Estimated Risks of Fatal Events Associated with Acetaminophen, Ibuprofen, and Naproxen Sodium Used for Analgesia

Kenneth J. Rothman* and Lee L. Lanza

RTI Health Solutions, 3040 Cornwallis Road, P.O. Box 12194, Research Triangle Park, NC 27709-2194, USA

Abstract

Objective: We assessed the net effect on risk of death for within-label use of acetaminophen and the two non-aspirin alternative oral non-prescription analgesics available in the U.S. (ibuprofen and naproxen sodium) in relation to upper gastrointestinal hemorrhage, liver failure, and renal failure.

Methods: For each drug we obtained estimates of recent general-population prevalence of use and the number of deaths in the US from acute liver injury, acute renal failure, and gastrointestinal hemorrhage for the years 2006-2008 in the population age 20 years or older. We searched the literature and reviewed all informative epidemiologic studies to obtain estimates of the relative risks for each analgesic-endpoint combination. From the estimates of prevalence, relative risk and total one-year risk for the U.S. population, we back-calculated the risk among unexposed, using it as a benchmark from which we could obtain the change in absolute risk related to using each analgesic.

Results: Under most assumptions for the relative risks among the different analgesics, acetaminophen use carried the smallest absolute increase in risk, the best estimate being about 35 deaths per million in one year. The comparable estimated increased risk of death related to use of ibuprofen or naproxen sodium was 64 deaths for ibuprofen and 118 deaths for naproxen sodium per million person-years respectively.

Conclusions: When non-prescription analgesics are used according to labeled instructions, acetaminophen use appears likely to be associated with smaller combined risks for upper gastrointestinal hemorrhage, liver disease, and renal disease than is use of ibuprofen or naproxen sodium.

Keywords: Analgesics; Non-steroidal anti-inflammatory agents; Ibuprofen; Naproxen sodium; Acetaminophen; Acute liver failure; Acute kidney injury; Gastrointestinal hemorrhage

Introduction

A considerable proportion of the U.S. population uses non-prescription analgesics on a regular basis [1]. Four oral medications are currently approved in the U.S. for non-prescription analgesia: acetaminophen, aspirin, ibuprofen, and naproxen sodium. As with any pharmaceuticals, these agents carry some risk of adverse events that must be weighed against their therapeutic benefits.

Some cases of acute liver failure have been attributed to nontherapeutic use or unintentional overdose of acetaminophen [2-5]. Acute liver failure is also theoretically possible for those with severely damaged livers who take acetaminophen at recommended doses, although this phenomenon has not been established. Recent recommendations designed to reduce excessive dosing with acetaminophen may also discourage some appropriate use of acetaminophen, diverting patients to use alternative analgesics [6]. These alternatives to acetaminophen carry their own risks and benefits. With nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs), there may be dose-related effects on the gastrointestinal lining and on cardiovascular disease risk [7]. Some of these effects are welcome; for example, aspirin in low doses is recommended to lower risk of myocardial infarction in high risk populations. Other effects, such as acute renal failure and gastrointestinal bleeding, are undesirable.

In this paper, we assess the net effect on mortality risk related to each of the non-aspirin over-the-counter analgesics approved for use in the U.S. There are four major fatal endpoints that are thought to be affected by therapeutic analgesic use. These endpoints are upper gastrointestinal hemorrhage, liver failure, renal failure and a sudden cardiovascular event (either stroke or myocardial infarction). The first three categories of risk convey much smaller risks than cardiovascular events. As a result, any attempt to weigh risks among alternative analgesics would be dominated by the cardiovascular effects of the analgesics. Although acetaminophen does not appear to have any association with cardiovascular mortality, alternative analgesics have effects that may be either protective or causative. Aspirin is used for chemoprevention of cardiac outcomes, although optimal cardiopreventive dosing is too low to offer effective analgesic relief. In contrast, other NSAIDs have been reported to increase cardiovascular mortality [8-10]; two of them, rofecoxib and valdecoxib, were withdrawn in 2004 and 2005 respectively because of an association with cardiovascular deaths [11,12]. Because cardiovascular deaths far outnumber deaths from gastrointestinal hemorrhage, liver failure or renal failure, even modest variations in relative risk for cardiovascular deaths would dominate any effects related to deaths from other endpoints.

Nevertheless, for someone who was already getting optimal chemoprevention against cardiovascular death, there remains the question of what the attendant risks might be for someone weighing the use of acetaminophen or an alternative analgesic. Thus, a patient taking 81 mg/day of aspirin to lower cardiovascular risk might still face...
the question of what non-prescription analgesic to use for pain. That
hypothetical patient could benefit from understanding the comparative
risks among the choices available. In this paper we compare the risks
for fatal outcomes caused by gastrointestinal hemorrhage, acute liver
failure or acute renal failure. We estimated risks for each of these three
outcomes for each of the non-aspirin non-prescription analgesics
approved in the U.S., in order to estimate the risk of death from these
causes related to use of each of these agents.

Methods

We studied the three oral non-aspirin drugs that are approved for
nonprescription analgesia in the US: acetaminophen, ibuprofen and
naproxen sodium. For each drug we obtained estimates of the recent
general-population point prevalence of use from the most recently
available data in the Slone surveys [13,14], which were conducted
during the period 2004 to 2007. The Slone Survey inquired about
analgesic use among adults age 18+ during the week before the survey.
For simplicity we assumed that users reporting that they used one
analgesic were nonusers of the others during the reporting period.

We obtained the number of deaths in the U.S. from acute liver
injury, acute renal failure, and gastrointestinal hemorrhage for the years
2006, 2007, and 2008 from the National Center for Health Statistics
Compressed Mortality File (CMF) [15]. The CMF uses counts of deaths
by cause from vital statistics registries and U.S. population estimates
from the Bureau of the Census. We restricted the mortality data to
age 20 years or older. Types of underlying cause of death were defined
by International Classification of Diseases, Tenth Revision (ICD-10)
codes [16]. Upper gastrointestinal hemorrhage was defined by codes
for gastrointestinal ulcer with hemorrhage or perforation (K25 through
K29 range, K92.2). Acute liver failure deaths were defined as codes
K72.0 (acute and subacute hepatic failure) and K76.7 (hepatorenal
syndrome). For acute renal failure we used code N17, which included
acute renal failure with tubular necrosis, or acute cortical necrosis,
or other or unspecified pathology. We converted the three years of
death data to one-year risks by dividing the average annual deaths in
each outcome category over the three years by the average U.S. adult
population age 20+ for those years (Table 1).

The total population one-year risk for each endpoint is a weighted
average of the risks among nonusers of analgesics and users of each of the
three analgesics. Most of the available literature on the risks associated
with non-prescription analgesic use compares the risk among users with
that of nonusers of that analgesic, and reports results as relative risks.
We searched the literature to obtain estimates of the relative risks for
each drug-endpoint combination. When more than one study reported
findings for a particular drug-endpoint combination, we combined the
results in a fixed-effects meta-analysis. For many combinations, there
was only one study reporting on the relation. We relied on population-
based or general practice studies whenever available, rather than
clinical trials and studies with comparison groups based on either no
NSAID exposure or past exposure. We used three estimates for each
of the 9 relative risks that we sought to estimate: we chose a central
estimate for our primary evaluation, and we also used a low estimate
and a high estimate for sensitivity analyses. Our estimates were based
on use of each product according to the label. We did not attempt to
incorporate risks stemming from accidental or deliberate overdoses,
although when low-dose or high-dose estimates were reported, we
used the high-dose result if it was within therapeutic guidelines. The
central estimate was either the only reported value or the result of a
meta-analysis of reported values. For the low and high estimates we
used the lower and upper confidence limits of the reported estimate
that we used for the central estimate, or the lower and upper confidence
limits of the meta-analysis, unless the lower bound was less than unity,
in which case we used unity instead.

For each relative risk, the nonusers could be defined either as
nonusers of that product or as nonusers of any analgesic. For our
calculations we considered nonusers to be those not using any analgesic.
If users of other analgesics are part of the referent group for the relative
risks, the estimates for the relative risk obtained may differ from what
would have been obtained with just nonusers of analgesics as the referent
group. Generally the inclusion of users of other products in the referent
group for a specific product would lead to slight underestimates of the
relative risk for that product compared with nonusers of any analgesic,
assuming that the analgesics elevate risks above the levels in nonusers.

From the relative risk values taken from the literature, we calculated
estimates of the absolute risk of each of the fatal endpoints for users
of each type of analgesic. We started from the overall risk of each
endpoint based on the deaths obtained from the National Center for
Health Statistics. That total risk for an endpoint is a weighted average
of the risks experienced by each category of analgesic user and the risk
among those unexposed to any of the analgesics. From the relative risks
and total risk, we back-calculated the risk among unexposed, from
which we could obtain the absolute risk for each analgesic category.
This calculation assumes that confounding between estimates is
comparatively unimportant.

Results

The prevalence of use of the three analgesics of interest among
people 18 years or older was 18% for acetaminophen [13], 17% for
ibuprofen, and 4.7% for naproxen sodium [14]. The one-year overall
risks of death are given in table 1 for the three endpoints. Risks are
low for all three categories, but about one order of magnitude lower
for acute liver failure than for acute renal failure or gastrointestinal
hemorrhage.

Table 2 gives the range of risk ratio estimates that we assembled
from the available literature. The first row indicates what we considered
the central estimate for each measure, based on either a fixed effects
meta-analysis or the use of a single study where only one was available.
The next two rows indicate lower and upper values that we took as the
plausible range. These values were either taken from the confidence
limits from the single study or meta-analysis, unless additional
information on dose or duration of use was available. The underlying
literature and reported values are summarized in table 3, which reports
values for any use of the NSAID, for low-dose use, and for high-dose
use. These categories are sometimes not available and, when they were,
not consistently defined across studies. In table 4, the number of deaths
predicted in a population experience of 1,000,000 person-years is
shown under three different scenarios, using the best estimates for the
risk ratios, the low estimates, and the high estimates.

<table>
<thead>
<tr>
<th>Underlying Cause of Death</th>
<th>Total Deaths</th>
<th>One Year Risk (cases/ 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Liver Failure</td>
<td>2,228</td>
<td>0.339</td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>24,323</td>
<td>3.696</td>
</tr>
<tr>
<td>Upper Gastrointestinal Hemorrhage</td>
<td>26,801</td>
<td>4.072</td>
</tr>
</tbody>
</table>

*The average number of deaths per year in 2006-2008 with the study condition
as underlying cause of death was 743 for ALF, 8,108 for ARF, and 8,934 for UGIH

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not consistently defined across studies. In table 4, the number of deaths
predicted in a population experience of 1,000,000 person-years is
shown under three different scenarios, using the best estimates for the
risk ratios, the low estimates, and the high estimates.
Under the best estimate scenario, use of any of the nonprescription analgesics is related to some increase in the overall risk of death from one of the three considered endpoints, compared with nonexposed. Acetaminophen use was estimated to carry the smallest increase in risk, about 35 deaths per million person-years of experience, most of the increase being attributed to an increase in risk of acute renal failure. Increased risk from using ibuprofen was estimated to be nearly twice as great as the increase for acetaminophen, at about 64 deaths per million person-years of experience, with a slightly larger increase in risk than acetaminophen for acute renal failure and a much greater risk for upper gastrointestinal hemorrhage. For naproxen sodium, the increase in risk for acute renal failure is smaller than the increase for either of the other two analgesics, but it is overshadowed by a much greater increase in risk for fatal upper gastrointestinal hemorrhage than the alternative drugs. The overall estimated increase in deaths related to naproxen sodium is 118 per million person-years. From the perspective of switching from acetaminophen to one of the alternatives, there would be an increase in the risk of a fatal adverse event in one of the three categories equal to about 29 deaths per million person-years if the switch is from acetaminophen to ibuprofen and 83 deaths per million person-years if the switch is from acetaminophen to naproxen sodium.

For the scenario based on using all the low estimates, switching from acetaminophen to ibuprofen would result in an estimated increase of 37 deaths per million person-years; for the high estimates, we estimated nearly the same number of deaths from using acetaminophen and ibuprofen. For naproxen sodium, low estimates resulted in an estimate of an increase of 86 deaths per million person-years for those switching from acetaminophen to naproxen, and 53 deaths per million person-years for the high estimates [17-27].

The risks for acute liver failure are so low from any of these drugs that this endpoint barely influences the calculations. Thus, if instead of a RR of 1.0 between acetaminophen and fatal acute liver failure, we had used a RR of 50, the risk of death among acetaminophen users from any of the three endpoints would have been 107 per million person-years instead of 93 per million person-years. The component due to acute liver failure increases from 2.7 to 16.8 deaths per million person-years, with the risk among unexposed changing from 2.7 deaths per million person-years to 0.34 deaths per million person-years. Under this scenario, the risks related to use of ibuprofen and naproxen sodium would be only slightly reduced from the values of 122 per million person-years and 177 per million person-years respectively, and there would be only a small change in the overall risk difference.

The other two endpoints, acute renal failure and upper gastrointestinal hemorrhage, are approximately equally common, with the overall estimated increase in deaths related to naproxen sodium being of similar magnitude.

Table 2: Range of Relative Risk Estimates for Three Nonprescription Analgesics in Relation to Three Fatal Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Published Relative Risk Estimates</th>
<th>First Author, Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>Any Use</td>
<td>1 (0.5, 2.0)</td>
</tr>
<tr>
<td>Low Use</td>
<td>assume 1.0</td>
<td></td>
</tr>
<tr>
<td>High Use</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Any</td>
<td>2.0</td>
</tr>
<tr>
<td>Low</td>
<td>1.4 (0.8, 2.4)</td>
<td>Perneger, 1994 [18]</td>
</tr>
<tr>
<td>High</td>
<td>2.1 (1.1, 3.7) (assume 3.0)</td>
<td>Perneger, 1994 [18]</td>
</tr>
<tr>
<td>UGI Hemorrhage</td>
<td>Any</td>
<td>1.3 (1.1, 1.5)</td>
</tr>
<tr>
<td>Low</td>
<td>1.00 (0.5, 2.0)</td>
<td>Garcia Rodriguez, 2001a [19]</td>
</tr>
<tr>
<td>High</td>
<td>3.4 (2.4, 4.8)</td>
<td>Garcia Rodriguez, 2001a [19]</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Acute liver failure</td>
<td>Any</td>
</tr>
<tr>
<td>Low</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Any</td>
<td>2.2 (1.9, 2.5)</td>
</tr>
<tr>
<td>Low</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>UGI Hemorrhage</td>
<td>Any</td>
<td>2.0 (1.6, 2.5)</td>
</tr>
<tr>
<td>Low</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Any</td>
<td>1.8 (1.6, 2.0)</td>
</tr>
<tr>
<td>Low</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>UGI Hemorrhage</td>
<td>Any</td>
<td>4.2 (3.4, 5.3)</td>
</tr>
<tr>
<td>Low</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

*Figures within parentheses are reported 95% confidence intervals.

Table 3: Published estimates of risk ratios for three nonprescription analgesics in relation to three fatal outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR Estimate</th>
<th>Acetamin.</th>
<th>Ibuprofen</th>
<th>Naproxen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Liver Failure</td>
<td>Best</td>
<td>1.0</td>
<td>2.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Low</td>
<td>1.0</td>
<td>1.8</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3.4</td>
<td>2.8</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>Best</td>
<td>2.0</td>
<td>2.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Low</td>
<td>1.4</td>
<td>1.9</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3.0</td>
<td>2.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Upper GI hemorrhage</td>
<td>Best</td>
<td>1.3</td>
<td>2.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Low</td>
<td>1.0</td>
<td>1.6</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>6.5</td>
<td>2.5</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Predicted Deaths per Million Person-Years by Cause of Death and Analgesic for Three Scenarios.
but the estimates from the literature of increased risk for each of the analgesics are more narrowly spread for acute renal failure than for upper gastrointestinal hemorrhage. Thus, the assumptions about the magnitude of effects for upper gastrointestinal hemorrhage dominate the risk calculations and projected differences in risk among these analgesics.

**Discussion**

This analysis is premised on an array of reported findings from the literature on analgesics, some of which are subject to considerable error. We also made a number of assumptions for ease of comparison. We assumed that all analgesics would be taken according to label directions. Thus, our estimate that acetaminophen likely does not increase risk of fatal liver failure is intended to describe the relation when users follow the instructions on the label. According to the FDA, “the risk of liver injury primarily occurs when patients take multiple products containing acetaminophen at one time and exceed the current maximum dose of 4000 mg within a 24-hour period” [28]. Nevertheless, even when the risk ratio for liver injury from acetaminophen was assumed to be 50 rather than 1, the overall risk of death from any of these three outcomes studied changed very little, because deaths from liver injury were so rare.

We also assumed that effects of analgesics were uniform over age, sex and other variables, and that there was no uncontrolled confounding that would have influenced the interpretation. Another assumption was that each person uses only one analgesic at a given time, although in reality there could be combination therapy. We ignored non-fatal adverse effects and limited attention among fatal outcomes to three endpoints, liver disease, renal disease, and upper gastrointestinal hemorrhage. Doing so involved what was perhaps the most important assumption, namely that the cardiovascular effects were constant across all the analgesics, and that all users were receiving minimal cardioprotective doses of aspirin. For someone who was not taking low-dose aspirin, the higher-dose of aspirin taken for analgesia might lower cardiovascular risk as a secondary effect and thus offset some of the increase in risk from upper gastrointestinal bleeding. But if the same person already takes low-dose aspirin, thus reducing the risk of cardiovascular death but not achieving analgesia, acetaminophen appears likely to be associated with a lower risk of death than ibuprofen or naproxen sodium, the other two non-aspirin non-prescription alternatives on the U.S. market.

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Use of nimesulide and other NSAIDs and the risk of upper gastrointestinal complications in Friuli Venezia Giulia, Italy. Analysis of cases with codes with high positive predictive value. Abstract 409. PDS 20: S178.


