxib > ibuprofen and low for rofecoxib. It is difficult to explain the interplay of NSAID-induced loss of pregnancy in terms of prostaglandin suppression.[11]

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