Non-Steroidal Anti-Inflammatory Drug (NSAID) Therapy in Patients with Hypertension, Cardiovascular, Renal, or Gastrointestinal Comorbidities: Joint APAGE / APLAR / APSDE / APSH / APSN / PoA Recommendations

Supplementary Text 1

(A) Methods

The Steering Committee Meeting

The steering committee meeting was organized in Osaka, Japan between April 7th and 8th, 2018. The principal investigator (FKL Chan) called a meeting with an interdisciplinary team from gastroenterology (K Fujimoto, and K Sugano), nephrology (CC Szeto), cardiology (JG Wang), and epidemiology (K Tsoi) to discuss the safety use of NSAID. The clinicians were from the Asia-Pacific Society for Digestive Endoscopy (A-PSDE), the Asia-Pacific Association of Gastroenterology (APAGE), the Asia-Pacific Society for Nephrology (APSN), and the Asia-Pacific Society of Hypertension (APSH). This meeting discussed the structure of the expert panel, focus of the adverse events, presentation format of the positional statements, and plan for academic publication. The steering committee members explored other associations in the Asia-pacific regions and agreed to invite experts in the field of rheumatology. The definitions of adverse events were agreed to focus on the life-threatening events, including the cardiovascular diseases, GI bleeding and renal failure. CC Szeto drafted the proposed position statements based on the evidence from the literature review. Each panel member independently reviewed the draft of statements and proposed modifications in advance of the expert panel meeting.

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The Expert Panel Meeting

The expert panel meeting was organized in Shatin, Hong Kong on Nov 23th, 2018. The expert panel comprised of three cardiologists, three gastroenterologists, three nephrologists, two rheumatologists and an epidemiologist. The clinicians represented six societies or associations in the Asia-pacific regions (Appendix 1). The meeting was chaired by the principal investigator from gastroenterology (F Chan). Panel members received the first draft of positional statements, a summary of the literature reviews, and the full lists of original papers before the meeting. All comments or concerns for the statements were marked on the draft. In the meeting, panel members reviewed the draft of the statements and in individual sections on hypertension, cardiovascular, renal and GI adverse effects. Each statement was discussed for the level of evidence available and the strength of the recommendation by using the classification system of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) (Supplementary Table 1) [1]. The full list of positional statements was endorsed at the end of meeting.

(B) Other cardiovascular effects of NSAID

In addition to congestive heart failure and atherosclerotic events, there is also evidence on the association between NSAID and other cardiovascular problems. For example, a meta-analysis found that COX-2 inhibitors are associated with increased risk of cardiac arrhythmia (relative risk 2.90) [2]. Liu et al [3] found that recent prescription of NSAID was associated with new onset atrial fibrillation (relative risk 1.53). Ungprasert et al [4] reported that NSAID is associated with venous thromboembolism (relative risk 1.80). Another systematic review by the same group found that the risk of hemorrhagic stroke is significantly increased for patients treated with diclofenac and meloxicam (relative risk 1.27 for both agents), but not other NSAIDs [5].

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(C) Other renal effects of NSAID

In addition to AKI, some observational studies suggest that NSAID is associated with a higher risk or more rapid renal function loss in CKD [6-8], although other studies revealed negative results [9-11]. It should be noted that chronic use of paracetamol has also been reported to be associated with CKD progression [12,13]. More recently, a meta-analysis of 3 cohort studies, with over 44000 patients, showed that NSAID at high dose, but not regular dose, is associated with more rapid CKD progression [14]. Taken together, it seems logical to avoid chronic use of high dose NSAID in patients with pre-existing CKD, even when there is no acute rise in serum creatinine immediately after the initiation of treatment.

NSAID may also increase the rate of renal function decline without causing AKI in patients with pre-existing CKD. However, 6 observational studies in this area report conflicting result regarding the risk of NSAID on the rate of renal function decline [7-9] and progression to dialysis-dependent ESRD [6-11]. In a case-control study, Kaewput et al [8] found that the rates of eGFR decline were -6.84 and -1.61 ml/min/1.73m2 in 1 year, respectively, amongst patients with and without COX-2 inhibitor therapy. In contrast, Möller et al [10] reported that the rate of eGFR decline were -0.87 and -0.67 ml/min per year, respectively, amongst patients with and without receiving NSAID. In a meta-analysis of 3 cohort studies with 44,479 patients, high dose NSAID was associated with 26% excess in risk of CKD progression [14].

In addition to the effect on kidney function per se, it is long believed that NSAID may be associated with the development of hyperkalemia. However, a large case-control study of 18326 cases and 355106 controls showed that NSAID may not by themselves carry a higher risk of moderate to severe hyperkalemia [15], and the development of hyperkalemia probably depends on the concurrent exposure to other agents.

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(D) Other gastrointestinal effects of NSAID

NSAID is also associated with increased risk of various abdominal symptoms [16-19] and lower GI events, which include diverticulosis and its complications (hemorrhage or perforation), and other causes of lower GI bleeding [18-26]. In addition, NSAID usage has been associated with the development of microscopic colitis, a chronic bowel disorder characterized by watery diarrhea. Contrary to its efficacy in peptic ulcer prophylaxis, concomitant use of PPI further increases the risk of microscopic colitis [27]. Acid suppression related gut dysbiosis may contribute to the detrimental effect of PPI [27].

The risk of small intestinal mucosal damage and bleeding is also increased following NSAID [28-30]. NSAID can induce injuries in the small bowel even in patients without any lesions in both the stomach and colon. In a retrospective study of 61 patients who received NSAID therapy and had undergone double-balloon endoscopy because of GI bleeding or anemia, multiple ulcers or erosions were observed in the ileum in 6 patients and in the jejunum in another one [31]. A subsequent study by the Japanese Study Group for Double-Balloon Endoscopy showed that non-specific mucosal breaks were detected in 51% patients who received NSAID treatment, but only 5% in the control group [32]. Symptomatic NSAID-induced small-bowel injuries exhibit a variety of patterns of ulcerative lesions, usually in the ileum but could also be present in the duodenum or jejunum [33]. The pathogenesis of NSAID-induced small bowel injury is not entirely clear. Nonetheless, microbiota probably plays a key role [7,34]. Indole, a gut microbiota-derived metabolite, decreases mucosal inflammation and injury in a murine model of NSAID enteropathy [35]. NSAID results in a drastic alteration in the gut microbiome, which is probably directly responsible for the pathogenesis of small bowel mucosal injury [36]. PPIs *per se* profoundly influence gut microbiota [37] and may further exacerbate NSAID-induced small intestinal injury by inducing dysbiosis [38-40].

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In addition to GI complications, NSAID can cause acute liver injury with variable severities [41,42]. The most common pattern of injury was hepatocellular, and auto-antibodies were detected in one-third of the cases [43]. Diclofenac is the most frequently implicated NSAID [44]. A number of genetic factors, including the polymorphism of cytochrome P450 (CYP) enzymes, uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7), glutathione S-transferases (GST) genes, as well as human leukocyte antigen (HLA) alleles, are specifically associated with NSAID-induced liver injury [42]. Although the hepatic safety profile of selective COX-2 inhibitors may be more favorable than traditional NSAIDs, direct head-to-head comparison study is not available [44].

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