HHS Public Access

Author manuscript

J Clin Pharm Ther. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

J Clin Pharm Ther. 2017 October ; 42(5): 656–660. doi:10.1111/jcpt.12592.

Use of Anti-inflammatory Analgesics in Sickle Cell Disease

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Summary

What is known and objective—Nonsteroidal anti-inflammatory drugs (NSAIDs) have been commonly used to treat pain in sickle cell disease (SCD), but NSAID use is associated with renal, gastrointestinal, and cardiovascular toxicities. Our objective was to evaluate the use of aspirin and non-aspirin NSAIDs in SCD.

Comment—Despite analgesic and anti-inflammatory benefits in SCD, non-aspirin NSAIDs are associated with renal, cardiovascular and gastrointestinal toxicities in this patient population. Aspirin may have less renal and cardiovascular toxicities. The different side effect profile of NSAIDs is related to the COX-1/COX-2 selectivity at their therapeutic doses. Individual risk factors and genetic biomarkers should be considered when selecting appropriate NSAIDs and their dose.

What is new and conclusion—NSAIDs have the potential to be an important component of pain regimens in SCD, but the use of NSAIDs should be individualized based on potential side effects and patient risk factors and the lowest effective dose should be prescribed with proper monitoring in patients with SCD.

What is known and objective

Sickle cell disease (SCD) is a hemoglobin disorder characterized by mutations in the beta hemoglobin genes that affect 25 million people worldwide.[1, 2] A combination of chronic, acute and neuropathic pain impairs the quality of life of SCD patients.[3] Potential treatment options include opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. Since the discovery of aspirin at the end of 19th century and development of indomethacin and ibuprofen in the 1960s,[4] NSAIDs have been used in many conditions for their anti-inflammatory and analgesic properties by inhibiting cyclooxygenase (COX) enzymes and suppressing the production of prostaglandins.[5] Inflammation is a key component in the pathophysiology of SCD, and NSAIDs have been used to treat both vaso-

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occlusive (VOC) pain episodes and chronic pain,[6] but NSAID use is associated with renal, cardiovascular, and gastrointestinal (GI) toxicities.[7] The focus of this commentary is to evaluate the use of aspirin and non-aspirin NSAIDs as potential anti-inflammatory analgesic options in SCD.

Comment

Clinical Efficacy

The evidence for using aspirin to treat VOC pain crisis is rather limited, although aspirin has been the mainstay of analgesics in SCD patients in parts of Africa and the Middle East.[8–10] One small trial showed that parenteral aspirin could be a safe and effective approach in treating VOC in the pediatric SCD patients.[10] Some studies reported that non-aspirin NSAIDs in combination with opioids in SCD patients reduce pain, shorten the length of VOC episodes, and decrease consumption of opioids,[11, 12] whereas other studies failed to show significant benefits.[13, 14] NSAIDs as a monotherapy were not effective as NSAIDs plus opioids in preventing 30-day emergency department (ED) revisits after treat-and-release ED visits for VOC.[15] According to the recommendations from National Heart, Lung, and Blood Institute (NHLBI), NSAIDs can be used as an adjuvant analgesic to treat mild to moderate pain during VOC, but the strength of the recommendation is moderate and the quality of evidence is low, and no references were provided to support the recommendations.[16]

Potential Toxicities

Despite the anti-inflammatory and analgesic benefits, the use of non-aspirin NSAIDs is associated with potential side effects when used in a variety of conditions other than SCD. Non-aspirin NSAIDs decrease renal blood flow, which can cause acute kidney injury (AKI).[17] Repeated AKI episodes are associated with increased risk of developing advanced chronic kidney disease (CKD).[18] Large epidemiological studies of healthy individuals have not consistently demonstrated an association between chronic non-aspirin NSAID use and CKD.[19–22] In contrast, high-risk individuals, such as the elderly, have a more rapid decline in estimated glomerular filtration rate (eGFR) after exposure to high doses of non-aspirin NSAIDs,[23] which was supported by other small cohort and case-control studies.[24] Non-aspirin NSAIDs can also reduce sodium excretion, increase intravascular volume, and increase systolic blood pressure by approximately 5 mmHg on average in a meta-analysis.[25] Due to medullary hypoperfusion, cortical hyperperfusion, and aberrant renal vascular responses to stress, patients with SCD are at increased risk of CKD.[26] Renal complications shorten the SCD patient's lifespan and account for 16–18% of overall mortality.[27] Therefore, non-aspirin NSAID use in SCD is of concern because of the potential to cause or exacerbate kidney disease in this high-risk patient population. Consistent with these concerns, non-aspirin NSAIDs were associated with a small but significant fall in eGFR and rise in urinary osmolality in SCD patients compared to healthy controls[28–30] and the use of non-aspirin NSAIDs has also been associated with albuminuria and acute kidney injury in SCD cohorts.[31–33] The use of hydroxyurea has been shown to reduce albuminuria in patients with SCD,[34, 35] but there is no current evidence showing that the renal toxicities associated with non-aspirin NSAID use may be attenuated by hydroxyurea.

In addition to the renal toxicity, non-aspirin NSAIDs, especially COX-2 selective inhibitors, are known to cause cardiovascular toxicity.[36, 37] Ibuprofen, a commonly used over-the-counter NSAID, increased the risk of developing major coronary events 2.2-fold and NSAIDs in general doubled the risk of hospitalization due to heart failure.[37] The most recent Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial showed that even the non-selective NSAIDs may not pose a lower cardiovascular risk compared to COX-2 selective NSAID.[38] It is recommended that non-aspirin NSAIDs should be avoided in patients at high risk of cardiovascular disease (CVD),[39] and may be only used for musculoskeletal pain as the last-line agents in patients with known CVD.[40] SCD is a hypercoagulable disease, and patients with SCD are at higher risk of developing ischemic stroke, pulmonary hypertension, and diastolic dysfunction.[41] Although there is no evidence showing that use of non-aspirin NSAIDs increases the CVD risk in the SCD patients, in theory it poses additional risks in this patient population. Additionally, the GI toxicity associated with non-aspirin NSAID use, including dyspepsia, peptic ulcer disease, and bleeding, is well documented in the general population,[42] as well as in SCD cohorts.[9, 12]

Compared to non-aspirin NSAIDs, aspirin has a lower risk of decreasing renal blood flow and GFR and does not increase the blood pressure significantly.[25, 43, 44] Most of the literature indicates that aspirin alone is not associated with increased risk of kidney injury, [19, 20, 45–47] even among heavy users to treat rheumatoid conditions,[48–51] but a few other studies have shown conflicting results.[52, 53] Furthermore, high intake of non-aspirin NSAIDs was associated with a nine-fold increased risk of developing end-stage renal disease (ESRD), whereas no increased risk was observed in the frequent aspirin users.[46] Aspirin also has cardioprotective effects due to its antiplatelet function and it is widely used for secondary prevention of CVD,[54] although its utility in primary prevention of CVD, especially stroke, is still controversial due to the increased bleeding risk.[55] Stroke is one of the major complications in SCD patients,[56] and the role of aspirin use in the treatment or prevention of stroke in SCD has not been established despite some efforts.[57] Additionally, decreased platelet aggregation induced by aspirin may ameliorate the frequency and severity of VOCs. There are small trials studying aspirin use for VOC or stroke prevention in SCD patients with mixed results on these outcomes but importantly no major side effects were reported.[57, 58] Similar to non-aspirin NSAIDs, use of aspirin may also cause upper and lower GI tract injuries, especially in patients with risk factors including a history of peptic ulcer or age >70 years.[59]

Despite its benefits in for preventing cardiovascular complications in conditions other than SCD, aspirin has several potential disadvantages compared to non-aspirin NSAIDs. First, the analgesic effect of aspirin appears to be weaker than non-aspirin NSAIDs.[60] The aspirin dose used for its cardioprotective effects is usually lower than the dose used for analgesic purposes although it is generally safe even among heavy users.[48–51] Secondly, due to the association between aspirin and Reye's syndrome, it is recommended that aspirin not be used in children and adolescents with varicella or influenza-like symptoms.[61] The incidence of Reye's syndrome is low and withholding aspirin from children with viral illness symptoms should minimize the risk.[61] Thirdly, approximately one-third of strokes associated with SCD are hemorrhagic in nature,[56] and aspirin use may increase the risk of

bleeding. Therefore, the use of aspirin in SCD patients with pre-existing arteriovenous malformations such as moya-moya syndrome and intracranial aneurysm should be avoided.

The different side effect profile of non-aspirin NSAIDs and aspirin is related to the COX-1/COX-2 selectivity at their therapeutic doses.[7] COX-1 is constitutively expressed in various tissues, and is the rate-limiting enzyme for the production of prostaglandins protecting gastric and duodenal mucosa;[62] therefore, inhibition of COX-1 is responsible for the GI toxicities associated with non-selective NSAIDs and aspirin use.[7] COX-1also mediates the production of thromboxane A2 (TxA2), a platelet activator, and the anti-platelet effect of aspirin results from the irreversible inhibition of COX-1 and TxA2 production.[63] COX-2 is an inducible enzyme, and the analgesic and anti-inflammatory effects of NSAIDs largely results from inhibition of the COX-2. In the vascular endothelium, COX-2 mediates the production of prostaglandin I2 (PGI2), which is a vasodilator and inhibitor of platelet aggregation.[63] The cardiovascular risk associated with non-aspirin NSAIDs is believed to result from COX-2-PGI2 inhibition.[64] The COX-2 selective NSAIDs shift the balance of PGI2 and TxA2 in favor of TxA2-induced platelet activation and arterial vasoconstriction, posing a greater cardiovascular risk. The vasoconstriction caused by inhibition of COX-2 and subsequent prostaglandins is also responsible for renal toxicity.[7] Understanding the selectivity of the COX-1/COX-2 at the therapeutic doses and their pharmacokinetic/pharmacodynamic properties can guide the selection of appropriate NSAIDs.

Genetic variations, especially in cytochrome P450 (CYP) enzymes may lead to the interindividual difference in response to non-aspirin NSAIDs. CYP2C9, a highly polymorphic enzyme, metabolizes several NSAIDs, and has been implicated in intersubject variability in NSAID metabolic clearance.[65] The CYP2C9 polymorphism is common in patients with SCD, and has been associated with different analgesic response to non-aspirin NSAIDs.[66, 67] In addition to genetic variation, the individual's clinical profile, particularly GI, renal, and cardiovascular risk factors, should be considered when selecting a NSAID and its appropriate dose. Certain preventive approaches, such as co-administering proton pump inhibitors with either non-aspirin NSAIDs or aspirin, have been used to avoid GI side effects.[68, 69] In addition, researchers have been trying to develop novel agents which associate non-aspirin NSAIDs/aspirin with protective mediators to counteract the toxicities. Phosphatidylcholine was conjugated with NSAIDs to improve the GI safety, and chemical moieties that release protective mediators such as nitric oxide was structurally linked to NSAIDs to attenuate GI and cardiovascular toxicities, and this area of research has shown some promise.[70]

What is new and conclusion

Anti-inflammatory analgesics have the potential to be an important component of the pain regimens for SCD. Due to various side effects associated with non-aspirin NSAIDs and aspirin, there are no risk-free anti-inflammatory drugs. Both non-aspirin NSAIDs and aspirin should be used cautiously in sickle cell patients, especially those with renal, GI, and cardiovascular risk factors. Aspirin may have a better cardiovascular and renal toxicity profile. Genetic biomarkers predisposing patients at higher risk to develop adverse events may also be considered when using non-aspirin NSAIDs. Anti-inflammatory analgesics

should be only used at the lowest effective dose for the shortest duration in this patient population, and regular monitoring of potential side effects is required for all patients receiving long-term treatment. A prospective study evaluating the efficacy and safety of aspirin and non-aspirin NSAIDs in pain management and stroke prevention in SCD is needed.

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