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Systematic review: the hepatotoxicity of non-steroidal anti-inflammatory drugs

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SUMMARY

Background: Non-steroidal anti-inflammatory drugs have been implicated in reports of liver injury. However, the precise risk of non-steroidal anti-inflammatory drugs for this rare complication is unknown.

Aim: To review systematically the published literature of population-based epidemiological studies reporting the incidence or comparative risk of non-steroidal anti-inflammatory drugs for liver injury resulting in clinically significant events, defined as hospitalization or death.

Data extraction: Duplicate extraction of the methodological quality, design, source, population, years studied, particular non-steroidal anti-inflammatory drugs studied, definitions, patient counts and follow-up, and the adjustment for confounders.

Results: Seven articles met inclusion criteria. The comparative risk of liver injury resulting in hospitalization for current non-steroidal anti-inflammatory drug users compared with past non-steroidal anti-inflammatory drug users ranged from 1.2 to 1.7, but none was statistically significant. The incidence of liver injury resulting in hospitalization ranged from 3.1 to 23.4/100 000 patient-years of current use of non-steroidal anti-inflammatory drugs, with an excess risk compared with past non-steroidal anti-inflammatory drugs users of 4.8–8.6/100 000 patient-years of exposure. There were zero deaths from liver injury associated with non-steroidal anti-inflammatory drugs use in over 396 392 patient-years of cumulative exposure.

Conclusion: These findings allow for the possibility of a small increase in the risk of clinically relevant hepatotoxicity with non-steroidal anti-inflammatory drugs use, but do not document that such a risk occurs.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used medications in the United States.[1, 2] The major adverse effect of NSAIDs, gastrointestinal (GI) mucosal injury, is well-known. Additionally, numerous case reports have described patients who develop fatal liver injury while taking NSAIDs.[3–7] In 1998, the NSAID bromfenac was withdrawn from the USA market due to four deaths and eight liver transplantations, with severe liver injury occurring in an estimated 1/10 000–20 000 users.[8]

The magnitude of clinically significant liver disease associated with NSAIDs is likely relatively small, and is therefore difficult to assess in controlled trials. Excessive spontaneous reports of adverse effects can signal a potential problem, but these spontaneous reports are inadequate to provide a true population-based incidence and are an unreliable measure of risk.[9] Therefore, we systematically reviewed the published literature for

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population-based observational studies assessing the incidence or comparative risk of clinically significant hepatotoxicity associated with NSAIDs.

NSAIDs may also be associated with asymptomatic elevations in liver tests, but these laboratory tests are variably performed and reported in population-based studies, the frequency of their use may be influenced by underlying patient disease or medication use (e.g. liver tests are more likely to be checked in patients using diclofenac than in those taking other NSAIDs), and asymptomatic liver test elevations are of unclear clinical significance. Therefore, we limited our search to studies with clinically meaningful outcomes: hospitalizations and deaths.

METHODS

Study selection

We selected population-based epidemiological studies reporting the incidence or comparative risk of hospitalizations or death because of hepatotoxicity among adult patients taking NSAIDs, including cyclo-oxygenase-2 (COX-2)-specific inhibitors. We accepted case–control, controlled cohort, and single cohort population-based studies. We excluded spontaneous reports of adverse drug reactions, studies examining only aspirin, or studies reporting only asymptomatic elevations in liver function tests or liver diagnoses without hospitalization.

Both investigators independently searched the Medline, Pre-Medline, and Embase electronic databases from 1966 to 2004 using a search strategy limited to humans with the following Medical Subject Headings: (i) non-steroidal anti-inflammatory agents, naproxen, ibuprofen, diclofenac, cyclooxygenase inhibitors, celecoxib, rofecoxib, valdecoxib, or meloxicam, and (ii) toxic hepatitis, liver, or liver diseases, and (iii) epidemiology, epidemiological methods, case–control studies, cohort studies, incidence, or prevalence. The titles and abstracts were reviewed to identify potentially relevant articles, and the full manuscript for each of those deemed by consensus to be potentially useful was obtained and reviewed. Citations from these articles and selected review articles were cross-referenced to identify additional potential articles. Studies presented only in abstract were not included. No attempt was made to contact study authors. Any discrepancies regarding whether articles met selection criteria were resolved by consensus.

Study assessment and data abstraction

The methodological quality of each article was assessed using criteria of the United States Preventive Services Task Force for case–control and controlled-cohort studies.[10] These criteria rate the internal validity of a study as 'good' (meaning all of the criteria are met), 'fair' (not all of the criteria are met, but there are no fatal flaws), or 'poor' (fatal flaw in at least one of the criteria). The criteria for controlled-cohort studies were modified for single-cohort studies: the first two criteria relating to assembly and maintenance of comparable groups were deleted and the third criterion was modified by removing the reference to a differential loss to follow-up. Both authors assessed each article independently, and any discrepancies were resolved by consensus.

Using a predesigned data abstraction sheet, data were abstracted by both authors on study design type, data source, country of population, years of data collection, particular NSAIDs studied, case and control definitions, numbers and follow-up of cases and controls, outcome and exposure definitions, outcome measures, and the presence of adjustment for potential confounders such as medications or illnesses.

Analysis

Wherever possible, we derived the incidence of hospitalizations per patient-years of exposure and rate ratios comparing incidences among individual NSAIDs from the data published.

Role of funding sources

None of the funding sources had any role in the design, performance, analysis, or reporting of this review.

RESULTS

Study characteristics

Literature searches of the electronic databases yielded 1141 unique citations. Review of the titles and abstracts left 16 articles potentially meeting selection criteria.[11–26] Cross-referencing the references listed in those articles and in selected review articles yielded only one additional potential article.[27] Of these 17 studies, 10 were found not to meet inclusion criteria because they were not population-based,[11, 19, 27] cases were ascertained by

spontaneous reporting of adverse reactions,[24] the exposure studied was not NSAIDs,[14, 20, 23, 27] the outcomes did not include hospitalizations or death from hepatotoxicity,[11, 14, 19–22, 25] or the study was not published as a full article.[19]

Characteristics of the seven remaining studies are shown in Table 1. There was one case–control study,[15] one nested case–control study,[16] two retrospective single-cohort studies that included nested case–control studies,[17, 26] and three retrospective single-cohort studies without nested case–control studies.[12, 13, 18] Three of the cohort studies had control groups that were defined as patients with prior exposure to NSAIDs (specified as 60 days after the NSAID prescription,[12] or 104 days[26] or 180 days[18] after the duration of the NSAID prescription); therefore, we classified these studies as single-cohort designs as no truly unexposed arm existed.

The internal validity of the studies is also shown in Table 1. One study was rated as good and six were rated as fair. Two of the articles reported different analyses from the identical data set.[12, 16] All of the studies attempted to exclude other probable causes of liver disease. All of the studies reported outcomes of hospitalizations with elevated liver tests, but not all reported deaths.

Study results

The incidence of liver injury resulting in hospitalization ranged from 3.1 to 23.4/100 000 patient-years of current use of NSAIDs in the cohort studies (Table 2). Three studies reported the incidence of hospitalization for liver injury in a control population (all used past NSAID users as controls), and it ranged from 0 to 14.8/100 000 patient-years. The excess risk attributable to NSAIDs ranged from 4.8 to 8.6/100 000 patient-years of exposure. Estimates of the comparative risk for current NSAID users ranged from 1.2 to 1.7 times the control populations, but the confidence intervals (CI) all crossed the null value, and the upper limit was as high as 3.7 (Tables 2 and 3).

Three cohort studies reported zero liver-related deaths among a cumulative exposure of over 396 392 - patient-years (95% CI: 0–0.9 deaths per 100 000 - patient-years).[13, 17, 26] No study mentioned any patient receiving an orthotopic liver transplantation.

The median interval from the time of the initial prescription to the admission was 11 days in one study.[26] Another study reported that the unadjusted relative risk for acute liver injury was 1.9 (95% CI: 0.8–4.9) for the first prescription compared with subsequent prescriptions, although these results are based on a combination of in-patients ($n = 8$) and out-patients ($n = 15$).[17]

Although older patients were at greater risk for liver injury in general,[18, 28] there was no association between age and NSAID hepatotoxicity *per se*.[17, 18, 28] Two studies reported no effect of gender,[17, 18] while a third study found men to be at increased risk when controlling for current NSAID usage and age.[28]

No study assessed the effect of concurrent illness on hospitalizations for NSAID-associated liver injury. However, one study, assessing in-patient ($n = 8$) and out-patient ($n = 15$) acute liver injury combined, found that patients whose indication for treatment was rheumatoid arthritis had a relative risk of 10.9 (95% CI: 2.4–50.2) compared to patients with osteoarthritis, adjusting for age, gender, duration of usage, and concomitant hepatotoxic medications.[17]

One study reported no difference in odds ratios (OR) for hospitalization for NSAID-associated liver injury among patients concomitantly exposed to other hepatotoxic medications compared with those not exposed.[15] In contrast, another study reported an OR of 5.9 (95% CI: 2.8–12.4) with the use of hepatotoxic medications other than NSAIDs, adjusted for current usage of NSAIDs, age, gender, and calendar year.[16] An additional study of out-patient and in-patient acute liver injury found a relative risk of 8.6 (95% CI: 3.3–22.8) with the use of hepatotoxic drugs, adjusted for age, gender, duration of NSAID usage, and treatment indication.[17]

Three studies reported the comparative risks of individual NSAIDs specifically for hospitalizations from liver injury, but each used different comparison populations (Tables 4 and 5). Traversa *et al.* reported comparisons with past users of any NSAIDs,[26] while the control population employed in the nested case–control study of Perez Gutthann *et al.* was current or past users of NSAIDs.[16] In the case–control study by Carson *et al.* the unexposed patients did not have a prescription for an NSAID within 30 days of admission, but might have had one earlier.[15] The different comparison populations and use of adjustment for other factors in the analyses makes it difficult to compare outcomes from the various studies. However, a statistically significant association with hepatotoxicity was only found for two NSAIDs in any of the studies: nimesulide and sulindac.

Table 1. Characteristics of studies included in systematic review

Study (Reference)	Design	Data source	Country	Years	NSAIDs studied	Quality rating	Reasons not good quality
Traversa *et al.*[26]	RSC* and NCC	National Health Service Database and chart review	Italy	1997–2001	Nimesulide compared with all other NSAIDs	Fair	Reviewed 72% of cases Controls had previous NSAID prescriptions
Lanza *et al.*[18]	RSC*	United Health Care (HMO) database and chart review	USA	1989–1991	Non-aspirin NSAIDs	Fair	Low-cost generics not automatically recorded No adjustment for potential confounders
Garcia Rodriguez *et al.*[17]	RSC and NCC	GPRD and follow-up doctor survey	UK	1987–1991	Ibuprofen, diclofenac, naproxen, mefenamic acid, indometacin (indomethacin), ketoprofen, piroxicam, fenbufen, diflunisal, tenoxicam, fenoprofen, sulindac	Fair	Controls had previous NSAID prescriptions
Carson *et al.*[15]	CC	Medicaid database and chart review	USA	1980–1987	Any	Fair	Reviewed ≈50% of cases
Perez Gutthann and Garcia Rodriguez[16]	NCC	Saskatchewan Department of Health databases and chart review	Canada	1982–1986	12 NSAIDs plus aspirin	Fair	All controls had previous NSAID prescriptions
Garcia Rodriguez *et al.*[12]	RSC*	Saskatchewan Department of Health databases and chart review	Canada	1982–1986	12 NSAIDs plus aspirin	Good	N/A
Jick *et al.*[13]	RSC	GPRD and chart review	UK	1988–1991	Diclofenac, piroxicam, and naproxen only	Fair	Did not strictly exclude other potential causes of liver disease or adjust for confounders, but did provide narratives for each case Report of outcomes is inconsistent

RSC, retrospective single cohort; NCC, nested case–control; CC, case–control; GPRD, General Practice Research Database; HMO, health maintenance organization; N/A, not applicable.
* Classified as single cohort because 'controls' were past users and not truly unexposed.

Table 2. Results of population-based cohort studies for any NSAID

Study (Reference)	Definition of exposure	Definition of controls	Pt-yrs cases/ Pt-yrs controls	Outcome definition	Case incidence (95% CI) per 100 000 pt-yrs	Control incidence (95% CI) per 100 000 pt-yrs	Rate ratio (95% CI)	Confounders
Traversa *et al.*[26]	Current use (≤ duration of Rx + 2 weeks)	Past use (3.5–12 months after duration of Rx) matched for sex, age, and date of admission	140 836/ 378 433	Admission for acute non-viral hepatitis with liver tests ≥2× ULN	23.4 (16.1–32.9)*	14.8 (11.1–19.2)*	1.4 (0.9-2.1)	Adjusted for age, gender
Lanza *et al.*[18]	Current or recent use (≤ 30 days after duration of Rx)	Distant past (>180 days after the duration of the Rx, up to 12 months after last dispensing)	20 893/ 13 303	Admission with signs or symptoms of new liver disease, abnormal liver tests, and no other potential causes	4.8 (0.1–26.7)*	0 (0.0–27.7)*	Not calculable	N/A
Garcia Rodriguez *et al.*[17]	Current use (≤ 60 days after Rx)	N/A	Approximately 260 000*/ N/A	Admission for acute liver injury with liver tests ≥2× ULN (all happened to be jaundiced)	3.1 (1.3–6.1)*		N/A	N/A
Garcia Rodriguez *et al.*[12]	Current use (≤ 60 days after Rx)	No current use (>60 days after Rx)	177 550/ 467 906	Admission for acute liver injury with liver tests ≥2× ULN	9.0 (6–15)	3.8 (2.1–5.6)*	1.7 (0.8–3.7)	Adjusted for age, gender (unadjusted was 2.3, 95% CI: 1.1–4.9)
Jick *et al.*[13]	Current use (≤ 90 days after Rx)	N/A	102 644 pts/N/A	Admission for liver disorder, and NSAID deemed 'definitely', 'probably', or 'possibly' causal	1.9–3.9/ 100 000 pts* or 0.6–1.1/ 100 000 Rx's*	N/A	N/A	N/A

Pt-yrs f/u, patient-years of follow-up; CI, confidence interval; Rx, prescription; ULN, upper limit of normal; N/A, not applicable; NSAID, non-steroidal anti-inflammatory drug.
* Derived from the published data.

Table 3. Results of population-based case–control study for any NSAID

Study (Reference)	Definition of cases	Definition of controls	Definition of exposure	Number of cases/number of controls	Odds ratio (95% CI)	Confounders
Carson *et al.*[15]	Admission for new acute liver disease with liver tests >2× ULN, not diagnosed incidentally during hospitalization	Matched by sex, age, state, without liver disease	NSAID dispensed ≤ 30 days prior to date of admission	107/428	1.2 (0.5–2.8)	Adjusted for age, gender, state, other drug exposure

CI, confidence interval; ULN, upper limit of normal; NSAID, non-steroidal anti-inflammatory drug.

Table 4. Risks of individual NSAIDs for liver disease (with liver tests ≥2× ULN) resulting in hospital admission: controlled-cohort study[26]

Drug	Rate per 100 000 patient-years (95% CI)	Rate ratio* (95% CI)
Celecoxib	15.1 (0.4–84.2)	1.0 (0.1–7.3)
Diclofenac	22.4 (9.7–44.1)	1.5 (0.7–3.2)
Ibuprofen	44.6 (5.4–160)	3.0 (0.7–12.4)
Naproxen	12.8 (0.3–71.1)	0.9 (0.1–6.2)
Nimesulide	33.1 (18.9–53.8)	2.2 (1.3–3.0)
Piroxicam	13.6 (4.9–46.4)	1.2 (0.4–3.4)

CI, confidence interval; ULN, upper limit of normal; NSAID, non-steroidal anti-inflammatory drug.
* Ratio for current use of individual NSAID vs. past use of any NSAID.

DISCUSSION

We systematically reviewed the published literature for population-based epidemiological studies of the risk associated with NSAIDs for clinically significant hepatotoxicity, which we defined as that resulting in hospitalization or death. The individual studies estimated a slight increase in risk for liver injury with NSAID use, resulting in a 20–70% higher incidence of hospitalization compared with controls, but the increase was not statistically significant in any study. The absolute incidence ranged from 3.1 to 23.4/100 000 patient-years of exposure, with an excess risk when compared with past NSAID users from 4.8 to 8.6/100 000 patient-years. No fatal cases of NSAID hepatotoxicity were reported, suggesting that the mortality rate is likely to be <1/100 000 patient-years.

Liver injuries associated with NSAIDs appear to be idiosyncratic reactions, and can present with hepatocellular or cholestatic patterns; the severity can range from asymptomatic elevations in liver tests to case reports of fulminant hepatic necrosis resulting in death or the need for transplantation.[3] Spontaneous reports of adverse drug events are helpful warning signals for rare toxicities, but do not allow determination of incidence or relative risk and can lead to spurious conclusions.[9] Reviewing epidemiological observational studies, we found that serious liver injuries associated with NSAIDs are quite rare, and that whether an increased risk is present at all is difficult to determine with certainty. While the case reports can be alarming, it is important to keep the hepatotoxicity of NSAIDs in perspective. In one of the studies reported, the odds of liver injury requiring hospitalization associated with known hepatotoxic medications was approximately sevenfold higher in the absence of NSAID use.[16] Clearly, on an individual patient level, NSAIDs do not pose a very large risk of hepatotoxicity.

The use of NSAIDs is exceedingly prevalent: 6% of the adult USA population report using a prescription NSAID in a month, and 24% report using non-prescription ibuprofen, albeit only 3% report using the ibuprofen for more than 14 days in the month.[25] Assuming 10% of the population is taking NSAIDs at any one time, even an excess risk of liver injury resulting in hospitalization of 4.8/100 000 patient-years would lead to 1200 excess annual cases of hepatotoxicity in the USA hospitals. Assuming 20% of the population is taking NSAIDs, an excess risk from NSAIDs of 8.6/100 000 patient-years would lead to 4300 excess annual hospitalizations. Nonetheless, the potential for hepatotoxicity pales in comparison with the upper GI toxicities from traditional non-selective NSAIDs, which confer an excess risk of 1000–1500/100 000 patient-years of exposure for upper GI complications.[28]

If there is a small increased risk for hepatotoxicity from NSAIDs, which patients are at risk? Women and the elderly have been suggested to be at higher risk,[3] but

Table 5. Risks of individual NSAIDs for acute liver disease (with liver tests >2× ULN) resulting in hospital admission

Drug	Cases (%) $n = 107$	Controls (%) $n = 428$	Odds ratio (95% CI)
(a) Case–control study with controls matched by gender, age and state[15]			
Ibuprofen	3 (2.8)	9 (2.1)	1.3 (0.2–5.5)
Naproxen	1 (0.9)	7 (1.6)	0.6 (0.01–4.5)
Piroxicam	1 (0.9)	2 (0.5)	2.0 (0.03–38.9)
Sulindac	4 (3.7)	4 (0.9)	4.1 (0.8–22.4)
(b) Nested case-control study[16]			
	Cases (%) $n = 34$	Controls (%) $n = 500$*	Adjusted odds ratio† (95% CI)
Diclofenac	1 (2.8)	13 (2.6)	2.0 (0.2–17.4)
Ibuprofen	1 (2.8)	6 (1.2)	1.2 (0.1–12.0)
Indometacin	4 (11.8)	30 (6.0)	2.6 (0.8–8.6)
Naproxen	3 (8.8)	27 (5.4)	1.7 (0.5–6.4)
Piroxicam	4 (11.8)	33 (6.6)	2.0 (0.6–6.8)
Sulindac	4 (11.8)	10 (2.0)	5.0 (1.3–18.5)

ULN, upper limit of normal; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug.
* Control population consists of current or past users of NSAIDs without hospitalization for acute liver disease.
† Adjusted for current use of NSAIDs, age, gender, year, other hepatotoxic drugs.

those assertions were not borne out by the evidence. Patients using certain NSAIDs may have a higher risk, with the best evidence present for nimesulide and sulindac, and patients being treated for rheumatoid arthritis may also be at higher risk than those treated for osteoarthritis. The evidence is mixed with regard to whether the concomitant use of other hepatotoxic drugs increases the risk from NSAIDs, but suggests that such an effect may indeed exist. The highest risk for liver injury may be within the first few weeks of taking the medication.

As with any systematic review, the major limitations of this review are the methodological qualities of the individual studies and the heterogeneity of designs, including study types, populations, exposures, and outcomes in each study. Most of the studies were prone to ascertainment bias of some sort. For instance, administrative claims databases generally do not include information on non-prescription NSAIDs, and testing for hepatitis C was not yet available during many of the study periods; both of these shortcomings could lead to incorrect assignment of liver injury cases. All of the studies were prone to misclassification bias, which is a distortion in the measure of effect because of inaccurate assignment of the status of subjects' exposure or outcome. Three studies used controls with exposure to NSAIDS in the more distant past, and none of the studies performed a manual chart review unless the outcome was present for the patient in the retrospective electronic database search. Finally, as with any observational study, any associations cannot be assumed to be causal relationships; for instance, the non-specific prodrome of a toxic hepatitis might have led doctors to prescribe NSAIDs, rather than the NSAIDs causing the toxicity.[12]

In summary, our findings allow for the possibility of a small increase in the risk of clinically relevant hepatotoxicity with NSAID use, but do not document that such a risk occurs. Additional carefully designed epidemiological studies would allow for more precise estimates of the risk, but would require very large populations given the rarity of clinically significant events.

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