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Over-the-Counter Analgesics: What Nurse Practitioners Need to Know

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ABSTRACT

Many patients and health care practitioners are unaware that over-the-counter (OTC) analgesics can cause potentially serious adverse effects when used in combination with other common medications and in certain patient populations. Recently, there has been a call from the United States Food and Drug Administration, consumer groups, and specialty medical groups for safer use of OTC analgesics. This article reviews the more common OTC analgesics, mechanisms of action, potential drug interactions, and approach to patient management, with consideration of special patient groups.

Keywords: acetaminophen, adult health, over-the-counter analgesics, pain, pain management, NSAIDs

INTRODUCTION

A landmark survey of medication use patterns in the United States found that > 82% of adults used at least one over-the-counter (OTC) or prescription medication each week, and that 30% used up to five OTC medications.[1-3] Acetaminophen, ibuprofen, and aspirin are among the most frequently utilized OTC analgesics medications.[4]

Because of the widespread availability and perceived safety of OTC analgesics, self-medication with these agents has become commonplace. Practitioners do not always inquire in the medication history about the use of nonprescription drugs or supplements. Many patients and practitioners are unaware of the potential for toxicity and adverse drug interactions associated with the long-term and inappropriate use of OTC analgesics. OTC analgesics may be used in higher-than-recommended doses or in combinations that increase the risk of adverse interactions. Practitioners should be aware of potential drug interactions with OTC analgesics when prescribing new medications, and should review all medications taken (prescription and OTC) with each office visit.

The ready availability of OTC products provides both challenges and opportunities for practitioners. The challenge is to understand the current recommendations for dosing, evaluate drug interactions, and educate patients on the safe use of OTC products. The purpose of this investigation is to review the more common OTC analgesics, mechanisms of action, potential drug interactions, and approach to patient management, including special patient groups (Table).

Acetaminophen, or paracetamol, was first synthesized in 1878, and was introduced for medical use in 1883.[5] It is commonly used as an analgesic and antipyretic, available in many preparations both OTC (oral, rectal, topical) and in prescription formulations, generally combined with opioids and as a branded IV preparation (ie, Ofirmev; Cadence Pharmaceuticals).

MECHANISM OF ACTION AND METABOLISM

Although its exact mechanism of action is not clearly understood, acetaminophen appears to produce analgesia by elevation of the pain threshold through central activation of descending serotonergic pathways.[5] It is thought, in part, to have a mechanism of action similar to that of nonsteroidal anti-inflammatory drugs, resembling in particular the cyclooxygenase-2 (COX-2) selective inhibitors.[6] Acetaminophen has been shown to produce antipyresis through inhibition of the hypothalamic heat-regulating center in the brain.[6] With oral intake, the majority of acetaminophen is metabolized in the

Table. OTC Analgesics Overview

Drug	Mechanism of Action	Safety Considerations	Drug-Drug Interactions
Acetaminophen	• ↑Pain threshold[5-7] • ↓Nitric oxide pathway[5-7] • Selectively inhibits COX-2[5-7] • + Interacts with the endocannabinoid system[8,9] • ↓PG in the CNS, inhibit endogenous pyrogens[5-7]	Dosing < 4 g/d[10-12] Hepatotoxicity[14] s/s toxicity = nausea/vomiting, abdominal pain, jaundice, fatigue, skin rashes and/or itching of skin, and/or fluid retention.[16]	CYP450: 1A2, 2E1 $T_{1/2}$ – 2-4 hours[7,32] Prokinetic GI drugs (increase gastric emptying)[7,32] Anticholinergics (decrease gastric emptying)[7,32] Cholestyramine Enzyme-inducing substances (phenytoin, barbituates, etc.)[7,32] Probenecid[7,32] Salicylamide[7,32] Oral anticoagulants[7,32] Chloramphenicol[7,32]
Ibuprofen	• Inhibits cyclooxygenase, reducing prostaglandin and thromboxane synthesis[17,19] • + Interacts with the endocannabinoid system[20]	Dosing <3,200 mg/d[19,21] • Gastrointestinal toxicity, bleeding[22] • CV toxicity = HTN, MI[17,19] • Renal toxicity[17,19,22] s/s toxicity = renal and hepatic dysfunction, hypertension, apnea, seizures.[17,19]	CYP450: 2C9 substrate $T_{1/2}$ = 2 hours[19,35] Antihypertensives (diuretics, ACEIs)[19,35] Loop diuretics[19,35] Calcium channel blockers[19,35] Aspirin[19,35] SSRIs[19,35] Antirheumatics/chemotherapy[19,35] Corticosteroids[19,35]
Aspirin	Nonselective and irreversibly inhibits cyclooxygenase, reducing prostaglandin and thromboxane A_2 synthesis, producing analgesic, anti-inflammatory, and antipyretic effects and reducing platelet aggregation.[26,27]	Dosing < 4 g/d[26,27] • Gastrointestinal toxicity, bleeding[26-29] • Platelet inhibition[26-29] • Hepatictoxicity[26-29] • Respiratory[26-29] s/s toxicity = diarrhea, abdominal pain, nausea, and/or vomiting, headache, lightheadedness, drowsiness (particularly in children), tachypnea or hyperpnea, flapping of the hands (in older adults), increased thirst, visual problems[26,28]	CYP450, gut, plasma $T_{1/2}$ = 0.25 hour (ASA), 2-6 hours (salicylates).[28] ACEIs[26,28,36] Anticoagulants/antiplatelet drugs[26,28,36] Antiglycemics[26,28,36] Calcium channel blockers[26,28,36] Corticosteroids[26,28,36] Loop diuretics[26,28,36] Methotrexate[26,28,36]

ACEI = angiotensin-converting enzyme inhibitor; ASA = American Association of Anesthesiologists; GI, gastrointestinal.

liver by glucuronidation and sulfonation to nontoxic metabolites, excreted with bile and urine. The remaining amount (< 10%) is metabolized through the CYP450 pathway to the hepatotoxic metabolite *N*-acetyl-*p*-benzoquinoneimine.[6–8] Research also suggests that acetaminophen plays a role in the endocannabinoid system.[8,9]

SAFETY CONSIDERATIONS

The generally accepted consensus is that, for the average healthy adult, the recommended maximum daily dose is no more than 4,000 mg from all sources. In some individuals, however, doses close to the 4,000-mg/d limit for adults could still be toxic to the liver. It is safest to take only what is needed and to not exceed 3,000 mg/day whenever possible.[10,11]

In 2006, the American Liver Foundation issued recommendations that patients not exceed 3 g/d of acetaminophen for any "prolonged period of time."[12] They pointed to a study that reported aspartate aminotransferase levels were elevated in healthy patients receiving 4 g/d for 14 days.[13] The