Nonprescription analgesics and their use in solid-organ transplantation: a review

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Objective-To review the pharmacology, adverse events, drug interactions, and use of the nonprescription analgesics in solid-organ transplant recipients. Study Selection and Data Extraction-Studies evaluating nonprescription analgesics in solid-organ transplantation were considered for evaluation. English-language studies were selected for inclusion.

Data Synthesis-Nonprescription analgesics (aspirin, choline salicylate, magnesium salicylate, sodium salicylate, ibuprofen, ketoprofen, naproxen sodium, and acetaminophen) are the most commonly purchased over-the-counter agents in the United States. These agents, although generally considered safe, have been associated with a number of toxicities. The salicylates and nonsteroidal anti-inflammatory drugs have been associated with gastrointestinal damage, hematologic changes, liver and kidney dysfunction, and breathing difficulties. Acetaminophen has been shown to induce hematologic changes and liver and renal dysfunction.

Conclusion-A closer look at the nonprescription analgesics reveals their potential for harm when used by solid-organ transplant recipients. In this patient population, the salicylates and nonsteroidal anti-inflammatory drugs should generally be avoided if possible, because of their potential toxicities, especially renal dysfunction. Low-dose aspirin, for the prevention of cardiovascular and cerebrovascular events, appears to be safe, but patients must still be followed closely. Acetaminophen is generally considered the nonprescription analgesic and antipyretic of choice in transplant recipients because of its favorable toxicity profile. However, it is imperative that patients and transplant practitioners are aware that this agent is not without toxicities and proper monitoring is advised.

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agents are also beneficial for the treatment of pyrexia, because of their ability to act on the hypothalamus heat-regulating center to reduce fever.2-4 Unlike other nonprescription analgesics, aspirin irreversibly acetylates platelets, resulting in decreased platelet aggregation.1 This unique mechanism of action provides an additional benefit of aspirin therapy in the prevention of cardiovascular and cardiocerebral events.2 Table 1 presents a list of common nonprescription analgesic brand names and doses.

Common Indications

Aspirin is indicated for the relief of mild to moderate pain, such as headache, dysmenorrhea, myalgia, arthralgia, and neuralgia,2-4 and is effective as an antipyretic for the temporary relief of fever. In patients with a history of myocardial infarction or unstable angina pectoris, aspirin is indicated for secondary prevention of further myocardial infarctions. Aspirin is also effective in reducing the risk of recurrent transient ischemic attacks or stroke and graft occlusion following aorta coronary bypass surgery.2-4 Table 2 shows a complete list of aspirin indications and associated doses.

Choline salicylate, magnesium salicylate, and sodium salicylate are indicated for the temporary relief of pain, inflammation, and fever. Rheumatoid arthritis, rheumatic fever, osteoarthritis, dysmenorrhea, and myalgias are some common ailments that respond to the nonacetylated salicylates.2,4

Dosing

Aspirin. The typical dose for mild-to-moderate pain and fever is 1.95 to 4 g/day in divided doses; patients should not take more than 4 g/day. For inflammatory disorders, aspirin needs to be dosed at 4 to 6 g/day; because this exceeds the maximum recommended daily aspirin dose, NSAIDs are often considered the first-line anti-inflammatory agents.2-4

Choline Salicylate. The recommended dose of choline salicylate is 435 to 870 mg every 4 hours, not to exceed 5325 mg/day. This agent is particularly useful in patients who have difficulty taking tablets or capsules, because choline salicylate is available in an oral solution. However, patients often complain of a fishy odor with this dosage form.2,4

Magnesium Salicylate. The recommended adult dose of magnesium salicylate is 650 mg every 4 hours, not to exceed 3900 mg/day.2,4

Sodium Salicylate. This agent has been shown to be less effective than aspirin (at equivalent doses) in reducing pain and fever. The recommended dose of sodium salicylate is 325 to 650 mg every 4 hours, with a maximum of 4 g/day.2,4

Major Adverse Reactions

Central Nervous System. Central nervous system (CNS) adverse events with the salicylates are rare, but are often present during salicylate overdose. In cases of overdose, some common CNS symptoms include headache, dizziness, mental status changes, fatigue, and lassitude.2-4

Endocrine and Metabolic. Salicylates alter uric acid secretion and reabsorption in the renal tubules; at low doses (aspirin 1-2 g/day), tubular uric acid secretion is inhibited and elevated uric acid levels are common; at moderate doses (aspirin 2-3 g/day), uric acid excretion is not altered; and at high doses (aspirin >5 g/day) uric acid levels are decreased through uricosuric effects. Unfortunately, at uricosuric doses, the risk of salicylism is high. Patients with a history of gout or hyperuricemia are recommended to avoid salicylates.2-4

Salicylates may increase the hypoglycemic effects of sulfonylureas. Diabetic patients receiving sulfonylurea and who require an antipyretic or analgesic should consider acetaminophen as a first-line agent.2,4

Patients with kidney impairment should avoid using magnesium salicylate because of the potential for magnesium accumulation and subsequent magnesium toxicity.2,4 In addition, sodium salicylate should be avoided in patients who require sodium restriction.2-4
Gastrointestinal. Salicylates have been associated with a number of gastrointestinal (GI) toxicities, including, nausea, vomiting, diarrhea, gastritis, and ulcer formation. These agents induce GI damage by 2 distinct mechanisms: (1) primary insult—as acidic molecules, Salicylates produce a local irritant effect by direct contact with gastric mucosa; and (2) secondary insult—by inhibiting the synthesis of prostaglandin E-2, an essential prostaglandin for the production of the stomach’s protective lining.2-5 The Food and Drug Administration (FDA) recommends that chronic alcohol consumers avoid concurrent salicylate use as it may increase the risk of GI bleeding.2

Hematologic. As discussed previously, prostaglandins are necessary for platelet aggregation. All salicylates alter platelet function; however, only aspirin irreversibly renders platelets dysfunctional through acetylation.2,4,6,7 All these agents increase the risk of bleeding, but the risk is higher with aspirin. Thus, aspirin therapy is contraindicated in patients with hypoprothrombinemia, vitamin K deficiency, hemophilia, history of any bleeding disorder, or peptic ulcer disease.2,6 In addition, neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia, eosinophilia, pure white blood cell aplasia, thrombocytopenia, and pancytopenia have been associated with salicylate use.2,4,6,7

Hepatic. Although rare, salicylates have been associated with elevations in liver function tests, hepatomegaly, and drug-induced hepatitis.2,4 One case of aspirin-induced hepatotoxicity has been reported in a pediatric liver transplant recipient.8

Otic. Ototoxicity, although rare, is a commonly known adverse event seen in salicylate overdose. Tinnitus and healing difficulty are 2 of the more common manifestations of salicylate-induced Ototoxicity.2,4,9 However, tinnitus is often not present in an overdose; therefore, it should not be used as the only indicator of salicylism.

Renal. In healthy adults, the short-term use of salicylates is generally not associated with changes in renal function. However, in patients with underlying renal dysfunction (eg, chronic renal insufficiency, glomerulonephritis, systemic lupus erythematosus), aspirin, even at recommended doses, has been shown to induce acute renal failure (ARF).2,4,10,11

Respiratory. Salicylates have been shown to induce bronchospasm, tachypnea, hyperpnea, respiratory alkalosis, and noncardiogenic pulmonary edema.2,4,12

Warnings and Precautions

Allergic Reactions. The incidence of aspirin allergy is rare, occurring in less than 1% of patients. However, true aspirin allergy is seen more often in patients with preexisting urticaria, asthma, and nasal polyps. Allergy to aspirin typically manifests as urticaria, edema, bronchospasm, or rhinitis. There is a significant cross-reaction rate in aspirin-allergic patients to other nonprescription analgesics, acetaminophen (6%), and NSAIDs (97%). Patients allergic to aspirin or NSAIDs can be safely treated with nonacetylated salicylates.2,4

Glucose-6-Phosphate Dehydrogenase Deficiency. The use of aspirin in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency may result in hemolysis. However, the true incidence of aspirin-induced hemolytic uremia in G6PD deficient patients is poorly understood.2,4

Pregnancy and Breast-Feeding. Salicylates have been associated with increased maternal morbidity and fetal morbidity and mortality. Women should be advised to avoid salicylates during pregnancy, especially during the last trimester, and while breast-feeding.2,4

Reye Syndrome. Salicylates should be avoided in children younger than 15 years of age with an influenza or varicella zoster infection because of the risk of developing Reye syndrome. This syndrome is an acute and potentially fatal illness, often manifesting as hepatotoxicity and CNS adverse events. The FDA requires all salicylate-containing products to be labeled with a warning on Reye syndrome. Neither the NSAIDs nor acetaminophen have been associated with this syndrome.2,4

Nonsteroidal Anti-Inflammatory Drugs
Mechanism of Action

The NSAIDs work similarly to salicylates, by blocking prostaglandin, prostacyclin, and thromboxane synthesis via COX inhibition. As with the salicylates, the administration of NSAIDs results in a reduction in the propagation of pain impulses and inflammation. These agents also have proven benefit in the treatment of pyrexia. NSAIDs, through reduced thromboxane biosynthesis, alter platelet aggregation, but not to the same extent as aspirin.2,4

Common Indications

Ibuprofen, ketoprofen, and naproxen sodium are indicated for the relief of mild-to-moderate pain, inflammation, and fever. In the general population, NSAIDs are usually considered first-line OTC agents for rheumatoid arthritis, ostcoarthritis, and dysmenorrhea. As mentioned above, NSAIDs do not irreversibly inhibit platelet aggregation; therefore, they are not useful in preventing cardiovascular or cardiocerebral events.2,4

Dosing

Ibuprofen. This agent is the only nonprescription NSAID approved by the PDA for children. It is indicated in this population (age 2-11 years) for the treatment of fever and the relief of pain associated with the common cold, influenza, sore throats, headaches, and toothaches. In children, the recommended dose is 7.5 mg/kg per day, not to exceed 30 mg/kg per day.2,4

In adults, the recommended analgesic dose of ibuprofen is 200 to 400 mg every 4 to 6 hours. It is recommended that patients not exceed 1200 mg/day. However, the dose needed to treat inflammatory disorders is 400 to 800 mg every 6 to 8 hours (maximum dose of 3200 mg/day). This dose exceeds the recommended nonprescription dosing.2,4

Ketoprofen. As an analgesic, this agent should be dosed at 12.5 mg every 6 to 8 hours, not to exceed 75 mg/day. As an anti-inflammatory, this agent should be dosed at 50 to 75 mg every 6 to 8 hours, with a maximum daily dose of 300 mg. As with ibuprofen, antiinflammatory doses of ketoprofen exceed the recommended maximum dose listed on the OTC product labeling.2,4

Naproxen Sodium. Naproxen should be dosed at 220 to 440 mg every 8 to 12 hours, not to exceed 660 mg/day, for pain relief. The anti-inflammatory dose of this agent is 275 to 550 mg every 8 to 12 hours (maximum recommended dose of 1650 mg/day). This antiinflammatory dose exceeds the recommended dose listed on the OTC product labeling.2,4

Major Adverse Reactions

Cardiovascular. It is well known that hypertension is a common manifestation in organ transplant recipients. Hypertensive patients may have elevations in angiotensin II and norepinephrine levels. As a compensatory mechanism in these patients, the body increases the production of prostaglandins. With inhibition of prostaglandin synthesis by NSAIDs, an escalation in blood pressure may be noted. Nonprescription NSAIDs antagonize the effects of antihypertensive medications, especially angiotensinconverting enzyme inhibitors and ß-blockers.2,4,13,14

Central Nervous System. Psychosis and cognitive impairment can be seen with NSAID use, especially in elderly patients.2,4 Indomethacin, a prescription NSAID, is particularly notorious for inducing these types of effects.15 Aseptic meningitis is a rare, yet serious, manifestation of phenylproprionic-acid NSAIDs (ie, ibuprofen and naproxen sodium). This toxicity is often associated with NSAID use in patients with systemic lupus erythematosus and rheumatoid arthritis.15,16

Endocrine and Metabolic. NSAIDs may potentially trigger sodium retention. This adverse event results in fluid retention, which may reduce the effectiveness of antihypertensive therapies, especially diuretics, and worsen congestive heart failure.2,4,17

Gastrointestinal. The etiology of NSAID-induced GI adverse events is similar to that of the salicylates. NSAIDs are associated with
abdominal cramps and pain, heartburn, indigestion, nausea, dyspepsia, vomiting, peptic ulcers, GI perforation, and bleeding.2,4,5

Hematologic. As discussed previously, prostaglandins are necessary for platelet aggregation. All NSAIDs alter platelet function and may increase the risk of bleeding.2,4,6 Blood dyscrasias have also been seen with NSAID therapy.2,4,18 Bleeding times have been shown to be prolonged in patients who ingest alcohol concurrently with NSAIDs.2,4

Hepatic. NSAIDs generally induce idiosyncratic hepatic injury. These agents have been associated with elevations in liver function tests, but rarely cause liver failure.2,4 However, a case of ibuprofen-induced hepatotoxicity in a 59-year-old woman has been reported. The patient developed subacute liver failure and eventually required an orthotopic liver transplant.19

Renal. NSAID-induced renal dysfunction generally presents in 2 distinct forms; hemodynamically mediated ARF and acute interstitial nephritis (with or without nephrotic syndrome).13 Under certain circumstances (ie, glomerular disease, renal insufficiency), prostaglandins are vital in the preservation of renal blood flow and glomerular filtration rate (GFR) by dilating the afferent arterioles. NSAID-induced prostaglandin inhibition may result in reversible renal ischemia, a reduction in GFR and subsequent ARF. Several case reports of nephrotoxicity secondary to NSAID-administration have been reported in solid organ transplant recipients. One case involved a 34-year-old kidney transplant recipient receiving ibuprofen who developed acute interstitial nephritis.20 Ketoprofen has also been associated with irreversible renal failure in a kidney transplant recipient.21 Two case reports of ibuprofen-induced ARF have been reported in liver transplant recipients.22

Respiratory. The use of NSAIDs has been associated with bronchospasm and constriction. Inhibition of COX by NSAIDs shunts arachidonic acid down the lipoxygenase pathway, resulting in increased leukotriene synthesis. Excessive leukotriene production may result in constriction and spasm of the bronchioles. These adverse events are rare in the general population, but are particularly noticeable in patients with underlying pulmonary disorders.2,4,12

Precautions and Warnings

Allergic Reactions. NSAIDs should not be administered to any patient with a history of aspirin allergy.2,4

Pregnancy and Breast-Feeding. Nonprescription NSAIDs are category-B rated for pregnant women, except during the third trimester when they are category D.2,4 NSAID use near term may inhibit labor. The American Academy of Pediatrics considers nonprescription NSAIDs to be compatible with breast-feeding.2,4

Acetaminophen

Mechanism of Action

Acetaminophen has a similar mechanism of action to the salicylates and NSAIDs, with one major exception; at normal doses, acetaminophen inhibits prostaglandin synthesis solely in the CNS.24 Notably, this difference in mechanism of action influences the indications and adverse events of acetaminophen.

Common Indications

Acetaminophen is an effective analgesic for the relief of mild-to-moderate pain. This agent is also effective in reducing fever. Because of its site of action, acetaminophen is not an effective anti-inflammatory drug, as treatment of inflammation generally requires decreased peripheral prostaglandin synthesis. However, acetaminophen may be used to treat pain associated with inflammation.2,4

Dosing

Acetaminophen can safely be administered to children. The typical dose in this population is 10 to 15 mg/kg per day. In adults, the recommended dose is 325 to 650 mg every 4 hours (maximum 4 g/day).2,4 This dose may need to be adjusted in liver transplant
recipients. Park et al. conducted a study to determine the alterations of acetaminophen metabolism in patients after liver transplantation. The authors concluded that the risk of acetaminophen-induced hepatotoxicity may be increased in the early postoperative period and that the maximum daily dose of acetaminophen may need to be reduced during this time.

Major Adverse Reactions

Hematologic. Hematologic changes with acetaminophen rarely occur, but may manifest as methemoglobinemia, hemolytic anemia, neutropenia, thrombocytopenia, pancytopenia, and leukopenia.

Hepatic. Acetaminophen is extensively metabolized in the liver to both sulfate and glucuronide conjugates. Approximately 10% of the therapeutic dose of acetaminophen is metabolized via the cytochrome P450 system to N-acetyl-p-benzoquinoneimine (NAPQI). NAPQI is a toxic metabolite that, under normal circumstances, is immediately conjugated with glutathione to form nontoxic compounds. In cases of excessive acetaminophen consumption (7.5-10 g acutely; 4 g/day chronically), glutathione stores become depleted and NAPQI accumulates causing hepatic injury. In the early postoperative period, NAPQI concentrations may be increased in liver transplant recipients through impaired glucuronidation and sulfation and enhanced NAPQI formation. In solid-organ transplant recipients especially, hepatotoxicity may be enhanced by the coadministration of cotrimoxazole, which competes with acetaminophen for glucuronidation.

Renal. The etiology of acetaminophen-induced renal injury is similar to acetaminophen-induced hepatotoxicity. NAPQI is also metabolized by the kidneys, where it binds to cellular macromolecules resulting in cellular injury or death. ARF is almost exclusively accompanied by liver failure, but it may occur by itself in patients with a history of alcoholism. In patients with underlying renal dysfunction, doses may need to be adjusted to avoid the accumulation of NAPQI.

Warnings and Precautions

Pregnancy and Breast-Feeding. Acetaminophen crosses the placenta and appears in breast milk. However, acetaminophen therapy is safe during all trimesters of pregnancy and the American Academy of Pediatrics considers acetaminophen to be compatible with breast-feeding.

Glucose-6-Phosphate Dehydrogenase Deficiency. The use of acetaminophen in patients with G6PD deficiency may result in hemolytic anemia.

Recommendations for Nonprescription Analgesics in Solid-Organ Transplant Recipients

Nonprescription analgesics are freely available to all patients. Although these agents are generally considered safe, they are not devoid of adverse events. This is particularly true in patients with underlying disease states that may predispose them to drug-induced toxicities. Solid-organ transplant recipients need to be especially cautious when choosing an analgesic, anti-inflammatory or antipyretic, for fear of complications. These patients, along with clinicians, need to be aware of the risks and benefits associated with each nonprescription analgesic (Table 3).

Salicylates

For the treatment of pain, inflammation, and fever, salicylates should generally be avoided in all solid-organ transplant recipients. At doses necessary to treat these ailments, salicylates are fraught with potential adverse events that can affect any transplant recipient.

* Salicylates have been shown to worsen hyperuricemia and gout, which is a common manifestation in patients with renal dysfunction and those patients receiving cyclosporine.

* Patients receiving either magnesium salicylate or sodium salicylate should be monitored closely for signs of electrolyte accumulation.
Salicylate-induced GI toxicities are common, even at the lowest doses. These adverse events may be amplified in patients receiving any oral immunosuppressant, especially mycophenolate mofetil and mycophenolate sodium.

A pharmacodynamic interaction would exist between salicylates and immunosuppressants (except for prednisone) as they have all been associated with blood dyscrasias.

Alone, salicylates are rarely hepatotoxic. However, this risk may be increased in patients with underlying hepatic dysfunction (liver transplant recipients) or those receiving other potential hepatotoxins (cyclosporine, tacrolimus).

All solid-organ transplant recipients taking a calcineurin inhibitor are at risk of developing renal dysfunction. This risk is increased when patients are receiving other nephrotoxic agents. Salicylates have been shown to induce ARF; therefore, would not be ideal for use in patients receiving cyclosporine or tacrolimus.

In patients with underlying respiratory conditions, including lung transplant recipients, salicylates may induce bronchoconstriction or bronchospasm.

The benefit of low-dose aspirin (Nonsteroidal Anti-Inflammatory Drugs)

NSAIDs are considered the OTC drugs of choice for inflammation in the general public. Along with acetaminophen, they are also used frequently for pain relief and in the treatment of fever. NSAIDs should generally be avoided in all solid-organ transplant recipients because of their potential to induce toxicities.

Hypertension is a common ailment after solid-organ transplantation. The use of NSAIDs has been shown to worsen hypertension and antagonize the effects of some antihypertensive medications.

Through similar mechanisms as listed above with the salicylates, NSAIDs may produce GI upset, hematologic changes, hepatic and renal dysfunction, and respiratory toxicities. Therefore, solid-organ transplant recipients must make an effort to avoid the unsupervised use of NSAIDs.

NSAIDs are effective for the treatment of inflammatory disorders, such as rheumatoid arthritis and gout. In these cases, alternative agents (ie, corticosteroids, disease-modifying antirheumatic agents, colchicine) should be sought before using NSAIDs. However, if NSAIDs are needed, they should be taken under the supervision of a transplant practitioner and patients should be monitored closely for NSAID-induced toxicities.

Acetaminophen

For the relief of mild-to-moderate pain and fever, acetaminophen is generally considered the nonprescription treatment of choice for solid-organ transplant recipients. Although it is generally considered to be free of major adverse events, acetaminophen has been associated with some serious toxicities that may be exacerbated in this specific patient population.

Excessive consumption of acetaminophen, either acutely or chronically, has resulted in liver dysfunction. This is of particular concern in liver transplant recipients, as well as patients receiving potentially hepatotoxic immunosuppressants. An analysis in liver transplant recipients has demonstrated that acetaminophen doses may need to be reduced in the early postoperative period.23

Acetaminophen-induced nephrotoxicity is rare. However, renal function should be monitored in any patient using acetaminophen for chronic disease. Dosing may need to be adjusted in patients with underlying renal dysfunction.

Conclusion
The use of nonprescription analgesics is common among Americans. Solid-organ transplant recipients need to be particularly vigilant in taking responsibility for their own well-being. These patients must not put themselves at undue risk of toxicity by self-medicating with potentially harmful agents, just because they are available without a prescription. It is imperative that transplant practitioners take an active role in identifying nonprescription medication use among their patients; are aware of possible complications, adverse events, or drug interactions; and educate their patients on the need for open communication regarding nonprescription analgesic use.

References

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