Evaluating the Safety of Non-Steroidal Anti-inflammatory Drugs use in Asthmatic Patients: A Systematic, Critical Review of Literature

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Abstract

Background: Evidence suggest avoidance of Non-steroidal anti-inflammatory drugs (NSAID) in aspirin-intolerant asthmatics due to the risk of triggering exacerbation attack; however, evidence around avoiding NSAIDs in all other asthmatic patients are unclear. This study aimed to evaluate the evidence surrounding the safety of using NSAIDs, including selective COX-2 inhibitors, among asthmatic patients.

Methods: A systematic review used Medline (OVID), Scopus and Embasefrom January-2008 to January-2019. Inclusion criteria includedEnglish, and human studies that evaluated the use of NSAID in asthmatics. Data was screened/extracted using a pre-designed data extraction form using Covidence®, thenwere critically appraised.

Conclusion: Of the 49 identified studies,eight were eligible. Prevalence of NSAID-induced asthma exacerbation was 9%(95%CI:6.0–12.0%)-9.9% (95%CI:9.4-10.5%). Asthmatics who were aspirin/NSAID intolerant had 37% higher risk of hospitalisation compared to tolerant patients (RR:1.37; 95%CI:1.12–1.67).Use of COX-2 inhibitors showed non-significant associations with worsening respiratory symptoms/exacerbation. Only low-quality evidence was found for the safety of topical NSAID. NSAIDs-induced respiratory reactions/symptoms is relatively uncommon with the majority of asthmatic patients could tolerate NSAIDs therapy. Asthmatic patients who suffer from aspirin-induced asthma or NSAIDs-exacerbated respiratory disease (NSAIDs intolerant) should be avoided NSAIDs prescribing but could be safely prescribed selective COX-2 inhibitors as an alternative.

Key words: *Asthma; Non-steroidal anti-inflammatory drugs; safety; analgesics; exacerbation*

Introduction

Asthma is a complex, heterogeneous airway disorder responsible for a variety of recurring symptoms, such as tightness of the chest,difficulty in breathing and wheezing, caused by bronchoconstriction, airway oedema, hyper-responsiveness and remodelling[1].Asthma is a prevalent chronic condition affecting over 300 million people, with its prevalence continues to increase with expectation that another 100 million people would be affected by 2025[2].In the UK, 5.4 million people currently suffer from asthma with one potentially life-threatening asthma attack every 10 seconds resulting In three asthma attack related deaths, on average, every day, giving the UK some of the highest asthmatic rates in Europe[3].

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Multiple factors have been identified as potential risk factors for triggering acute attack of asthmatic exacerbationsymptoms and these include poor medication compliance, allergies and exposure to some pharmacological agents such as non-steroidal anti-inflammatory drugs (NSAIDs)[4].Non-steroidal anti-inflammatory drugs are one of the most commonly prescribed analgesics, accounting for approximately 5-10% of all annual prescribed medications[5]. NSAIDs' pharmacological effectsare mediated via inhibition of prostaglandins via reversible inhibition of cyclooxygenase(COX) enzymes (both COX-1-responsible for the production of prostaglandins which maintain normal physiological functions and COX-2- involved only in production of pro-inflammatory prostaglandins)[6].Based on their selectively toward COX enzyme, NSAIDs can be classified into standard NSAIDs (these are non-selective inhibiting both COX-1 and COX-2) such as ibuprofen, and indomethacin and Coxibs (these are selective COX-2 inhibitor) such as celecoxib and etoricoxib[7].

Use of NSAIDs in asthmatics might trigger an acute asthma exacerbation attack which is known as aspirin-induced asthma (AIA) or Non-steroidal anti-inflammatory exacerbated respiratory disease (NERD)[5], which has an average prevalence of about 21% in adult asthmatics, even though it could vary between 4%-44%[8]. AIA/NERD is a common cause of life-threatening asthmatic exacerbations[9], and although its exact pathophysiology has not yet been fully understood, current evidence suggest the involvement of leukotrienes[10].Although it has been suggested that the majority of asthmatics can tolerate NSAIDs[8],the current international guidelines, including the UK National Institute for Health Care and Excellence (NICE)[11] recommend all asthmatics should be offered a NSAIDs provocation test before prescribing NSAIDs to assess patients' tolerability to NSAIDs; and subsequently avoid NSAIDs in asthmatics who are intolerant to NSAIDs (i.e. AIA/NERD sufferers). However, due to issues with the availability and feasibility/practicality of undertaking provocation test for all asthmatics, these recommendations mean that NSAIDs should also be avoided in all asthmatics with unknown sensitivity status which constitutes the majority of asthmatic patients. Accordingly, avoiding NSAIDs in this large population of untested asthmatics for NSAIDs sensitivity leads to many untested asthmatics being unnecessarily denied the multiple advantages of NSAIDs and being prescribed alternative analgesics such as paracetamol, and opioids/ opioid derivatives[12];this might be of particulate concern since the latter could be associated with potentially problematic long-term adverse effects and harms such as dependence, risk of abuse and reduced quality of life[13].

Similarly, although evidence suggest the safety and efficacy of selective COX-2 inhibitors in many sufferers of AIA/NERD, due to their selective inhibition of COX-2[14], NICEcontinues to recommend their avoidance due to non-lethal intolerance in a small number of AIA/NERD patients[11]. In order to avoid the unnecessary use of potentially harmful analgesics in asthmatic patients such as opioids, who could otherwise be prescribed NSAIDs, it is important to understand the current evidence around the safety of NSAIDs among asthmatic. Therefore, this study aimed to critically review and analyse the current scientific literature for the safety of NSAIDs in asthmatic patients including the safety and tolerability of selective COX-2.

Method

Data Source and Searches

This was a systematic review of the literature conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist[15]. The literature search was carried out inMedline (OVID), Scopus, and Embasefrom January 2008 to January 2019, using key terms related to asthma, NSAIDs, COX-2 inhibitors and aspirin induced asthma or NSAID exacerbated respiratory diseasebased on previously conducted systematic review in this area including the use of certain exclusion terms to limit the volume of irrelevant results. A population, intervention, comparison and outcome (PICO)[16] approach was adopted to assist with the search and selection of the relevant articles (Table 1). Reference lists ofthe eligible articles were also manually searched to identify any further relevant articles.

Table 1. Population, Intervention, Comparison and Outcome definition used in the study

Population	Intervention	Comparison	Outcome
All asthmatics of every age group including those asthmatics who suffer from AIA/NERD and those tolerant to NSAIDs	Use of NSAIDs and selective COX-2 inhibitors	As an alternative to NSAID avoidance or use of COX-2 inhibitors as an alternative to NSAIDs	Safety of NSAIDs and selective COX-2 inhibitors in terms of inducing exacerbation of asthma
(Note): COX-2: Cyclooxygenase enzyme 2; NSAIDs: Non-steroidal anti-inflammatory drugs			

Study Selection

Studies were considered eligible if they were conducted in human, published in English, without restrictions to study designs and studies that matched our PICO criteria (Table 1). All the identified records from the search strategy were exported from the databases and imported into Covidence®[17]whereby duplicate records were removed. The author (AK) independently undertook titles and abstract screening for relevance, followed by selecting records for full-text screening and data extraction; each of the above stages were validated by an independent reviewer (MM). Any discrepancy was resolved through discussion until consensus was achieved.

Data Extraction, quality Assessment, synthesis and analysis

After identification of the eligible studies, data from these studies were subsequently extractedinto a spreadsheet including information on the study characterises (study design, setting, sample size, population) and outcome measures including prevalence of NERD/AIA, differences in the risk of asthmatic morbidity in relation to NSAIDs and COX-2 inhibitors, differences in FEV1 after exposure to NSAIDs and COX-2 inhibitors, average doses provoking asthmatic response in NSAIDs and COX-2 inhibitors and the presence of symptoms induced by NSAID and COX-2 inhibitor exposure. Studies' quality and risk of bias was assessed using the National Heart, Lung and Blood Institute's quality assessment tool[18] for the various types of study design including observational studies, systematic reviews, meta-analyses and before-after studies except from case reports; whereby studies' were classified based on their quality into good, fair or poordependingon the total scores from each tool. The evidence from all the eligible studies were then critically reviewed and appraised using the Critical Appraisals Skills Programme (CASP)[19] checklists for the appropriate study design/type.

Literature Review Results

Overall, 316 articles were identified from the initial literature search, of which only eight studies were eligible for inclusion. A total of 50,086 patients were included in these eight records.

Study characteristics

The eligible eight studies comprised of two meta-analysis[20, 21], one retrospective cohort study[22], one before and after study[23], one expert opinion[24], and

three case reports[25-27]covering both adult and paediatric population, and short/acute and long-term complications.

In terms of outcomes, the eight included studies provided a wide range of information concerning the safety and use of NSAIDs in the general asthmatic population and those who suffer from AIA/NERD. Overall, the evidence indicated that the use of NSAIDs is associated with higher risk of asthmatic complications/ exacerbations in those who suffer from AIA/NERD (intolerant patients) compared to those are tolerant to NSAIDs (Table 3). Furthermore,asthmatics who are suffering from NERD showed poorer asthma control when taking NSAIDs and the average NSAIDs dose that found to provoke asthmatic reaction is even below the therapeuticNSAIDs dose. Moreover, asthmatic children, compared to adults, using NSAIDs were at higher risk of asthma associated morbidity and mortality. In terms of the safety of COX-2 inhibitors, the evidence from the meta-analysis[21] showed no harms or safety issues with the use of COX-2 inhibitors among asthmatic including those who suffer from AIA or NERD; this is despite some case report studies showed contradicted evidence as they reported an increase in the onset of asthmatic symptoms and a reduced FEV1upon exposure to COX-2 inhibitors but only among AIA or NERD asthmatics. In terms of the quality and risk of bias, two studies[20, 21] were classified as good quality, one study[22] as fair quality, and one[23] as poor quality.

Critical appraisal and analysis

Use of NSAIDs

The highest quality evidence about the safety use of NSAIDs in asthmatics came from a meta-analysis of 46 clinical trials and observational/population-based studies conducted by Morales *et al*[20]which included data from 20,162 patients with NERD and NSAIDs-tolerantasthma (NTA). This study determined the prevalence of NSAIDshypersensitivity (intolerance) measured either by oral provocation challenge tests (OPCTs)(9%) or a self-reported questionnaire (9.9%); the observed difference between NSAIDshypersensitivity (intolerance) prevalence was attributed to the vague respiratory reaction definitions used within the questionnaires which likely resulted in overestimation of NSAIDshypersensitivity (intolerance) prevalence. These estimates were significantly lower than what initially estimated in a previous systematic review since this study, unlike the previous stud[8] minimised bias by including only studies that used blinded and controlled OPCTs. Data on aspirin dose that provoked asthma symptoms in both adults and children was also assessed; then observational studies reporting asthma morbidity in those with NERD and NTA were compared.In regard to the former, the mean aspirin dose that provoked respiratory reactions in NERD patients was 85.8 mg (95%CI:73.9-97.6) which is a clinically relevant doses of oral aspiringiventhe 75-100 mg aspirin dose recommended by the US guidelines for the CVD prevention[28];although the potential risk reduction of using 75mg vs 100 mg aspirin was not possible to quantify due to lack of data, sub-group analysis results suggest a dose-response relationship between aspirin dose and the extent of fall in FEV1. Having said this, it should be noted that there were considerable variations in individual patients susceptibility to the low aspirin dose suggested other factors might play a role as well; accordingly, it could be concluded that using low-dose aspirin would not trigger clinically significant adverse respiratory symptoms in all asthmatics with NERDeven though the risk would be higher when higher loading aspirin dose (≥300 mg) is used; however, these risks should be weighed against the net clinical benefits of using aspirin in the management and prevention of CVD. In terms of asthma morbidity in those with NERD and NTA, compared to NTA, use of NSAIDs was associated with higher risk of all asthmatic morbidity including 50% higher risk of severe asthma and double the risk of uncontrolled asthma as well as 80%, and 40% higher risk of emergency visits and asthma hospitalisation, respectively, emphasising the importance of considering NERD diagnosis to direct the safe use of NSAIDs and aspirin among asthmatic patients. Although this meta-analysis provided valuable findings about the safety of NSAIDs use among asthmatic and it was of a good quality, it has certain limitations including investigating

the safety of aspirin only without considering the otherNSAIDs which do not exclude the possibility of selective hypersensitivity to aspirin and issues with generalisability to all the other NSAIDs.

The higher risk of asthmatic morbidity among NERD was further confirmed by another retrospective cohort study conducted by Lo *et al*[22]. who investigated risk of asthma exacerbation hospitalisation with the use of NSAIDs among 29,484 paediatric asthmatic patients of which 9,862 (33.4%) and 19,622 (66.6%) were NSAIDs users and non-users, respectively. After adjusting for potential confounders, use of NSAIDs was associated with 41% higher risk of hospitalisationcompared to non-user (aRR: 1.41; 95%CI:1.3-1.53) which equates to 9.2% vs. 6.3% in NSAIDs users and non-users, respectively. This study was of fair quality but still suffer from certain limitations such as failure to consider the over-the-counter use of NSAIDs as well as defining NSAIDs users as only those who were prescribed NSAIDs and anti-asthmatic therapy on the same day, both of which might have resulted in under-estimation of NSAIDs use and hence its risk. Overall, this study has clearly demonstrated the apparent safety risk of NSAIDs use among paediatric asthmatic patients.

Unlike the other identified studies, one of the studies[23] investigated the safety of topical NSAIDs among 11 NERD asthmatics; this was a "before and after" study in which asthma control was evaluated 6-months before and after starting and ceasing topical NSAIDs, respectively. The study findings indicated improvement in all the asthma control measurements after ceasing topical NSAIDs. However, this study was of poor quality with many methodological flaws, that question the validity of the findings, including a very small sample size, failure to disclose anti-asthmatic medications being taken by patients as well as considering the adherence to the topical NSAIDs. Accordingly, despite suggesting topical NSAIDs are hazardous in asthmatics with NERD, this evidence is inconclusive and as such a recommendation on the safety of topical NSAID use in NERD patients cannot bemade.

Furthermore, exacerbation of asthma symptoms upon exposure to NSAIDs was further reported by two case reports by King *et al*.[25] and Tang and Zhang[24]; however, evidence from case reports are only considered as hypothesis generating which in turn has been confirmed in subsequent studies such as those described earlier[20, 22].

Use of selective COX-2 inhibitors

The safety of using COX-2 inhibitors (e.g., celecoxib, rofecoxib) and selective NSAIDs (e.g., meloxicam) among NERD asthmatic was investigated in a meta-analysis by Morales *et al*[21]. The meta-analysis included a total of 426 NERD asthmatic patients from 14 clinical trials. Compared to placebo, the study found no significant differences in respiratory symptoms, FEV1, and nasal symptoms after exposure to COX-2 inhibitors but only a very small increase in respiratory symptoms (risk difference:0.08; 95%CI:0.02-0.14) after exposure to selective NSAIDs, suggesting the safety of using COX-2 inhibitors in asthmatic patients with NERD.

This study was of high methodological quality in which bias was minimised by including only blinded clinical trials; however, only low-moderate dose in patients with stable, mild-to-moderate persistent asthma was evaluated in this study; hence this observed safety might not be applicable to high doses of COX-2 inhibitors or those with unstable asthma or those who have experienced severe life-threatening reactions requiring intubation after aspirin or NSAIDs exposure.This is despite two case reports[26, 27] who reported respiratory reaction to COX-2 inhibitors in a uncontrolled 33-year old asthmatic with NERD and a controlled 25-year old NERD asthmatics, respectively; however, these hypothesis generating evidence were subsequently contradicted and disapproved by several clinical trials as summarised in the meta-analysis by Morales *et al.*[21].

Discussion

The current evidence from the literature indicated that the prevalence of AIA/NERD among asthmatic was relatively uncommon with a reported prevalence

of approximately of 9%, suggesting that the majority of asthmatic patients could tolerate NSAIDs; hence their safe prescribing among asthmatic with unknown history of hypersensitivity to NSAIDs.These findings might question the current guideline recommendations[1, 11] of avoiding NSAIDs in asthmatics unless they have proven to be NSAIDs tolerant through either NSAIDs provocation challenge test or self-reported questioning; however, both of the latter are problematic since, firstly, the NSAIDs provocation challenge test is not widely used in routine clinical practice due to issues with availability, practicality, feasibility[1, 11]; and secondly, due to variability of self-awareness of NSAIDs-induced symptoms in patients with asthma[29]which makes the self-reported intolerance to NSAIDs unreliable. Collectively, these guideline recommendations[1, 11] imply denying and withholding NSAIDs prescribing from the majority of asthmatics despite NSAIDs effective anti-inflammatory, analgesic, and antipyretic effects resulting in doctors prescribing alternatives analgesics to NSAIDs such as paracetamol, and opioids/opioid derivatives[12]; however, this is concerning since some of these alternatives such as opioids/opioid derivatives are associated with potentially problematic long-term adverse effects and harms such as dependence, risk of abuse and reduced quality of life[13].

Furthermore, there are high quality evidence for increasing asthma morbidity among AIA/NERD patients upon exposure to NSAIDs suggesting that NSAIDs should be avoided in these group of asthmatic patients. However, unlike NSAIDs, selective COX-2 inhibitors are shown to be safe in AIA/NERD patients and could be prescribed safely as an alternative to NSAIDs in AIA/NERD patients.Moreover, selective COX-2 inhibitors could also be a safe option for the general asthmatic patients who are unwilling to accept receiving NSAIDs due to the potential risk of their asthma exacerbation in response to NSAIDs exposure. There is lack of robust and high-quality evidence about the safety of topical NSAIDs among AIA/NERD patients leaving this an area for further research.

Strengths and limitations

To our knowledge, this is the first comprehensive systematic evaluation of the safety of using NSAIDs, including selective COX-2 inhibitors, among patients with asthma as well as asthmatics who suffer from AIA/NERD, without restrictions to study types across multiple databases over a 10-year period. Since the search was conducted up until January 2019 it is possible that we have missed potential studies that have been published after January 2019 which might have impacted our study findings.

Conclusion

In summary, it could be concluded thatNSAIDs-induced respiratory reactions/symptoms is relatively uncommon with the majority of asthmatic patients could tolerate NSAIDs therapy. Asthmatic patients who suffer from AIA/NERD should be avoided NSAIDs but could be safely prescribed selective COX-2 inhibitors as an alternative.

Acknowledgment: I would like to acknowledge Mr M. McGarry for his help with the data screening, extraction and quality assessment.

Conflicts of Interest: Nothing to declare

Funding : This study was not funded

Ethical Clearance: Ethical clearance was not required as the study was a systematic review of studies that have been already published.

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