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NEWS BRIEFS from the Aspirin Foundation

Aspirin and NSAIDs to prevent Alzheimer's disease - A BMJ review

Growing evidence from observational studies 'lends support to the hypothesis that NSAIDs may protect against the development of Alzheimer's disease.' This was the conclusion of a BMJ review of studies from 1996 to 2002 that examined NSAID use in preventing Alzheimer's. Nine studies looked at all NSAIDs in adults over 55 years old. Six were cohort studies involving 13,211 participants and three were case-control studies of 1443 participants. The pooled relative risk of Alzheimer's disease among NSAID users was 0.72 (95% confidence interval 0.56 to 0.94). The longer the people had used NSAIDs, the lower their risk of Alzheimer's, so that it fell from 0.95 in users for less than 1 month, to 0.83 to those taking NSAIDs for under 24 months and to 0.27 among users for more than 24 months. The pooled relative risk for aspirin alone for all studies and all users was 0.87 (95% confidence interval 0.70 to 1.07).

The authors concluded that use of an NSAID lowers the risk of developing Alzheimer's disease and that there is greatest benefit with long term use, especially over two years. They agree that the studies also show that aspirin has a protective effect, but the magnitude of the effect is less clear than for NSAIDs because few studies specifically evaluated the effects of aspirin. They state that there are not enough data on which to base a comparison between aspirin and other NSAIDs in the prevention of dementia.

They add that although a few randomised controlled trials have shown some benefit in cognition with NSAIDs in patients with established Alzheimer's disease, there are as yet no randomised controlled trials that have looked at prevention. They also add that the relative benefit of COX-2 selective inhibitors over traditional NSAIDs is purely speculative.

They wait for more trials on which to base the appropriate dose, duration and ratios of risks to benefits of anti-inflammatory agents in Alzheimer's.

Reference Etmnan M, Gill S, Samii A Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. Brit Med J 2003; 327: 128-131.

Reye's Syndrome – New UK Label Warning

From 1st October 2003 all aspirin products must carry the warning '**Do not give to children under 16 years of age unless on the advice of a doctor**'. From that date packs without such a warning should not be sold. Most aspirin manufacturers have been putting this warning on aspirin packs since March this year in anticipation of the change.

Pharmacists will have cleared incorrectly labelled stock from their shelves by the end of September. This requirement also applies to stocks in grocery and convenience stores and newsagents.

Background to the warning: Understanding of Reye's Syndrome

What is Reye's Syndrome?

Reye's Syndrome (RS), first described by Dr Ralph Reye in 1963, is an extremely rare, sometimes fatal, disorder. RS occurs almost exclusively in children with only 2 cases reported in the last 2-3 years. It can affect all organs of the body but is most harmful to the brain and the liver, where it may cause raised intracranial pressure or liver failure.

Signs and Symptoms:

The signs and symptoms of RS are almost always preceded by a viral illness such as flu or chicken pox. The most common signs and symptoms include recurrent or persistent vomiting, listlessness, personality changes such as irritability, disorientation or confusion. In the latter stages, breathing can become sluggish and the child can experience a loss of consciousness. Although severity varies, RS should be considered to be life threatening.

Can aspirin usage cause Reye's Syndrome?

A causal link between aspirin and RS has not been proven. The exact causes of RS remain a mystery. Some studies have shown that ingestion of aspirin by children during and after a viral illness, such as chickenpox or flu, have been associated in the development of Reye's syndrome. However, a high percentage of Reye's cases reported occurred without aspirin usage.

New Labelling

The Medicines and Health products Regulatory Agency (MHRA) has announced new labelling for the use of aspirin in 12-15 year olds. The MHRA has taken this step as a purely precautionary measure following advice from the Committee on Safety of Medicines (CSM), in relation to the yet unproven link between aspirin and RS in children.

The change in legislation is an extension of the current situation restricting the use of aspirin in under 12 year olds, to include 12-15 year olds.

The wording on the packs of aspirin containing products will be, **'Do not give to children under 16 years of age, unless on the advice of a doctor'**. A causal link between aspirin and Reye's syndrome remains unproven and people aged 16 and above should be re-assured that this is an extremely cautious approach and should not affect the way they take the product.

Facts about aspirin

- Aspirin has been available for over 100 years and is used by millions of people to effectively treat pain, reduce inflammation and to reduce fever/raised temperatures.
- Aspirin is the most widely used medicine in the world with an estimated 100 billion tablets swallowed every year.
- Aspirin substantially reduces the risk of heart disease and stroke in millions of people in the UK alone, by virtue of its anticoagulant properties.
- Even now research scientists are still finding out more about the effects of aspirin in the body and their discoveries are opening up further possibilities for future applications. Probably the most significant of these is the role aspirin plays in the prevention of blood clots. Small daily doses of aspirin may help prevent diseases such as heart attacks, strokes and the blindness and kidney damage suffered by many patients with diabetes. Here clots blocking a major blood vessel cause the damage.
- There has been a small number of clinical studies set up recently to look at the effect of taking aspirin in the prevention of deep vein thrombosis.
- Aspirin research continues and in the future we may see aspirin being used for the treatment of cancers and Alzheimer's disease.
- Most of the drugs that were launched at the same time as aspirin have long since disappeared, replaced by newer and more effective drugs. But aspirin goes from strength to strength. And given the pace of current research

into new uses for the drug it seems likely that it will still be available long into the next century.

Night time aspirin lowers blood pressure

The time of day that an aspirin is taken may make a significant difference to its effect on blood pressure. Dr Ramon C Hermida and colleagues of the University of Vigo, in Spain, have reported that taking aspirin at night lowers blood pressure more than doing so in the daytime.

They studied the effects on blood pressure in 100 untreated mildly hypertensive mainly middle aged men and women who took aspirin at different times of the day. They were randomly divided into 3 groups. One was given only recommendations on lifestyle and diet. Another was given the same plus aspirin 100 mg per day in the morning, and the third was given the same recommendations and the same dose of aspirin before bedtime. Blood pressure was measured every 20 minutes during the day and every 30 minutes at night for 48 consecutive hours before starting, and 3 months after starting their treatment.

After 3 months, patients in the lifestyle/diet group with no aspirin showed a small, nonsignificant reduction of blood pressure. Their results did not differ significantly from those also given morning aspirin. However, there was a highly significant fall in blood pressure (of 6mm Hg systolic and 4mm Hg diastolic pressure – $p < 0.001$) for those receiving their aspirin before bedtime. The authors suggested that night time low dose aspirin has an extra benefit in lowering blood pressure over the same dose of aspirin given in the morning to patients with mild hypertension. They add that there is a need to determine in more detail aspirin effects in patients using it along with antihypertensive drugs.

(Hermida RC et al. Administration time-dependent effects of aspirin on blood pressure in untreated hypertensive patients. Hypertension 2003; 41(6):1259-67)

Aspirin kills H. pylori and increases its susceptibility to antibiotics

In vitro, aspirin inhibits the growth of H pylori and enhances the bacterium's susceptibility to antimicrobial agents. Dr Benjamin Wong of Hong Kong found these properties of aspirin could be used to develop anti-H.pylori treatments in the future. It also suppresses the mutagenic effect of metronidazole.

Dr Wong states that aspirin and related compounds may induce programmed cell death in newly cancerous cells: this may explain the inverse relationship between them and gastric cancer. However, the effect on H pylori may also be anti-carcinogenic, as infection with it puts patients at higher than normal risk of gastric cancer. Aspirin inhibited growth of all 63 strains of H pylori tested at a

concentration of 100g/ml and was lethal at 400g/ml.

As well as directly affecting *H pylori* strains at a wide range of pH, aspirin also lowered minimum inhibitory concentrations (MICs) of amoxicillin, metronidazole and clarithromycin in strengths comparable to those found in plasma after therapeutic aspirin doses. It also brought down the MICs for four strains of *H pylori* resistant to metronidazole and one to clarithromycin respectively. In contrast, the MICs for *Escherichia coli* rose after exposure to aspirin.

Giving aspirin and metronidazole together was strongly synergistic in decreasing *H pylori* colony formation. Dr Wong suggests that incipient mutant bacteria might first be weakened by metronidazole then killed by aspirin. However, he adds that because aspirin may cause peptic ulcer it will not be used along with antibiotics against *H pylori* or as a prophylaxis against it. It is a pointer to the use of similar drugs in the future that may have less ulcerogenic effects. The team is currently studying the effects of COX-2 inhibitors.

Reference Wong BCY Aspirin kills H pylori and increases its susceptibility to antibiotics. Gut 2003; 52: 490-5.

Flaws in the DVT Best Study debated

The BEST study examined prospectively the incidence of deep vein thrombosis in people taking long haul flights. It used venous scans and raised D-dimer levels to detect DVTs and people with increased risk of DVT in 899 passengers, 180 of whom travelled in business class.

Of the 434 subjects who underwent a full venous scan, none had any evidence of DVT. Seventy-four of the 899 passengers had raised D-dimers after their journeys: they included 22 of the 180 in business class (12%) and 52 of the 719 in economy class (7%). None had a DVT. Of 505 passengers followed up in the next 6 months, none had had any symptoms of DVT or pulmonary embolus. None of the passengers had used compression stockings.

The class of travel made no difference to the risk from DVT, which was extremely low in this study – much lower than in other studies of DVT in airline passengers.

There was no association between smoking or sleeping tablet use and D-dimer level, but those who had taken aspirin did have higher D-dimer levels than those who had not. The

authors, Barry F Jacobson and colleagues, of the Universities of the Witwatersrand and the Guy's King's and St Thomas's Schools of Medicine, state in the publication that aspirin is unlikely to cause thrombosis. Instead it might have falsely elevated D-dimers in patients who reacted to it with gastritis, or patients who used it might have been in a higher risk group in the first place. However, Professor Jacobson was reported to have said in a comment to the press that while aspirin prevents clots in arteries, the evidence for its preventing venous thrombosis is far less convincing.

Professor Colin Prentice, author of the report of the Pulmonary Embolism Prevention (PEP) Trial Collaborative Group (The Lancet 2000; 355: 1295-1302) strongly disagreed with this statement. His report showed a significant benefit in the prevention of deep vein thrombosis following surgery for hip fractures – aspirin reduced post-operative DVT by 36% and pulmonary embolism by 43%. Professor Prentice asked for aspirin to be given routinely in all surgical and medical groups at high risk of venous thromboembolism. Commenting on the interpretation of the BEST study's results for Aspirin Briefs, he said that the authors had 'fallen into the trap of surrogate endpoints'. Professor Prentice would not place any reliance on a study looking at D-dimer alone without clinical events. The results on aspirin use, he said, were invalid as that part of the study was not controlled with a randomised aspirin versus placebo trial. He and his colleague, Professor Rory Collins of the CTSU, Radcliffe Infirmary, Oxford are preparing an article for the Lancet to re-affirm the usefulness of aspirin for persons taking long haul flights.

Reference: Jacobson BF Munster M Smith A et al. The BEST study – a prospective study to compare business class versus economy class air travel as a cause of thrombosis. South African Medical Journal 2003; 93: 7, 521-8.

Pharmacists improve aspirin prophylaxis in diabetes in primary care practice

Since 1997 the American and British authorities in diabetes have been promoting aspirin prophylaxis against cardiovascular events in high risk patients with diabetes. However, only a small minority of them have actually been given aspirin. Only around 20% of patients with diabetes were found to be taking aspirin in the most recent United States National Ambulatory Medical Care (NAMC) survey.

Pharmacists working in a New York State rural primary care clinic therefore set out to see if they could improve aspirin prophylaxis in their population of diabetics. Eighty five diabetic patients identified from their records and clinic visits were advised, either at interview or by telephone, to take enteric coated aspirin 81 mg per day. Only 28 (33%) had been taking it at the baseline. By the end of the study, 70 (82%) were taking daily aspirin or had accepted the recommendation to start the therapy. Two patients declined to take it, eight had contraindications to its use, and two were found not to have an indication to take it.

The authors proposed that their method of improving aspirin prophylaxis in their primary care environment would be a template for patients with diabetes in other settings. Pharmacists may be more important than doctors in persuading patients with diabetes to improve their compliance with the guidelines.

Reference: Faragon JJ Waite NM Hobson EH et al. Pharmacotherapy 2003; 23(1): 73-9.

Aspirin and ibuprofen – a help for people who can't stop smoking

People who absolutely can't stop smoking may be helped by using aspirin or ibuprofen daily. This proposal comes from a study of C-reactive protein (CRP) levels in non-smokers and in current smokers and ex-smokers ("ever-smokers"). Raised CRP is a marker for systemic inflammation and for cardiovascular disease. Data from 8,850 adults over 17 years old established that the ever-smokers (who included quitters and current smokers) had higher CRP levels than never-smokers. However, the ever-smokers who regularly took aspirin or ibuprofen had lower CRPs than the ever-smokers who did not. This was so even when the use of aspirin or ibuprofen was low. In particular, low use of ibuprofen was related to a lower risk of having a raised CRP than no use of ibuprofen alone.

Smoking is certainly a high risk factor for cardiovascular disease. If people can't stop smoking then they should consider ibuprofen or aspirin prophylaxis against it.

Reference: Mainous AG Pearson WS Aspirin and ibuprofen: potential mediators of the cardiovascular risk due to smoking? Family Medicine 2003; 35(2): 112-8

'Aspirin and Cancer' Conference: Bart's Hospital

The Aspirin Foundation will be holding a one day conference in the Great Hall at Bart's on Monday 10th November to highlight some of the established and potential new areas of aspirin and cancer.

Professor Gordon McVie, ex Director General of Cancer Research UK will chair the meeting and a team of highly distinguished scientists will make presentations on subjects including aspirin in the treatment of bowel cancer, prostate and bladder cancer, mammary cancer and cancer of the skin. We will also be looking into current research support and progress in cancer control.

Members of the medical and pharmaceutical media will be invited to attend the meeting as the Aspirin Foundation believes that the medical and paramedical professions will benefit from an up to date story of the current position in this area of treatment and research. Medical students will also be invited to attend the conference and professional accreditation is being applied for.

Aspirin Foundation website

A reminder of the Aspirin Foundation's website located at www.aspirin-foundation.com

You can find information on the history of aspirin over the last 100 years; details of its current therapeutic uses; things you should know before taking aspirin; the chemistry of aspirin; conference proceedings and publications as well as news stories and earlier Aspirin News Briefs.

Further information from:

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