

DECEMBER 2003

Malignant melanoma: another risk reduced by NSAIDs?

Epidemiologists at Ohio State University have reported several analyses demonstrating that regular use of NSAIDs is associated with a reduced risk of certain tumours, notably cancers of the breast, lung and prostate. Using a case-control design, the Ohio investigators have also explored the factors that may contribute to the development of melanoma (*Oncol Rep* 2001;8:655-7).

They identified 110 middle-aged women with melanoma among patients attending cancer centres in New York and Ohio. They compared sun exposure and use of NSAIDs by each woman to that of six controls without melanoma matched for age, race and place of residence.

As expected, they found that melanoma was associated with increased episodes of sunburn before age 21 (3.2 in cases vs. 1.6 in controls; $p < 0.01$) and current sun exposure (10.6 vs. 6.2 hours/week; $p < 0.01$). Perhaps more surprisingly, regular NSAID use was associated with a 55% lower risk of melanoma: compared with no NSAID use, the odds ratio for melanoma in women who took at least one dose of an NSAID per day for at least 2 years was 0.45 (CI_{95%} 0.22, 0.92). The odds ratios for daily use of OTC ibuprofen (0.42) and aspirin (0.55) were not statistically significantly different but paracetamol was not associated with a reduction in risk (OR 0.95; CI_{95%} 0.45, 1.98).

There was also evidence of a dose-

response relationship, with greater NSAID use associated with decreasing risk. Adjustment for sun exposure or age did not alter the risk reductions.

Observational studies such as this do not prove that NSAIDs cause the reduced risk of melanoma. However, the association is strengthened by the dose-response relationship and a plausible hypothesis for the mechanism of action. The enzyme COX-2 is induced by exposure of human skin cancer cells to UV B and is inhibited by NSAIDs such as ibuprofen. The fact that paracetamol, which does not inhibit COX peripherally, had no apparent effect lends further support to a central role for COX-2.

'Little risk of serious GI toxicity' with OTC ibuprofen

Intermittent use of low-dose ibuprofen does not increase the risk of serious gastrointestinal (GI) toxicity for most people, say investigators at Stanford University, California (*J Rheumatol* 2003;30:2226-33). Their study provides scientifically robust evidence of the low risk associated with OTC ibuprofen.

The investigators determined the rates of serious GI events (e.g. GI bleeding, gastritis, GI-related admission to hospital) among 5692 patients with rheumatoid arthritis (RA) and 3124 patients with osteoarthritis (OA), who had taken ibuprofen, aspirin or paracetamol over a 6-month period.

In patients who were not taking other NSAIDs or corticosteroids, the three analgesics were associated with similar

modest rates of serious GI events per 1000 patient-years of use (ibuprofen: 3.1 for RA patients and 2.4 for OA patients; aspirin, 4.0 and 2.9; paracetamol, 2.6 and 2.1). Event rates were higher among patients who were also taking concurrent NSAIDs treated with other analgesics or corticosteroids but still not significantly different. However the rate of serious GI toxicity in these patients was significantly greater with paracetamol (15.0 per 1000 patient-years for RA and 12.0 for OA patients) than with ibuprofen (6.1 and 5.4) or aspirin (8.7 and 4.7). This finding could not be explained by preferential use of paracetamol by patients at increased risk and the investigators admitted it was a surprise.

Outcomes were then analysed according to the dose of analgesic; for ibuprofen, the categories were up to 100 mg/day, 101 - 1100 mg/day, 1101 - 2200 mg/day and over 2200 mg/day. The investigators assumed that the lowest daily doses were most likely to reflect intermittent use of OTC ibuprofen. Numbers were too small to estimate dose-response relationships but for ibuprofen there was evidence to distinguish between low and high doses. Event rates tended to be higher at doses of >2200 mg/day, and this difference was statistically significant for patients with RA who were taking NSAIDs and corticosteroids.

Overall, the investigators concluded that serious GI toxicity in these patients was largely attributable to known risk factors, such as other drug therapy and a history of GI disease. Among people taking analgesics alone at the lowest doses, there were 'low or even no GI event rates' - only one event occurred in either RA or OA patients in over 900 patient-years of use. This study supports the relative safety of ibuprofen, aspirin and paracetamol at OTC doses, the investigators conclude, particularly in patients not taking other drugs for their arthritis.

NSAIDs 'may delay or prevent onset' of Parkinson's disease

NSAIDs are associated with a reduced risk of developing Parkinson's disease (PD)

and their use may delay or prevent onset of the disease, say US investigators (*Arch Neurol* 2003;60:1059-64).

Using data from two large cohort studies - the 14-year Health Professionals Follow-up of 44,057 men and the 18-year Nurses' Health Study of 98,845 women - they compared the incidence of PD in NSAID users with that in non-users. 'Use' was defined as taking an NSAID (ibuprofen, indomethacin, naproxen, diflunisal, tolmetin or sulindac) 2 or more times per week for men or in most weeks for women.

A total of 415 new cases of PD were identified. Overall, the risk of PD was reduced by half among men and women who regularly used NSAIDs (Relative risk, RR, 0.50; CI_{95%} 0.29, 0.89, after adjustment for arthritis status). The risk declined with longer duration of NSAID use for up to 5 years. Similar analyses found that aspirin was associated with a statistically borderline risk reduction but paracetamol was not associated with a reduced risk of PD.

The investigators note that their findings support what is known about the effects of NSAIDs in experimental models of PD. An accompanying editorial suggests that the mechanism of action is probably a reduction in neuropathological inflammation secondary to COX inhibition (*Arch Neurol* 2003;60:1043-4). The author estimates that the number needed to treat (NNT) with NSAIDs to prevent one case of PD in 10 years is 98, which is comparable with currently established interventions such as preventing breast cancer with tamoxifen for 5 years (NNT 97).

Meta-analysis confirms NSAIDs protect against Alzheimer's

A new meta-analysis has confirmed that NSAIDs and aspirin are associated with a reduced risk of developing Alzheimer's disease, though the appropriate dose and duration of treatment remain unclear (*Br Med J* 2003;327:128-32).

The analysis, conducted by Canadian epidemiologists and a US neurologist,

included nine observational studies (six cohort plus three case-control) involving a total of 14,654 participants over 55 years old. NSAID use was defined very broadly as any use at any time during the study period.

Compared with non-users, NSAID use was associated with a relative risk (RR) of developing Alzheimer's disease of 0.84 (CI_{95%} 0.54, 1.05) in the cohort studies and 0.62 (CI_{95%} 0.45, 0.82) in the case control studies. Combining these data, the overall risk was significantly reduced (RR 0.72; CI_{95%} 0.56, 0.94); by contrast, the combined risk reduction with aspirin was not statistically significant (RR 0.87; CI_{95%} 0.70, 1.07), probably because of the relatively small number of participants involved.

Only one study investigated the possible effect of duration of use of NSAIDs: there was a significantly lower risk with long-term (>24 months) use (RR 0.27; CI_{95%} 0.13, 0.58) but not with short (<1 month) or intermediate (1 - 24 months) duration of use.

The authors acknowledge that methodological problems may have influenced their findings. Nevertheless, they conclude that their review of observational studies supports the hypothesis that NSAIDs may protect against the development of Alzheimer's disease, though the ratio of benefit to risk is still unclear.

Evidence 'insufficient' for advice on taking ibuprofen with aspirin

There is still insufficient evidence to formulate definitive advice about the use of ibuprofen by people taking low-dose aspirin, according to a *BMJ* editorial (2003;327:1298-9). The comment follows publication of another observational study showing that prescribed ibuprofen is not associated with an increased risk of myocardial infarction among older people taking aspirin prophylaxis (*Br Med J* 2003;327:1322-4).

The new study was carried out at Yale University in the United States. Investigators used a Medicare database to

identify 66,739 patients aged 65 or older who had been prescribed low-dose aspirin alone, or with ibuprofen (844 patients) or another NSAID (2,733 patients), when they were discharged from hospital following a myocardial infarction. They then compared the number of patients in each group who had died during the following year.

Overall, 17.5% of patients prescribed only aspirin, 14% of those prescribed aspirin and ibuprofen, and 15.8% of those prescribed aspirin and another NSAID, died within a year. After adjustment for risk factors such as medical history, there was no statistically significant difference between the groups in the risk of death (hazard ratio for ibuprofen plus aspirin vs. aspirin alone 0.84; CI_{95%} 0.70, 1.01).

The *BMJ* commentary notes that two other observational studies have reported an increased risk among people taking both aspirin and regular (but not intermittent) ibuprofen, but points out that both suffer from a small sample size and other methodological weaknesses. The latest study also has its problems - for example, it did not account for use of over-the-counter drugs. With these misgivings, the authors say it is not yet possible to make a definitive recommendation about the use of ibuprofen by people taking prophylactic aspirin. Until firm evidence becomes available, they conclude, efficacy and the risk of bleeding should determine the choice of analgesic and anti-inflammatory medication.

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