Short-term use of nonsteroidal anti-inflammatory drugs and adverse effects

An updated systematic review

Anita Aminoshariae, DDS, MS, Dipl (American Board of Endodontics); James C. Kulild, DDS, MS, Dipl (American Board of Endodontics); Mark Donaldson, BSP, PharmD, ACPR, FACHE

In July 2015, the US Food and Drug Administration (FDA) strengthened warnings about the risk of heart attack and stroke associated with nonsteroidal anti-inflammatory drugs (NSAIDs).[1] In patients with NSAID-exacerbated respiratory disease (NERD), NSAIDs are considered the greatest infractor, with reactions typically occurring within 3 hours of ingestion.[2] Thus, the FDA lists the use of NSAIDs as a contraindication in patients suspected of having NERD.[3]

Although long-term use of NSAIDs may be associated with adverse cardiovascular (CV),[4-7] renal,[8-11] gastrointestinal (GI),[12-14] and respiratory[15] events, preoperative and postprocedural dental pain are usually short-term episodes with the dental procedure itself, or the normal healing process, being the final disease-modifying entities, and therefore requiring limited (fewer than 10 days) NSAID exposure. A systematic review of the peer-reviewed literature focusing on the evidence regarding the CV, renal, GI, and respiratory adverse effects and safety of these medications in patients taking routine NSAIDs for 10 days or fewer, which is within the usual time for dental patients exposed to an NSAID, compared with patients who were not exposed to these medications, has yet to be published.

Because the potential benefits of pain reduction always must be balanced against the potential adverse effects of medications, the goal of this investigation is to report the available scientific evidence regarding potential adverse effects of short-term use of NSAIDs and CV,

ABSTRACT

Background. In this article, the authors examine the available scientific evidence regarding adverse effects of short-term use of nonsteroidal anti-inflammatory drugs (NSAIDs). Short-term use was defined as 10 days or fewer.

Methods. The authors reviewed randomized controlled clinical trials and cohort and case-controlled clinical studies published between 2001 and June 2015 in which the investigators reported on the safety of nonselective cyclooxygenase inhibitors and of cyclooxygenase-2 selective inhibitor NSAIDs.

Results. The systematic review process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines allowed the authors to identify 40 studies that met the inclusion criteria.

Conclusions. On the basis of the available scientific evidence, NSAIDs may be considered relatively safe drugs when prescribed at the most effective dose and for the shortest duration of time, which was defined to be 10 days or fewer.

Practical Implications. Although the US Food and Drug Administration recommends the use of NSAIDs beyond 10 days to be accompanied by a consultation with a health care provider, the use of NSAIDs may be considered relatively safe when prescribed at the most effective dose and for the shortest duration of time, which was defined as 10 days or fewer. Exceptions would be for patients at risk of developing NSAID-exacerbated respiratory disease, patients with prior myocardial infarction who are receiving antithrombotic therapy, patients with asthma, and patients with a history of renal disease.

Key Words. NSAIDs; cardiovascular risk; myocardial infarction; gastrointestinal; renal; respiratory; randomized controlled clinical trials; cohort studies; case-controlled studies; vascular events.

JADA 2016:147(2):98-110

http://dx.doi.org/10.1016/j.adaj.2015.07.020

renal, GI, and respiratory complications. Short-term use is defined as 10 days or fewer.

METHODS

Formulating the review question. We developed the following problem, intervention, comparison, and outcomes (PICO) framework for this systematic review: What is the evidence regarding adverse effects and safety of NSAIDs in patients taking them routinely for 10 days or fewer compared with that in patients who are not exposed to these medications?[16] Table 1[17,18] identifies the recommended doses of NSAIDs available in the United States.[19,20]

Inclusion and exclusion criteria. Inclusion criteria were as follows:

- randomized controlled clinical trials (RCTs) and case-controlled studies of patients ingesting NSAIDs for 10 days or fewer;
- publications from 2001 to June 2015;
- human adult patients 18 years or older;
- head-to-head comparisons between different NSAIDs;
- the end point of adverse effect or safety as a primary objective;
- quantitative results reported.

We excluded published study results if they were not vetted in the peer-reviewed literature or if they did not meet any of the inclusion criteria.

Search methodology. We registered the protocol for this systematic review in the PROSPERO database (registration number CRD42015023343). We included the following databases in this review: the Cochrane Oral Health Group Trials Register to June 2015, the Cochrane Central Register of Controlled Trials to June 2015 (Cochrane Library 2015), MEDLINE via Ovid to June 2015, EMBASE via Ovid to June 2015, and the meta-Register of Controlled Trials to June 2015. We searched the bibliographies of relevant clinical trials, the gray literature, and review articles individually.[21] *Gray literature* generally is defined as material that is not published formally. We applied no language restriction to the searches of the electronic databases as long as a translation was provided in English. We used the Assessing the Methodological Quality of Systematic Reviews checklist; the Oxford Systematic Review Appraisal Sheet, Critical Appraisal Skills Programme; and the Grading of Recommendations Assessment, Development and Evaluation system for grading evidence to ensure the accuracy of this data analysis in this systematic review.[16,22-24]

Search and key words. Using the PICO-formatted question, the authors generated methodological medical subject heading terms to make the search strategy more sensitive in identifying studies. We reviewed RCTs and cohort and case-controlled clinical studies reporting the safety of nonselective cyclooxygenase (COX) inhibitors and COX-2 selective inhibitor NSAIDs. Two of the authors (A.A., J.C.K.) systematically reviewed research evidence published between 2001 and 2015 pertaining to the topic. In the case of any disagreement over inclusion or exclusion of a particular article, these authors would come together to discuss the divergence and then agree on the final outcome. There were no disagreements between the 2 authors. Key search terms included "NSAIDs," "cardiovascular risk," "myocardial infarction," "randomized controlled clinical trials," "cohort and case-controlled studies," "hypertensive effects," "cardiovascular effects," "respiratory effects," "renal effects," "GI effects," and "gastrointestinal effects."

RESULTS

On the basis of all of the different study methodologies, it was not possible to perform a meta-analysis. The figure[16] presents a flowchart of the systematic review process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We identified 11 studies that met the inclusion criteria for CV safety.[19,25-34] We identified 6 studies that met the inclusion criteria for renal safety.[33,35-39] We identified 14 studies that met the inclusion criteria for GI safety.[17,18,30,40-50] We identified 9 studies that met the inclusion criteria for respiratory safety.[51-59]

Tables 2-5[17-19,25-60] detail the risk of bias assessment as performed according to guidelines outlined by the Cochrane Collaboration for CV, GI, and renal safety, respectively.[61] We graded evidence according to the Grading of Recommendations Assessment, Development and Evaluation system.[24]

DISCUSSION

We found 40 publications published within the past decade in the peer-reviewed literature that met the PICO framework for this investigation to address the deficit of such articles and that demonstrated remarkable consonance in their conclusions (Tables 2-5).[17-19,25-60]

CV risk with the short-term use of NSAIDs. A comprehensive search of the literature failed to indicate that short-term use of NSAIDs for 10 days or fewer was associated with myocardial infarction or any other major

ABBREVIATION KEY. **ASA:** Acetylsalicylic acid (aspirin). **COI:** Conflict of interest. **COX:** Cyclooxygenase. **CV:** Cardiovascular. **DM:** Double masked. **FDA:** Food and Drug Administration. **GI:** Gastrointestinal. **LSS:** Low sample size. **MPP:** Masking of participants and personnel. **MS:** Manufacturer sponsored. **NERD:** NSAID-exacerbated respiratory disease. **NSAID:** Nonsteroidal anti-inflammatory drug. **OTC:** Over the counter. **PICO:** Problem, intervention, comparison, and outcomes. **RCT:** Randomized controlled clinical trial. **RSG:** Random sequence generation. **Rx:** Prescription required for certain strengths. **SM:** Single masked. **SR:** Selective reporting. **SS:** Sample size.