Science Vision

Magic Powders

Sadaf Sheikh[1], Mohammad Saeed[2]
Aga Khan University, Karachi, Pakistan[1], Northwestern University, Chicago, USA.[2]

Aspirin's gender bias

Aspirin reduces the risk for myocardial infarction (MI), but not stroke, in men.[1] These researchers from Harvard aimed to determine whether aspirin would be effective primary prevention for cardiovascular events in women who are at higher risk for stroke than for MI.

They randomized about 40 thousand women (mean age 55 years) without heart disease, prior stroke, or other major chronic health conditions to take aspirin (100 mg every other day) or placebo and followed them for an average of 10 years. The main endpoint was major cardiovascular outcomes (nonfatal MI, nonfatal stroke, and fatal cardiovascular events).

There were 391 ischemic strokes (170 with aspirin, 221 with placebo), 92 hemorrhagic strokes (51 aspirin, 41 placebo) and 424 transient ischemic attacks (186 aspirin, 238 placebo). Overall, there was a 17% decrease in stroke risk attributable to aspirin use and a nonsignificant increase in hemorrhagic stroke risk (relative risk, 1.24; 95% confidence interval, 0.82-1.87). Women older than 65 years derived the greatest benefits. Compared with placebo recipients, aspirin users had 26% fewer major cardiovascular events and 30% fewer ischemic strokes. In a meta-analysis of this study and five other antiplatelet primary-prevention trials, the authors demonstrated that aspirin was effective in reducing stroke risk in women and MI risk in men.[2]

These findings support a sex-specific reduction in risk for first stroke or TIA with low-dose aspirin, particularly in women older than 65 years. However, it is quite plausible that the ineffectiveness of aspirin for MI prevention in women may be due to the low dosage employed in this study.[3] Additionally the majority of women included in this study had a less than 5% risk of MI and would not have received aspirin for primary prophylaxis.[3]

1. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med. 1989 20;321:129-35.
2. Ridker PM. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352:1293-304.
3. Schwartz D J. Aspirin in the Prevention of Cardiovascular Disease in Women. N Engl J Med 2005;352:2751-2.

NSAID-Induced Small Bowel Pathology

It is commonly believed that NSAIDs cause ulcerations only in the stomach and duodenum. Using video capsule enteroscopy (in which a tiny video camera is swallowed and transmits images of to an external recorder) the present study[1] demonstrated that NSAIDs cause ulcertions also in the jejunum, ileum, and colon.

Forty healthy volunteers received a 2-week course of slow-release diclofenac (75 mg twice daily) along with omeprazole for gastric protection. Capsule enteroscopy was carried out on the day before starting diclofenac and repeated on day 14. Sixty-eight percent of subjects developed new small-bowel pathology. The commonest lesions were mucosal breaks, seen in 40%, which were seen to be bleeding in 5%, reddened folds in 35%, petechiae 33%, denuded mucosa 20% and blood in the lumen without a visualized source in 8%. Fifteen of the 27 subjects had more than one lesion concurrently.

These results suggest a high incidence of small-bowel pathology after a short course of NSAID therapy.

1. Maiden L. A quantitative analysis of NSAID-induced small bowel pathology by capsule enteroscopy. Gastroenterology 2005;128:1172-8.

New Drug for Type 2 Diabetes

Successful management of Type 2 Diabetes (DM2) remains a tight rope walk. For patients on metformin therapy who require further glycemic control, a new injectable drug was recently approved by the FDA. Exenatide (Byetta) is a Glucagon-like peptide 1 (GLP-1) receptor agonist. GLP-1 is an intestinal peptide secreted in response to meals and stimulates insulin secretion. In a moderate sized randomized controlled trial, 336 patients with suboptimally controlled DM2 during metformin monotherapy (mean glycosylated hemoglobin [HbA_{1c}] level, 8.2%) received placebo or exenatide (5 or 10 μg), injected subcutaneously twice daily. Metformin therapy was

continued. At 30 weeks, mean HbA_{1c} levels increased by 0.1% in the placebo group and decreased by 0.4% and 0.8%, respectively, in the 5-µg and 10-µg exenatide groups. Compared with placebo, exenatide reduced postprandial glucose excursions and induced weight loss (mean of 2 kg). The difference between placebo and exenatide groups was statistically significant for all these endpoints. Exenatide frequently caused nausea, but this adverse effect tended to lessen over time. The incidence of hypoglycemia was similar in all groups.

Although injectable, exenatide adds another option for patients with type 2 diabetes who require additional therapy. The authors suggest more data on longer-term outcomes are needed. This is the second injectable noninsulin diabetes drug to be FDA-approved in recent months: The other is pramlintide (Symlin; a synthetic analog of the pancreatic hormone amylin), which lowers blood glucose levels by several mechanisms.

1. DeFronzo RA. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005;28:1092-100.

Do "Seizures beget seizures"?

A major issue in treatment of epilepsy is to start a patient on medication after the first seizure summarized in the famous quote of Sir William Gowers[1], "seizures beget seizures". In other words, repeated seizures might make chronic epilepsy more likely. Marson and colleagues[2] conducted a large and adequately powered study that examined several issues associated with starting medication at first-seizure presentation. Their major finding is that, in this group of patients, delaying medication does not increase the risk of chronic epilepsy. Other findings of the study included the lack of improvement of the quality of life with immediate treatment and a minute decreased risk of proximate seizures with little long-term gain in starting medications immediately. This conclusion applies to the practical problem of starting therapy after the first or few seizures- it does not imply that withholding therapy in the face of ongoing multiple seizures is appropriate.

In terms of demographics, the study population was mainly teenagers and young adults. Whilst this age is typical of the first-seizure patients seen by neurologists, new-onset epilepsy is actually most common in young children and the elderly. Findings of Marson et al. broadly apply to these populations. Additionally, it should be acknowledged that "epilepsy" is not a single condition. Aggressive early treatment of certain progressive epilepsies might be beneficial, but this is an area for future research. This study contributes good quality evidence for the discussion with patients and families about the advisability of medication. In what is often a difficult situation, good data coupled with a clinical synthesis of the risks and benefits that are tailored to the patient's circumstances will contribute to optimum treatment decisions.

1. Gowers WR. Epilepsy and other chronic convulsive disorders: their causes, symptoms and treatment. London: J&A Churchill, 1881.
2. A Marson, A Jacoby, A Johnson, L Kim, C Gamble, D Chadwick. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomized controlled trial, Lancet 2005; 365:2007-13.

COX-2 inhibitors and neuronal death

A recent report in Nature Medicine by Kukar et al has raised an interesting question: Can NSAIDs be detrimental in Alzheimer's disease? The authors found that COX-2 inhibitors increased the production of toxic amyloid-ß (Aß) peptide, which is widely accepted as having a key role in the progression of Alzheimer's disease, by inhibiting Y-secretase activity.

COX-2 is increased during inflammation, resulting in the synthesis of pro-inflammatory prostanoids, whereas COX-1 is constitutively expressed and may be involved in the physiological production of prostanoids. Kukar et al[1] show that some NSAIDs can increase Aß42 production while lowering levels of the less toxic shorter Aß40 peptides. Interestingly, NSAIDs with high specificity for COX-2 often increased Aß42 levels, whereas specificity for COX-1 tended to reduce them. Acute delivery of celecoxib to mice for three days resulted in almost twofold higher levels of Aß42 than in control mice. In contrast to previously described Aß42 lowering NSAIDs with low brain penetrance, celecoxib levels were 2-3 fold higher in the brain than in plasma-suggesting different drug metabolism at these sites or selective uptake in the brain.

Other compounds including the lipid-lowering drug Fenofibrate were found to increase Aß42 production. These compounds seem to target the gamma-secretase complex, increasing gamma-secretase-catalyzed production of Abeta42 in vitro. Thus the chronic pharmacological modulation of Y-secretase to augment Aß42 production may promote Alzheimer's disease. Understanding these modulators may help in the design of new inhibitors of Aß production and the development of new drugs for the treatment of Alzheimer's disease while at the same time increasing caution at the use of COX-2 inhibitors. The effects of NSAIDs on Aß production open the possibility that these drugs affect Alzheimer pathogenesis more directly and independent of inflammation.

1. Kukar T. Diverse compounds mimic Alzheimer disease-causing mutations by augmenting Abeta42 Production. Nat Med 2005;11:545-50.