Naproxen sodium did not lead to substantially more upper gastrointestinal tract bleeding than ibuprofen during short term use as an analgesic


Question
Do patients who use naproxen sodium as an over the counter analgesic have an increased risk of upper gastrointestinal tract bleeding compared with those who use ibuprofen?

Design
A case cohort study in which exposure to naproxen sodium and ibuprofen was compared in patients from a claims database who had upper gastrointestinal tract bleeding and in a subcohort of patients from the database.

Setting
Michigan and Ohio, USA.

Participants
Patients were eligible if they had received benefits from Ohio Medicaid or Michigan Medicaid and had received naproxen sodium or ibuprofen, but not both drugs. From a cohort of 378,919 patients in the Computerized On-Line Medical Pharmaceutical Analysis and Surveillance System (COMPASS), 59 patients (54% men) who were admitted to hospital for upper gastrointestinal tract bleeding within 14 days of their first prescription for naproxen sodium (n=26) or ibuprofen (n=33) were selected as case patients; a random sample of 37,891 patients (71% women) was selected as a subcohort to determine relative prescription rates (n=10,024 for naproxen sodium; n=27,867 for ibuprofen).

Main outcome measures
Inpatient diagnoses recorded in COMPASS were used to identify patients who had upper gastrointestinal tract bleeding within 14 days of their first prescription of ibuprofen or naproxen sodium.

Commentary
Epidemiological studies of patients taking prescribed non-steroidal anti-inflammatory drugs (NSAIDs) show that these drugs are associated with a three to 10-fold increased risk of bleeding, perforation, hospitalisation and death.1 Primary studies and meta-analyses also show that NSAIDs differ in their risk. Ibuprofen is consistently associated with lower risks than the group as a whole whereas other NSAIDs such as piroxicam and azapropazone seem to be associated with relatively high risks.

In recent years a number of NSAIDs have become available over the counter. This may partly reflect patent expiry, anticipation of a new generation of NSAIDs (COX-2 selective or NO-NSAIDs) and recognition that the absolute risks of short term, low dose treatment are relatively low.

The problem has been to assess the safety of drugs in this setting. In their study Strom et al have attempted to quantify the risks of over the counter naproxen sodium by reference to a prescribing situation that tried to replicate intended patterns of over the counter use. Information was gathered from the Computerized On-Line Medical Pharmaceutical Analysis and Surveillance System (COMPASS) database for Michigan and Ohio, USA. Patients were eligible for study if they had received benefits from Ohio or Michigan Medicaid and had received naproxen, sodium or ibuprofen but not both drugs. Age, sex, race, US state, inpatient and outpatient diagnoses, drugs dispensed for outpatients, and any over the counter drugs that were paid for by Medicaid were extracted from COMPASS.

Main results
The incidence of inpatient upper gastrointestinal tract bleeding was 0.026% (95% CI 0.017% to 0.038%) for patients who were prescribed naproxen sodium and 0.012% (CI 0.008% to 0.017%) for patients who were prescribed ibuprofen. Patients with uncertain Medicaid eligibility, long-term NSAID use, and use of non-steroidal anti-inflammatory agents (NSAIDs), or concomitant use of other NSAIDs were excluded from the analysis (n=10 for the case patients; n=7,989 for the subcohort) and the results were adjusted for the state of residence, age group, sex, and presence of pre-existing gastrointestinal tract bleeding. Compared with patients who received ibuprofen, those who received naproxen sodium had an increase in the adjusted relative risk of upper gastrointestinal tract bleeding that required hospital admission (adjusted relative risk 2.0, 95% CI 1.1 to 3.8), but no increase in the adjusted absolute risk occurred (adjusted absolute risk difference 0.0011%, CI −0.0001% to 0.0023%).

Conclusions
The incidence of upper gastrointestinal tract bleeding was low for naproxen sodium and ibuprofen. Although patients who used naproxen sodium as an analgesic had an increase in the relative risk of upper gastrointestinal tract bleeding that required hospital admission, no increase occurred in the absolute risk.

The relative risk of upper gastrointestinal tract bleeding that required hospital admission was calculated. A modified version of the Cox proportional hazards method was used to adjust for the fact that the case group and the subcohort were not independent.

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Commentary

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