The Use and Effect of Analgesics in Patients Who Regularly Drink Alcohol

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Abstract

Analgesic consumption poses special risks for regular users of alcohol. Among the numerous adverse health effects are acetaminophen toxicity and gastrointestinal (GI) bleeding associated with nonsteroidal anti-inflammatory drug (NSAID) use. An alcohol-acetaminophen hypothesis contends that alcohol enhances acetaminophen toxicity. Because 22% of adults use acetaminophen each week and 5% to 10% of the population is alcoholic, the healthcare implications of serious adverse interactions are considerable. However, such interactions are rare when NSAID doses remain in the therapeutic range. Although clinical studies fail to support anecdotal case reports of liver damage associated with consumption of therapeutic doses of acetaminophen by alcohol users, such reports are probably inaccurate because of the uncritical acceptance of patient history by the clinician and a lack of well-designed prospective trials. Over-the-counter (OTC) NSAIDs, such as aspirin, naproxen, and ketoprofen, are other analgesic options, but each carries the risk of GI bleeding. Unanswered questions about the newer "second-generation" NSAIDs, such as celecoxib and rofecoxib, make them less desirable than acetaminophen and OTC NSAIDs. Because the risk of GI bleeding or ulceration may be higher in alcoholic patients, the optimal strategy in prescribing pain relievers to those who consume alcohol is to use 1 drug at a time and to clearly communicate its generic name. Acetaminophen is the safest OTC analgesic and is recommended as first-line treatment for osteoarthritis. OTC NSAID users should be carefully advised as to recommended dose, and all patients should be reminded to stay within the dosing limits regardless which OTC analgesic is used.

Most people use over-the-counter (OTC) analgesics. Telephone surveys indicate that 22% of the adult population in the United States use acetaminophen in a given week.[1] In adults, the most common reason for acetaminophen use is to control pain. Acetaminophen has been shown to be effective for the treatment of headache, osteoarthritis, acute musculoskeletal injury, dental pain, and many other painful conditions.

Alcohol is also used commonly in the United States. Alcoholism affects 5% to 10% of the population and many more people drink alcohol on a regular basis. Alcoholism is associated with decreased overall health of the individual patient.

Pain treated by OTC analgesics may be of short or long duration. Medications approved in the United States for OTC use have minimal adverse effects after one or several doses, however, safety issues arise when repeated dosing is needed.

Alcohol Use and Nonsteroidal Anti-inflammatory Drugs

Chronic use of alcohol produces multiple adverse health effects. One proposed adverse effect is susceptibility to acetaminophen toxicity. Another is an increased incidence of gastrointestinal (GI) bleeding in association with nonsteroidal anti-inflammatory drug (NSAID) use. How does the clinician make prudent analgesic recommendations to the alcoholic patient or the patient who consumes alcohol regularly? The primary choices available to these patients include acetaminophen and NSAIDs such as ibuprofen or aspirin as well as the newer NSAIDs such as celecoxib or rofecoxib.

The efficacy of these products is similar. Individual studies have reported advantages for some specific conditions,

but the data overall are mixed. It is important to understand that NSAIDs do not inhibit inflammation in OTC doses. Although there may be some intermittent inflammatory response in patients with osteoarthritis, the treatment is aimed at pain relief and not specifically at reduction of inflammation.[2] As a result, the use of simple analgesics or NSAIDs in doses that produce only analgesia can be used. Overall, it is the patient's preference that determines the choice in regard to efficacy. Often, the osteoarthritis patient tries many OTC and prescription medications in the course of a year.

Alcohol-Acetaminophen Syndrome

Safety is an important consideration for each of these agents. Acetaminophen is used by millions of people each week.[1] Many of these patients suffer from alcoholism or consume alcohol regularly. In recent years an "acetaminophen-alcohol syndrome" has been proposed. The alcohol-acetaminophen hypothesis contends that acetaminophen toxicity is enhanced by alcohol. An interaction between a drug used by 22% of adults each week and a disease that affects up to 10% of the population would have important healthcare implications. Fortunately, serious adverse effects are rare, suggesting that if such an interaction exists, it requires considerably higher doses than the therapeutic dose.

The theory behind the alcohol-acetaminophen hypothesis involves the induction of the enzyme that metabolizes acetaminophen. CYP2E1 is an isozyme in the hepatic cytochrome P450 system that metabolizes about 5% of a typical dose of acetaminophen. The product of metabolism is a reactive metabolite named N-acetyl-p-benzoquinone imine (NAPQI). The remainder of a therapeutic acetaminophen dose is conjugated to nontoxic forms of glucuronide and sulfate. Ingestion of alcohol induces the activity of CYP2E1 and may briefly double or triple the activity of CYP2E1 in people.[3] At normal doses of acetaminophen, the production of NAPQI has not been considered important because it is quickly detoxified by the sulfhydryl groups provided by glutathione. The amount of NAPQI produced by an overdose, however, is capable of overwhelming the glutathione detoxification mechanism. The result is necrosis of liver cells and potentially fulminant hepatic failure in severe cases. Because of the induction of CYP2E1, some individuals have proposed that the alcoholic patient may suffer injury at therapeutic doses of acetaminophen.

There are several reasons to question the concept that true therapeutic doses of acetaminophen can cause toxicity, even in the patient with induced CYP2E1. Although liver toxicity is well known in overdose, there are strikingly few reports of toxicity at lower doses in the medical literature, particularly for a drug that is used so frequently throughout the world. Further, clinical toxicologists treat large numbers of patients suffering from both alcoholism and acetaminophen ingestion. If an interaction exists, why do we not see more cases of unexpected liver injury?

My coworkers and I investigated this phenomenon directly by administering maximum therapeutic doses of acetaminophen (4 g/day) to alcoholic patients in a randomized, double-blind, placebo-controlled trial.[4] The newly abstinent alcoholic patient should be the most vulnerable to acetaminophen because of induced CYP2E1 and perhaps because of lower levels of glutathione. Induction of CYP2E1 wanes after discontinuing alcohol consumption, but takes several days to return to normal. We treated patients within the first 18 hours to assure that induction did not wane substantially before acetaminophen was administered. To assess injury, we observed serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) as well as the international normalized ratio (INR). We found that acetaminophen had no effect on the AST, ALT, or INR of alcoholic patients. Increases in AST as small as 14 IU/L could be detected in the study.

Related articles also support the concept that the alcoholic patient is not at risk from therapeutic doses of acetaminophen. Benson[5] administered acetaminophen 4 g/day to patients with various forms of hepatitis and cirrhosis, including alcoholic cirrhosis and hepatitis. He found no change in ALT despite treatment for 13 days.

In contrast to these prospective controlled studies, some retrospective reports have expressed concern because fulminant hepatic failure followed the use of acetaminophen.[6] Some of these reports state the doses ingested were within the 4-g/day maximum recommended by manufacturers. Like all retrospective data, these reports have serious limitations. One fundamental issue is the accuracy of the history from a seriously ill alcoholic patient. These reports used history as the only estimation of dose and many of the reports included data that conflicted with the conclusion that a therapeutic dose was ingested. The discrepancies included remarkably high serum levels of acetaminophen, a history that suggested a suicidal ingestion was involved, and histopathology that was not consistent with a diagnosis of acetaminophen hepatotoxicity. The patient claimed a therapeutic intent, but actually ingested much higher doses or a different liver toxicant. Other sources of inaccuracy include the lack of studies needed to exclude other causes of liver injury (hepatitis, other drugs or liver toxins, liver ischemia/hypoxia, and many others).

In short, prospective clinical studies have not verified concerns raised in anecdotal case reports of liver injury associated with a history of ingesting therapeutic doses of acetaminophen. It is likely that these reports are incomplete or inaccurate because of uncritical acceptance of patient history.

These retrospective reports raise an important question, but only prospective trials can answer the question. Our study produces the first prospective data that directly addresses the question of whether therapeutic doses of acetaminophen can produce liver injury in the alcoholic patient. We found no effect, even when post hoc analysis of putative high-risk subgroups was examined.[4] Currently, there are no adequately designed prospective trials that indicate a risk of liver injury from therapeutic doses of acetaminophen.

Our study produces the first prospective data that directly addresses the question of whether therapeutic doses of acetaminophen can produce liver injury in the alcoholic patient.

The other analgesic choices available to the alcoholic patient are OTC NSAIDs: aspirin, ibuprofen, naproxen, and ketoprofen. Each of these drugs causes GI bleeding during therapeutic use and has been associated with an increased mortality rate. The data are clear that aspirin 650 mg is the most likely NSAID to cause GI bleeding or ulceration. Ibuprofen is the least likely to produce these effects.[7]

NSAIDs and Acetaminophen

It is difficult to compare the safety of NSAIDs and acetaminophen during therapeutic use. It is clear that the risk is extraordinarily low with acetaminophen if the patient actually ingests therapeutic doses rather than repeated supratherapeutic doses (more than 4 g/day). The risk is also low with an OTC NSAID for 1 or 2 days. However, there are several conditions in which NSAIDs are contraindicated (asthma, history of GI ulceration, hypertension, renal failure, and others). When the patient can tolerate an OTC NSAID, it is surprisingly common for healthcare providers to recommend doubling or even tripling the OTC dose in the belief that this will provide a safe,

cost-effective alternative to prescribing a prescription dose of NSAID. Although it may be less costly, the risk also increases quickly. Approximately 1% to 2% of patients treated with a prescription dose of an NSAID will suffer from GI bleeding. NSAIDs are associated with up to 16,000 deaths per year.[8] It is important to realize that not all of these events were caused by the NSAID involved, but the frequency of bleeding is clinically important.

Acetaminophen is the safest OTC analgesic and many patients find it effective for nearly any painful condition for which an OTC analgesic is appropriate.

Aspirin is the poorest choice for treatment of pain with an OTC analgesic. Even the low dose of aspirin used for coronary prophylaxis is associated with a statistically significant increase in the frequency of GI bleeding.[9] Although this risk is reasonable in the patient in whom cardioprophylaxis is justified, the larger risk associated with analgesic doses of aspirin is not justified when other equally effective alternatives are available.

The "second-generation" NSAIDs (celecoxib and rofecoxib) have efficacy profiles similar to the first-generation NSAIDs. Initially thought to be safer than the earlier NSAIDs, serious questions about the safety of both agents have emerged.[10] In the future it is likely that these agents will have some role in the treatment of various painful conditions. Until the safety and appropriate use of these agents is clarified, however, they should remain third-line agents to treat painful conditions behind acetaminophen and the OTC NSAIDs.

The risk of GI bleeding or ulceration during treatment with an NSAID may be even higher in the alcoholic patient. The ability of alcohol alone to induce gastric mucosal injury is well known in animals and has been described in people.[11] Furthermore, the odds ratio for upper GI tract bleeding is 2.8 with alcohol alone compared with a nondrinker, but increased to 6.0 when combined with a nonaspirin NSAID and 8.1 when combined with aspirin.[12]

Recommendations

What is the appropriate treatment for the alcohol-using patient with painful conditions such as osteoarthritis? Many individuals influence the patient's choice of an OTC analgesic. These include the patient, the patient's physician, pharmacist, and other healthcare providers as well as their family and friends. The plethora of trade names and combination products makes selection difficult and can create confusion. The best strategy is to use 1 drug at a time with clear communication of the generic name. A pharmacist, nurse, or physician should be involved if use exceeds the recommendations on the package labeling or if multiple products are used. Manufacturers are encouraged to clearly label their proprietary products with the active ingredient.

Acetaminophen is the safest OTC analgesic and many patients find it effective for nearly any painful condition for which an OTC analgesic is appropriate. It can be used in all patients if the package labeling is followed. Because of safety considerations, professional medical societies in both Europe and the United States recommend acetaminophen as first-line treatment of osteoarthritis.[13,14]

An NSAID will often be used or added if acetaminophen is not completely effective. It is important during patient counseling to accurately determine the OTC analgesics and the doses used by the patient. Some patients confuse aspirin and acetaminophen. This could increase their risk of GI bleeding or the patient could inadvertently ingest 2 different acetaminophen-containing products simultaneously. Further, preliminary evidence suggests that patients tend to think they

should take 2 pills for each dose of OTC analgesic 4 times per day. This can lead to OTC NSAID dosages that markedly exceed the recommended OTC dose.[15] Overall, more educational materials for patients using OTC analgesics are needed. This need increases as the number of agents available without prescription increases.

For the alcoholic patient with mild-to-moderate pain, therefore, acetaminophen is the preferred drug followed by ibuprofen. All patients should be reminded to stay within the dosing limits indicated on the package labeling for all OTC analgesics.

Patients with a history of medication abuse should avoid all OTC analgesics. Many of these patients have alcoholism among their health problems.

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