Adverse Effects of Analgesics Commonly Used by Older Adults With Osteoarthritis: Focus on Non-Opioid and Opioid Analgesics

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ABSTRACT

Background: Osteoarthritis (OA) is the most common cause of disability in older adults, and although analgesic use can be helpful, it can also result in adverse drug events.

Objective: To review the recent literature to describe potential adverse drug events associated with analgesics commonly used by older adults with OA.

Methods: To identify articles for this review, a systematic search of the English-language literature from January 2001 to June 2012 was conducted using PubMed, MEDLINE, EBSCO, and the Cochrane Database of Systematic Reviews for publications related to the medical management of OA. Search terms used were "*analgesics*," "*acetaminophen*," "*nonsteroidal anti-inflammatory drugs*" (NSAIDs), "*opioids*," "*pharmacokinetics*," "*pharmacodynamics*," and "*adverse drug events.*" The search was restricted to those articles that concerned humans aged ≥65 years. A manual search of the reference lists from identified articles and the authors' article files, book chapters, and recent reviews was conducted to identify additional articles. From these, the authors identified those studies that examined analgesic use in older adults.

Results: There are limited data to suggest that non-frail elders are more likely than their younger counterparts to develop acetaminophen-induced hepatotoxicity. However, decreased hepatic phase II metabolism in frail elders may result in increased risk of hepatotoxicity. It is now well established that older adults are at higher risk of NSAID-induced gastrointestinal toxicity and renal insufficiency. Insofar as opioids, the data that suggest an increased risk of falls, fractures, or delirium need to be tempered by the potential risk of inadequately treating severe chronic OA-related pain.

Conclusions: Acetaminophen is the mainstay frontline analgesic for treating OA-related pain in older adults. NSAIDs should be limited to short-term use only, and for moderate to severe OA-related pain, opioids may be preferable in individuals without substance abuse or dependence issues. (*Am J Geriatr Pharmacother*. 2012;10: 331–342)

Key words: adverse drug events, aged, analgesics, osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder in the United States and is the leading cause of disability in the elderly.[1] Pain caused by OA may lead to decreased health-related quality of life, reduced sleep quality, interference with social relationships, diminished cognitive function, limitations in activities of daily living, reduced productivity, and increased anxiety and depression.[2] Thus, adequate pain control is an essential component of successful management of OA in older adults. Analgesics, including non-opioids and opioids, are the most common type of pharmacotherapy used in the treatment of OA.[3] However, various adverse drug events (ADEs), that is, injuries due to medication, have been reported with these analgesic classes.[4]

Several clinical guidelines are currently available for the management of OA. Most recently, in April 2012, the

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American College of Rheumatology published expert-guided consensus guidelines as an update to the 2000 guidelines.[5] In addition, OA guidelines and recommendations have been published by several other groups including the American Geriatrics Society, the European League Against Rheumatism, the National Institute of Clinical Excellence, the American Association of Orthopedic Surgeons, and the Osteoarthritis Research Society International.[6–12] However, the focus of these guidelines is primarily on analgesic efficacy, with little attention to potential ADEs that may occur with analgesic use in older adults. Much of the pharmacoepidemiologic safety data available on analgesic use in older adults comes from the primary literature. Thus, the objective of the present study was to review the recent literature to describe the potential ADEs associated with analgesics commonly used by older adults with OA. We hoped to highlight the current gaps in the literature and suggest practical ways in which clinicians can optimize analgesic use in older adults with OA.

METHODS

A systematic search of the English-language literature from January 2001 to June 2012 was conducted using PubMed, MEDLINE, EBSCO, and the Cochrane Database of Systematic Reviews for publications relating to analgesic management of OA. The start date (2001) coincided with publication of a recent review of this topic written by one of the authors (J.T.H.).[4] Searches were performed using a combination of the terms "*analgesics*," "*acetaminophen*," "*nonsteroidal anti-inflammatory drugs*" (NSAIDs), "*opioids*," "*pharmacokinetics*," "*pharmacodynamics*," and "*adverse drug events*." A manual search of the reference lists from identified articles and the authors' article files, book chapters, and recent reviews was conducted to identify additional articles. From these, the authors identified those studies that examined analgesic use in older adults. Of note, only analgesics currently available in the United States are discussed in this review. Excluded were studies that included adults aged <65 years or that focused on analgesics other than acetaminophen, NSAIDs, or opioids or that focused only on efficacy or effectiveness.

DATA SYNTHESIS

The following sections on non-opioid (ie, acetaminophen and NSAIDs) and opioid analgesics provide an overview, information about age-related pharmacokinetic and pharmacodynamic properties, data about specific ADEs, and a section summary.

Non-Opioid Analgesics

Acetaminophen

Overview

Acetaminophen (APAP) is recommended in current guidelines as a first-line analgesic for mild to moderate pain due to OA of the knee and hip.[6–12] The analgesic activity of APAP results from the central inhibition of prostaglandin synthesis. However, the primary mechanism of prostaglandin synthesis inhibition by APAP remains unknown.[13]

Recently, there has been increasing concern about APAP hepatotoxicity. Thus, the US Food and Drug Administration commissioned a working group within the Center for Drug Evaluation and Research to recommend interventions to reduce APAP-induced liver toxicity.[14] An assembly of 3 advisory panels reviewed the report of the working group and endorsed the following recommendations: reduction of the maximum daily dose from 4 g/d to possibly 3250 mg/d; a ban on prescription narcotic-APAP combinations; and reduction of the maximum single nonprescription dose from 1 g to 650 mg, thus relegating the 500-mg dose strength prescription status.[14] Although the Food and Drug Administration has not implemented all of the suggestions of the advisory panel, they have required expanded warnings about hepatotoxicity on nonprescription products containing APAP, required companies to limit the APAP component of combination analgesic prescription products to 325 mg per dosage form, required a black box warning about liver injury, and mandated 1 concentration of APAP liquid (160 mg/5 mL). The question remains as to whether the data support a greater risk of hepatotoxicity in older adults.

Acetaminophen is a dose-dependent hepatotoxin, and excessive dosages (intentional or unintentional) may lead to irreversible acute liver failure. Glucuronidation and sulfation are the major metabolic pathways for APAP metabolism in usual dosages in healthy adults.[15] These phase II pathways become saturated after an APAP overdose, causing a shift to phase I metabolism and creation of a toxic metabolite, *N*-acetyl-p-benzoquinone imine (NAPQI), that binds to glutathione. When glutathione is depleted, NAPQI accumulates, binds to hepatic cells, and causes hepatic necrosis. Even in therapeutic dosages, APAP may cause transient elevations in liver enzyme levels and possibly hepatotoxicity, in particular in individuals who are malnourished (due to glutathione reduction) and in those using hepatic enzyme inducers (eg, regular and heavy alcohol use, rifampin, phenytoin, carbamazepine, and barbiturates), which increase phase I metabolism and NAPQI concentrations.[15]