

Newsletter



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

New evidence suggests that ibuprofen - but not other NSAIDs, aspirin or paracetamol - may delay or prevent the onset of Parkinson's disease (PD).

The finding comes from a preliminary analysis of a large prospective study of 146,565 participants in the American Cancer Society's Cancer Prevention Study II Nutrition Cohort, presented on April 14th at the American Academy of Neurology meeting in Miami Beach.

Between 1992 and 2000 there were 413 new cases of PD in the cohort. Ibuprofen was associated with 35 percent lower risk of PD (relative risk, RR, 0.65; CI_{95%} 0.48 - 0.88), with similar risk reductions for men and women and regardless of age or smoking status.

There was a significant trend for lower risk with increasing consumption of ibuprofen (from RR 0.73 with fewer than 2 tablets per week to RR 0.61 for daily use) but duration of use made little difference. No significant associations were found for aspirin, other NSAIDs (though numbers were low) or paracetamol.

The authors commented that their study confirms their earlier analysis of the Health Professional's Study and the Nurses Health Study, which showed that non-aspirin NSAIDs were associated with a 45 percent lower risk of Parkinson's disease (*Arch Neurol* 2003;60:1059-64).

Ibuprofen may act by reducing the inflammation in areas of the brain affected by PD, though whether such changes are contribute to, or are caused by, PD is presently unclear.

NSAID plus PPI preferred over coxib for high-risk patients

A non-selective generic NSAID plus gastroprotection with a proton pump inhibitor (PPI) is more cost effective treatment than a coxib for patients at high risk of gastrointestinal (GI) complications or a cardiovascular event, say US economists (*Arthr Rheum* 2005;53:185-97).

There are several reasons why older treatments may be preferable to a coxib, they argue. Coxibs only offer a small absolute reduction in the risk of ulcer complications compared with older NSAIDs and this is not enough to offset their higher costs. They have not been shown to be confer a lower GI risk than an NSAID plus a PPI in high-risk patients. The risk reduction is abolished by concurrent aspirin, so the coxibs offer no GI benefit for patients at increased cardiovascular risk. Furthermore, the coxibs have been associated with an increased risk of cardiovascular events.

The analysts constructed an economic model to compare the cost effectiveness of three strategies - a non-selective NSAID alone or combined with a PPI, or a coxib alone - for treating a cohort of patients aged 60 who had moderate to severe arthritis pain.

They found that, over one year, an NSAID cost \$650 per patient treated and 96.1 percent of patients were free of ulcer complications. Treatment with an NSAID plus PPI cost \$1557 and, compared with NSAID monotherapy, prevented an ulcer in an additional 2 percent of patients at a cost of \$45,350 per additional ulcer avoided. Treatment with a coxib cost \$1572 and was less effective in preventing ulcers than an NSAID plus PPI (97.3 percent). The cost per quality-adjusted life-year (QALY)

gained by using an NSAID plus PPI was \$302,333.

Subgroup analysis showed that an NSAID plus PPI and a coxib were equally cost effective in patients at low risk of GI complications, with each ulcer avoided costing >\$60,000 and each QALY gained >\$300,000 compared with an NSAID alone. However, in patients at high risk of GI complications, whether or not they were taking low-dose aspirin (and therefore at risk of cardiovascular events), an NSAID plus PPI was more cost effective than a coxib: the additional cost per ulcer avoided fell to \$4,000 - \$16,000 and the cost per QALY gained to \$28,000.

The authors conclude that an NSAID plus PPI is the preferred treatment for high-risk patients and an NSAID alone remains the most cost effective option for low-risk patients.

MHRA recommends alternatives to co-proxamol

Following its decision to withdraw co-proxamol by February 2006, the Medicines and Healthcare Products Regulatory Agency (MHRA) has published guidance to prescribers on selecting analgesics - including ibuprofen (http://medicines.mhra.gov.uk/ourwork/monitor-safequalmed/safetymessages/co-proxamol_healthprofessional.pdf). The guidance is intended for doctors switching patients from co-proxamol during the forthcoming months and to recommend alternative drugs for the treatment of new cases of mild to moderate pain.

The MHRA classifies pain as acute and self-limiting, either alone or against a background of chronic pain (Class I - for example, due to low back pain or osteoarthritis); or as chronic pain (Class IIa) which may be stable (Class IIa - osteoarthritis) or progressive (Class IIb - cancer pain, diabetic neuropathy).

The management of Class I pain is a 4-step process:

- Step 1 paracetamol
- Step 2 substitute ibuprofen
- Step 3 add paracetamol to ibuprofen
- Step 4 continue paracetamol but replace ibuprofen with a different NSAID

The low potency opioids codeine and dihydrocodeine are alternatives to an NSAID at

Steps 2 and 3, and may be added at Step 4 if pain is not controlled.

Class IIa pain is treated in a similar way except that the use of a low potency opioid should be considered earlier; if this does not control pain, a tricyclic antidepressant or an anticonvulsant should be considered. The treatment of Class IIb pain is similar to that for Class IIa except that a tricyclic or anticonvulsant should be considered earlier. Strong opioids such as morphine are also indicated for patients with severe Class IIb pain but the MHRA says this is outside the scope of its guidance.

Ibuprofen better for OA pain

A French clinical trial has shown that OTC doses of ibuprofen are more effective than paracetamol in relieving pain in patients with osteoarthritis (*Ann Rheum Dis 2004;63:1028-34*).

The IPSO study (Ibuprofen, Paracetamol Study in Osteoarthritis) randomised 222 patients with osteoarthritis of the knee (70 percent) or hip (30 percent) to treatment with ibuprofen 400 mg or paracetamol 1,000 mg, each taken three times daily. Six hours after the first dose, ibuprofen reduced pain scores by significantly more. After 14 days, ibuprofen was associated with significantly greater reduction in pain intensity, stiffness and pain and significantly greater physical functioning. There was no difference in adverse effects.

Ibuprofen was therefore the more effective analgesic in single or multiple doses (though the total daily dose of paracetamol was lower than is used in the UK). The authors conclude that ibuprofen has a superior efficacy/tolerability ratio.

NSAIDs linked to lower breast cancer risk

Long-term use of ibuprofen or aspirin is associated with a lower risk of breast cancer in women with hormone receptor-positive tumours say US epidemiologists (*J Am Med Assoc 2004;291:2433-40*).

They compared the use of ibuprofen, aspirin or paracetamol in 1,442 women with breast cancer and 1,420 controls. After adjusting for age at diagnosis, body mass index and use of other medicines, those who reported taking ibuprofen or aspirin at least once weekly for at least 6 months had a significantly lower risk of breast cancer than controls (odds ratio, OR,

0.80; CI_{95%} 0.66 - 0.97). The risk was even lower among those who took 7 or more tablets per week (OR 0.72; CI_{95%} 0.58 - 0.90) and among regular users (OR 0.74, CI_{95%} 0.59 - 0.92) but duration of use was not significant. There was no reduction in risk associated with paracetamol.

Subgroup analysis revealed that statistical significance was maintained for aspirin alone but not for ibuprofen, which was taken by fewer women. The reduced odds with aspirin occurred in women with hormone receptor-positive tumours, suggesting that NSAIDs may reduce breast cancer risk via COX inhibition, reducing the synthesis of prostaglandins that induce aromatase activity and therefore reducing the synthesis of oestrogen.

Ibuprofen for migraine in children

New US guidelines on the management of migraine in children state that ibuprofen is effective and should be considered as a first-line agent for acute treatment (*Neurology* 2004;63:2215-24).

The American Academy of Neurology (AAN) defines the objectives of treatment as:

- rapid and consistent headache relief without recurrence
- restore the patient's ability to function
- minimise use of back-up and rescue medication
- optimise self-care and minimise use of resources
- cost effective
- minimal or no adverse effects

The AAN cites two randomised trials which provide strong evidence to support its recommendation for ibuprofen. One found a response rate (headache relief at 2 hours) of 68 percent vs. 37 percent with placebo in 4 - 16 year-olds at a dose of 10 mg/kg (p<0.05); the other, conducted in 6 - 12 year-olds treated with 7.5 mg/kg, reported a response rate of 76 percent vs. 53 percent with placebo (p=0.006). Adverse effects are described as 'infrequent'.

The principles of treating migraine in children are the same as for adults, says the AAN. In particular, agents such as the triptans should be used when an NSAID fails to provide relief of headache. The alternatives to ibuprofen are paracetamol, which is considered 'probably effective', and nasal sumatriptan; there are no data on the efficacy of oral triptans in children and adolescents.

Stop ibuprofen the day before surgery?

A study of the effects of ibuprofen on platelet activity has concluded that it may be sufficient to stop ibuprofen on the day before surgery rather than one week ahead (*Ann Intern Med* 2005;142:506-9).

It's not unusual for surgeons to recommend stopping regular ibuprofen treatment one week before surgery to avoid the risk of bleeding complications - but there's no evidence to support this practice. US investigators have now studied the duration of platelet inhibition after discontinuing ibuprofen following a week's administration of 1,800 mg/day to health volunteers. (The usual dose of OTC ibuprofen is 200 - 400 mg three times daily.)

They measure platelet activity with a platelet function analyser, which records the time taken for platelets to aggregate after exposure to a membrane coated with collagen and adrenaline. This is denoted as the closure time; a value of 167 seconds is the threshold corresponding to abnormal platelet function.

Before taking ibuprofen, all participants had normal platelet function (median closure time 130 seconds). Forty minutes after taking the last dose of ibuprofen, median closure time was 225 seconds, though it was below the critical value of 167 in 4 of the volunteers. After 8 hours, median closure time was reduced to 138 seconds, with 7 participants now below the threshold for abnormality. After 24 hours, the median closure time had returned to baseline (120 seconds) and all participants were within the normal range.

The authors acknowledge that they did not measure actual bleeding time but they say their method is more accurate. They also found that oral contraceptive use mitigated the effects of ibuprofen on platelet activity.

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