Comparative Safety Evaluation of Non-narcotic Analgesics

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ABSTRACT. Both spontaneous reports and single outcome studies may distort the overall safety evaluation of drugs. We identified epidemiologic studies, published from January 1970 to December 1995, that investigated the association of serious adverse effects with aspirin, diclofenac, acetaminophen, and dipyrone to determine and compare the excess mortality associated with short-term drug use. The estimated excess mortality due to community-acquired agranulocytosis, aplastic anemia, anaphylaxis, and serious upper gastrointestinal complications was 185 per 100 million for aspirin, 592 per 100 million for diclofenac, 20 per 100 million for acetaminophen, and 25 per 100 million for dipyrone. The estimates were largely influenced by the excess mortality associated with upper gastrointestinal complications. A relative risk estimate of 300 or more for the association of dipyrone with agranulocytosis would have been necessary for the excess mortality of dipyrone to be comparable to that of aspirin or diclofenac. Based on published epidemiologic evidence used to determine the excess mortality associated with short-term use of these four non-narcotic analgesics, the current regulatory ranking of the drugs appears inappropriate.

KEY WORDS. Aspirin, dipyrone, diclofenac, mortality, acetaminophen

INTRODUCTION

Comprehensive risk evaluations should include comparisons of the safety of the agent to other drugs with similar indications. Comparative evaluations are of particular importance to avoid regulatory and clinical decisions based on single adverse events that are uncommon (e.g., those events with a low baseline incidence).

A comparative safety evaluation of drugs should employ an objective measure to incorporate and quantify the impact of a range of drug-specific adverse effects, with varying degrees of seriousness. For those effects that are life-threatening, an appropriate estimate for the comparative assessment is the excess mortality.

We reviewed the published epidemiologic literature to estimate and compare the excess mortality of four agents indicated for the short-term relief of pain: aspirin, diclofenac, acetaminophen, and dipyrone. In the 1970s, dipyrone was banned in the United States and several European nations, after reports of fatal agranulocytosis among users [1]. At the time dipyrone was banned, little information was available to quantify the risk associated with its use. In addition, no standards were established to compare agent-specific adverse effects.

Since the 1970s, considerable epidemiologic data have been published on the safety of non-narcotic analgesics. The association of the nonsteroidal anti-inflammatory drugs, such as aspirin and diclofenac, with serious upper gastrointestinal complications has been well documented [2–12], but has not affected their availability. In the United States, diclofenac is available with a prescription, and aspirin and acetaminophen are available over the counter. Because these agents are representative of non-narcotic analgesics commonly administered for pain, they are appropriate agents for comparison of safety with dipyrone. We sought to determine the appropriateness of the current regulation of these agents through a comparative evaluation of the number of deaths over a 1-week period attributable to a short-term course of therapy with each agent.

METHODS

We performed a search of the English language literature using the Medline database to locate all epidemiologic studies published from January 1970 to December 1995 that
investigated the association of potentially fatal adverse effects with aspirin, diclofenac, acetaminophen, and dipyrone. Life-threatening, drug-related adverse events that are predominantly reported were reviewed through the database, searching for the following terms: adverse effects, toxicity, gastropathy, peptic ulcer, gastrointestinal hemorrhage, gastrointestinal perforation, hepatotoxicity, hepatic disease, liver, renal failure, renal disease, kidney, blood dyscrasia, aplastic anemia, agranulocytosis, skin, toxic epidermal necrolysis, Stevens–Johnson Syndrome, anaphylaxis, anaphylactoid reactions, in conjunction with the aforementioned agents/drug class: aspirin; diclofenac (anti-inflammatory drugs, nonsteroidal); acetaminophen (paracetamol); dipyrone. We reviewed the abstracts of all articles to identify epidemiologic studies (cohort and case-control studies) investigating the associations of the analgesics with adverse events.

To be selected for the comparative evaluation, articles had to satisfy the following criteria. First, they investigated end points that were evaluated in published epidemiologic reports for all of the four agents (aspirin, diclofenac, acetaminophen, dipyrone). Four end points were identified that were evaluated in the literature for the four agents, including agranulocytosis, aplastic anemia, anaphylaxis, and serious upper gastrointestinal complications (hemorrhage and/or perforations). Second, they provided the requisite data to evaluate the excess mortality. For cohort studies, the necessary data included estimates of the risk difference and the case-fatality rate. For case control studies, the required data included estimates of the relative risk associated with drug exposure compared to non-exposure, the percentage of cases exposed to the drug, the overall incidence of the disease in the source population, and the case-fatality rate. When all necessary data were not included in the original article, we performed a Medline literature search to locate auxiliary reports by the study investigators that presented estimates of the overall risk of disease in the study population and/or estimates of the case-fatality rate.

For each study, we calculated the excess mortality attributable to short-term use (a 1-week period) by multiplying the estimate of the 1-week excess risk, or the risk difference (RD), by the case-fatality rate of each adverse effect. One-week risks of death in the general population were estimated from risk estimates for longer time periods under the assumption of a constant rate of disease.

The calculation of the 1-week risk difference from the case-control studies involved the following procedure [13,14]: The etiologic fraction (EF), the proportion of events in the study population than can be attributed to drug use, was calculated using the formula \( (RR-1)/RR \), where \( RR \) is the relative risk of an event in the exposed users compared to the non-exposed (non-users of the drug) and \( P_e \) is the percentage of cases who were exposed to the drug. Multivariate RR estimates were used in the calculations, when provided. The risk of becoming a case in non-users (\( R_n \)), was calculated as \( (1-EF)R_T \), where \( R_T \) is the overall incidence in the population. The risk of the event in users (\( R_u \)) was then estimated by multiplying the risk in the non-exposed by the estimate of the relative risk of the event in the exposed, \( (RR) \) (\( R_u \)).

The excess mortality was summed across adverse events to determine the overall excess mortality attributed to short-term use of each agent. When more than one study was located that assessed the association between an agent and a given adverse event, we used the median excess mortality estimate for the respective event. We evaluated the influence of age and history of peptic ulcer disease on the overall estimates, using the reported estimates of incidence, relative risk, and case-fatality rate, when available.

We assessed the influence of the baseline mortality rate and relative risk of events associated with the agents on the overall excess mortality estimate. To derive plausible estimates of the baseline mortality rates from the epidemiologic studies, estimates of the incidence of disease in those unexposed to the drug(s) were multiplied by the corresponding case-fatality rates.

**RESULTS**

We selected nine case-control studies that assessed the risk of agranulocytosis (one study) [13], aplastic anemia (one study) [13], anaphylaxis (one study) [15], or serious gastrointestinal complications (seven studies) [4–10] associated with aspirin, diclofenac, acetaminophen, or dipyrone. Of the seven studies examining gastrointestinal complications, six studies investigated the association with aspirin [5–10], three the association with diclofenac [4,6,9], three the association with acetaminophen [6,8,9], and one the association with dipyrone [10]. Three studies [4,7,9] restricted analyses to hospitalizations and/or deaths due to bleeding or perforated peptic ulcer, and another study [5] provided data to evaluate bleeding due to peptic ulcer exclusively. Estimates of the overall incidence and/or the case-fatality of the gastrointestinal complications were obtained from auxiliary reports [16–20] for five studies [5,7–10]. Table 1 presents the study estimates for the evaluation of the excess mortality associated with each of the agents [56].

Studies evaluating the association between the four analgesics and agranulocytosis, aplastic anemia, and upper gastrointestinal complications reported higher incidence rates and case-fatality rates in older age groups [6,9,13,15,16,18–20]. Table 2 presents the study estimates for the evaluation of the excess mortality associated with the agents among patients 60 years of age and older, reported in five studies evaluating the association between the analgesics and upper gastrointestinal complications [6–10] and the International Agranulocytosis and Aplastic Anemia Study, evaluating the association between the analgesics and agranulocytosis and aplastic anemia [13,21]. Age-related differences in the esti-
mates were not reported in the studies evaluating the associations of these agents with anaphylaxis [15].

**OVERALL EXCESS MORTALITY**

The overall excess mortality from agranulocytosis, aplastic anemia, anaphylaxis, and upper gastrointestinal complications was 185 per 100 million for aspirin, 592 per 100 million for diclofenac, 20 per 100 million for acetaminophen, and 25 per 100 million for dipyrone, using the median estimates of excess mortality due to gastrointestinal complications for each agent and the higher estimate of excess mortality due to agranulocytosis for dipyrone (Figure 1). The excess mortality associated with gastrointestinal complications was 185 per 100 million for aspirin, 592 per 100 million for diclofenac, 20 per 100 million for acetaminophen, and 25 per 100 million for dipyrone, using the median estimates of excess mortality due to gastrointestinal complications for each agent and the higher estimate of excess mortality due to agranulocytosis for dipyrone (Figure 1). The excess mortality associated with gastrointestinal complications was 185 per 100 million for aspirin, 592 per 100 million for diclofenac, 20 per 100 million for acetaminophen, and 25 per 100 million for dipyrone, using the median estimates of excess mortality due to gastrointestinal complications for each agent and the higher estimate of excess mortality due to agranulocytosis for dipyrone (Figure 1). The excess mortality associated with gastrointestinal complications was 185 per 100 million for aspirin, 592 per 100 million for diclofenac, 20 per 100 million for acetaminophen, and 25 per 100 million for dipyrone, using the median estimates of excess mortality due to gastrointestinal complications for each agent and the higher estimate of excess mortality due to agranulocytosis for dipyrone (Figure 1).
tions exerted the major influence on the overall estimate, contributing to 99% of the excess mortality in users of aspirin and diclofenac, 96% of the excess mortality of acetaminophen, and 69% of the excess mortality in users of dipyrrone. Substitution of the estimates from studies [6,10] with the smallest excess mortality due to gastrointestinal complications decreased the overall excess mortality estimate to 75 per 100 million for aspirin, 194 per 100 million for diclofenac, and 15 per 100 million for acetaminophen. If the highest estimates in the range were substituted, the excess mortality increased to 326 per 100 million with aspirin use, to 2120 per 100 million with diclofenac use, and to 64 per 100 million with acetaminophen use.

For aspirin, acetaminophen, and dipyrrone, the overall excess mortality estimates for individuals 60 years of age and older were higher than those estimates for the entire population.

### TABLE 2. Risk of agranulocytosis, aplastic anemia, anaphylaxis and serious upper gastrointestinal complications associated with nonnarcotic analgesics among patients 60 years of age and older

<table>
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<tr>
<th>Analgesic</th>
<th>Relative risk</th>
<th>Proportion of exposed cases</th>
<th>Overall annual incidence (10^8)</th>
<th>Weekly excess risk in users (10^8)</th>
<th>Case-fatality rate</th>
<th>Weekly excess mortality in users (10^8)</th>
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*a* Age-related differences in the estimates were not reported.

*b* Pooled estimate for the years 1987 and 1988, using method outlined by Greenland [56].

*c* Serious upper gastrointestinal complications, including hemorrhage and perforations.
population. Nevertheless, the relative ranking of the estimates for the three agents remained the same. The estimates were 417 per 100 million for aspirin, 613 per 100 million for diclofenac, 47 per 100 million for acetaminophen, and 74 per 100 million for dipyrone, using the median estimates of excess mortality due to gastrointestinal complications.

Laporte et al. [6] evaluated the risk of gastrointestinal complications associated with analgesic use among individuals without a history of peptic ulcer disease. Assuming a case-fatality rate of 2.3%, the excess mortality in individuals without a history of peptic ulcer disease was 79 per 100 million for aspirin, 138 per 100 million for diclofenac, 3.6 per 100 million for acetaminophen, and 5.4 per 100 million for dipyrone. Assuming the risk of agranulocytosis, aplastic anemia, and anaphylaxis would not be affected by a history of peptic ulcer disease, the overall excess mortality estimates were 80 per 100 million for aspirin, 144 per 100 million for diclofenac, 4.4 per 100 million for acetaminophen, and 13 per 100 million for dipyrone.

Figure 2 illustrates the sensitivity of our results to changes in the estimates of the relative risk and the baseline mortality of gastrointestinal complications, evaluating the range of estimates found in the selected studies. The median values for the relative risks (3.1 for aspirin, 7.9 for diclofenac, 1.5 for acetaminophen, and 1.6 for dipyrone) associated with drug use and the weekly baseline mortality rates (1 per million) give excess mortality estimates of 211 per 100 million for aspirin, 696 per 100 million for diclofenac, 51 per 100 million for acetaminophen, and 68 per 100 million for dipyrone. The minimum value of the baseline mortality (20.5 per 100 million) yielded excess mortality estimates for aspirin and diclofenac which were more than two-fold higher than that of dipyrone and acetaminophen, 44 per 100 million for aspirin, 147 per 100 million for diclofenac, 11 per 100 million for acetaminophen, and 20 per 100 million for dipyrone. Substitution of the minimum values for the relative risk estimates yielded similar disparities in the estimates. Assuming the median estimates of excess mortality associated with gastrointestinal complications, relative risk estimates of 300 to 1100 for the association of dipyrone with agranulocytosis would be necessary for the overall excess mortality of dipyrone to be comparable to that of aspirin and diclofenac, respectively. Alternatively, a baseline annual mortality rate of 6 to 20 per million for agranulocytosis, at least 20 times higher than that estimated, would be necessary for the excess mortality estimate of the drugs to be similar.

Figure 3 presents estimates of the overall annual incidence of a number of additional adverse effects reported
with the use of one or more of the evaluated analgesics [22–34]. The majority of adverse event rates were evaluated in populations for which dipyrone had been banned. The estimated mortality rates associated with each of these diseases (including Stevens–Johnson syndrome, toxic epidermal necrolysis, toxin-induced renal failure, acute idiopathic hepatic disease, and acute pancreatitis), that have rarely been reported with short-term use of the evaluated analgesics, are at least 10-fold less than that of serious upper gastrointestinal complications. Thus, further evaluation of these events would likely have little impact on the overall study results.

**DISCUSSION**

The absolute risk of mortality associated with dipyrone appears to be similar to acetaminophen and substantially lower than the risk associated with aspirin and diclofenac, other agents commonly used for short-term pain relief. The estimated excess mortality due to agranulocytosis, aplastic anemia, anaphylaxis, and serious upper gastrointestinal complications was 185 per 100 million for aspirin, 592 per 100 million for diclofenac, 20 per 100 million for acetaminophen, and 25 per 100 million for dipyrone. The estimates were largely influenced by the excess mortality associated with upper gastrointestinal complications, an adverse effect more commonly associated with use of aspirin and diclofenac than with use of dipyrone or acetaminophen. While the absolute values of the excess mortality varied according to patient age and history of peptic ulcer disease, the disparity in estimates between the agents remained.

No combination of plausible estimates for the relative risk and the baseline mortality of gastrointestinal complications or agranulocytosis associated with drug use resulted in excess mortality greater with dipyrone than with the selected nonsteroidal anti-inflammatory drugs. A relative risk estimate of 300 or more for the association of dipyrone with agranulocytosis, or a baseline mortality of agranulocytosis 20 times greater than that estimated, would be necessary for the excess mortality of dipyrone to be comparable to that of aspirin or diclofenac.

Several limitations are apparent with our quantification of total risk associated with drug therapies. First, the analysis was limited to epidemiologic investigations of adverse effects assessed with each of the agents. Because potential adverse effects not evaluated in the epidemiologic literature or not evaluated for each of the agents were not incorporated [28,32,35–37], the overall excess mortality was likely to be underestimated for each of the agents. However, the relatively small mortality rates for acute idiopathic pancreatitis, idiopathic hepatic disease, toxin-induced renal disease, and serious dermatologic reactions would be expected to have a minor effect on the overall estimation of risk (Fig. 3). For example, the weekly excess mortality due to hepatic disease among users of diclofenac was approximately 5 per 100 million, 100-fold less than the excess mortality due to upper gastrointestinal complications [27].

Restriction of our analysis to epidemiologic studies that provided adequate information to evaluate the excess mortality may have influenced our findings. For diclofenac, the relative risk estimates for the association with upper gastrointestinal complications included in our analyses were moderately higher than generally observed in epidemiologic investigations, which have indicated a 3- to 5-fold increase in risk [38–45]. For aspirin and dipyrone, the relative risk estimates that were included in our analyses are similar to those reported in other epidemiologic investigations [38,39,41,43,44,46–50]. The associations of the non-nar-
cotic agents with agranulocytosis, aplastic anemia, and anaphylaxis were each based on one study only [13,15].

Another major limitation of our evaluation was the use of relative risk estimates that did not account for the drug dose, duration of therapy, or previous therapy with the drugs under study. We were not able to assess the excess mortality according to drug dose, although a number of studies have reported a progressively increased risk of gastrointestinal complications with increasing dose of nonsteroidal anti-inflammatory drugs [9,10,38,39,42,51]. In addition, we assumed that the risk of adverse effects was constant throughout therapy, which is unlikely to be true. The majority of anaphylactic reactions occur within 1 hour after drug exposure [52]. The risk of gastrointestinal hemorrhage is higher early in nonsteroidal anti-inflammatory drug therapy (within 1 week to 1 month after the initiation), with a decreasing risk over time [9,17,51,53–55]. Non-constant hazards of agranulocytosis and aplastic anemia over a course of drug therapy are also likely. The relative risk estimates upon which we relied are drawn from studies that included both early (higher risk) and later (lower risk) periods of use of all the drugs. Thus, the short-term use for acute pain relief envisioned in the present analysis is likely to carry higher risks for all adverse effects and all drugs, and to accentuate the difference among drugs.

Our analysis is restricted by the validity of the estimates reported in the published literature. The data may be flawed, due to confounding or other biases. We used the data reported from all studies without rating the quality of the study design and analysis.

Considerable heterogeneity in the estimates of excess mortality due to upper gastrointestinal complications existed between studies, resulting from the disparate estimates.
of relative risk, total incidence in the population, and the percent of patients exposed to the agent being evaluated. The wide variation in estimates may be a function of differences in the predispositions of the study populations or in the diagnostic criteria among studies. The data necessary for the evaluation of the precision of the overall risk estimates were not available for many of the studies, precluding appropriate assessment of the precision of the excess mortality estimates and the differences between the estimates. Thus, we used the median estimates of excess mortality and evaluated the influence of the baseline mortality rate and relative risk estimates used in our assessment, rather than performing a meta-analysis to calculate summary estimates.

The current regulatory positions of these four non-narcotic analgesics bear an inappropriate relation to their hazards in users. At the time of regulatory action banning dipyrone, information was unavailable to quantify and compare the safety of the agent to other non-narcotic analgesics. However, the considerable epidemiologic evidence now available suggests that appraisal of the overall safety of the agents in users. At the time of regulatory action banning dipyrone, information was unavailable to quantify and compare the safety of the agent to other non-narcotic analgesics. However, the considerable epidemiologic evidence now available suggests that appraisal of the overall safety of the agents should incorporate examination of the baseline incidences of the adverse events rather than evaluation of relative risk estimates and spontaneous reports exclusively.

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References


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